Nutrition compartments are important factors in healthy life and stress biology. Not only modification on the diet but also changes in frequency of nutrition intake cause changes in endocrine and monoamine synthesis. These changes may affect the susceptibility to stress. Increased brain serotonin activity appears to be a prerequisite for maintaining control over cognitive information processes and involvement in learning and memory. Dietary modification may affect the availability of L-Trp, which has been reported to result in increased brain levels of L-Trp and elevated rates of serotonin synthesis and metabolism. The presence of large amounts of omega-3 PUFAs in the brain is indicative of the major role that these compounds play in the structure and function of this organ.

The effects of meal size on attention and mood indicated that subjects who ate a larger than usual lunch made more errors on attention and search tasks than those who ate a normal-sized lunch or one smaller than usual. Performance improved to a greater degree after the small lunch in subjects who typically ate a heavy lunch than in those who ate a light lunch. Further, afternoon snacks may also have positive effects on cognitive performance. For positive influences on stress, mood and cognitive function foods of plant origin have to be preferred. They are rich in minerals, phytochemicals, trace elements and vitamins, which show wide variety of positive effects on health.

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Impression

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11ß-HSD 1	11ß-hydroxysteroid dehydrogenase type 1
5-HT	5-Hydroxytryptamine (Serotonin)
ACTH	Adrenocorticotropic hormone
AD	Alzheimer Disease
ALA	α-Linolenic Acid
ALC	Acetyl-L-carnitine
AN	Anorexia Nervosa
BCAA	branched-chain amino acids
Bcl-2	B-cell lymphoma 2
BDNF	Brain-derived neurotrophic factor
BED	binge eating disorder
BMI	body mass index
BN	Bulimia Nervosa
cAMP	cyclic AMP
CBG	corticosteroid-binding globuline
CCK	Cholecystokinin
CeA	Central nucleus of the amygdala
CMA	Chronic Metabolic Acidosis
cNOS	constitutive Nitric Oxide Synthase
CNS	Central nervous system
CR	Caloric Restriction
CRF	corticotrophin Releasing Factor
CRH	Corticotropin-releasing hormone
DA	Dopamine
DHA	Docosahexaenoic acid
DHT	Dihydrotestesterone
DOPA	Dihydroxyphenylalanine
EMS	Eosiniphilia myalgia syndrome
eNOS	enothelial Nitric Oxide Synthase
EODF	every-other-day fasting
EPA	Eicosapentaenoic acid
ERK	Extracellular signal-regulated kinase
FA	fatty acid
FFA	Free Fatty Acids
FSH	follicle-stimulating hormone
fT3	Free Triiodothyronine
fT4	Free prohormone thyroxine
GABA	γ-Aminobutyric acid
GC	Glucocorticoid

GD50	Gestation Day 50
GH	Growth Hormone
GIT	Gastrointestinal Tract
Glu	Glutamine
GnRH	Gonadotropin releasing hormone
HD	Huntington's Disease
HIAA (5-HIAA)	5-hydroxyindolacetic acid
His	Histidine
HPA	hypothalamic-pituitary-adrenal
IGF	Insulin Growth Factor
IL	Interleukin
INF	Interferon
iNOS	inducible Nitric Oxide Synthase
IQ	intelligence quotient
LC-PUFA	Log chain PUFA
LH	Luteinizing Hormone
LNAA	large neutral amino acids
LPS	Lipopolysaccharides
Lys	Lysine
MDD	Major depressive disorder
MHC	Major Histocompatibility Complex
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI	Magnetic resonance imaging
MSG	Monosodium glutamate
MUFA	Mono unsaturated fatty acid
NE	Norepinephrine
NK	cell natural killer cell
nNOS	neuronal Nitric Oxide Synthase
NO	Nitric Oxide
NPC	Neural precursor cells
NPY	Neuropeptide Y
OCD	Obsessive Compulsive Disorder
OS	Oxidative Stress
PBLs	peripheral blood leokocytes
PC	Phosphatidylcholine
PD	Parkinson's disease
Phe	Phenylalanine
PS	Phosphatidylserine
PS60	prenatal stress

PUFA	Poly Unsaturated Fatty Acids
PVN	paraventricular nucleus
REM	Rapid eye movement
ROS	Reactive oxygen species
rT3	Reverse Triiodothyronine
SHB	Sex hormone binding
T3	Triiodothyronine
T4	Prohormone thyroxine
TNF	Tumor necrosis factors
TRH	thyrotropin-releasing hormone
TSH	thyroid-stimulating hormone
Trp	Tryptophan
TSST	Trier Social Stress Test
Tyr	Tyrosine
WHR	Waist Hip ratio

1. Introduction

The term "stress" describes the state of the organism under the influence of external or internal forces or "stressors", which threaten to alter its dynamic equilibrium or homeostasis. Stress needs stressful stimuli. This can be anatomical, mental, physical or physiological reactions. Stress can be positive or negative. While distress is the most commonly referred to have negative implications, eustress is a positive form of stress, usually related to desirable events in person's life.

Distress and eustress are cumulative in nature, depending on a person's way of adapting to a change that has caused it. The adaptive changes occurring in response to stressors are both behavioural and physical. Stress may lead to illness through e.g. unhealthy changes in nutritional behaviour. Food choices have often been considered as one of a range of health-related behaviours that might be responsive to life stress or emotional well-being, either inadvertently, or as a deliberate strategy for coping with stress (1,2). Also, stress may affect health not only through its direct biological effects but also through changes in health behaviours (3,4).

Stress is associated with biological changes, such as adrenaline-induced glycogenolysis, slowed gastric emptying, autonomic shunting of blood from gut to musculature, and activation of the hypothalamic-pituitary-adrenal (HPA) axis (5,6). The HPA axis is activated during stress, resulting in the release of glucocorticoids (GC) from the adrenal cortex in blood, and subsequently the appearance in saliva (7). Increases of CRH, ACTH and cortisol levels in anticipation of or during stressful stimulation are interpreted as allostatic (8).

There is evidence that the HPA axis as well as peripheral cortisol metabolism may be differently regulated according to sex, and age factors (9, 10). The diversity of health implications now associated with control, and consequences of the release of cortisol, together with its sensitivity to psychological stress, has given this major human adrenal GC hormone much importance in behavioural medicine (11). Also, the HPA axis is closely associated with systems responsible for caloric flow in the body (12,13,14). HPA axis function can profoundly influence expression of appetite, and regulation of body weight (6), whereas HPA axis activity can be modified by changes in feeding patterns (15). In humans the fasting induced changes in

adrenocortical responsiveness (16). In sheep isolated from the flock compared with stressed sheep fed ad libitum a prolonged fasting of 4 days decreased cortisol responses to stress (17). Further rats fasted for 14–24h showed a blunted corticosterone response to novelty (18), and reduced ACTH levels following restraint stress compared with controls (19,20). However, despite lower ACTH levels, restraint stress after fasting was associated with an increased corticosterone response (20). Systematic studies demonstrated an association between meals and the midday increase in plasma cortisol (21). Also, increases in plasma cortisol could occur in some subjects after breakfast, the midday meal or an evening meal, the greatest effect occurred after the midday meal (22).

Stress may lead to illness through unhealthy changes in nutritional behaviour (22a). There is evidence that stress may evoke a change in diet, although taken together the data is inconsistent and suggests that the stress effects on the diet are dependent on the type of stress and individual responses. While an identical stressor may cause in some people an increase in food intake whilst others to decrease their intake (23). However irrespective of whether eating increased or decreased, sweet foods and chocolate intake increased in both groups whilst fruit, vegetables, meat and fish intake decreased in both groups (24).

Recent studies indicated that consumption of high carbohydrate/low protein meals raise the plasma ratio of Tryptophan (Trp), which produced anti-depressant effects on clinical populations (25). In the randomised placebo controlled clinical study in high stress prone subjects a high carbohydrate/low protein meal, which increased plasma ratio of Trp:LNAA (large neutral amino acids) by 42%, reduced the cortisol response to a laboratory stressor (26). In other randomised placebo controlled study a dietary protein enriched in Trp (in the form of lactalbumin) had a similar effect in reducing cortisol responses to a laboratory stressor (27). Trp is the precursor to the neurotransmitter serotonin. Also, the availability of this amino acid to brain neurons that synthesize serotonin directly influences the rate at which it is converted to a neurotransmitter (28). Administering either the amino acid itself (29) or meals that raise Trp access to serotonin neurons (30, 31) rapidly stimulates serotonin production. Increases in brain serotonin appear to modulate adrenocortical reactivity probably through alterations in Trp1a and Trp2 receptor sites located at the hypothalamic and pituitary brain area (32).

2. Importance of Macronutrients

Meal compartments can be divided in macronutrients, micronutrients, and phytochemicals. Chemically macronutrients are classified in three categories carbohydrate, fat and protein. Diets have to contain adequate amounts of macronutrients for physical and mental growth and development. Not only the meal composition but also food ingestion is a well-known inducer of several peptides that may, in turn, directly influence the activity of the HPA axis (33). Animal studies indicated that both food intake and the light-dark cycle represent independent synchronizers for the circadian periodicity of cortisol secretion (34). Also, not only the food composition but also the meal timing and the duration of pre-meal fasting have been shown to exert an important effect on cortisol secretion (22,35).

In humans normal physiological variations in cortisol have a significant direct influence on macronutrient metabolism (36,37). Cortisol seems to increase lipolysis and proteolysis, as well as increasing gluconeogenesis, thereby raising the contribution of protein and fat to energy substrate supply, while protecting glycogen stores. Further, the ability of cortisol to increase plasma free fatty acid (FFA) levels may underlie the emerging link between cortisol and abdominal obesity, together with its associated metabolic syndrome (38).

In humans, stress may alter macronutrient selection. Women tend to prefer high fat or sweet foods when moderately stressed (39,40). Cortisol reactivity may be a marker for vulnerability to stress induced eating and thus may help to explain who eats more versus who eats less after stress (41). Women who were high cortisol reactors to stress ate more food than low reactors during recovering from stress (41). On the rest day, however, high reactors tended to eat less and low reactors tended to eat more, eliminating the difference between groups. Interestingly the high cortisol reactors tended to consume more sweet foods than low reactors across days (41). Animal experiments show that adrenal steroids influence macronutrient selection by increasing appetite for carbohydrate, primarily, and for fat and regulating the timing of eating (42, 43). In humans it has been found that food ingestion, particularly proteins, can stimulate α1-adrenoreceptors possibly via the activation of neurotransmitter amines (44).

Previous studies indicated that post meal plasma cortisol levels could be affected by the proportions of macronutrients consumed. Meals containing 20-40% protein (as % total energy) produced a greater plasma cortisol response

than meals with high carbohydrate or fat levels (45). By comparison, meals containing 10% protein resulted in weaker secretion of plasma cortisol (46) and protein-free glucose or fat loads did not stimulate cortisol release (34). There is some evidence that maintaining a very high-protein diet may chronically stimulate the HPA axis (47) and increase release of vasoactive hormones (48). Further, reducing the carbohydrate:protein ratio of diets chronically has also been associated with deterioration in mood (49,50).

2.1. Importance of Carbohydrate

Carbohydrate consists of monosaccharide sugars or larger molecules of these unit joint together:

- Disaccharides (two units of monosaccharides),
- Oligosaccharides (a few units of monosaccharides) and
- Polysaccharides (many units of monosaccharides).

For instance, glucose is a monosaccharide and starch is a polymer of glucose units. Polysaccharides are sometimes called complex carbohydrate and sugar simple carbohydrate. Carbohydrate or saccharides fill numerous roles in living things such as the storage and transport of energy in form of glycogen and starch and structural components in form of cellulose[1] in plants and chitin[2] in animals. Carbohydrate supplies around 4 kilocalories per gram.

Diets with high carbohydrate content may prevent deterioration of mood in stress-prone subjects when submitted to a stressful task (51). Different studies indicated that carbohydrate supplementation result in significantly lower plasma levels of Trp and the branched-chain amino acids (BCAA; leucine, isoleucine and valine) by 120 minutes of exercise (52,53). The decrease of plasma Trp concentration can be caused by higher brain Trp uptake. Early studies indicated that carbohydrate ingestion stimulate brain Trp uptake and serotonin synthesis (31). Further, carbohydrate supplementation causes attenuation in FFA levels. Increasing levels of plasma FFA result in increased plasma levels of Trp by displacing Trp from albumin (53,54). In contrast, declines in plasma BCAA levels during carbohydrate supplementation and

[1] Cellulose is a polysaccharide consisting of a linear chain of several hundred to over ten thousand D-glucose units. It is the structural component of the primary cell wall of green plants, many forms of algae and the oomycetes. About 33% of all plant matter is cellulose (the cellulose content of cotton is 90% and that of wood is 40–50%). Some animals can digest cellulose with the help of symbiotic microorganisms that live in their guts. Also, humans can digest cellulose to some extent.

[2] Chitin is a long-chain polymer of N-acetylglucosamine, a derivative of glucose. It is the structural component of the primary cell wall of many animals. Chitin may be compared to the polysaccharide cellulose.

exercise are thought to be due to the maintenance of plasma insulin levels during exercise (54,55). Further, carbohydrate supplementation during prolonged exercise attenuated increases in plasma cortisol and decreases in plasma insulin (52,56).

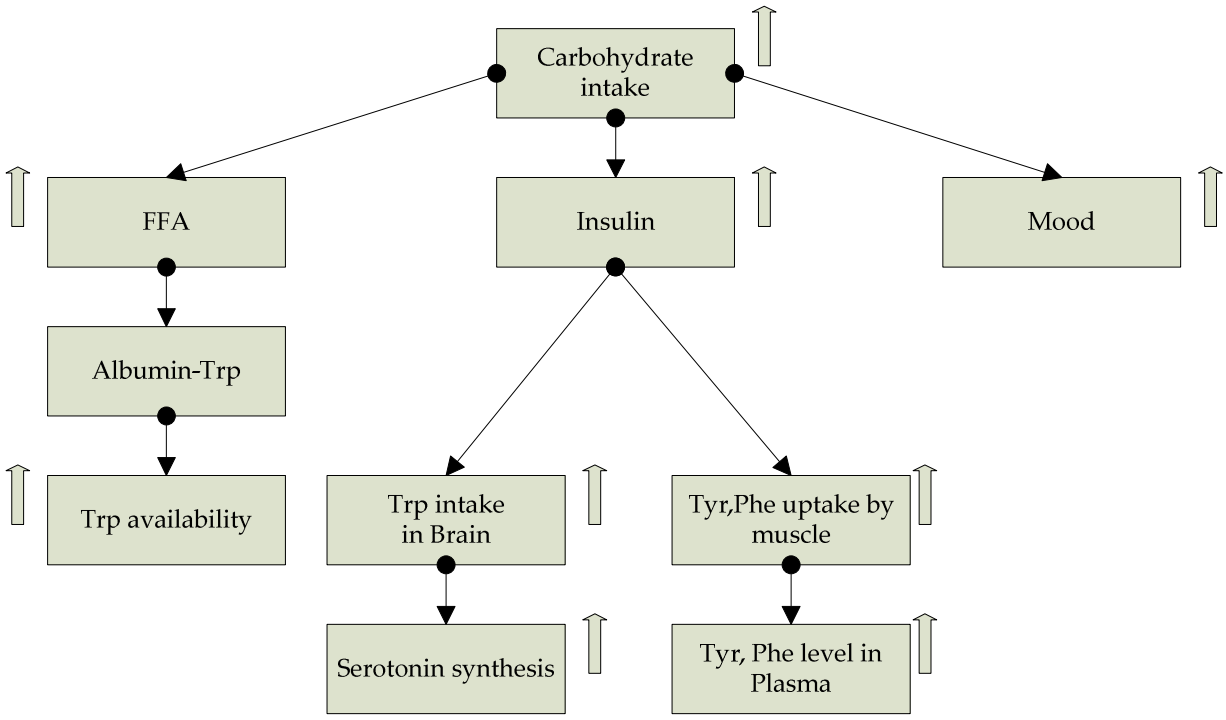

FIG. 1. Effect of high carbohydrate intake

Different studies indicated that carbohydrate supplementation result in lower plasma levels of both amino acids tyrosine and phenyalanine. Since movement of these amino acids into the muscle and the liver can also be enhanced by insulin (53,57). Also, glucose load leads to a rapid rise in insulin levels in nondiabetics and thereby to an increased transport of Trp into the CNS. This is followed by an increased synthesis of serotonin, which is known to have a stimulatory influence on the HPA axis at the hypothalamic level (58). Human studies suggest that ready availability of energy is a prerequisite for significant acute stress responses of the HPA axis (13). Following Trier Social Stress Test (TSST) subjects with high blood glucose levels showed the well-established response pattern of a 2-fold increase in free cortisol levels (59,60). Further, brain derived neurotrophic factor (BDNF) expression can be inhibited by a diet high in saturated fat and sucrose (61,62).

2.1.1. Importance of Sucrose

Sucrose (saccharose) is a disaccharide of glucose and fructose. It is formed only by plants. Sucrose prevents a marked reduction in caloric intake after stress. The effects of sucrose are to damp subsequent activity in the HPA axis (63). Nutritive sweet drinks also block stress-induced effects on avoidance behaviour in rats (64,65), reduce pain perception (66,67) and reduce perceived exertion and the hormonal responses to intense exercise (68). The interaction of sucrose with stress-induced ACTH secretion depends on whether the studies use acute or chronic stress. In rats (19) and man (69) sucrose or glucose have been shown to augment ACTH responses to acute stress.

2.2. Importance of Fat

Fats in diets consist largely of a heterogeneous mixture of triacylglycerol molecules that are each combined with three fatty acids (FAs). Dietary fat has long been recognized as an important source of energy for mammals. The FAs can be divided into two categories, based on chemical properties: saturated FAs and unsaturated FAs.

TABLE 1

Fat composition of some Nutrition (in 100 g)

	Fat (g)	MUFA (g)	PUFA (g)	n6 FA* (g)	n3 FA** (g)
Buckling	15.8	8	3	0.3	1.4
Flounder	3.8	0.8	1.1	0.2	0.4
Greenland halibut	14.6	3.4	4.6	1	1.8
Halibut	2	0.5	0.7	0.1	0.3
Lye rolls	2.6	0.7	0.8	0.6	0.1
mackerel	13.9	5.4	3.6	0.3	1.8
Olive (green)	13.9	9.9	1.3	1.2	0.1
Red perch	4.3	1	1.1	0.2	0.6
Salmon	6.3	2.4	1.6	0.1	0.9
Stockfish	2.9	0.3	1.1	0.1	0.7
Trout	2.9	0.9	1	0.2	0.6
Tuna	17.3	4.5	5.8	0.5	3.9
Walnut	62.5	10.1	42.7	35.8	6.3
White bread	3.3	1	0.9	0.5	0.3

* Sum of Arachidonic acid and linolic acid

** Sum of α-linolenic acid, DHA and EPA

Unsaturated FAs can be monounsaturated FAs (MUFA), or polyunsaturated FAs (PUFAs). PUFAs can be categorized according to their chain length. Mammalian cells can introduce double bonds into all positions on the FA chain except the n-3 and n-6 position. Thus, the shorter-chain α-linolenic acid (18:3 n-3) and linoleic acid (18:2 n-6) are essential FAs. The 18-carbon n-3 and n-6 shorter-chain PUFAs are precursors to the longer 20- and 22-carbon PUFAs, called very-long chain PUFAs. Despite their differences in structure, all fats contain approximately the same amount of energy (9kcal/g).

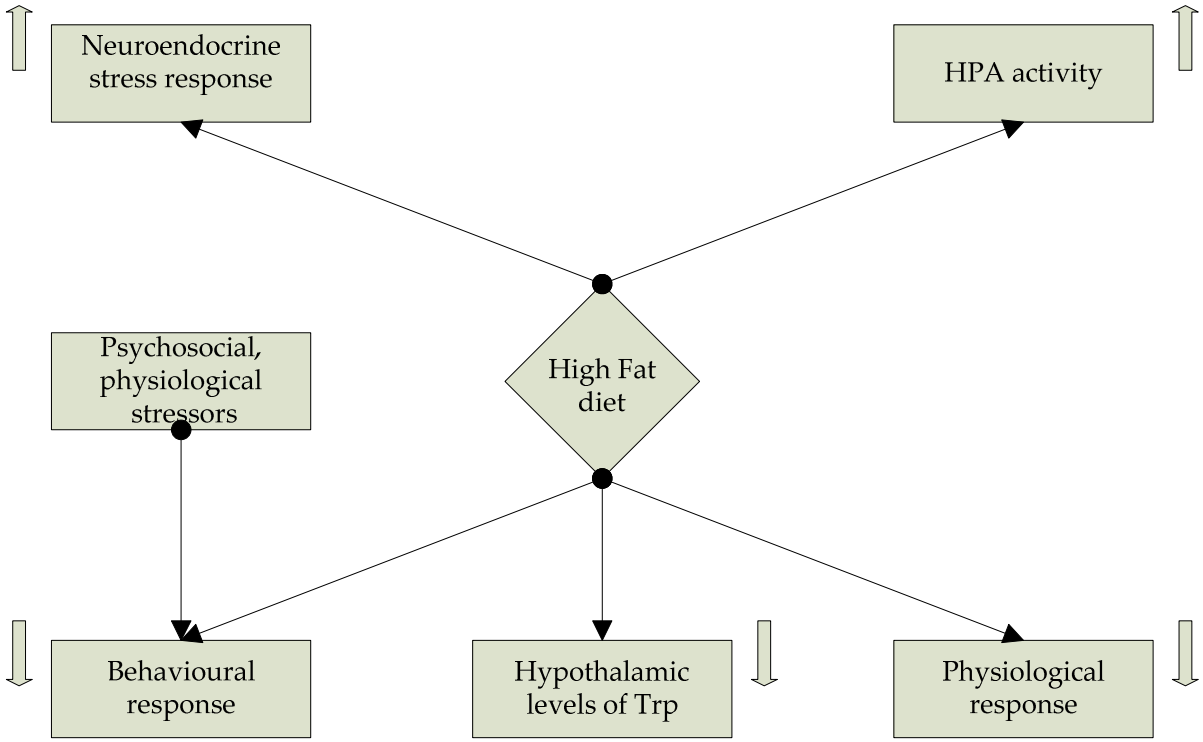

FIG 2. Effect of high fat diet on neurological and physiological response

FAs play a variety of physiological roles. The specific biological functions of a FA are determined by the number and position of the double bonds and the length of the acyl chain. A high-fat diet has suppressive effects on the thermoregulatory and behavioural responses to the stress (70). Feeding rats with a high-fat diet reduces some of the behavioural and physiological responses to the psychosocial and physiological stressors such as social defeat and administration of the endotoxin Lipopolysaccharides (LPS) (70). Also, feeding rats chronically a high-fat diet increased their basal and stress-induced HPA activity (71). Continuous high-fat feeding may act as a chronic stressor, not only enhancing baseline adrenocortical activity but also increasing the neuroendocrine stress responses. Feeding rats with a high-fat diet resulted in a lower anxiety level in an elevated plusmaze paradigm compared to feeding

with a high carbohydrate diet (72). Also, consumption of a high-fat diet decreases the hypothalamic levels of Trp immediately (73). Further, the defeat-induced desensitization of central nervous Trp1a receptors is absent in animals on a high-fat diet (70).

2.2.1. Importance of Saturated Fat

Consumption of a diet high in saturated fat and sucrose inhibited the BDNF expression (61,62). Saturated fats did not enhance the affinity constant of corticosteroid-binding globuline (CBG) for cortisol, whereas oleic acid enhances this three-fold (74). The Italian Longitudinal Study on ageing (5632 subjects) has shown that high intakes of total fat, saturated fat and cholesterol, have been associated with an increased risk of dementia (75).

2.2.2. Importance of MUFA

In-vitro the addition of physiological concentrations of the exogenous FFAs confirms that the stimulation of CBG binding properties is mainly due to MUFA (the primary constituents of olive and canola oils) classes. Addition of MUFA to purified human CBG enhanced CBG binding activity in a concentration dependent fashion (76). Also, oleic acid alone mimicked the in-vivo situation by increasing the affinity constant of CBG for cortisol (three-fold) and reducing the number of binding sites (two-fold), whereas saturated fats did not enhance the binding (74).

The Italian Longitudinal Study on Ageing has shown that a typical Mediterranean diet, with high MUFAs intakes, appear to be protective against age-related cognitive decline (77).

2.2.3. Importance of PUFA

PUFAs are long chain omega-3 and omega-6 FAs of plant (the primary constituents of corn, sunflower, flax seed and many other vegetable oils) and marine origin. These essential FAs cannot be synthesized in the human body. Due to their greater availability and low cost, there is excessive consumption of omega-6 FAs in developing countries. Junk foods are also loaded with omega-6 FAs and trans-FAs. The omega-3 FA (α-linolenic acid) can be metabolized in the liver to the longer-chain eicosapentaenoic (EPA) and docosahexaenoic acid (DHA). This conversion is limited in human beings. It is estimated that only 5–15% of α-linolenic acid is ultimately converted to DHA

(78). Ageing, illness and stress, as well as excessive amounts of omega-6 rich oils (corn, safflower, sunflower, and cottonseed) can all compromise this conversion (79). The ideal dietary ratio of omega-6 to omega-3 has been recommended by an international panel of lipid experts to be approximately 2:1 (80). It is reported that corn oil has an omega-6:omega-3 ratio of 60:1, and safflower a ratio of 77:1 (81).

The biological importance of PUFA derives in part from their role as precursors of important second messengers (prostaglandins, prostacyclins and leukotrienes) (82,83) and as constituents of structural lipids in cellular membranes, which influence the activities of membrane-linked functional molecules (receptors, enzymes and transporters) (84,85). The presence of large amounts of omega-3 PUFAs in the brain is indicative of the major role that these compounds play in the structure and function of this organ (86). About 50 to 60% of the dry weight portion of the human brain consists of lipids. PUFAs constitute approximately 35% of that lipid content (87). Omega-3 FAs, particularly EPA and DHA play important roles in the development and maintenance of normal CNS structure and function. Along with the omega-6 FA, arachidonic acid, DHA is a major constituent of neuronal membranes, making up about 20% of the brain's dry weight (88). Synapses contain a high concentration of DHA, which appears to play a role in synaptic signal transduction (89). DHA is also important for normal cognitive development (90). In transgenic mouse models, dietary DHA improved memory, increased synapse density and decreased amyloid-ß toxicity, thus providing evidence of protection against the Alzheimer Disease (AD) and cognitive decline (91,92). The omega-3 FAs are an essential component of CNS membrane phospholipid-acyl chains and, as such, they are critical to the dynamic structure of neuronal membranes (93). DHA is continuously secreted by astrocytes, bathing the neuron in omega-3 FA (94). Fish provide varying amounts of omega-3 PUFA in the form of DHA and EPA.

2.2.3.1. Effects of PUFA on CNS membrane Fluidity

PUFAs in general play important roles in structural and functional maintenance of neuronal membranes, neurotransmission and eicosanoid biosynthesis (87,95), as well as in the maintenance of membrane fluidity and flexibility and in the modulation of ion channels, receptors and ATPases. Omega-3 PUFA can alter neuronal fluidity by displacing cholesterol from the membrane (96). Alterations in the membrane lipids can alter their function by changing fluidity. An optimal fluidity is required for neurotransmitter binding and the signalling within the cell (97). In healthy adults, higher concentrations

of plasma DHA predict higher cerebrospinal fluid 5-hydroxyindolacetic acid, a metabolite that reflects serotonin turnover, particularly in the frontal cortex (98). Numerous studies link low cerebrospinal fluid 5-hydroxyindolacetic acid with psychiatric conditions, including violent and suicide attempts during depression (99). Animal studies with an omega-3 PUFA deficient diet showed reductions in DHA levels although reductions are particularly pronounced in the frontal cortex (40% reduction). Another area with a marked DHA reduction is the olfactory bulb (35% reduction), which may also have behavioural consequences (100).

Omega-3 PUFAs are essential components of CNS membrane phosphor-lipidacyl chains and as such they are critical to the dynamic structure of neuronal membranes (93). DHA is continuously secreted by astrocytes, bathing the neuron in omega-3 PUFA (94). Reduction in omega-3 PUFA intake (in the form of α-linolenic acid) results in a reduction of omega-3 PUFA content throughout the brain cells and organelles along with a compensatory rise in omega-6 PUFA acid content. This alteration is accompanied by a 40% reduction in the Na-K-ATPase of the nerve terminals, an enzyme that controls ion transport produced by nerve transmission and that consumes half the energy used by the brain (86). There is also a 20% reduction in 5'-nucleotidase activity, a decrease in fluidity in the surface polar part of the membrane (101) and a significant reduction in the cell body size of the hippocampal CA1 pyramidal neuron (102). A 30% reduction in the average densities of the synaptic vesicles in the terminals of the hippocampal CA1 region has also been observed as a result of an omega-3 deficiency combined with a learning task (103). Deficiency of omega-3 PUFA also results in a 30-35% reduction in phosphatidylserine in the rat brain cortex, brain mitochondria and olfactory bulb (104).

2.2.3.2. Effects of PUFA on Monoamines

A number of studies have specifically examined the effect of an omega-3 deficient diet on the DA and serotonin levels in animals. In animal studies omega-3 PUFA deficient diet resulted in a reduction of the dopaminergic vesicle pool (105) along with a 40-60% decrease in the amount of DA in the frontal cortex and an increase in the nucleus accumbens (105,106). Although overall DA levels in the nucleus accumbens are higher in an omega-3 deficiency. Function of the nucleus accumbens-dopaminergic system appears to be abnormal. In rats omega-3 PUFA deficiency reduced the release of DA from the vesicular storage pool under tyramine stimulation by 90% compared to receiving an adequate omega-3 PUFA intake (105). In the animal model of

depression, although overall nucleus accumbens-DA levels are higher, the extracellular levels of DA in the nucleus accumbens are lower than normal controls and do not respond to normal serotonin stimulation (107). The increase in DA in the nucleus accumbens of omega-3 deficient rats is thought to be a result of loss of normal inhibitory control by reductions in frontal cortex DA input (108). Also, omega-3 PUFA deficiency induces changes at several levels of the dopaminergic mesocortico limbic pathway (109).

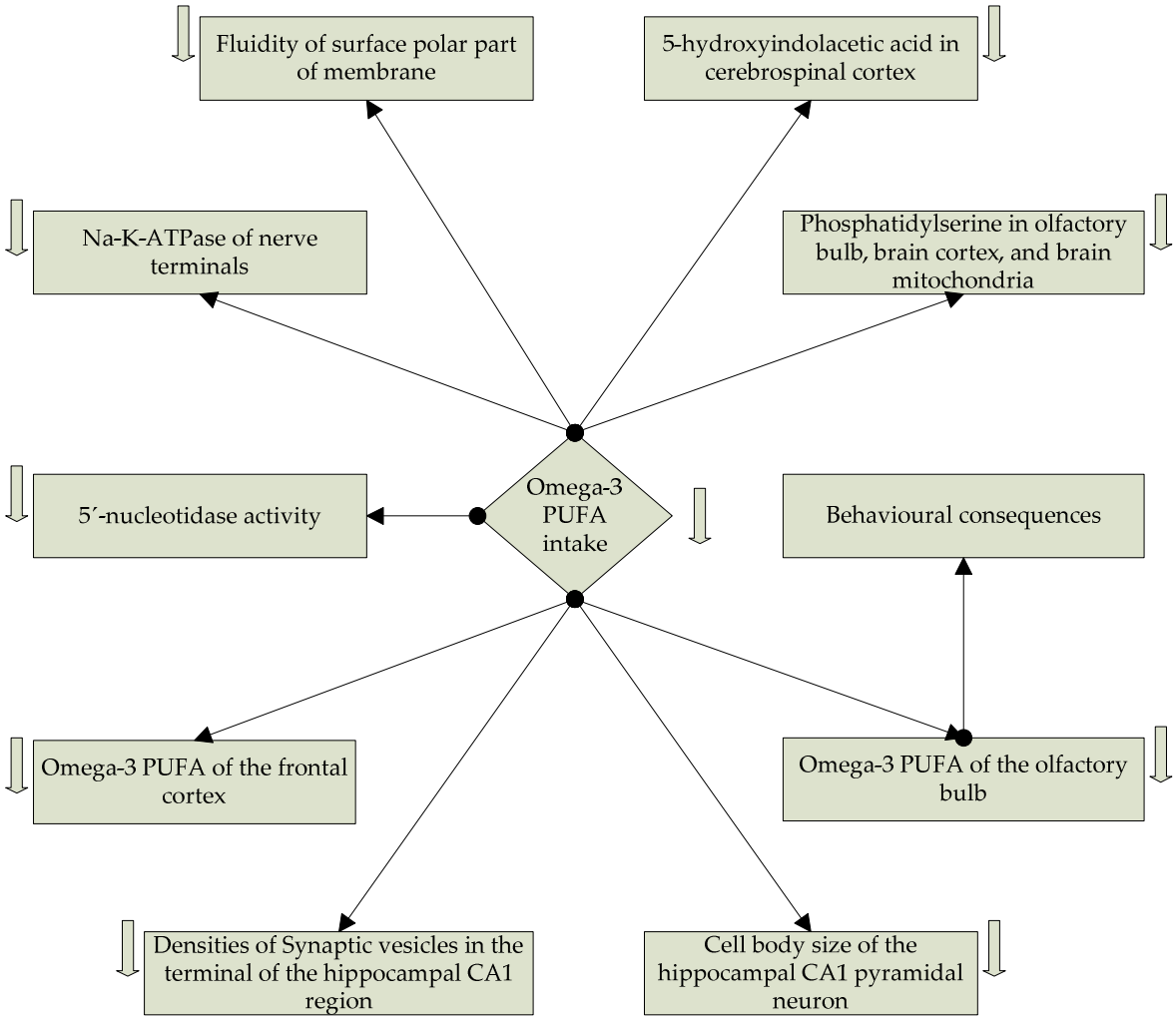

FIG 3. Consequences of reduced omega-3 FA intake for a long time on CNS

The binding of serotonin to the astroglial 5-HT2A receptor can mobilize DHA to supply the neuron (110). Also essential FAs can act as sources for second messengers within and between neurons (111).

TABLE 2.
Effect of omega-3 deficiency in the CNS

Parameters showing decrease	Parameters showing increase
1. 5′-nucleotidase activity. 2. Blood-brain barrier integrity. 3. Cell body size of the hippocampal CA1 pyramidal neuron. 4. Cerebrospinal fluid 5-hydroxyindolacetic acid. 5. Dopamine (DA) content in frontal cortex. 6. DA content in olfactory bulb. 7. DA vesicle pool. 8. DA release from vesicle storage. 9. Fluidity at surface polar membrane. 10. Glucose uptake by neurons. 11. Hippocampal CA1 pyramidal neuron cell body size. 12. Neuronal cytochrome oxidase activity. 13. Normal cerebral microperfusion. 14. Normal inhibitory control over nucleus accumbens[3] dopamine. 15. Phosphatidylserine in cortex, olfactory bulb, and mitochondria. 16. Pre/post synaptic dopamine receptor DR2 in frontal cortex. 17. Sodium/potassium ATPase at nerve terminal. 18. Vesicular monoamine transporter.	1. DA content in nucleus accumbens. 2. Pre/post synaptic DA receptor DR2 in nucleus accumbens. 3. Serotonin receptor density in frontal cortex.

2.2.3.3. Effects of PUFA on densities of synaptic vesicles

A 30% reduction in the average densities of synaptic vesicles in the terminals of the hippocampal CA1 region has also been observed as a result of an omega-3 PUFA deficiency combined with a learning task (103). Chronic dietary deficiency in α-linolenic acid impairs performance in learning ability

[3] The nucleus accumbens is a collection of neurons within the striatum. Each half of the brain has one nucleus accumbens. It plays an important role in addiction, aggression, fear, laughter, pleasure, reward, and the placebo effect. The nucleus accumbens and the olfactory tubercle collectively form the ventral striatum, which is part of the basal ganglia. The nucleus accumbens can be divided into two structures: the nucleus accumbens core and the nucleus accumbens shell.

and motivational processes (112). Also, deficiency of omega-3 PUFA results in a 30-35% reduction in phosphatidylserine concentration in the rat brain cortex, brain mitochondria and olfactory bulb (104).

2.2.3.4. Effects of PUFA on gene expression

The amount of omega-3 PUFAs in the diet might act on the regulation of cerebral gene expression (109,113).

2.2.3.5. Effects of PUFA on CBG

Addition of PUFA to purified human CBG enhanced CBG binding activity in a concentration dependent fashion (76). A clinical study in burn patients showed that low-fat nutrition support (i.e., 15% of total calories as fat) modulated CBG and the concentration of free circulating cortisol after a severe stress. In contrast to in-vitro studies additional intake of fish oil did not seem to add clinical benefit to low-fat solutions (114).

2.2.3.6. Effects of PUFA on phosphatidylserine

Animal studies in rats indicated that fish oil supplementation can increase phosphatidylserine (PS) composition of the cerebral membrane (115). PS has antidepressant activity in adults (116,117). PS can activate various enzymes, including protein kinase C, Na-K-ATPase and tyrosine hydroxylase, as well as regulating calcium uptake. It is therefore suggested that altering PS in cerebral membranes can alter neurotransmission (115).

2.2.3.7. Effects of PUFA on neuronal functional activity

An omega-3 PUFA deficiency has also been shown to decrease glucose uptake of brain cells by 30% and decrease cytochrome oxidase activity by up to 40% (118). Glucose uptake and cytochrome oxidase activity are indicators of neuronal functional activity. Also, an omega-3 PUFA deficiency can alter the delivery of amino acids and sucrose across the blood-brain barrier (119). Further, this deficiency may compromise normal cerebral microperfusion, whereas supplementation may improve cognitive abnormalities related to cerebral hypoperfusion (120,121).

2.2.3.8. Effects of PUFA on neuronal protection

PUFAs protect neurons directly by preventing neuronal apoptosis (122) and suppressing the production of neurotoxic TNF[4] (123,124). TNF is believed to have a role in these conditions by inducing the death of neurons (123).

[4] TNF (Tumour necrosis factors) refers to a group of cytokines family that can cause cell death.

Moreover, PUFAs augment acetylcholine and endothelial nitric oxide formation and release in the brain, enhance glucose uptake by neuronal cells and thus improve memory (125). The findings of epidemiological studies suggest that a high fish intake reduces the risk of dementia (50). Recently, a seven-year follow-up study of 1600 elderly people also showed that those who ate fish or seafood at least once a week were less likely to develop any form of dementia (126).

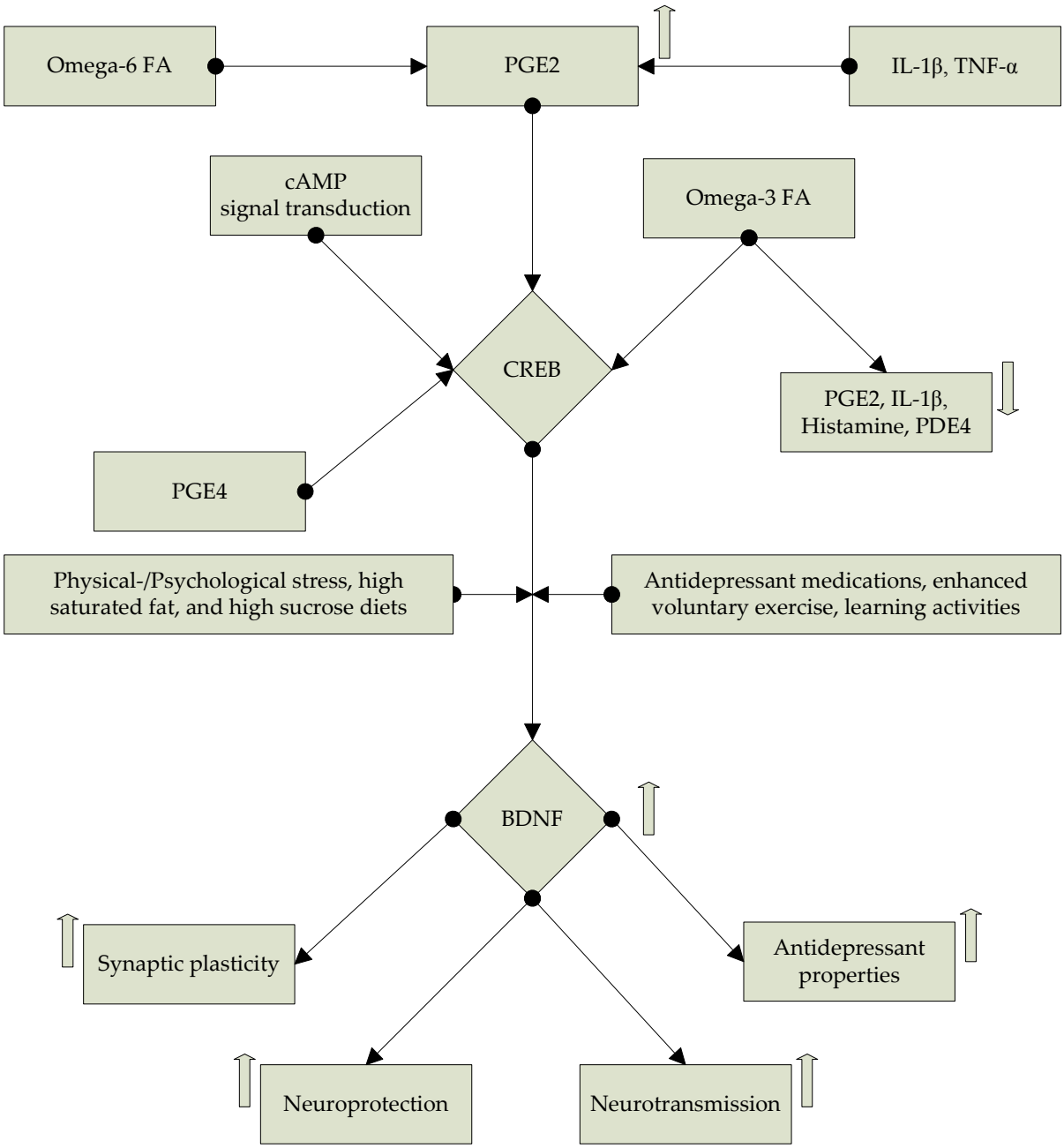

FIG. 4. Possible mechanisms of omega-3, and omega-6 FA in BDNF

2.2.3.9. Effects of PUFA on Depression

Case reports in the literature indicate flaxseed oil which is a source of α-linolenic acid may be of benefit in the treatment of bipolar depression and agoraphobia (127).

One well-designed trial demonstrated four months of treatment with 9.6 g omega-3 PUFA can be of benefit in the treatment of bipolar disorder. This study showed a highly significant effect of omega-3 PUFA in lengthening remission and a highly significant effect in treating depression ($p < 0.001$ Hamilton Rating Scale for Depression scores) (128). One double-blind, placebo-controlled study (n=22) showed that the addition of 2 g EPA to standard antidepressant medication enhance the effectiveness of that medication compared to the medication plus placebo after three weeks of treatment (129). EPA had an effect on insomnia, depressed mood and feelings of guilt and worthlessness (129). In a 12-week, randomized, double-blind, placebo-controlled trial, patients who experienced persistent depression, despite ongoing standard pharmacotherapy received 1 g EPA. The patients showed a 53% reduction on Hamilton depression scores. Intake of 1 g EPA dose led also to improvements in depression, anxiety, sleep, lassitude, libido and suicidal ideation (130). The 2-g/d group showed little evidence of efficacy, whereas the 4-g/d group showed non-significant trends toward improvement.

A number of investigations have also found decreased omega-3 PUFA content in the blood of depressed patients (131-134). Further, there is a significant negative correlation between worldwide fish consumption and prevalence of depression (135). Frequent fish consumption in the general population is associated with a decreased risk of depression and suicidal ideation (136). Also, fish consumption is significantly associated with higher self-reported mental health status (137). Separate research involving a random sample within a nation confirms the global findings, as frequent fish consumption in the general population is associated with a decreased risk of depression and suicidal ideation (136). In addition, a cross-sectional study from New Zealand found that fish consumption is significantly associated with higher self-reported mental health status (137). In fact, EPA content in red blood cell phospholipids is negatively correlated with the severity of depression, while the ratio of omega-6 PUFA arachidonic acid to omega-3 PUFA EPA positively correlates with the clinical symptoms of depression (131). In addition, a negative correlation between adipose tissue DHA and depression has been

observed. In a clinical study mildly depressed subjects had 34.6% less DHA in adipose tissue than non-depressed subjects (138). Depressive symptoms associated with premenstrual syndrome have also been shown to be responsive to marine oil extracted from Antarctic krill. Krill oil is particularly rich in phospholipids as well as EPA and DHA (240 mg and 120 mg per g, respectively). Canadian researchers compared 2 g krill oil to 2 g standard fish oil capsules (180 mg EPA and 120 mg DHA per g) in the treatment of premenstrual syndrome and dysmenorrhoea. In the three-month trial (n=70), patients took 2 g krill oil or fish oil capsules daily for one month, then for eight days prior to, and two days during menstruation for the following two months. Evaluations at 45 and 90 days revealed the patients taking krill oil showed a significant improvement in depressive symptoms of premenstrual syndrome. The same effect was not observed with the standard fish oil capsules, indicating that the presence of the phospholipids and/or higher amounts of EPA may be responsible for the therapeutic effect of krill oil (139). Another possibility is the presence of some naturally occurring substances in the Krill oil with positive health effects in contrast to the fish oil capsules.

Logistic regression analysis indicated that a 1% increase in plasma DHA is associated with a 59% reduction in the reporting of depressive symptoms (140). It is well known that during pregnancy there is a significant transfer (up to 2.2 g/day) of PUFA to the developing foetus (79). Also, increased risk of post-partum depressive symptoms has recently been associated with a slower normalization of DHA levels after pregnancy (141). Higher concentrations of DHA in mother's milk and greater seafood consumption both predicted lower prevalence of post-partum depression (142).

MRI studies indicated a decrease in volume of various areas of the brain in depressed patients (143,144). Omega-3 PUFA can augment antidepressant pharmacotherapy and alleviate depression by entirely different means than standard medications (130). With regard to DHA or a combination of EPA and DHA, there have been three negative reports. In a trial on DHA alone as mono-therapy in the treatment of MDD[5] 2 g pure DHA or placebo was administered to 36 patients with depression for six weeks. The response differences between the groups, as measured by scores on the "Montgomery-Asberg Depression Rating Scale" did not reach statistical significance (145). Further, in an open label pilot study the combination of 1.7 g of EPA and 1.2 g

[5] Major depressive disorder is a mental disorder characterized by an all-encompassing low mood accompanied by low self-esteem and by loss of interest or pleasure in normally enjoyable activities.

of DHA failed to show benefits among seven women with a past history of post-partum depression. The omega-3 PUFA mono-therapy was initiated between the 34th – 36th weeks of pregnancy and was assessed through 12 weeks post-partum. In these women the fish oil combination did not reduce the risk of relapse (146). Finally, a pure DHA supplement, at low doses of 200 mg per day for 4 months post-partum, did not improve self-rated or diagnostic measures of depression over placebo. However, the women enrolled (n = 89) in the study were not clinically depressed as a group, which precludes interpretation that DHA is ineffective in post-partum depression (147).

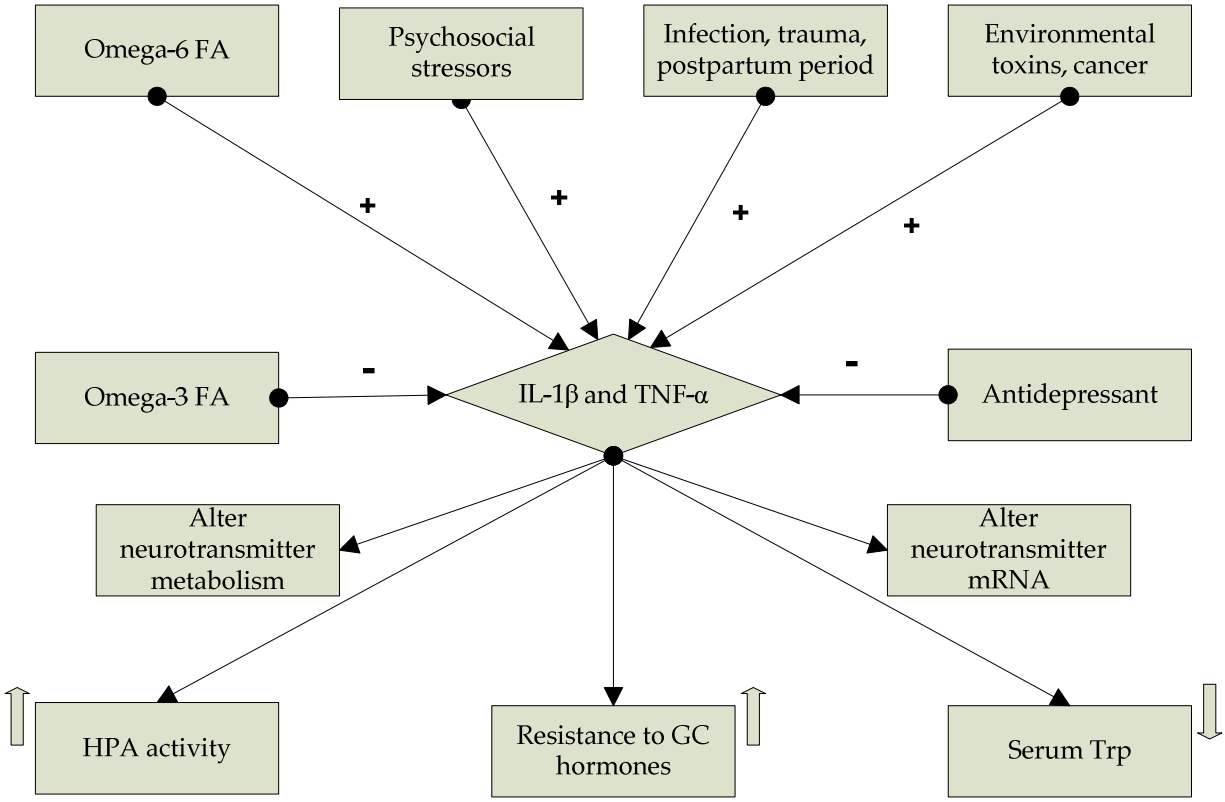

FIG. 5. Potential interactions between omega-3 FA, omega-6 FA, and inflammatory cytokines

2.2.3.10. Effects of PUFA on BDNF

Omega-3 PUFA may exert significant influence in major depression via cytokine modulation. A growing body of research has documented an association between depression and the production of these pro-inflammatory immune chemicals. These cytokines, including IL-1β, -2 and -6, INF-γ and TNF-*α*, can have direct and indirect effects on the CNS. Some of the documented activities of these cytokines include lowered neurotransmitter

precursor availability, activation of the HPA axis and alterations of the metabolism of neurotransmitters and neurotransmitter mRNA (148).

Recent data indicated that elevations of IL-1β and TNF-α is associated with the severity of depression (149). It has been suggested that the anti-inflammatory role of omega-3 PUFA may influence BDNF in depression (150). BDNF is a polypeptide that supports the survival and growth of neurons through development and adulthood. Serum BDNF has been found to be negatively correlated with the severity of depressive symptoms (151). Antidepressant medications and voluntary exercise can enhance BDNF (150). In contrast BDNF expression can be inhibited by:

- Physical and psychological stress (152) and
- A diet high in saturated fat and sucrose (61,62).

2.2.3.11. Effects of PUFA on cognitive function

In a single prospective cohort study that evaluated the effects of omega-3 PUFA on cognitive function in normal ageing, there was no significant association between omega-3 PUFA intake in the form of fish consumption and cognitive decline (153).

2.2.3.12. Effects of PUFA on incidence of dementia

Among three prospective cohort studies that assessed the effects of omega-3 PUFA on the incidence of dementia, fish consumption was associated with a statistically and clinically significant reduction in the incidence of the non-Alzheimer's dementia (126,154,155). Also, fish consumption was significantly associated with a reduced risk of the Alzheimer's dementia (155) and nearly so in the two other studies (126,154). While total omega-3 PUFA consumption and consumption of DHA were associated with a significant reduction in the incidence of AD for the general population consumption of α-linolenic acid and EPA were not (154).

2.2.3.13. Effects of PUFA on Suicide

In a study involving 100 suicide attempt cases in China compared to 100 hospital admission controls, there was an eightfold difference in suicide attempt risk between the lowest and highest red blood cells EPA level quartiles (156). Also, low level of EPA in red blood cells was associated with suicide attempts.

2.2.3.14. Effects of PUFA on Aggression

In a small pilot study (n = 30), the intake of 1 g EPA could reduce aggression (modified Overt Aggression Scale) and depressive symptom scores (Montgomery-Asberg Depression Rating Scale) among borderline personality disorder patients (157).

2.2.3.15. PUFA sources and requirements

Both α-linolenic acid and linoleic acid are present in a variety of foods. The major dietary sources of α-linolenic acid and linoleic acid are PUFA-rich vegetable oils. Linoleic acid is present in high concentrations in many commonly used oils, including corn oil, safflower, soy and sunflower. α-Linolenic acid is present in some commonly used oils, including canola and soybean oil and in some leafy green vegetables. The proportion of linoleic acid to α-linolenic acid as well as the proportion of those PUFAs to others varies considerably by the type of oil.

Table 3

Omega-3 and omega-6 FA content (%) of some dietary oils

Dietary source	Omega-3 FA	Omega-6 FA
Canola oil	9	20
Corn oil	1	60
Cottonseed oil	0	50
Flax oil	57	14
Peanut oil	0	32
Safflower oil	1	77
Sesame oil	0	45
Soybean oil	7	51
Sunflower oil	0	65
Walnut oil	10	52

2.2.4. Importance of L-Carnitine

Carnitine transports long-chain acyl groups from FAs into the mitochondrial matrix. In the mitochondrial matrix they can be broken down through oxidation to actetate and energy. It plays an important role in diseases associated with metabolic compromise, especially mitochondrial-related disorders. Humans take in carnitine primarily from diet 75% with the remaining 25% coming from endogenous synthesis. It is synthesised from L-lysine and L-methionine (158).

A deficiency of carnitine is known to have major deleterious effects on the CNS. Carnitine possesses neuro-protective ability in conditions of mitochondrial dysfunction, oxidative stress and possibly in neurodegenerative disorders such as PD and AD (159). Carnitine deficiency can be caused due to:

- Decreased natural synthesis of carnitine in the body,
- Altered transport of carnitine across the cellular membrane,
- Dietary lack,
- States causing abnormal loss or
- Overutilization of carnitine (160).

L-Carnitine and acetyl L-carnitine possess unique neuroprotective, neuro-modulatory and neurotrophic properties among their neurophysiological roles that are relevant in counteracting various disease processes (161). Neuro-protective actions of L-carnitine have also been reported against 3-nitropropionic acid induced neurotoxicity (162,163). The common underlying process in neurodegenerative processes is the increased metabolic stress due to mitochondrial dysfunction and formation of reactive oxygen species which has been linked to neurodegenerative disorders such as PD and AD (164,165). Part of the neuroprotective actions of carnitines could be related to their neurotrophic actions. For instance acetyl L-carnitine has been shown to accelerate regeneration of neurons in various in-vitro and in-vivo studies (166).

2.2.5. Importance of Choline-lecithin

Choline is the precursor of neurotransmitter acetylcholine. The synthesis of acetylcholine is influenced by the availability of choline within the cholinergic neurons. Neuronal choline concentrations can be altered by dietary choline intake, in the form of either free choline or phosphatidyl choline (lecithin) (167,168). Also, the lecithin is a mixture of various phospholipids and the composition depends on the dietary origin of the lecithin. The main phospholipids from soy and sunflower are phosphatic acid, phospahtidyl choline, phosphatidyl ethanolamine and phosphatidyl inositol. Oral choline and phosphatidyl choline have been used to treat Huntington disease without any success (169,170). Further, in patients with AD neither choline nor phosphatidyl choline offers much improvement in memory (171-173).

2.3. Importance of Protein

The protein content and the amino acid composition of the diet play a crucial role for human health. The net protein utilization is profoundly affected by the

limiting amino acid content (the essential amino acid found in the smallest quantity in the foodstuff) and somewhat affected by salvage of the essential amino acids in the body. A relationship between fluctuations in serum amino acids and appetite in humans has been showed (174,175). Dietary protein induces satiety in the short term (176) and consumption of protein-deficient diets leads to increased appetite for protein-containing foods (177). Increase consumption of high protein diet by reducing the carbohydrate:protein ratio of diets chronically has also been associated with deterioration in mood (49,50). Further, maintaining a very high-protein diet may chronically stimulate the HPA axis (47) and increase release of vasoactive hormones (48). Increased HPA activity and cortisol release have been linked to increased risk of insulin resistance, hypertriglyceridemia and hypercholesterolemia (178,179). Also, hypercholesterolemia can be caused by high intake of animal proteins (180).

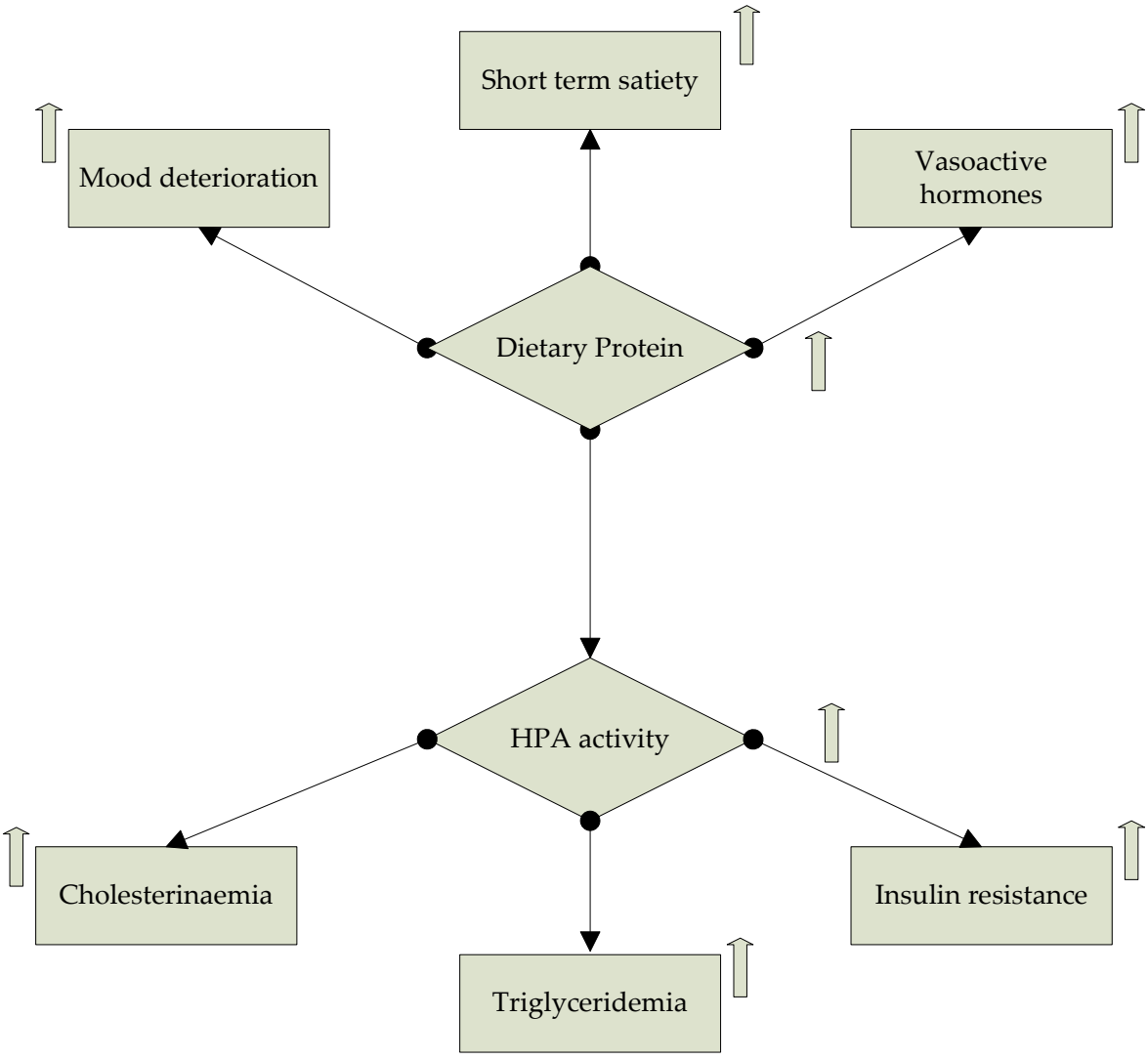

FIG. 6. Effect of high dietary protein

Amino acids may influence food intake either via direct actions within the CNS, via receptors located in the liver or portal vein (181). The rates of synthesis and release of the neurotransmitters DA, norepinephrine (NE) and epinephrine are directly modified by the brain concentrations of their amino acid precursors, Trp, Phe (phenylalanine) and Tyr (tyrosine; catecholamines), which in turn are influenced by their availability from blood (182). Physiologic and pathophysiologic factors that influence blood concentrations of Trp, Phe, Tyr and others that compete with them for a common transporter across the blood brain barrier are LNAA. Also, LNAA predictably alter aromatic amino acid concentrations in brain, the formation and release of these monoamine transmitters and consequently brain function (28,182). Also, administration of amino acids such as Phe and Trp that are precursors to monoamine neurotransmitters suppresses food intake in humans (183). The ratio of plasma Trp to other amino acids may influence brain serotonin levels, which are known to have an inhibitory influence on food intake (184). In animal studies deficiencies of certain amino acids in the diet of rats lead to rapid reduction of food intake that is mediated via specific pathways in the brain (185).

2.3.1. Effects of dietary protein on cortisol

There is some evidence that maintaining a very high-protein diet may chronically stimulate the HPA axis (47) and increase release of vasoactive hormones (48). After a protein-rich meal (30 to 40% energy as protein) salivary cortisol increases substantially (approximately one and one-half- to two-fold on average). Also, a meal intake of at least 20 g of protein may be necessary to show an effect. The higher the intake of protein, the greater the secretion of cortisol is likely to be (46,186). The increase begins toward the end of a 30-minute meal period and peaks at approximately 1 hour after the start of the meal. After approximately 2 hours, salivary cortisol levels declined and were no longer significantly different from those seen either in the absence of a meal or after a low-protein meal. Changes greater than 5% protein (as percent total energy) are required to detect a reliable increase in salivary cortisol (186). Results of studies measuring plasma cortisol suggested that at least 10% protein (as percent total energy) may be needed for reliable stimulation of cortisol (46). This acute stimulation of cortisol release may be part of a homeostatic mechanism in response to a high influx of amino acids (186).

2.3.2. Importance of Essential Amino Acids

Essential amino acids are called essential not because they are more important to life than the others, but also because the body does not synthesize them. It is essential to include them in one's diet in order to obtain them. Nine amino acids are generally regarded as essential for humans: histidine (His), isoleucine (Ile), leucine (Leu), lysine (Lys), methionine (Met), phenylalanine (Phe), threonine (Thr), tryptophan (Trp) and valine (Val). In addition, the amino acids arginine (Arg), cysteine (Cys), glycine (Gly), glutamine (Glu) and tyrosine (Tyr) are considered conditionally essential, while they are not normally required in the diet, but have to be supplied exogenously to specific populations that do not synthesize them in adequate amounts.

TABLE 4.
Essential and Non-essential Amino Acid content of some Nutrition (in 100 g)

	Essent. AA (g)	Non-essent. AA (g)	His (g)	Try (g)
beef	15,7	12,6	1	0,3
boletus	17,1	7,5	2,1	2
Codfish	10,5	8,8	0,5	0,2
Flax seed	12,2	12,1	0,5	0,4
gelatine	20,4	59,5	0,5	0,1
liver pie	9,2	7,7	0,6	0,2
Peanut	10,2	9,9	0,5	0,2
Pork	9,8	8,6	0,7	0,2
pumpkin seed	14	10,3	0,6	0,4
Salami	10,3	8,8	0,7	0,2
soya bean	18,3	17,8	0,9	0,4
Trout	12,4	10,3	0,6	0,2
Wheat germ	12,8	13,5	0,7	0,3

Dietary inadequacy of an essential amino acid leads to nonspecific signs of protein deficiency, such as lowered resistance to disease, decreased blood proteins and stunting in children. Low protein or amino acid poor diet yields degeneration of both filiform and fungiform papillae of taste buds (187) and decreases serum Zn^{2+} concentration (188). It has been shown that somatostatin containing inter-neurons are widely distributed in the anterior piriform cortex (189), an area thought to be responsible for the perception and recognition of essential amino acid levels in the diet (185). Animal studies indicate that rats reduce food intake if they are pre fed a low-protein basal diet and then switched to a diet with an imbalance or lack of essential amino acids (191-192).

Also, animal studies indicate that lack of an indispensable amino acid in the diet induces a decrease in food intake that leads to impaired body weight gain and growth and in the long term may result in death (193-195). Further, it has previously been reported that rats rapidly recognize the adverse metabolic effects of a diet lacking an indispensable amino acid and learn to avoid this diet (193,194,196).

Ligand binding studies have suggested that Trp is involved in the anorectic response to an amino acid deficient diet (195,197). Moreover, there is a specific involvement of the central nucleus of the amygdala (CeA) in the learned aversion to a threonine-imbalanced diet (198,199). The CeA Trp is involved in the conditioned taste aversion response to an amino acid deficient diet (200).

An important characteristic of the behavioural response to the lack of an essential amino acid is the delay of the establishment of the aversive response depends on the nature of the limiting amino acid. The most often quoted hypothesis is a direct brain detection of the decrease in the plasma and brain level of the limiting amino acid that usually follows the ingestion of a meal lacking this amino acid (185,190,200). An alternative mechanism could be alterations in the postprandial catabolism of the amino acids which may generate signals sensed in the brain to stop food intake. These signals may also be endotoxic signals through production of large amounts of ammonia (201,202) or physiological satiety signals produced through an increased postprandial amino acid oxidation, generating an aminostatic (174), an energostatic (203) or an ischymetric signal (204).

2.3.2.1. Importance of Glutamate

Glutamic acid (Glu) is one of the dispensable amino acids. Glu functions in all cells in the body as a metabolic intermediate and protein constituent. In the brain, it has the added role of being an excitatory neurotransmitter (205). Neurons utilizing excitatory amino acids as neurotransmitters participate in hypothalamic function, particularly in the control of pituitary hormone secretion (206,207). Thirty years ago, a link was forged between dietary MSG (monosodium glutamate) and brain function through the report that the repeated injection of very large doses of the amino acid into neonatal rodents could produce visible brain damage, notably in the hypothalamus (208). Glu occurs naturally in many foods (e.g., tomatoes, cheeses) and in prepared stocks and soups (in meat, soups and fish stocks the Glu released by protein hydrolysis becomes a key flavouring agent). The flavour attributed to MSG becomes more complex and the tongue's sensitivity to it is enhanced markedly

in the presence of certain nucleotides. This taste is readily identified in Asian cultures as being distinct from the four basic tastes (sweet, sour, salty, bitter) and has been named "umami" by the Japanese (209). The importance attached by the body to the perception of this taste appears underscored by the identification in the hypothalamus and the orbital prefrontal cortex of neurons that respond selectively to the application of MSG to the tongue (210,211). Glu receptors likely occur on the tongue, on vagal afferent fibres and also on a variety of other cell types in the periphery, where they may have subserve signalling functions (212,213).

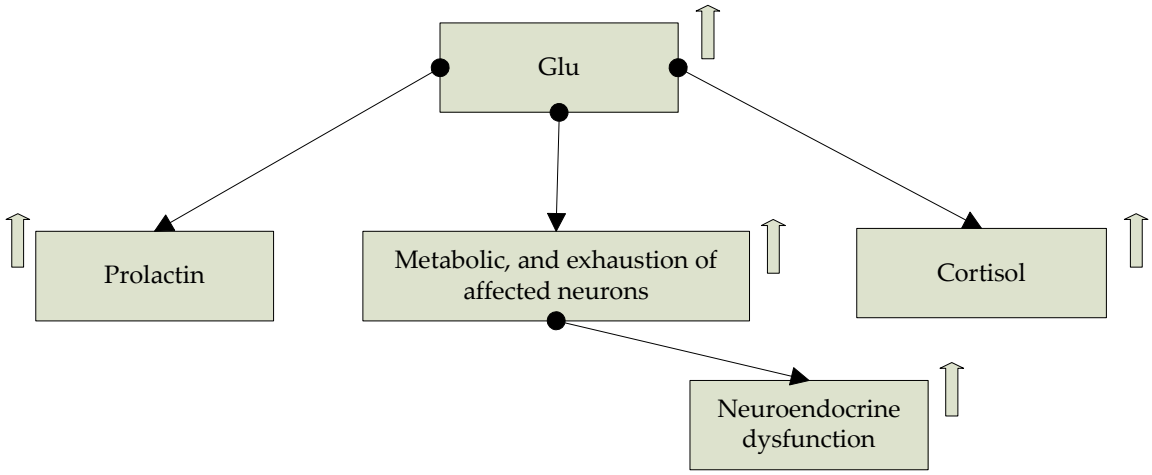

FIG. 7. Effect of high dietary Glutamic acid (Glu) intake

Dietary Glu is a major energy source for the intestines, accounting for half of the energy consumed during digestion (214). From big importance is the role of Glu as a co-substrate in the trans-amination and de-amination of several other amino acids which provide carbon skeletons for gluconeogenesis or ATP generation (215). The Glu is present in the brain and is used by it as a neurotransmitter. It has been found to be synthesized within neurons and actively removed from the synapses. The glial cells are primary participants in the process of synaptic Glu removal and recycling (216,217). In the face of large Glu influxes secondary to greatly elevated blood Glu concentrations the Glu concentrating power of Tanycytes, a specialized glial cell present throughout the median eminence, may fail, leading to local Glu increases and neuronal toxicity (218).

In humans a high oral dose of Glu (10 g, ~150 mg/kg body weight) caused a rise of plasma Glu to 500nmol/mL over baseline values, a 5- to 10-fold increment over typical values (219). Increments in plasma prolactin and cortisol were noted (219). This dose of Glu, given as a single load, is extremely

large, approximating the amount of Glu a human would ingest over an entire day as a component of 100 g of dietary protein. Also, the administration of excitatory amino acids (at very high doses) or their more active analogue has been reported previously in monkeys to stimulate the secretion of one or more pituitary hormones (prolactin, GH, ACTH, cortisol, and LH and/or FSH) (220-224). Further, arcuate neurons bearing Glu receptors thus become exposed to high local Glu concentrations are subjected to excessive excitation. Such excitation is postulated to produce metabolic and functional exhaustion of the affected neurons and subsequently neuronal death. Such effects might possibly lead to neuro-endocrine dysfunction in humans (225).

2.3.2.2. Importance of Histidine

His is an extremely bioactive essential amino acid which has multiple physiological functions. Some of His derivatives such as carnocine are endogenous antioxidants that are stimulated by stress (226). The neurotransmitter histamine is synthesized in the brain by the enzymatic decarboxylation of His. Systemic administration of His in large doses has an increasing effect on histamine concentration in the rodent brain (227,228). Conversion of His to histamine in the hypothalamus is necessary to produce the suppressive effect of His on feeding behaviour. His induces suppression of food intake by a direct effect on zinc metabolism (229-231). It plays a major role in zinc metabolism acting as the major zinc binding moiety in serum (229-231). Normally, zinc is bound to one or two of the available 16 His moieties on albumin (229,230). His administration to animals (231) or humans (232) strips zinc from its albumin binding sites initiating a Zn-His complex which produces significant tissue zinc depletion. It also causes zinc deficiency leading to functional losses of taste, smell, appetite, food intake and other neurological abnormalities (232). These effects are reversed completely by zinc administration while maintaining His intake at any given level, indicating that His-induced suppression of appetite relates specifically to this mechanism of zinc depletion (232). Indeed, loss of appetite with His administration through this induced zinc deficiency was used as a novel technique to induce reduced food intake in humans and to induce weight loss (233,234). With this use there can be significant side effects due to the effects of zinc depletion on multiple organ systems (232).

Natural foodstuffs such as marine products including tuna, sardine, Pacific saury and so on are quite rich in L-His.

2.3.2.3. Importance of Isoleucine, Leucine and Valine

The branched-chain amino acid Ile (Isoleucine) participates directly and indirectly in a variety of important biochemical functions in the brain. These include protein synthesis, the production of energy, the compartmentalization of the neurotransmitter glutamate in the brain and the synthesis of the neurotransmitters serotonin and the catecholamines DA and NE, which are derived from the aromatic amino acids Trp, Phe and Tyr (182,235,236). 15–20% of the amino acid content of animal-based dietary proteins contains considerable amounts of the branched-chain amino acids (237). While a major fraction of the ingested branched-chain amino acids is not metabolized by the liver and passes into the systemic circulation after a meal, causing plasma concentrations to rise appreciably (238,239). Also, the ingestion of the branched-chain amino acids causes:

- Rapid elevation of their plasma concentrations,
- Increases their uptake into brain and
- Decrease the brain uptakes and levels of the aromatic amino acids (240).

Reductions in the brain levels of the aromatic amino acids that follow the ingestion of amino acid mixtures containing the branched chain amino acids diminish the synthesis of some neurotransmitters (241-243). Also, the synthesis and the release in the CNS of serotonin and the catecholamines vary directly and rapidly with changes in concentrations of their precursor amino acids (Phe, Trp and Tyr) (182). In human studies with bipolar subjects during periods of mania, daily administration of the branched chain amino acids (60 g) for 7 d produced a significant reduction in manic symptoms, consistent with an effect on brain catecholamines (244).

2.3.2.4. Importance of Lysine

Lys is the one of all indispensable amino acid most strongly conserved, due to its capacity for storage and slower catabolism (236). A diet deficient in Lys decreases the whole-brain content of Lys (245) and affects NE activity in the hypothalamus (246). Animal studies indicated that rats are sensitive to changes in dietary Lys concentration (as small as 0.01%), when adapted to a Lys-deficient diet (247). The neural modifications that have been detected consistently in Lys-deficient rats (248) and the participation of Lys and its metabolites in normal brain functions (249) raise the possibility of psycho behavioural alterations during Lys-deficiency. The whole-brain content of Lys has been shown to be lower in Lys-deficient rats, with no specific modifications in the amygdala (200,245).

In animal studies within 24 h after a Lys-deficient diet no changes in daily food intake volume were found, whereas a significant decline was found during 4 days period of deficiency (246). Inhibition of protein synthesis (due to the low content of Lys) is improbable, but direct effects of Lys and/or its metabolites on Trp neurotransmission in the CeA or in other functionally interconnected brain areas are possible (250). The increased CeA Trp activity in the Lys-deficient rats triggered an anxiogenic effect in Lys-deficient rats but not in controls. The rats fed a Lys-deficient diet for 4 days, compared with normally fed rats, were characterized by increases in circadian release of CeA Trp, stress-induced anxiety and faecal excretion (251). Also chronic intake of a Lys-deficient diet affects the amygdala Trp and alters complex behaviours, such as stress perception. Further, a dietary deficiency of Lys increased stress-induced colonic transit and anxiety, because of an enhanced transmission of Trp in the amygdala. Further, increased anxiety and stress-induced faecal excretion were found in Lys-deficient rats (251). In contrast prolonged Lys treatment had anxiolytic effects in normally fed, stressed rats (252) and the metabolic effects of Lys were stress-specific (253,254). Moreover, a part of the Lys effect is traced to the Trp system (251). Lys blocks stress-induced faecal excretion and reduces the severity of diarrhoea in a manner similar to the action of synthetic Trp receptor antagonists (255).

Microbial synthesis of Lys was shown in the gastrointestinal tract (GIT) (256). This Lys is made available through protein breakdown and its intestinal uptake. Also, it is possible that the high dietary Lys load block this protein breakdown in an unspecified way (255). A partial blocking effect of Lys on anxiolytic responses but not on normal behaviour has been shown (255). In contrast to Lys-deficiency there is an improvement of stress responses in rats and pigs receiving Lys loads (252,257). Prolonged Lys supplementation reduced plasma cortisol in animals by inhibiting long-term anxiety (257) but without directly affecting the adrenal gland (258). Further, it has been shown that Lys fortification did not reduce normal levels of alertness and social apprehension (259). The anxiogenic response to Lys inadequacy in rats was mediated via serotonin alterations in the central amygdala (251).

Daily requirement for lysine is 1–1.5 g. It is in all cereal grains and in all pulses (legumes).

2.3.2.5. Importance of Trp

Trp serves as the immediate precursor for serotonin synthesis and Trp-induced serotonergic activity in the brain has been implicated in the regulation of many behavioural and physiological processes such as mood, aggression, susceptibility to stress, sleep patterns and food intake (27,260-263). Trp administration is also known to enhance serotonin release in neurons that are actively firing (264). The availability of Trp to brain neurons that synthesize serotonin directly influences the rate at which it is converted to a neurotransmitter (28). Trp has been shown to affect brain and nervous system function through interference with serotonergic neurotransmission (262,265,266). Administering either the amino acid itself (29) or meals that raise Trp access to serotonin neurons rapidly stimulates serotonin production (30,31). In clinical populations an elevated plasma Trp:LNAA ratio has been shown to improve mood (25,267). In healthy subjects such evidence has been weak and often inconsistent (268,269). In stress-vulnerable subjects the plasma Trp:LNAA ratio increased after a carbohydrate rich – protein poor diet and prevented a stress-induced rise in depressive mood and cortisol (51). Such functional effects are also reputed to accompany the ingestion of carbohydrates (270). In rats carbohydrate ingestion stimulated brain Trp uptake and serotonin synthesis (31). The dietary Trp may reduce aggression and alleviate stress in many species such as pigs (271), rats (260) and chickens (272-274).

Reduced serotonin concentrations resulting from the exhaustion of its plasma precursor Trp was found to provoke sleep abnormalities seen in depression (275,276), whereas increases in available plasma Trp for uptake into the brain improved sleep in different subjects (277-279). In humans administration of oral Trp can modify sleep and mood via its actions to stimulate neuronal serotonin production and release (280,281). Also, dietary Trp supplementation increased both Trp and 5-HIAA (5-hydroxyindolacetic acid) concentrations in the hypothalamus of piglets. The turnover of serotonin or the activity of the serotonergic nervous system is generally expressed as the ratio between Trp and its direct metabolite 5-HIAA (282). Reduced alertness after poor sleep often deteriorates cognitive-behavioural functioning (283). Sleepiness progressively reduces attention and efficient stimulus detection (284), as evidenced by lower behavioural responsiveness and reduced attention processing (285).

An increased availability of Trp and brain serotonin can be reached with dietary proteins containing high Trp. As a consequence, the serotonergic

system may become more sensitive because of compensatory receptor sensitization (286,287). α-lactalbumin has the highest Trp concentration of all bovine protein fractions (288). α-lactalbumin enriched whey protein increased the plasma Trp:LNAA ratio in subjects both highly vulnerable and relatively invulnerable to stress (27). In contrast, a protein-rich diet decreases the plasma Trp:LNAA ratio, because proteins are poor in Trp (1–2%) but rich in the LNAAs valine (Val), Tyr, Leu, Ile and Phe (25%). These dietary effects on the plasma Trp:LNAA ratio have frequently been shown (25,51,289).

Table 5.
Trp, LNAA und Trp:LNAA of some Nutrition (in 100 g)

	Energie	Trp (g)	LNAA (g)	Trp:LNAA
almond	569,6 kcal	0,2	4,5	0,04
Boletus	148,9 kcal	2	4,5	0,44
cashew nut	594,6 kcal	0,3	4,5	0,07
chanterelle	120,2 kcal	0,5	4,1	0,12
cocoa	342,5 kcal	0,2	3,5	0,06
flax ssed	372,4 kcal	0,4	6	0,07
Hen's egg	154,4 kcal	0,2	4,1	0,05
Liver pie	299,5 kcal	0,2	4,5	0,04
Meat	223,0 kcal	0,3	7,2	0,04
milk	64,3 kcal	0	1,1	0,00
Soya bean	416,3 kcal	0,4	8,5	0,05
Soya milk	152,2 kcal	0,2	4	0,05
Sunflower ssed	574,8 kcal	0,3	5,5	0,05
Whole-grain bread	187,9 kcal	0,1	1,4	0,07
Yeasts	288,0 kcal	0,4	9,4	0,04

Following dietary components may have Trp raising ability:

- Carbohydrate ingestion show no or only small behavioural effects due to modest Trp alterations (269,290).
- The rise in Trp:LNAA show 20–45% increases after the consumption of foods such as carbohydrates (290).
- A carbohydrate-rich, Protein-poor diet raise the ratio of plasma Trp-LNAA ratio and give Trp the advantage in the competition for access to the brain (30,291,292).
- Evening consumption of α-lactalbumin (4.8 g/100 g Trp) resulted in a 130% increases in the plasma Trp:LNAA ratio as compared with placebo (293).

While Trp binds to albumin in blood (294) the free Trp pool in blood ranges between 5–50% of the total Trp pool, depending on the physiologic or pharmacologic conditions (295-299). Albumin-bound Trp molecules in blood are readily available for transport across the blood-brain barrier. In blood nonesterified FAs also bind to albumin which is competitive with Trp (300). The proportion of Trp in blood that associates with albumin is thus affected by changes in blood nonesterified FA concentrations. Hence, as serum nonesterified FA concentrations influence the binding of Trp to albumin, changes in serum nonesterified FA should directly influence the free Trp pool and thus brain Trp uptake and levels (295,301). While insulin reduces plasma nonesterified FA concentrations the ingestion of a carbohydrate meal by rats rapidly would raise brain Trp levels and stimulate serotonin synthesis, which is linked to insulin secretion (30). Ingestion of a carbohydrate meal containing either 0 or 45% fat (or remained fasting) to overnight-fasted streptozotocin diabetic rats showed that the 45% fat meal raised serum nonesterified FA and produced a 2-fold rise in serum free Trp concentrations (compared with values in fasting rats or rats ingesting the 0 percent fat meal) and no changes in serum total Trp or the summed concentrations of the other LNAAs in serum (302). The changes in serum nonesterified FA and free Trp are as great as those seen following exercise in rats (303-306). The ingestion of a fat-containing meal rapidly raises plasma nonesterified FA concentrations. This effect is dose dependent. Hence, the response of brain Trp soon after fasting rats consumed a meal containing 20% protein (307) and one of several levels of fat (0, 15, 30, or 45%) showed that as the fat content of the meal increased, serum nonesterified FA concentrations and free Trp concentrations rose and yet brain Trp concentrations did not (307). The rise in plasma nonesterified FA caused by forced treadmill exercise in rats (20m/min for 1 h) was also associated with an increase in plasma free Trp, but not total Trp concentrations, as well as increases in brain Trp concentrations and the principal serotonin metabolite, 5-HIAA (304,305). Exercise-induced rise in plasma nonesterified FA is caused by sympathetic activation (308).

Recent investigations indicated that the intake of commercial available Trp causes toxic reactions, which was termed as eosiniphilia myalgia syndrome (EMS). It is characterized primarily by an increased blood eosinophil count and an often debilitating myalgia (309,310) and in some cases with neurological and pulmonary complications (311). This syndrome was appeared to be correlated with the use of Trp from a single manufacturer. Also, a contaminant in a production batch could be responsible for EMS (312). The absence of EMS in subjects ingesting pharmaceutical-grade Trp, which

meets high standards of purity, is consistent with this assessment (54). Also, pharmaceutical-grade Trp preparations in humans have never been associated with symptoms of EMS (54,313).

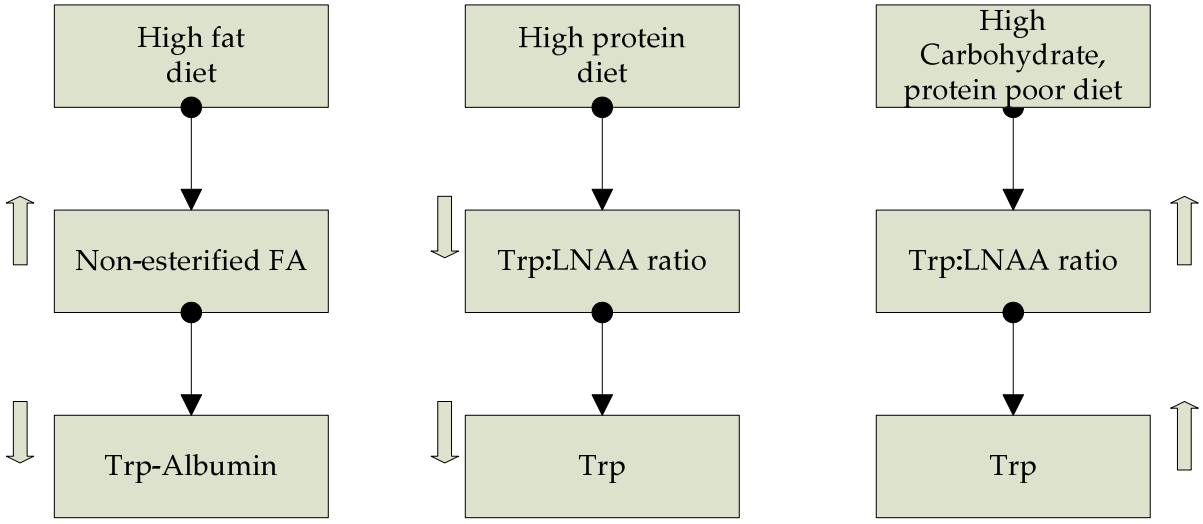

FIG. 8. Effect of macronutrients on Trp level in brain

2.3.2.6. Importance of Tyr

Tyr is the precursor to the catecholamine neurotransmitters DA, NE and epinephrine. Elevating Tyr concentrations in brain can stimulate neurotransmitter production in catecholamine neurons (particularly DA and NE neurons). It is observable in catecholamine neurons in both rat retina and brain in response to the large changes in Tyr concentrations produced either acutely or chronically by the ingestion of protein-containing foods (314,315). This effect occurs in actively firing neurons but not in catecholamine neurons that are quiescent or firing slowly (316,317). Brain Tyr concentrations raise as dietary protein content of diet increases from very low (2% energy) to moderate (10% energy) levels, with catecholamine synthesis following the change in Tyr (315). The ingestion of a protein-containing meal was known to produce a rapid increase in Tyr concentrations in the brain (318). Also, raising brain Tyr concentrations could rapidly stimulate L-3,4-dihydroxyphenyl-alanine (DOPA) synthesis in rat brain (319). Further, Tyr administration could stimulate DA synthesis in the corpus striatum, but pre-treatment of animals with a DA receptor antagonist to activate the neurons was required (320). Tyr concentrations in the brain are influenced by protein ingestion when the protein content of the diet is modified over several days or more (321,322). Physiologically, this relation might have the potential as a signal to inform the brain about the animal's success in acquiring protein in its diet (323). Tyr administration appears to improve cognition and performance in soldiers

under stressful conditions (324,325). In depressed patients the Tyr administration enhanced catecholamine production without any effects on mood (326).

In patients with PD Tyr administration elevated the DA production in the CNS (327). Variations in Tyr supply affect not only Tyr hydroxylation rate (DOPA synthesis) but also affect overall catecholamine production and release (328-330). In rats, Tyr depletion by itself does not appear to reduce DA (prefrontal cortex) or NE (hippocampus) release (329,331). However, it reduced the increase in DA and NE release produced by drugs either block catecholamine reuptake or receptors (329,331) and attenuates in rats the behavioural activation produced by amphetamine (332). In normal humans, Tyr depletion increases plasma prolactin concentrations (333), impairs features of spatial recognition memory and performance (333) and attenuates subjective psychostimulant effects of amphetamine (334,335). Tyr depletion has also been reported to reduce clinical ratings of manic symptoms in patients diagnosed with mania (335) and to lower some indices of mood in normal subjects that are reputedly consistent with the DA depletion (336,337). It has been observed that Phe inhibits Tyr hydroxylation (338). Reducing Tyr levels in brain can be accomplished by providing an oral dose of a mixture containing amino acids in addition to the LNAA, because this combination lowers plasma concentrations of Tyr (an effect originally unanticipated) while raising those of the other LNAA, thus enhancing the antagonism of competitive Tyr transport across the blood-brain barrier (243,339). The Tyr depletion paradigm, when applied to humans, seems to moderate striatal DA release (244).

3. Importance of Micronutrients

Micronutrients are essential constituents of diets needed in small quantities. These are vitamins, minerals and trace elements. Deficiencies and over doses of any micronutrients cause debility, disease and eventually death.

3.1.Importance of Vitamins

Chronically insufficient vitamin supply for vitamin C, thiamin, riboflavin, cobalamin and folate causes many unfavourable psychometric changes (340). In volunteers with an initial mild to moderate vitamin C deficiency, vitamin supplementation led to decreased nervousness, less depression and decreased emotional instability (340). In a clinical trial administration of folic acid, vitamin C and to a lesser extent thiamin, as compared to placebo, in men with an initial suboptimal folate status, led to a decreased emotional instability, increased activeness and concentration, higher extroversion and lower introversion, greater self-confidence and a markedly improved mood (340).

3.1.1. Importance of Folic Acid

Folate is important in 1-carbon metabolism (341), contributing carbon atoms to purines, thymidine and amino acids. In addition, methylation reactions involving folate may be important in the formation and maintenance of neuronal and glial membrane lipids (342). Folate is involved in maintaining adequate methionine pools for the synthesis of S-adenosylmethionine (343), a cofactor in methylation reactions in catecholamine synthesis and metabolism (344). Folic acid is important for functioning of the nervous system at all ages (345-348). It has also been linked to the maintenance of adequate amounts of tetrahydrobiopterin (349), a key cofactor in the synthesis of serotonin and the catecholamine neurotransmitters (344). Little information is available to illuminate the mechanisms by which folic acid deficiency causes the improper formation of the spinal cord. Folate supplementation produced a 72% protective effect against the occurrence of neural tube defects (350). Numerous studies have shown a high incidence of folate deficiency correlated with mental symptoms, especially depression and cognitive decline in epileptic, neurological, psychiatric, geriatric and psycho-geriatric populations (347,348). In neonates, infants, children and adolescents, inborn errors of folate transport and metabolism are associated with developmental delay, cognitive deterioration, motor and gait abnormalities, behavioural or psychiatric

symptoms, seizures, signs of demyelination[6] or failure of myelination and vascular changes seen on magnetic resonance imageing or postmortem examination (348).

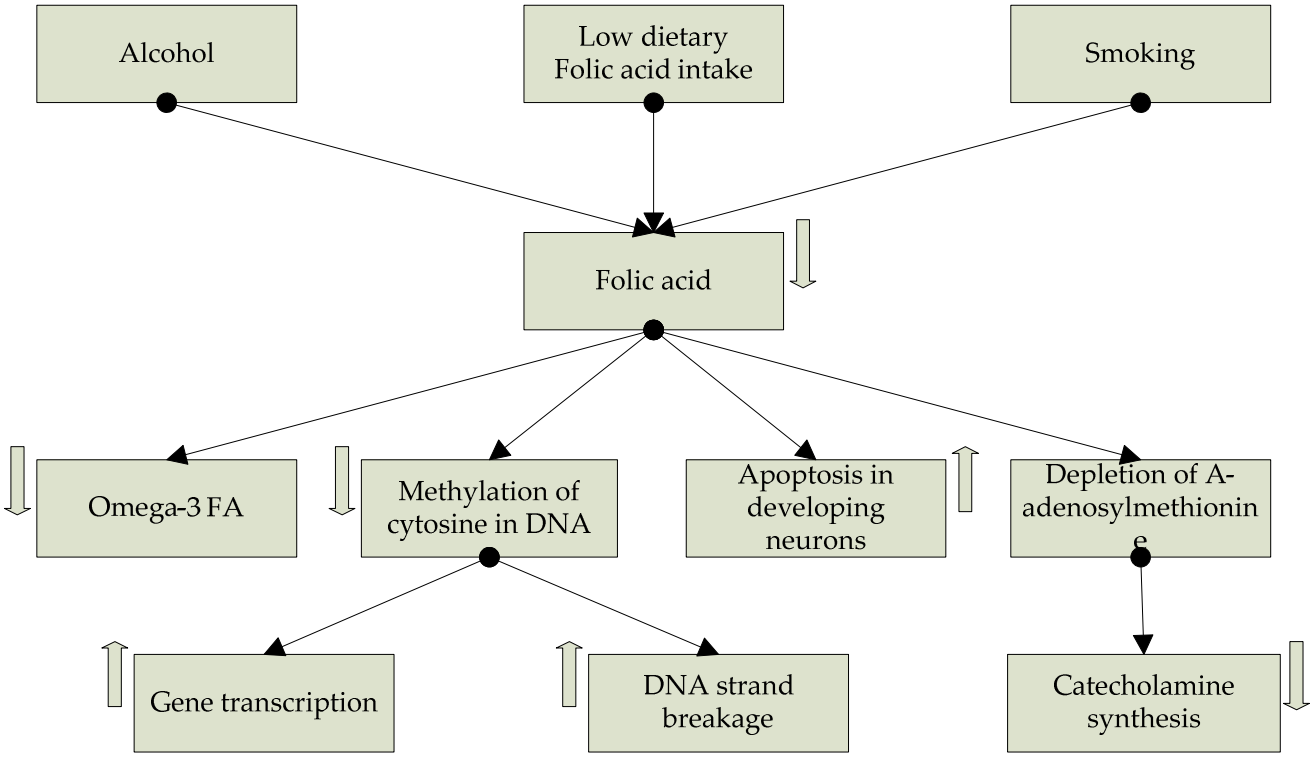

FIG. 9. Effect of low folic acid level

Patients with megaloblastic anemia who had a clear folate deficiency in the absence of vitamin B12 deficiency showed an incidence of affective (mood) disturbances of >50% (351). Depressed patients may have low plasma and red blood cell folate concentrations (352-354). Low intake of folic acid has been linked to other psychiatric conditions as well as to deficits in learning and memory, particularly in the elderly (355). The few controlled clinical trials of vitamin therapy in addition to standard psychotropic medication have all reported positive effects on patient's mental state. There are small clinical trials showing a beneficial effect of folic acid in depression and its ability to enhance the effectiveness of antidepressant medications (356,357). In a double blind placebo controlled trial in depressive patients treated with lithium, the addition of 200 μg/d of folic acid for one year significantly improved affective morbidity (358). Similarly, the addition of 500 μg/d of the vitamin to fluoxitine for 10 weeks significantly improved antidepressant response, especially in women (357). In folate deficient depressed and schizophrenic groups addition of 15 mg methylfolate to standard psychotropic

[6] The damage of the myelin sheath of the neurons is a demyelinating disease. This disease of the nervous system impairs the conduction of signals in the affected nerves, causing impairment in sensation, movement, cognition, or other functions depending on which nerves are involved.

medication over six months showed significant and increased clinical and social recovery (359). Earlier studies indicated improvement in both mood and neuropsychological function in a controlled trial of 15 mg daily intake folic acid alone for four months in depression (346). In a survey of nutritional status and cognitive functioning in 260 healthy elderly subjects aged 60 to 94 years in the community, there was a significant relation between impaired abstract thinking ability and memory and lower folate levels and intake (360). In the New Mexico ageing process study of 137 community residents aged 66 to 90 years, weak but significant associations were found between measures of abstract thinking and folate concentration (361). Several of the earliest reports of neurological disease associated with severe folate deficiency emphasise that dementia and depression are reversible with vitamin therapy (346,362-364).

The mechanism by which folate modifies mood is hypothesized to be related to its role in 1-carbon metabolism (341). In the form of methylentetrahydrofolate, the methyl donor in methionine synthesis from homocysteine, folate may help maintain adequate methionine pools for S-adenosylmethionine synthesis (343). The link to mood involves S-adenosylmethionine's role as a cofactor in methylation reactions in catecholamine synthesis and metabolism (344). Folic acid deficiency results in depletion of S-adenosylmethionine and a reduction in the methylation of cytosine in DNA. The decreased DNA methylation that can result from folic acid deficiency may enhance gene transcription and DNA strand breakage which can trigger malignant transformation (365,366). Recent studies have demonstrated direct consequences of folic acid deficiency on neurons by showing that simply depriving cultured embryonic brain cells of folate can induce apoptosis in developing neurons (367). Folic acid has been shown to increase omega-3 PUFAs status when supplemented and decrease omega-3 PUFAs status when it is in deficiency in the animal model (368). In addition, a folic acid deficient diet can enhance lipid peroxidation (369). A deficiency of folate can occur:

- When folate requirement is increased due to e.g. smoking and alcohol,
- When dietary intake is inadequate and
- When folate loses is more than usual.

Medications that interfere with body's ability to use folate may also increase the need for this vitamin. Major sources of folate are green vegetables, citrus fruits, liver and whole grains.

3.1.2. Importance of Vitamin A

Vitamin A actually refers to the family of retinoids. Its important part the retinyl group can be found in several forms. Vitamin A and its derivates, the retinoids, have been implicated in the synaptic plasticity of the hippocampus and might, therefore, play a role in associated cognitive functions (370). While adequate levels of vitamin A are required for appropriate CNS development and either too much or too little is equally harmful (370).

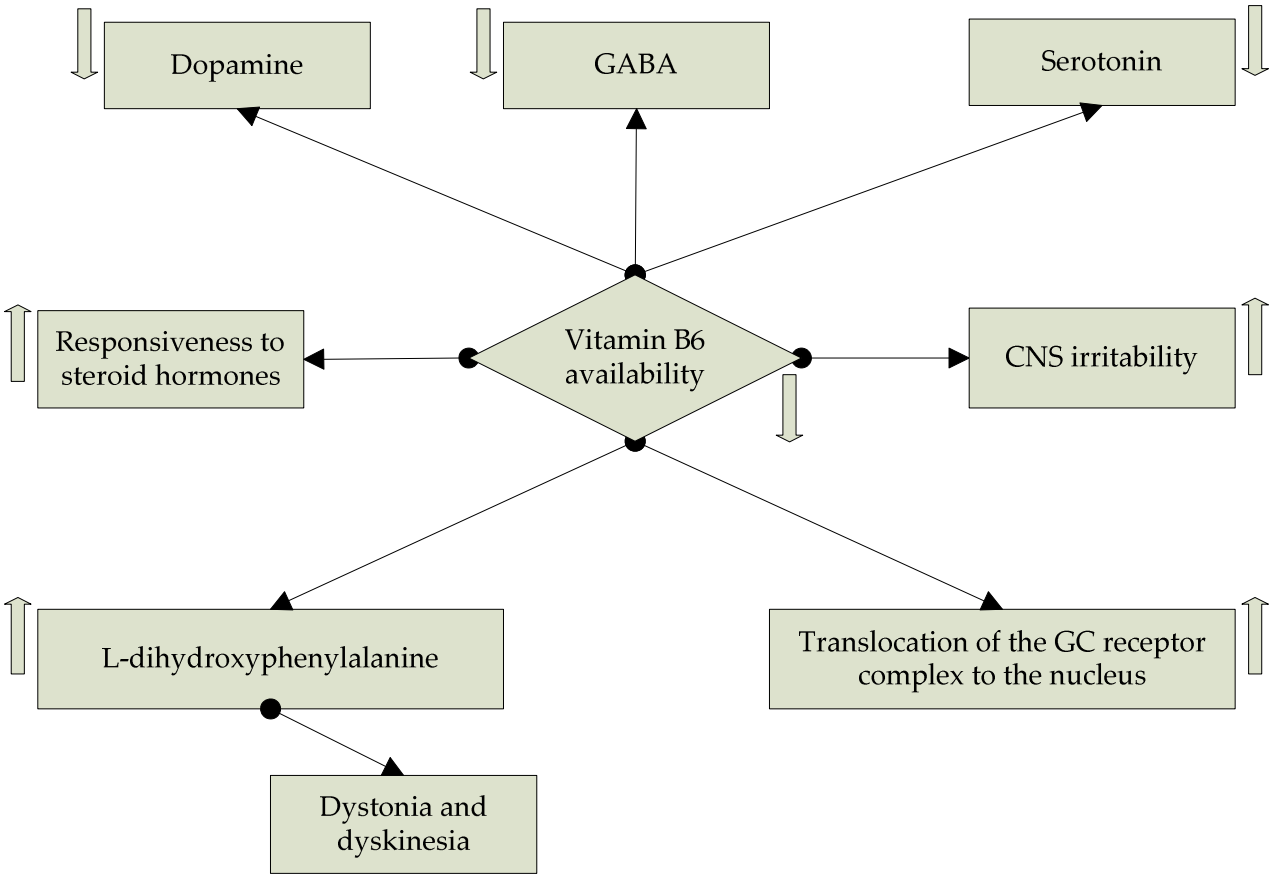

FIG. 10. Physiological effects of vitamin B6 deficiency

3.1.3. Importance of Vitamin B6

Dietary deficiency of vitamin B6 affects tissue concentrations of amino acids and neurotransmitters in rats and humans (371,372). The physiologically active forms of vitamin B6 are enzymatic cofactors in many reactions of mammalian nitrogen metabolism, including the metabolism of most amino acids and neurotransmitters. In general, vitamin B6 deficiency leads to a decrease in the concentrations of most amino acids. Most commonly affected brain amino acids by deficiency are serotonin, DA and GABA (371,372). In human plasma vitamin B6 concentration is associated with the best performance on the "Backward Digit Span Test" and performance improved on the "Activity Memory Test" with increased plasma

vitamin B6 concentration (373). Early studies indicated that excess dietary vitamin B6 affect brain and serum concentrations of some amino acids and binding properties of cortical serotonin receptors in a biphasic pattern (374). Also, large doses of vitamin B6 can affect CNS function (374,375) and neurotransmitter concentration (376). Further, high concentrations of pyridoxal phosphate suppress activation of transcription, while vitamin deficiency enhances responsiveness to steroid hormone (377) and increased CNS irritability (378). Vitamin B6 is a cofactor in the production of neurotransmitters including DA, NE, serotonin and GABA. Taurine deficiencies in vitamin B6 have been associated with defects in the CNS in rats (379). Also, pyridoxine is essential in the conversion of L-dihydroxy-phenylalanine to DA. Side effects of excessive L-dihydroxyphenylalanine include dystonia and dyskinesia (378).

3.1.4. Importance of Vitamin B12

Vitamin B12 is important for the normal functioning of the brain and nervous system and for the formation of blood. Vitamin B12 is required as coenzymes in the synthesis of serotonin and catecholamine neurotransmitters and also of S-adenosylmethionine, which has antidepressant properties (380-382). Further, it is involved in the metabolism of every cell of the body, affecting DNA synthesis and regulation FA synthesis and energy production. Lack of cobalamin causes a wide variety of neurologic symptoms and signs such as ataxia, loss of dermal sensation, diminished or hyperactive reflexes, dementia, memory loss, psychoses and disturbances of mood (383,384). Vitamin B12 deficiency may lead to severe neurologic disorders, which have been described in strict vegetarians, especially in infants and toddlers (385,386). Also, its deficiency may result in demyelination (387). In contrast vitamin B12 supplementation improves complete or partial memory loss (384), depression (388) and psychosis (389). Vitamin B12 level can be affected e.g. in following cases:

- Alcohol intake decrease vitamin B12 absorption from the GIT.
- The effects of most antibiotics on gastrointestinal bacteria can have clinically negative significant effects on vitamin B12 levels.
- An increased bacterial load can bind significant amounts of vitamin B12 in the gut and thus preventing its absorption.
- Nicotine can reduce serum vitamin B12 levels.

3.1.5. Importance of Vitamin C

Ascorbic acid is required for a range of essential reactions in all animals and plants. In living organisms, ascorbic acid is an antioxidant, since it protects the organism

against oxidative stress and is a cofactor in several vital enzymatic reactions. It is essential for optimal steroid hormone functions and this suggests an involvement of ascorbic acid in steroid synthesis mechanisms (390). Also, it affects the regulation of the levels of the circulating thyroid and adrenal cortical hormones (391). In animal studies, ascorbic acid deficiency caused an increase in plasma cortisol concentration (392) without an increase in ACTH (393). In rats, vitamin C pre-treatment enhanced the release of endogenous GCs such as to delay the turnover of the tracer cortisol in plasma (394). In humans about 2h after vitamin C application there was a distinct increase of plasma cortisol which was associated with an increase in urinary 17-hydroxycorticosteroids (395).

3.1.6. Importance of Vitamin D

The actions of 1,25-dihydroxy vitamin D3 at the plasma membrane and nuclear level may effectively enhance local cortisol availability and action in adipose tissue and may suppress pathways designed to limit expansion of adipose tissue stores (396). In vitro, cortisol promotes adipocyte triglyceride accumulation by reducing basal and catecholamine-stimulated lipolysis while also enhancing the activity of lipoprotein lipase (397). Suppression of 1,25-dihydroxyvitamin D3 levels by increasing dietary calcium may reduce local cortisol levels by reducing expression of 11ß-hydroxysteroid dehydrogenase and, thereby, attenuate local GC action specifically in the truncal region (398).

3.1.7. Importance of Vitamin E

Vitamin E, as the major chain-breaking lipid-soluble antioxidant, would be expected to be important for functional integrity of all biological membranes. It is apparent from the information currently available that the primary role of vitamin E in nutrition is that of a biological antioxidant. As such, vitamin E is thought to play an integral role in maintaining membrane integrity in nearly all mammalian cells (399). In vitamin E deficient rats a defect in the fast anterograde and retrograde axonal transport has been reported (400). Cerebellum seems to be active in the metabolic utilization of vitamin E. This could be the reason for cerebellar damage during experimental vitamin E deficiency and for the incidence of cerebellar symptoms in clinical vitamin E deficiency (401). The neuropathological changes of vitamin E deficiency in humans are very similar to those in rats and rhesus monkey (402). The resulting neurological syndrome is characterized by areflexia, peripheral neuropathy, cerebellar involvement with gait and limbio ataxia and decreased propioception and vibration sense (403).

3.2. Importance of Minerals, and trace elements

Dietary minerals and trace elements are required by living organisms. At least seven minerals are required to support biochemical processes, many playing a role as electrolytes or in cell structure, and function. Deficiencies of micronutrients have been shown to be associated with behavioural and developmental problems (404,405). Certain minerals balance is crucial for a healthy nervous system and neuronal susceptibility. Several reports suggested that the body electrolytes (calcium, chloride, magnesium, phosphorus, potassium and sodium) and the level of some trace elements (cobalt, copper, fluorine, iodine, iron, molybdenum, nickel, selenium, sulphur and zinc) play an important role in stress susceptibility.

3.2.1. Importance of Calcium

Low-calcium diets accelerate body weight and fat gains in animals fed an obesity-promoting diet and impede fat loss during energy restriction (398,406). In contrast, high-calcium diets suppress fat deposition and fat loss during modest energy restriction (398). Increasing intracellular Ca^{2+} using a variety of agonists, including 1,25-dihydroxyvitamin D3, results in a marked augmentation of human adipocyte cortisol production (406). Higher calcium intakes are associated with higher rates of whole-body fat oxidation measured in a whole-room calorimeter, with significant effects noted over a 24-hour period, during sleep and during light exercise. Also, dairy sources of calcium were shown to exert significantly greater anti-obesity effects than supplemental calcium carbonate, possibly due to the effects of other bioactive compounds in milk (407). Observational studies have found an inverse relationship between dairy and calcium intake and body fat in both younger and older women (408,409), calcium and BMI in African-American women (410), dairy products and obesity in children (411) and dietary calcium and body fat accumulation in preschool children (412). Reanalysis of a randomized controlled trial has demonstrated a calcium treatment effect of 0.325 kg weight loss/yr over 4 years with no intentional change in caloric intake (413). Increasing dietary calcium from 400 to 1000 mg/d for 1 year resulted in a 4.9 kg reduction in body fat (406). Indeed, there have been several isolated reports over the last 18 years of an inverse relationship between dietary calcium and/or serum calcium and indices of obesity (414-417).

Increasing intracellular Ca^{2+} results in an increase in human adipocyte energy storage and fat mass by stimulating de novo lipogenesis and inhibiting lipolysis (418-420), whereas treatment of obesity-prone mice with a calcium channel antagonist (nifedipine) results in significant reductions in adipose tissue mass (421). A clinical trial for determining the effects of dietary calcium on body weight and fat loss, secondary to energy-restriction diets producing an energy deficit of

500 kcal/d indicated that the high-dairy diet exhibited a significant increase in insulin sensitivity, as indicated by reductions in both circulating insulin and the area under the glucose tolerance curve (422).

3.2.2. Importance of Iodine

Epidemiological studies indicate that school-aged children living in iodine-deficient villages were found to have poorer levels of IQ, cognitive and motor function than school children in iodine-sufficient villages (423-428). Hypothyroid patients show slowing of intellectual function and speech and have memory deficits (429). Also, intrauterine iodine deficiency is well established as the cause of cretinism and lesser degrees of cognitive and motor disability (430). There is a suggestion that low serum thyroxine (T4), secondary to iodine deficiency, is linked to poor intellectual performance of the people residing in iodine-deficient areas (431). Triiodothyronine seems to be the active hormone with respect to neurological development in the foetus and is synthesised in the brain from thyroxine transported from foetal plasma across the blood-brain barrier (432). In case of severe hypothyroidism maternal transfer is insufficient for foetal requirements (433), while maternal thyroxine contributes substantially to foetal thyroxine in the later weeks of pregnancy (434).

3.2.3. Importance of Iron

The physiological manifestation of iron deficiency has also been noted in immune function, thermoregulatory performance, energy metabolism and exercise or work performance (435,436). Iron is involved in numerous neurological functions. Iron deficiency is strongly related to the severity of anaemia with a 50% decreases in muscle myoglobin content, cytochrome oxidase activity and electron transport capacity in skeletal muscle, concurrent with a 50% decreased oxygen transport capacity due to anaemia (437). Restless legs syndrome has been described as being causally related to iron-deficiency anaemia (438).

The mechanisms of Fe transport in the brain commonly involve transferring and transferrin receptors, as well as the divalent metal transporter 1 (439). Iron in neurons is stored as ferritin (440). The developing brain can be particularly sensitive to changes in iron status not only because of its rapid growth and development, but also because certain developmental events occur in a small window of time during which the timing and duration of a nutrient insult can have a significant, long-term effect on brain maturation and function (441). Several epidemiologic studies suggest that for anaemic children, iron supplementation is

correlated with improved performance outcomes, including attention and learning (442-445), as well as motor development (442). A study of non-anaemic adolescent girls also demonstrated a positive correlation between iron supplementation and improved verbal learning and memory (446). Short-term trials (<15 d) of iron supplementation among anaemic infants have shown no differences in children's motor or mental performance (447). In contrast, long-term iron supplementation trials have shown a significant improvement in children's behaviour (448). Also, the iron supplemented children were more socially interactive and displayed more positive affect than did the non-supplemented children (448).

Iron deficiency is reported to have an effect on cognition (449). Iron deficiency is thought to affect myelination, neurotransmitter metabolism and Fe-containing enzymes (450). Rats with postweaning iron deficiency had significantly lower concentrations or activity levels of myelination markers than controls (451). Post-weaning iron deficiency was also associated with changes in the PUFA content in myelin fractions (451,452). Both neonatal and postnatal iron deficiency in rats affected D1, D2 receptor and levels of DA transport in the striatum and prefrontal cortex (453,454). Also, Iron deficiency during lactation in the rat results in significant loss of regional brain iron that is distinct from those regions that lose iron with dietary restrictions later in life (455). Restoration of brain iron with later aggressive dietary iron repletion also resulted in incomplete restoration of abnormalities in DA metabolism and in behaviours related to DA (455,456). The rate of iron uptake into the brain is increased when the iron status of the subject is low and is decreased when the iron status is higher (457). Interestingly, regions of the brain rich in iron, i.e., the substantia nigra, globus pallidus and nucleus accumbens, are far less affected by dietary iron deficiency than are other regions such as the cortex or the striatum that have less iron content (458).

3.2.4. Importance of Magnesium

Extra- and intracellular magnesium levels have been shown to be genetically controlled in humans (459) and genetic differences in magnesium utilization may account for differences in vulnerability to magnesium deficiency and differences in body response to stress (460). Magnesium supplementation has beneficial effect in a wide variety of conditions, such as neuropsychiatric disorders, ischemic heart disease, cardiac arrhythmias, asthma, diabetes and chronic fatigue, in which magnesium deficiency has not always been substantiated (461,462).

3.2.5. Importance of Selenium

The preferential retention of selenium in the brain suggests that it has an important function. It seems to influence compounds with hormonal activity and neurotransmitters and this is postulated to be the reason why selenium affects mood in humans and behaviour in animals. Lowered levels of selenium have been associated with negative mood scores in at least 5 studies (463). It has been reported that a low selenium intake was associated with anxiety, depression and tiredness and that selenium therapy for five weeks alleviated these symptoms. Selenium deficiency can interfere with the normal conversion of α-linolenic acid into EPA and DHA and results in an increase in the omega-6:omega-3 ratio (464).

3.2.6. Importance of Zinc

Zinc is a trace mineral that is involved with RNA and DNA synthesis and is critical to cellular growth, differentiation and metabolism (465,466). Zinc levels are lower among patients with depression and a recent study found that 25 mg zinc supplementation may improve depressive symptoms (467). Zinc is known to be essential element for neurogenesis and also to play an important role in neurotransmission. The hippocampus, which participates in spatial learning and memory, contains the highest concentration of zinc of any other brain region. Zinc is concentrated in the synaptic vesicles of specific glutaminergic neurons, which are found primarily in the forebrain and connect with other cerebral cortices and limbic structures. During synaptic events, zinc is released and passes into postsynaptic neurons, serving as a neurotransmitter (468). Further, Zn^{2+} may participate in the storage, release and uptake of glutamate and modulation of glutamate receptors (469). The following 3 types of Zn^{2+} signals have been proposed (470):

1) Transmitter-like signals involving action potentials, the release of Zn^{2+} from synaptic vesicles and its binding to glutamate or GABA receptors.
2) The flux of Zn^{2+} into postsynaptic neurons during long-term potentiation.
3) Intracellular signalling for sequestration of Zn^{2+} into vesicles.

The involvement of vesicular Zn^{2+} in cognitive functions such as memory and learning has been suggested (468). Therefore, zinc deficiency may affect cognitive development by alterations in attention, activity, neuropsychological behaviour and motor development. Zinc deficiency may compromise behaviours necessary for cognitive functioning including activity and attention (465,471). In psychiatric patients zinc deficiency may affect emotionality and response to stress (472,473). Studies of severe zinc deprivation in monkeys before weaning showed that zinc-

deficient animals were emotionally less mature this was demonstrated by their difficulty with separation and the increased protective behaviour by their mothers (474). The association between zinc deficiency and an increased risk of anxiety and depression may be related to the stress reaction observed in zinc-deprived animals (475). Weekly administration of a micronutrient supplementation containing iron and zinc had a beneficial effect on infant motor development and exploration (orientation-engagement) (476). Trials in Chinese children and Mexican-American children from Texas have found that zinc-supplemented children demonstrated superior neuropsychological performance, particularly in reasoning, when compared with controls (477,478). Also, supplementation of 25 mg of zinc for two months has also been shown to significantly increase omega-3 status in the plasma phospholipids at the expense of saturated fat (479).

4. Importance of Phytochemicals

Fruits, vegetables and common beverages as well as herbs have been shown to be rich sources of the micro chemicals with the different healthy effects. Due to the absence of consideration they are not identified as nutrients and essential. The food chemists and natural product scientists have identified hundreds of the phytochemicals e.g., carotenoids, chlorophyll, flavonoids and sulphides. They have the potential e.g., to modulate stress. Persons who eat green or yellow vegetables every day show a lower incidence of the stress syndrome (irritation, sleeplessness) than those who do not eat them daily. Extracts of various fruits and vegetables exhibit neuroprotective properties in cell culture, and animal models that are relevant to the pathogenesis of many neurodegenerative conditions including stroke, AD and PD (480). The previous findings have suggested that reversals in age-related declines might be accomplished by increasing the dietary intake of the fruits and vegetables (481,482). Several studies have shown, that aqueous strawberry, spinach and particularly blueberry extracts were able to reverse several parameters of the brain ageing (e.g., deficits in cell communication) such as DA release (483,484) and age-related motor and cognitive deficits when fed to rats from 19 to 21 months of age (483-486).

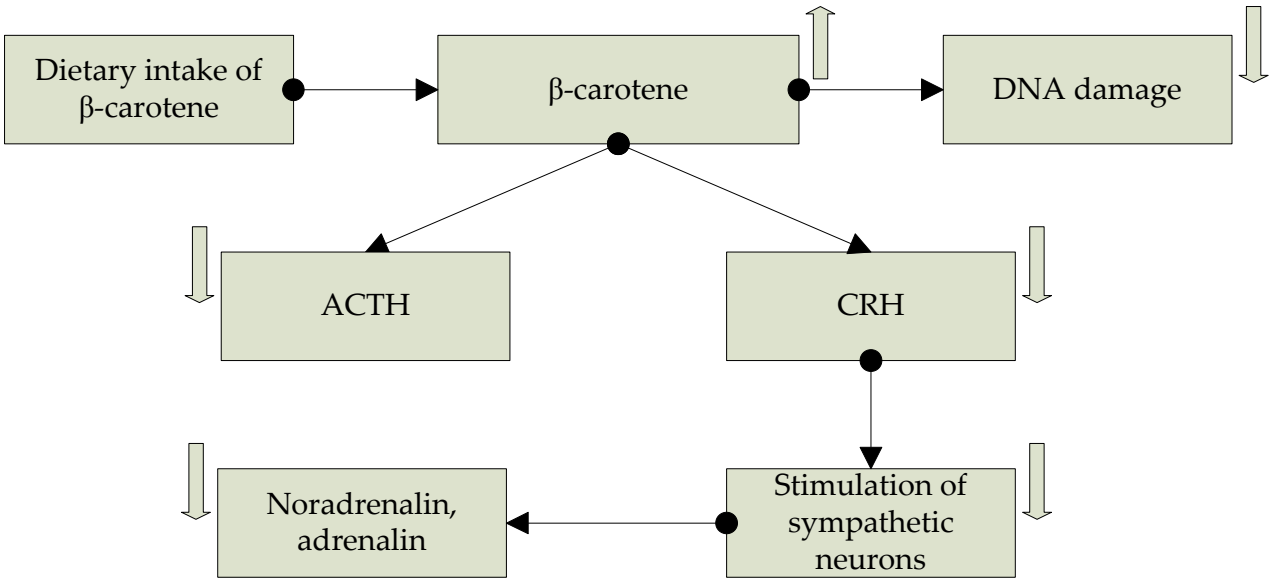

FIG. 11. Effect of high dietary β-carotene intake

4.1. Importance of Carotenoids

Carotenoids include compounds as diverse as α- and ß-carotene, lycopene, lutein and xanthophylls. Carotenoids are found in almost all coloured vegetables. They are a diverse group of over 600 structurally related compounds synthesized by the bacteria and plants. Several studies have shown that α-carotene prevents DNA

damage induced by carcinogenic chemicals (487-490). Also, α-carotene has been shown to attenuate hepatic drug metabolising enzymes (491). Human studies indicated that β-carotene suppresses the secretion of CRH dose dependently (492). It is also suggested that the effective site of β-carotene is the hypothalamus, where β-carotene suppressed the secretion of CRH induced by the exercise stress and consequently the secretion of ACTH in the pituitary. As CRH stimulates the sympathetic neurons (493), β-carotene also inhibited the stimulation of noradrenaline and adrenaline secretion through the suppression of CRH secretion (492).

4.2. Importance of Polyphenols

Flavonoids are the most abundant polyphenols in our diets with antioxidant activity. They can be divided into the several classes according to the degree of oxidation of the oxygen heterocycle: flavones, flavonols, isoflavones, anthocyanins, flavanols, proanthocyanidins and flavanones. They are involved in the photosensitization and energy transfer, the actions of plant growth hormones and growth regulators, the control of respiration, photosynthesis, morphogenesis and sex determination, as well as defence against infection. After consumption, the plant flavonoids undergo many metabolic conversions by the intestinal bacteria and both the metabolites and parent compounds are absorbed into the blood and then excreted, mainly in the urine (494). Rats fed diets containing extracts high in the both falvanoid as well as total antioxidant activity for 6 weeks before being subjected to 48h of exposure to 100% normobaric O2 showed no loss in the striatal muscarinic or cerebellar GABAergic receptor sensitivity (495). These oxygen-induced decreases in the neuronal function have been shown to be sensitive to ageing and have been associated with the behavioural deficits (496). Flavonoids have been shown to be effective in protecting the neurons against the oxidative insults, possibly by acting selectively within the protein and lipid kinase signalling cascades and not through their potential to act as the antioxidants (497,498).

Flavonoids may have a multiplicity of the direct and indirect effects that can profoundly affect the different neuronal parameters that lead to alterations in the motor and cognitive behaviours (499). In support to the concept of the multiple and complementary flavonoid effects beyond the simple antioxidant function, a prospective study of dementia in the subjects older than 65 years reported an inverse relation between the baseline intake of dietary flavonoids and development of dementia (500). Some flavonoids also have anti-inflammatory properties by being potent inhibitors of the nitric oxide synthase-2 induction and also increase the endothelial nitric oxide synthase-3 activity (501). Multiple studies have shown that the protein kinase activity is important in the memory formation in the

particular spatial memory (502) and that ERK (Extracellular signal-regulated kinase) is involved in the striatal-dependent learning and memory (503) and the hippocampal-dependent spatial memory (504). Changes in the hippocampal plasticity parameters such as the hippocampal neurogenesis, extracellular receptor kinase activation, insulin-like growth factor-1 (IGF-1) and IGF-1 receptor levels were increased in the blueberry-supplemented aged animals (505). Therefore, the cognitive improvements afforded by the polyphenolic-rich fruits such as blueberries appear in part to be mediated by their effects on the hippocampal plasticity (506).

In a neuronal cell model resveratrol activated the ERK-1 and ERK-2 (507). Recent studies have shown that resveratrol stimulates sirtuins and can exert anti-ageing effects at the cellular level. Interestingly, resveratrol is the phytochemical responsible for the health benefits of red wine (508,509).

4.3. Importance of Sulphides

The organosulphur compounds present in the Allium vegetables, which are either lipid or water soluble, are considered responsible for the beneficial effects of these herbs. The Allium genus includes approximately 500 species, the most widely used of which are onions (Allium cepa), garlic (Allium sativum), leeks (Allium porrum), chives (Allium schoenoprasum) and shallots (Allium ascalonicum). Recent studies indicated preventive effects of the garlic extracts for the brain atrophy (510) as well as the learning and memory impairments (511) in the senescence-accelerated mouse.

5. Importance of Functional foods

Functional foods are any fresh or processed foods with a health-promoting or disease-preventing property beyond the basic nutritional function. Also, they contain a wide variety of the compounds with such a property.

5.1. Importance of Acetyl-L-Carnitine

Acetyl-L-carnitine (ALC) is an orthomolecule which offers major metabolic benefits to the brain. ALC is a metabolic cofactor for the conversion of the FAs into energy within the mitochondria of the nerve cells, thereby helping to keep them supplied with energy (512). ALC also provides acetyl equivalents for the production of acetylcholine, one of the chemical transmitters. In controlled trials, ALC improved depression as well as cooperation, sociability and attention to personal appearance, though it did not consistently improve anxiety (513). A number of double-blind clinical trials suggested ALC may have clinical utility for the management of some forms of cognitive dysfunction (514-518). In one double-blind trial conducted with cognitively impaired ex-alcoholics aged 30-60 years, ALC improved memory, visuo-spatial capacity and vocabulary recall when given at two grams per day over a test period of three months (519). ALC's beneficial effects on the brain also extend beyond cognition enhancement. In the trials with cognitively impaired subjects, intakes ranged from 1.5 to 3 grams per day, with most trials using two grams or more. At these intake levels, ALC can intensify dream activity and it may be contraindicated for subjects with epilepsy or bipolar conditions (512).

5.2. Importance of Phosphatidylserine

Phosphatidylserine (PS) has been first obtained from bovine cortex. An alternative PS product has been made by enzymatic head group exchange from soy phosphatidylcholine. Animal studies demonstrated that soy PS has absolutely similar effects on cognitive performance as compared to bovine PS (520-522). Human studies with 300 mg soy PS (523) and 400 mg soy lecithin phosphatidic acid and PS complex (524) have shown positive effects on stress and mood. In a recently performed clinical investigation 300 mg of milk PS in a drink matrix have resulted in dampening psychological and endocrine stress response (525). Another human study indicated that the daily intake of phospholipid concentrate rich in PS and sphingomyelin compared to placebo-exposed individuals showed a tendency for shorter reaction times in the working memory task, suggesting better performance in phospholipid-treated subjects. The two treatment groups did not significantly differ in their endocrine stress response. However, phospholipid-treated subjects with a higher stress load showed a blunted psychological stress response (526).

5.3. Importance of Probiotics

Psychological stress can alter the integrity of indigenous micro-flora for several days (527). In primates after maternal separation GIT micro-flora was evaluated in 20 infant rhesus Macaques ages 6-9 months who were separated from their mothers for the first time. All infant monkeys were found to have typical faecal bacterial concentrations at baseline. A brief increase in Lactobacilli[7] shedding on the first day post separation ($p<0.05$) was followed by a significant decrease in the concentration of Lactobacilli in the faeces ($p<0.001$). An inverse relationship was also found between the faecal concentration of shed pathogens and shed Lactobacilli. Also, on the first day of stress there is an increased shedding of Lactobacilli, followed by a dramatic decrease in numbers of Lactobacilli over the next six days (527). The Lactobacilli population responds to stress-induced changes in GIT physiology, such as:

- Inhibition of gastric acid release (528),
- Alteration in GIT motility (529) or
- Increased duodenal bicarbonate production (530).

The micro-flora of the GIT represents an ecosystem of the highest complexity (531). The micro-flora is believed to be composed of over 50 genera of bacteria (532) accounting for over 500 different species (533). The adult human GIT is estimated to contain 1014 viable microorganisms, which is 10 times the number of eukaryotic cells found within the human body (534). The micro-flora plays many critical roles in the body such as:

- Stimulation of the immune system,
- Synthesis of vitamins (B group and K),
- Enhancement of GIT motility and function,
- Digestion, and nutrient absorption,
- Inhibition of pathogens (colonization resistance),
- Metabolism of plant compounds/drugs and
- Production of short-chain FAs and polyamines (531,535,536).

Many factors can harm the beneficial members of the GIT micro-flora:

- Use of antibiotic is a significant cause of major alterations in normal GIT micro-flora (537).

[7] Lactobacillus is a genus of gram-positive bacteria. They are a major part of the lactic acid bacteria group. In humans they are present in the vagina, and the GIT. The production of lactic acid makes its environment acidic, which inhibits the growth of some harmful bacteria.

- The potential for an antimicrobial agent to influence gut micro-flora is related to its spectrum of activity (537), pharmacokinetics and dosage (538) and length of administration (539).
- Oral antimicrobials well absorbed in the small intestine have minor impact on the colonic flora, whereas agents that are poorly absorbed can cause significant changes. In general, the greater the dosage and length of administration are the larger the impact on the micro-flora (539).
- Use of antimicrobial agents for parenteral administration is not free from these consequences, as some of these agents can be secreted in their active forms in bile, saliva or from the intestinal mucosa and result in considerable alterations in the colonic flora (540).
- Psychological stress can alter the integrity of indigenous micro-flora for several days (527).
- Physical stress, radiation, altered GIT peristalsis and dietary changes alter the GIT micro-flora.

Since both mucin and acidic mucopolysaccharides are important for inhibiting adherence of pathogenic organisms to the gut mucosa and their decrease contributes significantly to successful colonization by pathogenic organisms (541). Exposure to psychological stress has been shown to result in a significant reduction in the production of mucin and a decreased presence of acidic mucopolysaccharides on the mucosal surface (542). Further, exposure to stress results in decreased production of immunoglobulin-A (542).

In response to anger or fearful situations a 20-30% rise in the proportion of Bacteroides fragilis subsp. thetaiotaomicron[8] in the faeces of individuals has been noted. After resolving these situations the concentration of these organisms in the faeces decreased to normal levels (543). As growth of B. fragilis subsp. thetaiotaomicron is enhanced by bile, this may partly explain the increased numbers of organisms in response to increased epinephrine release (544).

The composition of the diet has been shown to have a significant impact on the content and metabolic activities of the human faecal flora (545). Sulphur compounds, including sulphate and sulphite have been shown to increase production of potentially harmful bacterial products in the GIT. In the colon there

[8] Bacteroides fragilis is a gram-negative bacillus of the gut. Bacteroides fragilis acts primarily at the surface of the mucosa. Bacteroides species also benefit their host by excluding potential pathogens from colonizing the gut. Some species are opportunistic human pathogens, causing infections of the peritoneal cavity, gastrointestinal surgery, and appendicitis via abscess formation, inhibiting phagocytosis and inactivating beta-lactam antibiotics. Bacteroides thetaiotaomicron can harvest.

is a specialized class of gram-negative[9] anaerobes known as sulphate-reducing bacteria (546). Reduction of sulphite to sulphide by sulphate-reducing bacteria (547) results in the production of a potentially toxic hydrogen sulphide which can contribute to abdominal gas-distension (546). These hydrogen sulphides can also damage colonic mucosa by inhibiting the oxidation of butyric acid[10], which is essential for absorption of ions, mucus synthesis and lipid synthesis for colonocyte membranes (548).

The amount of dietary sulphate that reaches the colon appears to be the primary factor in determining the growth of sulphate-reducing bacteria. On the other hand, endogenous sources of sulphate (e.g., sulphated glycoproteins and chondroitin sulphate) appear to have little impact on sulphate-reducing bacteria levels (549). Ingestion of foods rich in sulphur-containing amino acids encourages both the growth of sulphate-reducing bacteria and the production of sulphide in the large bowel (547). Sources of dietary sulphate include:

- With sulphur dioxide preservatives and dried fruits,
- Dehydrated vegetables,
- Shellfish (fresh or frozen) (550),
- Packaged fruit juices,
- Baked goods (551),
- White bread and
- The majority of alcoholic beverages (552).

Consumption of a high-protein diet can also increase the production of potentially harmful bacterial metabolites. Consumption of large amounts of sulphur-containing amino acids may significantly increase sulphide production in the colon (548). Elimination of milk, cheese and eggs from the diet of ulcerative colitis sufferers resulted in substantial therapeutic benefit, suggesting that reducing the intake of sulphur-containing amino acids decreases colonic production of sulphide (553).

In the GIT undigested protein is fermented by the colonic micro-flora with the resultant end-products of short chain FAs, branched-chain FAs and potentially harmful metabolites (ammonia and amines) (548,554,555). Ammonia production

[9] Gram-negative bacteria do not retain crystal violet dye in the gram staining protocol. On the other hand, gram-positive bacteria will retain the crystal violet dye when washed in a decolorizing solution. Gram-negative bacteria have pathogenic capability. It is often associated with certain components of Gram-negative cell walls, in particular, the lipopolysaccharide. Lipopolysaccharide triggers an innate immune response characterized by cytokine production and immune system activation.

[10] Butyric acid is produced as end-product of a fermentation process solely performed by obligate anaerobic bacteria in the gut.

and accumulation is also involved in the pathogenesis of portal-systemic encephalopathy (556). Ammonia has been shown to alter the morphology and intermediate metabolism, increase DNA synthesis and reduce the lifespan of mucosal cells (552). It is also considered to be more toxic to healthy mucosal cells than transformed cells and, thus, may potentially select for neoplastic growth (554). The production of these potentially harmful by-products can also be attenuated by the consumption of diets high in fibre (557) and/or indigestible starch (558). They will reduce intestinal pH.

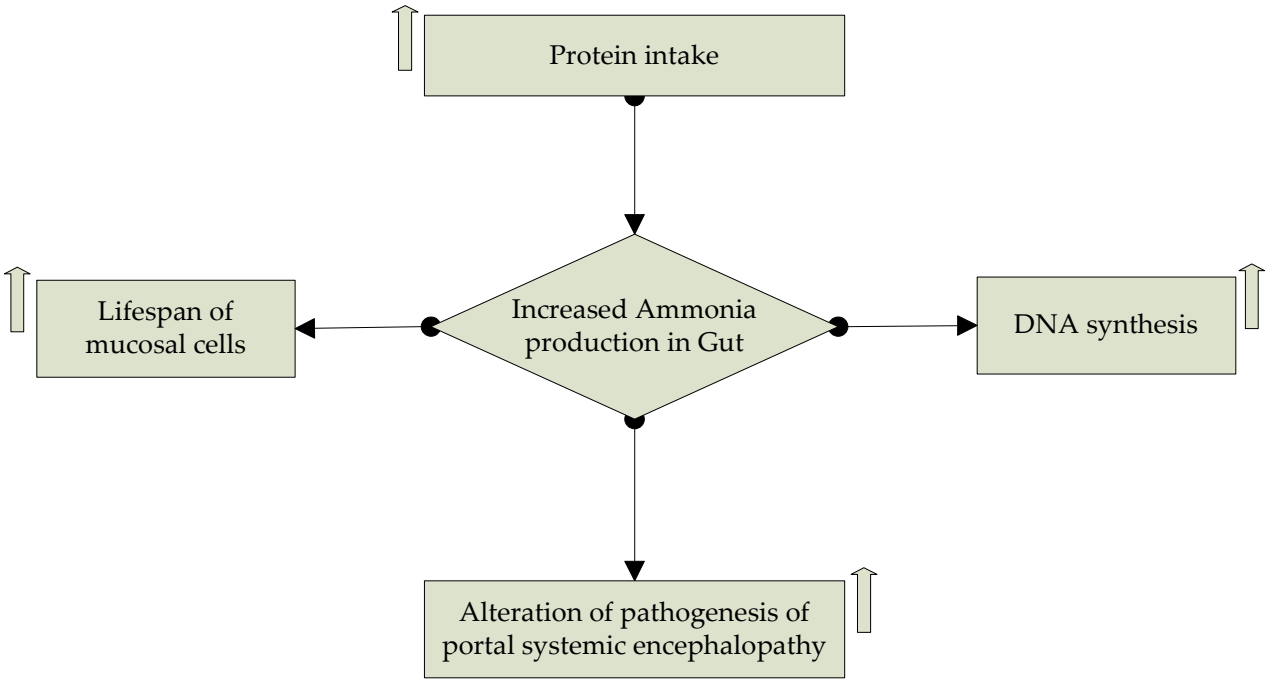

FIG. 12. Negative effects of high protein diets on gut.

Diets high in simple sugars slow bowel transit time, increase fermentative bacterial activity and faecal concentrations of total and secondary bile acids in the colon (559). A consequence of slower bowel transit time may be an increased exposure to potentially toxic bowel contents (560). Refined sugars are metabolized quickly in the ascending colon. In contrast foods containing substantial amounts of insoluble fibre are metabolized more slowly, releasing fermentation end-products (e.g., hydrogen gas and short chain FAs) more gradually (561).

6. Importance of Endocrine

The endocrine system is instrumental in the regulation of development, growth, metabolism, puberty and tissue function. It plays as a part in determining mood and stress.

6.1. Importance of CCK

Cholecystokinin (CCK) is a hormone of the GIT. It was originally identified in the gut, where it is involved in the secretion of pancreatic enzymes, gallbladder contractions and gut motility. Some known facts about CCK are:

- CCK production is located in the CNS.
- CCK is localized in several brain areas involved in food intake regulation (562). - CCK is released from hypothalamic neurons during feeding (563,564).
- CCK is released by the duodenum in the presence of digestive products of fats and proteins in the intestine (565).
- CCK is involved in the control of food intake in both man and animals (566-568).
- CCK mediates gastric emptying under physiological conditions (569).
- CCK inhibits food intake and increase satiety in humans (570).

In humans, CCK pathways modulate sensations induced by gastric distension (571). It has also been hypothesized that CCK plays an etiologic factor in panic disorder and anxiety (572). CCK is more abundant in the brain than in the periphery and is one of the most abundant neuropeptides in the brain (573,574). Its concentration in cortex and limbic regions (575,576) supports its role in the regulation of many behavioural phenomena, including satiety and appetite (577), anxiety (577-582), memory (583), sexual behaviour (580,581), thermoregulation (578,579) and response to drugs of abuse (584). It is localized in cell bodies and terminals with many other neurotransmitters such as GABA (585,586), DA (587), serotonin and opiates (588). Also, there is evidence of a major corticostriatal CCK-containing pathway that is thought to contain glutamate as well (589). It meets the criteria for designation as a neurotransmitter (573).

CCK is responsible for stimulating the digestion. It acts as a hunger suppressant and plays a major role in inducing drug tolerance to opiates. CCK is likely to transmit vagal afferent signals to the hindbrain by acting on receptors located in the pylorus and liver. There is a large body of data from studies investigating the role of CCK in food intake regulation (590,591). Also, CCK is a potent inhibitor of gastric emptying (592), some of its effects to limit food intake may be indirectly mediated by the retention of food in the stomach. Both depression and chronic

tension can present with abdominal symptoms (593,594). It is known that CCK or CCK receptors interact with other neurotransmitters in the CNS (monoaminergic, serotonergic, GABAergic) known to be involved in anxiety and affective disorders (595-597). CCK-B receptor plays an important role in anxiety states and panic attacks (572,598,599). CCK-B receptors can modulate activity within the HPA axis (599,600), which is involved in the stress response. Psychological stress is widely believed to precipitate exacerbation of symptoms in functional dyspepsia. Inhibition of gastric emptying and stimulation of colonic transit is the most consistent motility response of the GIT to acute stress (601). Early life stress and trauma in the form of abuse, neglect or loss play a major role in the vulnerability of individuals to develop functional GI disorders. It is proposed that in the genetically predisposed individual both early life stress and severe life-threatening stress can result in permanent alteration in central stress circuitry and predisposes the individual to the development of functional disorders later in life (601). Although CCK reduces meal size, long-term peripheral administration of CCK does not reduce overall energy intake or induce sustained weight loss (602).

6.2.6.2. Importance of Cortisol

Cortisol has been implicated as a potential mediator for increased energy intakes in healthy males (603) and females (41). It is involved in appetite regulation (604) and energy balance by increasing available energy through gluconeogenesis and lipolysis (41). Studies in dogs suggest that cortisol treatment enhances de novo glucose synthesis through increased amino acid uptake in the liver (605,606). In animals, GC administration (607) and corticosterone replacement (608) led to hyperphagia and weight gain. Corticosterone also increased fat intake in a dose-dependent fashion in rats (608).

Depression is positively related to basal cortisol levels (609). Although the acute elevation of cortisol plays a protective role during stress, chronic elevations can promote insulin resistance and cause abdominal obesity (610,611). A ‘chronic stress-response network’ in rats, based on greater consumption of sucrose following administration of GCs, leaded to increased abdominal fat depots. In humans overeating of ‘comfort foods’ may be stimulated by cortisol in response to stress, which can result in abdominal obesity (612).

After acute stressor, the rapid increase in HPA activity interacts with elevated epinephrine, glucagon, and sympathetic neural activity to elevate blood glucose concentrations, ensuring adequate substrate for brain and muscle that may be life-saving. Also, high cortisol secretion in response to an acute laboratory stressor is related to voluntary increases in sweet, high-fat food ingestion after the stressor.

Individuals with high cortisol responses consumed more calories on the stress day compared to low reactors, but ate similar amounts on the control day (41).

Stress and negative affect are the most frequently cited precursors of binge eating (613). However, negative emotions have been associated with both increased and decreased food intake (614,615). Stress reactivity may distinguish stress overeaters from stress under-eaters (616). Cortisol secretion is a major component of the stress response (617) and could play a role in binge eating, given that exogenous GCs induce obesity by increasing food intake (603). An exaggerated cortisol response after laboratory stress tests has been observed in women with anorexia nervosa (AN) (618), bulimia nervosa (BN) (617,619) and obesity (620), although a blunted cortisol response has been found (621).

Cortisol is released during stress and can increase hunger and feeding behaviour (603). Also endogenous cortisol release stimulated by stress may mediate stress-induced eating. Among lean women, high cortisol reactors ate significantly more food after a stress task (41). Stress plays a confirmed role in the onset and maintenance of BN (616) and in the initiation of binge eating episodes (622,623).

Increased cortisol is positively related to central fat distribution in both obese and lean individuals (624,625) and morning cortisol has been shown to be positively associated with waist-hip ratio (WHR) and insulin (626). A large WHR, reflecting central obesity, appears to be a health risk factor independent of obesity (624) and is related to greater HPA activation (611), associated with increased cortisol levels and vulnerability to stress (620,625). Obese women with binge eating disorder (BED) have higher morning basal cortisol levels compared with non-BED (627). Additionally, a greater cortisol area in the BED group is observed during a cold stress test (627). Women with BED have similar to those with BN greater basal cortisol levels (621,627,628) and increased cortisol after stress (617,619,627,629). In relation to health, dysfunction of the HPA axis has been implicated in particular in dysphoric disorders, such as major depression (630), whereas hypercortisolemia in Cushing's syndrome is accompanied by physical symptoms, such as accumulation of abdominal adipose tissue, together with muscular atrophy of the limbs, providing powerful evidence of the well-established metabolic and nutritional consequences of chronic hypercortisolemia (178). Normal physiological variations in cortisol level in humans have a significant direct influence on macronutrient metabolism (36,37). Also, the ability of cortisol to increase plasma FFA levels may underlie the emerging link between cortisol and abdominal obesity, together with its associated metabolic syndrome (38). Cushing's patients with elevated cortisol levels selected high-fat foods twice as often as normal weight subjects and three

times as often as overweight controls (608). Laboratory test indicated that among healthy women, high cortisol reactors ate significantly more food following a cognitive stress task compared to low cortisol reactors (41). In an earlier study (631) subjects undergoing a stressful task before a meal showed increased plasma cortisol during the task, which was then followed by a suppressed cortisol response to the meal.

In healthy men administration of cortisol for four days led to slightly increased energy expenditure. In contrast to this slight increase the food intake increased dramatically (603). Approximately 90-95% of plasma cortisol is bound to CBG, albumin and erythrocyte membranes (632) whereas only the free fraction is thought to be physiologically active. Cortisol in saliva is a valid measure of free cortisol levels and is easily sampled repeatedly without distress (11,632).

6.3. Importance of CRF

Corticotrophin-releasing factor (CRF) is a peptide that is released in the brain by stress to integrate the endocrine, behaviour, autonomic and visceral responses (633,634). CRF functions both as a neuroendocrine hormone and neurotransmitter, via the HPA axis and hypothalamic and extra-hypothalamic neuronal pathways (635). CRF also modulates the actions of other neuropeptides and hormones that regulate food intake, such as neuropeptide Y (NPY) and leptin (636). For instance, blockade of CRF signalling in the brain by selective antagonists or CRF antibody enhances NPY-induced food intake in rats (637,638). Further, CRF acts in the brain to induce a rapid onset reduction of food intake, gastric emptying in rodents and plays a role in stress-related alterations of food intake and gastric motor function (634,639-641).

CRF cells in the amygdala innervate monoaminergic neurons in brainstem. In the locus coeruleus, CRF increases the basal firing rates of the locus coeruleus neurons and NE secretion in the forebrain (642), probably increasing arousal and attention. Moreover, the electrical response of the locus coeruleus to hypotension requires amygdala CRF input and chronically stressed rats have increased CRF tone in the locus coeruleus (643,644). Activity of serotoninergic neurons in the dorsal raphe is similarly affected by CRF and stress (645-647). Both the locus coeruleus and dorsal raphe had greater c-Fos responses in chronically stressed rats than in naive rats provided with a novel acute-restraint stress (648). Possibly it is elaborating behavioural, autonomic and neuroendocrine motor outputs characteristic of chronic stress by administering CRF (649-651). The amygdala appears to be a very important component of the chronic stress-response network, both because of its

far-reaching innervation of cortical, subcortical and brainstem structures and its important role in memory consolidation (652).

6.4. Importance of CRH

Corticotropin-releasing hormone (CRH) is a neurotransmitter as well as a neuro-hormone (653). Stressors increase the firing rate of regions in the brain stem, particularly noradrenaline–NPY neurones in the A1 (VLM), A2 (NTS) and A6 (locus coeruleus; LC) regions. There are synaptic contacts between noradrenaline–NPY nerve fibres and CRH perikarya in the paraventricular nucleus (PVN), although there have been no confirmatory retrograde or anterograde double-labelled studies to confirm the location of the perikarya of these axons (654).

6.5. Importance of Cytokines

Peripheral or central administration of a number of cytokines, including IL-6 and TNF, inhibit food intake (655). Cytokines may also influence food intake indirectly via actions on insulin sensitivity (656) or leptin production (657,658).

6.6. Importance of Glucocorticoids

GCs were named by Hans Selye for their major combined actions on both mobilization of small substrate molecules from peripheral fat and muscle stores and augmented gluconeogenesis in the liver (659). GCs are also known to affect development (660,661), memory (662,663), fear, anxiety (7) and the immune system (664-666). GCs as prime regulators of both energy balance and stress (667) are controlled by a wide range of variables, including hunger (668), feeding (669,670), aversive stimuli, expectancy (669,671,672) and circadian factors (667,670,673). Adaptive anorexia (674), anxiety symptoms (675) and increased HPA responsiveness (648) indicate facilitation of centrally driven defensive strategies. Elevated GCs stimulate appetitive activities, such as drug-taking behaviours (676,677), result in dose-dependent increases in wheel running (678) and palatable feeding (612,679,680) and may generally reduce thresholds for pleasurable stimulation. The HPA response is blunted in rats consuming high-calorie diets (63,681), a finding paralleled in some human subjects (26,682). Many studies find a positive correlation between plasma GCs and the expression of feeding behaviour. Food intake is normally highest at the time of day when baseline GCs show a peak and intensity of feeding can be shifted with GC treatment (12). Food intake may be mediated through GC-induced stimulation of NPY (14,683-685) and catecholamines (14) or through inhibition of the anorexigenic peptide CRF (686,687).

GC levels above the seasonal baseline are generally correlated with protein utilization and muscle tissue breakdown (688,689). Experimental manipulations confirm the involvement of elevated GC levels in such metabolic changes: induces protein loss and muscle atrophy in a variety of species (690-693). Further, GCs may promote gluconeogenesis through enhanced substrate delivery. Studies in a variety of vertebrate species verify the role of GCs in the acute provisioning of glucose. Treatment with GC equivalents increases plasma glucose in birds (694,695) and can reverse hypoglycaemic effects of insulin injections (696). In contrast, a characteristic change in transformed cells is a 5- to 7-fold increase in glucose uptake and utilization (697,698). Also, GC manipulations may not always affect plasma glucose levels (699,700). In many peripheral tissues GC decrease glucose uptake (701). The size of the GC stress response can either be enhanced, diminished or remain the same (702,703). GCs support a heightened physiological state by promoting availability of lipid energy from adipose tissue stores (12,664). For example, cortisone administration significantly reduces the stored triglyceride fraction of adipose tissue in lizards (704). Also, GCs increase lipogenesis and fat deposition in the liver (695,704,705). GCs may contribute to the process of FA oxidation by making available amino acids for use as citric acid cycle intermediates (706). Further, GCs may promote fat mobilization by inhibiting glucose uptake in adipose tissue (664).

In healthy males, exogenous GC administration increased daily food intake compared to placebo (603). Adrenalectomy and GC receptor antagonists prevent or reverse obesity (707), whereas administering corticosterone leads to increased appetite for sucrose (680), hyperphagia and weight gain (708). In cancer patients, prednisolone significantly increased appetite, compared to a control group (709).

GCs decrease DA and NE transporter activity and consequently increase signalling by these transmitters (710,711). In relation to health, dysfunction of the HPA axis has been implicated in particular in dysphoric disorders, such as major depression (630).

- Chronically high concentrations of GCs act in three ways that are functionally congruent (612).
- GCs increase the expression of CRF mRNA in the central nucleus of the amygdala, a critical node in the emotional brain.
- CRF enables recruitment of a chronic stress-response network.
- GCs increase the salience of pleasurable or compulsive activities (ingesting sucrose, fat and drugs or wheel-running). This motivates ingestion of “comfort food.”
- GCs act systemically to increase abdominal fat depots. This allows an

increased signal of abdominal energy stores to inhibit catecholamines in the brainstem and CRF expression in hypothalamic neurons regulating adrenocorticotropin.

Under a persistent stressor or long after administration of a single stressor of high intensity, there is marked diminution of the efficacy of GC feedback inhibition of stimulated, but not basal, ACTH secretion (712,713). After the first 24-h period of the onset of a chronic stressor, the direct long-term effects of GCs on brain are to enable the "chronic stress-response network" and thus modify a variety of mechanisms associated with coping, including enhancing stimulus salience and its attendant compulsions (612). There are three modes of GC action that are important during stress (612):

- Canonical,
- Chronic direct and
- Chronic indirect.

In rats high levels of GCs inhibit growth hormone secretion, reducing linear growth, reducing sympathetic neural outflow and reducing some types of fat mobilization (684,714). Adrenalectomized rats replaced with clamped corticosterone concentrations for 5 days and allowed to drink sucrose ad libitum showed a significant positive relationship between corticosterone and sucrose ingestion and corticosterone and mesenteric fat (680). By contrast, neither chow intake nor sc white fat depot weights were affected by corticosterone (680). Also, passively increasing corticosterone concentrations into the stress range in rats redistributes stored energy toward an intra-abdominal distribution (715).

6.7. Importance of Ghrelin

Ghrelin is a recently discovered peptide hormone which is structurally related to motilin.

- Ghrelin is also produced in the hypothalamus (716).
- Circulating ghrelin concentrations increase during fasting (717).
- Circulating ghrelin concentrations are reduced by the nutrient's presence in the stomach (717).
- Circulating ghrelin concentrations are in obese lower versus lean human subjects (718).
- Central ghrelin administration also increases hypothalamic expression of the NPY (719).

6.8. Importance of Insulin

Physiological amounts of insulin are required for normal neuronal activity but the sudden exposure to bolus insulin injections will activate the HPA axis, as will many other stressors, for example, transport, restraint or isolation. The HPA axis responds together with acute increases in insulin after meals in both rats and man (22,720,721). In vitro, insulin synthesis and secretion from the pancreas are directly inhibited by the actions of GCs (722). In vivo, increasing GCs are associated with increasing insulin secretion (723), possibly because of a marked anti-insulin effect on liver (723), which appears to be particularly vulnerable to the negative effects of GCs on insulin action (724). Hepatic insulin resistance is strongly associated with abdominal obesity (725). The relatively selective increase of abdominal fat in the presence of elevated GCs and insulin may be a consequence of the differentiating effects of these hormones on stromal fat precursor cells (726), as well as increased abundance of GC receptors on omental compared with sc adipocytes (727). In cases of very low energy stores and high GCs, the normal inhibitory effects of GCs on HPA axis activity are reduced, if not abolished (728). This should enhance GC elevations and their effects on omental fat.

6.9. Importance of Leptin

The adipose-derived hormone leptin is thought to regulate energy homeostasis by stimulating coordinated changes in energy intake and expenditure in response to changes in energy stores (729-731). Leptin is synthesized in fat cells and secreted into the bloodstream in concentrations that are proportional to total adipose stores (732-735). Leptin also increases release, from adjacent neurons, of anorexigens α-melanocyte stimulating hormone and cocaine- and amphetamine-regulated transcript, which are also coexpressed (736). Plasma leptin concentrations in humans correlate strongly with adiposity (732,733,735). Additional functions for leptin among his roles are signalling the neuroendocrine response to starvation (737-739), the timing of puberty (740-742) and regulation of the HPA axis (743-745). Several lines of evidence suggest that leptin can regulate the HPA axis at the level of hypophysiotrophic CRH and the adrenal gland (743-745). Since the circadian rhythm of the HPA axis is affected by feeding (746,747) and diurnal levels of leptin are also influenced by food intake (737,748).

Studies in spontaneously feeding rodents and humans have revealed an inverse relationship between the levels of leptin and GCs (737,749,750). In normal adult mice housed under 12-h light and 12-h dark cycles and fed ad libitum, maximum food intake occurs during the dark cycle (737). GCs increase early in the dark cycle, coinciding with the onset of feeding and decrease to a nadir at the beginning of the light cycle (737,746,747). In contrast, plasma leptin peaks late in the dark cycle and

decreases during the light cycle (737,748). Also, plasma leptin levels appear to be pulsatile and circadian (750) and leptin peaks early in the dark cycle, whereas cortisol peaks before wakefulness (749,750).

Fasting results in a decrease in leptin and an increase in corticosterone in adult mice (734,737,751). Further, diet-induced weight loss causes leptin concentrations to fall in proportion to the loss of adiposity (732). During acute weight loss (during fasting), however, leptin concentrations fall much more than expected from the amount of fat lost (735), suggesting that negative energy balance reduces the amount of leptin secreted per unit of fat mass.

6.9.1. Effects of Dietary Fat on Leptin

Inducing obesity by feeding rodents a high-fat or high-energy diet by changing diet from chow to a high-fat diet was associated with leptin resistance. This leptin resistance occurred rapidly and was apparent before any change of body composition could take place (752). Also, dietary fat, per se, can induce leptin resistance. Importantly, in rats maintained on chow, leptin sensitivity predicts the development of diet-induced obesity when the animals are subsequently placed on a high-energy diet (753).

6.10. Importance of SHBG

Depressed plasma testosterone levels consistently occur as a result of obesity. This could be caused due to the elevated metabolism of testosterone in fat tissue and a decrease in binding capacity of the sex hormone-binding globulin (SHBG) (754). Also, a low protein diet may elevate SHBG levels in elderly men (755). Further, the levels of growth hormone and IGF are reduced, which inhibit SHBG production in hepatocytes (756).

6.11. Importance of Thyroid Hormones

The liver and to a lesser degree the kidneys play a dominant role in the metabolism of thyroid hormones. As the liver and to a lesser extent kidney have primary influence on the circulating levels of thyroid hormone metabolites, the health and function of these organs play a critical and under-appreciated role in thyroid hormone function (757). The majority of the most metabolically active thyroid hormone, 3,5,3'-triiodothyronine (T3), is generated in peripheral tissue. Similarly, the preponderance of its competitive inhibitor, 3,3',5'-triiodothyronine (rT3; reverse T3) is generated outside the thyroid gland. Further transformations to T2 and T1 isomers also occur almost exclusively in peripheral tissue. These transformations are all catalyzed by deiodination enzymes. This stepwise deiodination results in

both active and inactive metabolites (758). People subjected to cold exposure-induced stress responded with an increase in serum rT3 (759). In an academic anxiety examination twenty-two male and 27 female medical students were monitored. Both male and female students experienced an increase in rT3 levels on examination days. The increase among female students was substantially higher than observed in the male students (760). In other study with military cadets the combination of several stressful situations showed a synergistic and dramatic effect on altering thyroid hormone metabolism. During a training exercise the cadets had been subjected to a combination of sleep deprivation, calorie deficiency and intense physical activity. Parallel to increased levels of cortisol along with abolition of circadian rhythm T4, fT4 and T3 consistently declined. While T4 and fT4 returned to normal levels within 4-5 days following the cessation of the training exercise, T3 and fT3 remained depressed (761). A correlation between increased rT3 and elevated levels of IL-6 has been reported in elderly patients undergoing emergency surgery (762). Elevated levels of IL-6, TNF-α and interferon-α have also been reported to have a strong association with the reduced T3 and increased rT3 found under stressful conditions (763,764). On the other hand, IL-6 administration also results in a significant increase in cortisol levels (765). In any type of situation characterized by increased endogenous secretion of cortisol, a predictable pattern of altered thyroid hormone metabolism may occur. The generalized pattern is characterized by a trend toward lowered thyroid-stimulating hormone (TSH) production and a blunted TSH response to thyrotropin-releasing hormone (TRH), a decline in T3 and an increase in rT3 (760,766-773). Even changes in serum cortisol levels within the normal range can cause significant alterations in thyroid hormone parameters (774). Abnormal plasma levels of the thyroid hormones are typically associated with reproductive deficiency (775). Hypothyroidism as well as hyperthyroidism also can modulate the reproductive capacity of experimental animals. Excessive levels of plasma thyroid hormones stunts growth and development, inhibits sexual behaviour (776), decreases plasma LH levels and thus impairs gonadal function (777). In accordance with hyperthyroidism hypothyroidism is associated with abnormal menstrual cycles and disrupted follicular development (775,778).

Enzyme activity can be modulated by numerous foreign compounds, such as common chemicals and drugs (779). Many of these enzyme inducers can increase the glucuronidation of T4, resulting in a decrease of serum T4 and a subsequent increase in TSH (780). Specific drugs and environmental toxins have been shown to influence the sulphotransferase activity responsible for thyroid hormone metabolism. While the role of most nutrients on sulphation of thyroid hormones is unknown, in rats selenium deficiency significantly increases the mean serum

concentrations of sulphated T4, T3 and rT3 (T4S, T3S, rT3S) secondary to reduction in 5'-deiodinase activity (781). Exposure to toxic metals such as cadmium or lead can result in an alteration in peripheral metabolism of thyroid hormones. A substantial reduction in T3 without any significant alteration of serum T4 concentrations has consistently been observed in animal models (782-784). Also, activity of hepatic 5'-deiodinase has decreased by as much as 90% subsequent to exposure to toxic metals. Coupled with the decline in T3 and hepatic 5'-deiodinase activity and the impairment in antioxidant enzyme systems, a concomitant increase in lipid peroxidation by as much as 200% has also been reported (782-784).

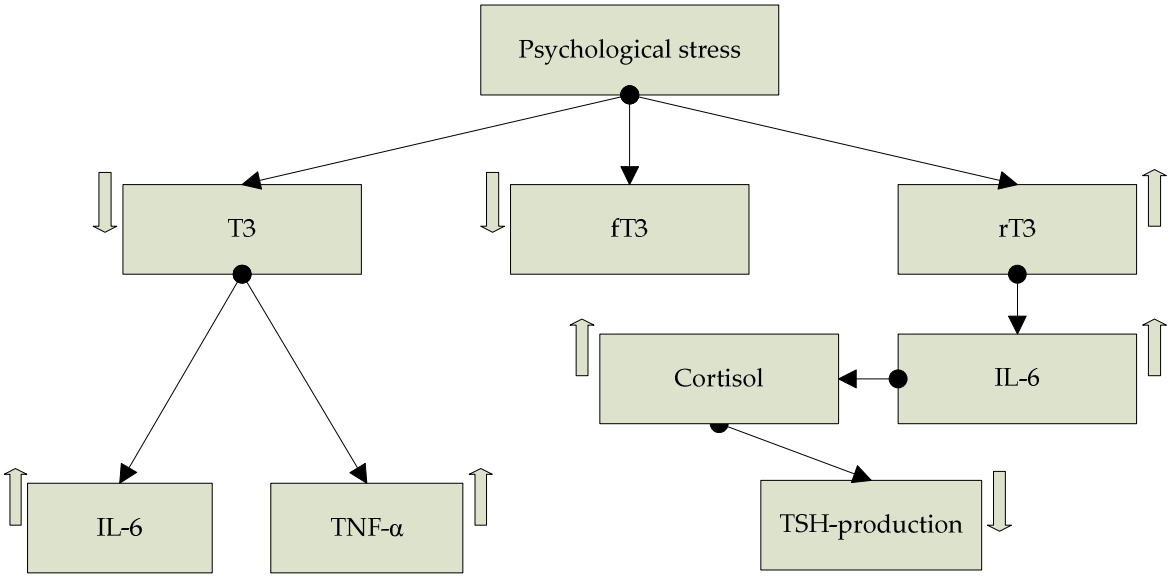

FIG. 13. Effect of psychological stress on thyroid hormone

Nutritional status and caloric expenditure influences thyroid function centrally at the level of TSH secretion, at the level of monodeiodination and possibly elsewhere. Since an increase of rT3 is found at the expense of T3 during caloric restriction, it is possible the hepatic peripheral pathways play a substantial role in metabolic control during energy balance. Also, the increase in rT3 during fasting might be a result of increased production of and decreased clearance of this metabolite (785). In healthy male subjects following a 30-hour fasting serum T3 levels were significantly lower than in the non-fasting state, while rT3 levels increased during fasting. After re-feeding, TSH tended to increase and rT3 to decrease slightly, these values remained perturbed when compared with values observed prior to fasting (786). In contrast to short periods of fasting caloric restrictions longer than three weeks cause a return of T4 and rT3 levels to normal values (787).

Serum thyroid hormones are sensitive to marginal changes in energy intake and expenditure. A hypo-caloric, low carbohydrate diet consisting of 800kcal/day for four days resulted in a striking decrease in both T3 and fT3 and an increase in rT3 (788). In a study of obese individuals, irrespective of carbohydrate content of the diet, when caloric content of the diet dropped to 600kcal/day T3 levels were compromised. Reverse T3 was not significantly influenced by the carbohydrate content of the diet and seemed to be most impacted by the caloric content (787). In a study with the non-obese subjects, T3 levels decreased and rT3 levels increased when carbohydrate intake was dramatically reduced (789).

In animal models, ethanol intake was associated with impaired hepatic 5'-deiodination (790). Among patients with alcohol-induced liver cirrhosis, low T3 and T4, elevated rT3 and normal TSH values have been observed. In these subjects an abolished circadian rhythm and elevated cortisol levels have frequently been observed (791).

6.12. Importance of Testosterone

Sex hormones can influence regions of the CNS which contain hormone receptors. Two decisive phases have been identified in the effects of testosterone on brain structures and consequently on behaviour. Testosterone is qualitatively the most potent androgen in males (792), which is also present in females at approximately one-tenth of the male serum concentration (793). During foetal and neonatal life relatively high concentrations of testosterone are thought to influence brain development by organizing the undifferentiated brain in a sex-specific manner. It has been shown that the hypothalamus, the hippocampus, the preopticseptal region and the limbic system are important target areas for sex steroid action (794-796). These brain structures and hence the corresponding behavioural repertoires are then thought to be activated at the beginning of puberty when the production of sex hormones increases (797). Stressful situations as experienced during work, before tournaments or anticipating exams have been shown to decrease testosterone levels (798-804). The same effect was seen in men undergoing workplace reorganisation and threatened by unemployment. After the workplace situation changed for the better, testosterone levels clearly rose with a marked variation between subjects (805). Studies exploring the relationship between gonadal function and depressive episodes showed that testosterone secretion as well as mean levels was decreased significantly in patients (806,807). Decreased testosterone levels in depressive illness can be seen as a permanently down-regulated secretion, partially maintaining a state of mood that initiated it in the first place. Contrary, stress release can have an elevating effect on androgen levels, which is demonstrated by a controlled study involving volunteers practicing

transcendental meditation (808). Strength training can have an acute effect on endocrine functions. Measurements immediately and 5 minutes post-exercise show an age-dependent increase in testosterone levels (809-813). Regardless of the kind of sport, maximal or submaximal exercise (5–30 min) normally results in significant increases in testosterone levels in males which are independent of luteinizing hormone (LH) and follicle-stimulating hormone secretion (814). The apparent disagreement between the effects of submaximal, prolonged exercise and 5–30 minutes exercise on testosterone levels in males are explained by the early (non-LH dependent) rise in testosterone concentrations (815) and a decreased metabolism of testosterone due to a drop in hepatic blood flow (816). Acute effects of submaximal, prolonged exercise in marathon runners or cross-country skiers resemble hormonal changes found in endurance-trained men during the resting state. A highly significant decline in testosterone concentrations compared with pre-competition baselines was observed (817-819). In contrast to men young sportswomen had significantly increased testosterone levels after a long-distance run (820). Testosterone concentrations of trained subjects were only 60–85% of the age-matched untrained men, although no difference in mean plasma SHBG capacity could be detected between the trained and untrained men (821).

In settings combining the mental and physical aspects of stress, testosterone can drop to clearly hypogonadal levels (822,823). External administration of testosterone is considered for the treatment of depressive states (824,825). In a representative study, ten cynomolgus monkeys received injections of either testosterone propionate or a sham solution. Testosterone administration led to a significant increase in aggression, which was mediated by social status. Dominant animals were much more likely to present aggressive behaviour than subordinate ones (826). To determine a possible role of testosterone in status ranking, chess players were tested before and after competition. Before and after tournaments, winners/ winners-to-be had higher testosterone levels than losers (827). Similar results in regard to post-competition levels were described during tennis matches and wrestling competitions (828,829). Also a history of previous success or membership in the host team can lead to an elevation of testosterone levels after the match (830). Interestingly in a socially homogeneous group of German volunteers, levels of saliva testosterone did not change during exposure to aggressive and violent films (831).

Any sexual behaviour can significantly alter sex hormone levels. The majority of data on eugonadal men refer to effects on ejaculation. Orgasmic frequency in males, whether through sexual intercourse or masturbation, correlated positively

with free, biologically active testosterone, serum testosterone or dihydro-testosterone (832-834).

6.12.1. Effects of Alcohol on Testesterone

Excessive alcohol consumption has toxic effects on hepatocytes and leads to hypothalamic dysfunction associated with lower testosterone levels. In general, alcohol consumption leads to a significant decrease in testosterone and DHT levels in males, regardless of whether beer or wine is consumed. Even 10–20 hours after drinking testosterone levels can still be significantly suppressed (754). Moderate consumption of alcohol will have no effect, but a personality trait of sensation-seeking behaviour has been described as associated with higher testosterone levels and higher frequency of alcohol consumption (835).

6.12.2. Effects of Nutrition and Testesterone

Nutrition has the potential to affect testosterone production and metabolism. Depressed plasma testosterone levels also consistently occur as a result of obesity, due to the elevated metabolism of testosterone in fat tissue and a decrease in binding capacity of the SHBG (754). Urinary secretion of androgens (representing a fraction of bio-available testosterone) in black and white North American men and rural black South African men was found to be significantly higher in those subjects living on a meat-rich western diet (836). Comparing total serum testosterone levels in omnivorous men to those on a vegetarian diet showed no differences, but in the latter group there were significantly higher levels of SHBG, leading to decreased levels of bio-available testosterone (837). Also, the kind of diet is most likely to influence the fraction of bio-available testosterone, but not total levels of this hormone (838-842).

7. Importance of Ageing

There is ample evidence that intelligence (843,844), life span (845-847) and the risk of various neurological disorders (848-850) would be determined, in part, by heritable factors. One gene that appears to have an influence on ageing in general and on the risk of age-related neurodegenerative disorders is apolipoprotein E (851). Other genes linked to life span that may influence brain ageing are those encoding the growth hormone (852) and major histocompatability complex (MHC) proteins (853). Growth hormone levels decrease with ageing and this change is ameliorated by caloric restriction. The density of micro-vessels in the brains of rodent decreases during ageing and this can be reversed by treating the animals with growth hormone, which may increase production of IGF-I in the brain (854).

During ageing in many brain regions, there is very little or no decrease in numbers of neurons, while in some brain regions neuronal loss may occur but may be compensated by expansion of dendritic arbors and increased synaptogenesis in the remaining neurons (855). It is thought that many neurons remain in the brain for a lifetime, although in some brain regions such as the olfactory bulb and dentate gyrus of the hippocampus, there may be a continuous replacement of neurons from a pool of progenitor (stem) cells (856,857). Changes in the cellular structure of the brain and the functions of its neuronal circuits are controlled by an intricate array of intercellular signalling molecules and intracellular signal transduction pathways. Signalling mechanisms affected by ageing include e.g.:

- Cellular calcium homeostasis (858),
- Gene transcription (859) and
- Protein phosphorylation (alterations in kinases, and phosphatases) (860).

The major classes of signal molecules important in brain ageing include neurotrophic factors, neurotransmitters, cytokines and steroids. In addition to their roles as mediators of synaptic transmission, neurotransmitters such as glutamate, acetylcholine and DA also play important roles in regulating the formation of neuronal circuits during development and in influencing the neurodegenerative process in brain disorders during ageing (858). Among neurotransmitter systems, dopaminergic signalling appears to be consistently altered during ageing with a progressive decrease in signalling (861). Three major classes of intercellular signalling proteins that regulate neuronal survival and synaptic plasticity are neurotransmitters, neurotrophic factors and hormones. Glutamate and GABA play pivotal roles in regulating neuronal survival (862) and synaptic plasticity (863). By inducing the expression of neurotrophic factors such as BDNF, glutamate can promote neuronal survival (864). On the other hand, over-activation of glutamate

receptors can cause neuronal death, particularly under conditions of increased levels of oxidative and metabolic stress, as occurs during ageing and in age-related neurodegenerative disorders (865). GABA can protect neurons in experimental models of neurodegenerative disorders by reducing neuronal excitability (862). Other neurotransmitters that can modify neuronal vulnerability in cell culture and animal models of neurodegenerative disorders include acetylcholine, DA, NE and serotonin (866-868).

Increased oxidative stress and accumulation of oxidatively damaged molecules (proteins, nucleic acids and lipids) promote dysfunction of various metabolic and signalling pathways (869). Neurons may also face energy deficits as the result of alterations in the cerebral vasculature and in mitochondrial function (870). DNA and RNA bases are subject to oxidative modification with a prominent example being the formation of 8-hydroxydeoxyguanosine (871). Further, the double bonds in membrane lipids are oxidized resulting in the production of a variety of lipid peroxides and aldehydes (872). These modifications of proteins, nucleic acids and lipids are greatly exacerbated in neurodegenerative disorders such as AD and PD consistent with a major role for oxidative stress of ageing in the pathogenesis of those disorders (873).

There are numerous dietary factors that have been reported to affect brain physiology in ways that could modify brain ageing and the pathogenesis of neurodegenerative disorders (874). These range from amino acids such as Trp (875), caffeine and related stimulants (876) and omega-3 PUFA (877).

7.1. Importance of Dietary restriction in brain ageing

The mean and maximum life spans of many different organisms including yeast, roundworms, rodents and monkeys can be increased by up to 50% simply by reducing their food intake (878-880). Data from clinical and epidemiological studies in humans support the anti-ageing and disease prevention effects of dietary restriction. Thus a low-calorie diet decreases the risk of the most prominent age-related diseases in humans including cardiovascular disease, diabetes and cancers (881-883). Biochemical and molecular analyses of the brains of old rats and mice that had been maintained on calorie-restricted diets reveal a retardation of changes that occur during ageing of animals fed ad libitum including increases in levels of Glial fibrillary acidic protein and oxidative damage to proteins and DNA (884,885). Oxidative stress and energy metabolism are counteracted by dietary restriction. Dietary restriction attenuates age-related deficits in learning and memory ability and motor function in rodents (886,887). In animal studies where restricted animals are given food pellets that contain 30–40% fewer calories than the pellets given to

the control animals there was an increase in the life spans of restricted rats and mice by 30–40% (880,888). Further, when rats were maintained for several months on dietary restriction, damage to hippocampal neurons was decreased. Further, learning and memory were preserved compared with rats fed ad libitum (889). Also, the motor function was improved in the restricted mice (890). In human individuals with a low calorie intake have lower risk of the developing AD, PD and stroke (891,892). There is a strong correlation between per capita food consumption and the risk for AD (893). Population-based case-control studies indicated that individuals with the lowest daily calorie intakes had the lowest risk of AD (892) and PD (894). Interestingly, the risk of PD and AD was more strongly correlated with calorie intake than with weight or body mass index. Other population-based longitudinal prospective study indicated that the incidence of AD increases among individuals living in industrialized countries compared with genetically similar individuals that live in non-industrialized countries (895). Evidence for an important role for neurotrophic factors in the beneficial effects of dietary restriction in the brain is suggested by studies showing that infusion of a BDNF blocking antibody into the lateral ventricles of dietary restriction mice significantly attenuates the protective effect of dietary restriction (896). In animal studies levels of BDNF are increased in neurons in the cerebral cortex, hippocampus and striatum maintained on dietary restriction (896,897). It is known that BDNF can protect neurons in culture and in vivo against excitotoxic, metabolic and apoptotic insults (898). Also, BDNF and other neurotrophic factors might counteract the adverse effects of ageing on synaptic function because they can modify synaptic plasticity in ways that facilitate learning and memory (899,900). In every neurodegenerative disorder increased oxidative stress, perturbed cellular calcium homeostasis and impaired energy metabolism occur (901,902). It has been shown that dietary restriction can stabilize mitochondrial function and reduce oxidative stress in brain cells of rodents (903). Also, caloric restriction can increase neurogenesis in the brains of rats and mice (897,904).

8. Importance of Foods

There are some known effects of foods on mental performance and stress susceptibility which will be discussed here.

8.1. Importance of Caffeine

Caffeine is a mild stimulant that may improve mental alertness and performance (905). In humans, coffee, tea and soft drinks, as well as cocoa, chocolate and certain medications are the major sources of caffeine (906). The content of caffeine of the various food items ranges from 40 to 180 mg/150 ml for coffee, 24 to 50 mg/150 ml for tea, 15 to 24 mg/150 ml for cola, 2 to 7 mg/150 ml for cocoa and 1 to 36 mg/28 g for chocolate (907,908). Caffeine absorption from the GIT is rapid and reaches 99% in humans in about 45 minutes after ingestion (909-912). Due to the hydrophobic properties of the drug, it can cross the placenta and the brain-blood barriers. Caffeine half-life is lower in rodents than in humans and it is increased during pregnancy and the neonatal period (876). Also, very large doses of caffeine have toxic effects, with an LD50[11] of about 200 mg/kg in rats (913). Deaths have been reported after the intravenous, oral and rectal administration of caffeine or coffee (914), the lethal dose being about 100 or 170 mg per kg, which is equivalent to 75 cups of coffee, 125 cups of tea or 200 cans of cola. There are no differences in caffeine half-life in young and elderly humans (911). The half-life of caffeine is about 80 ± 23 h for the full-term newborn infant (915,916) and can be over 100 h in premature infants (917). In adult smoker males, caffeine half-life is reduced by 30 to 50% compared with non-smokers (918-920). It is approximately doubled in women taking oral contraceptives (921) and greatly prolonged (up to 15 h) during the last trimester of pregnancy (922-924). Only at extremely high doses caffeine is teratogenic in mammals with the threshold dose for malformations appearing to be within the range of 80–100 mg/kg/day, depending on the method of administration and the species tested (925).

Caffeine may be a potential drug of abuse (926) and more recently caffeine has been described as "a model drug of abuse" (927). Also, the possibility that caffeine abuse, dependence and withdrawal should be added to diagnostic manuals has been seriously considered (928-931). Reduced foetal body weight and delayed skeletal ossification have been observed at relatively high doses of caffeine (932). The primary action of caffeine may be to block adenosine receptors, which leads to very important secondary effects on many classes of neurotransmitters, including

[11] LD50 (the median lethal dose) of a toxic substance is the dose required to kill half the members of a tested population after a specified test duration.

noradrenaline, DA, serotonin, acetylcholine, glutamate and GABA (933). Further, it cause a dose-dependent (30-75 mg/kg) increase in DA in the striatum (934). Caffeine as a potent adenosine antagonist is a CNS stimulant that easily crosses the blood-brain barrier due to its lipophilic properties (935). It has also been shown to counteract most of the inhibitory effects of adenosine on arousal (936), neuro-excitability (876,937), neurotransmitter release (938) and spontaneous activity (939). Adenosine concentrations increase in muscle and plasma during muscular contraction. Also, adenosine concentrations increase progressively in the brain during wakefulness and than decrease during sleep (936,940). Further, adenosine plays an important role in regulation of blood flow and as an inhibitory modulator of neuronal excitability and synaptic transmission of the brain via activation of adenosine receptors (941). It inhibits the release of most brain excitatory neurotransmitters (876,938), especially DA (942). These inhibitions are associated with reduced arousal, increased sleep (936) and suppression of spontaneous behavioural activity (939,943).

A caffeine withdrawal syndrome is well described. Withdrawal symptoms include headache and fatigue. Anxiety, impaired psychomotor performance, nausea and vomiting or an intense desire for coffee occurs less commonly (944).

8.1.1. Effects of caffeine on behaviour

Caffeine is well known to cause nervousness, restlessness, anxiety and insomnia. The effects of caffeine on children's behaviour have been of interest for several years (945-947). In boys with a mean age of 10.6 years 10 mg/kg of caffeine resulted in increased vigilance (sustained attention), motor activity and ratings of fidgetiness (945). Further, caffeine intake at concentration of 10 mg/kg in 7- to 12-year-old children increased motor activity and sustained attention (948). Caffeine has only small and inconsistent effects on the behaviour of young children (949).

8.1.2. Effects of caffeine on Anxiety

A disorder known as "caffeinism" was first described in 1974. Caffeinism is currently listed in the Diagnostic and Statistical Manual of Mental Disorders (950,951). It refers to a constellation of symptoms associated with very high caffeine intake that are virtually indistinguishable from severe chronic anxiety (951). Coffeinism is usually associated with daily intakes of between 1000 and 1500 mg caffeine. A study based on case reports suggested that symptoms of "caffeinism" can be indistinguishable from anxiety neurosis (952). A double blind placebo crossover study of 19 pre-pubertal and 20 college-age boys showed no significant

differences on self-reported anxiety symptoms after administration of caffeine (953). Also, caffeine ingestion potentiates the slowed reaction time induced by alcohol consumption, so coffee is not an "antidote" for intoxication (914,954-958).

8.1.3. Effects of caffeine on Sleep

Caffeine has substantial effects on sleep. Ingesting caffeine 30 to 60 minutes before sleep will increase sleep latency, decrease total sleep time and substantially worsen subjective estimations of sleep quality. There are large variations in sensitivity to sleep disturbance, with the effects being greater in persons who do not drink caffeinated beverages regularly (959). Several studies have shown that blood flow is decreased by caffeine-induced cerebro-vascular vasoconstriction (960,961).

8.1.4. Effects of caffeine on cognitive performance

The effects of caffeine on psychomotor and cognitive performance have been investigated in different studies. Also, caffeine alters hand steadiness, reaction times and tapping rate (962). It is more likely that caffeine acts by facilitating the sensory input and motor output rather than the central processing functions (963). Also, minimal abstinence duration of 1 hour affects mental performance and a low dose of caffeine after this brief abstinence gives improvements in attention, problem solving and delayed recall compared to the control condition (964).

8.1.5. Effects of caffeine on Anxiety

Human studies indicate that caffeine reduces self-rated depression when administered in moderate doses (965). Individuals who choose a high dose of caffeine reported positive mood changes whereas non-choosers reported anxiety and dysphoria (966). Caffeine reduces fatigue but also lead to increased tension and nervousness (967). Further, caffeine intake either 3 or 6 mg/kg increased anxiety (968,969).

8.1.6. Effects of caffeine withdrawal

Data indicated that caffeine withdrawal was associated with feelings of fatigue and decreased feelings of alertness (970). Indeed, about 10% of volunteers with a moderate daily caffeine intake (235 mg per day) reported increased depression and anxiety when caffeine was withdrawn (971). Also, the withdrawal symptoms include anxiety, apathy, decreased motor behaviour, headaches, increased heart rate, increased muscle tension, weakness and weariness and occasionally tremor,

nausea, vomiting and flu-like feelings (929,970-975). Withdrawal symptoms generally begin about 12 to 24 h after sudden cessation of caffeine consumption and reach its peak after 20 to 48 h. However, in some individuals, these symptoms can appear within only 3 to 6 h and can last for 1 week (962,973,976,977).

8.1.7. Effects of caffeine tolerance

In humans and experimental animals it is known that tolerance develops to some, but not to all effects of caffeine (978,979). Following long-term caffeine consumption the number of adenosine A1 receptors is increased (980). A change in adenosine A1 receptors occurs when animals are fed or injected with higher doses of caffeine that are still able to produce tolerance (981,982). This effect appears to be due to the blockade of a down-regulation induced by the endogenous agonist adenosine (983).

8.1.8. Effects of caffeine abuse

The effective dosage of caffeine, without apparent adverse effects, ranges from 3 to 9 mg/kg. At this dose, caffeine can increase exercise time to fatigue by 20-50% in humans during intensive running and cycling (984-990). The lethal dose for caffeine has been estimated to be in the range of 10 g (991), which would correspond to about 100 strong coffees. In case of providing adequate emergency measures patients appear to survive levels up to 1mM or even slightly above, but still higher levels are fatal (992).

8.1.9. Effects of caffeine on mood

There is ample evidence that lower doses (20-200 mg) of caffeine are reliably associated with "positive" subjective effects i.e. feel energetic, imaginative, efficient, self-confident and alert (972,975,993). Schoolchildren consuming more than 50 mg of caffeine per day, mainly from soft drinks, report higher wakefulness than a control group consuming less than 10 mg per day (994).

8.1.10. Effects of caffeine on anxiety

There are well-documented effects of caffeine on anxiety in humans (995). Outpatients undergoing treatment for psychiatric disorders who consumed more than 1000 mg of caffeine per day had symptoms of generalized anxiety (618). In human studies the administration of high doses of caffeine leads to a clear increase in measures of anxiety (966). Patients who report being anxious in response to

caffeine had higher pre-study anxiety scores (996). Interestingly subjects with high anxiety scores tended to have a lower caffeine intake (996,997). There are reports that high caffeine intake can exacerbate the symptoms of schizophrenia (998). Also, among psychiatric patients, caffeine consumption is highest among patient's diagnosed schizophrenics and lowest among depressed patients and those with anxiety disorders (997). The anxiogenic effects of caffeine are related not only to the dose of caffeine but also to its plasma levels (999).

8.1.11. Effects of caffeine on information processing

There is a complex interaction between the effects of caffeine on performance and parameters such as personality and time of day (1000). In a vigilance test where caffeine significantly improved performance, caffeine caused neither increasing nor decreasing changes on the mood that occur after such stressful tasks (1001). Also, increases in caffeine consumption over an already high normal level (400-1000 mg/day) did not impair performance even in a complex setting (1002).

8.5. Importance of Coffee

Coffee was first discovered around 850 AD by Khaldi in Abyssinia (Upper Egypt). The coffee bean is a seed. The seeds are hulled and dried from berries of coffee tree blossoms. The best coffees are picked just as the berries ripen. The outer skin is immediately scraped loose, exposing the bean. There are hundreds of coffee species. Instant coffee differs chemically from regular coffee. The "instantiation" process conserves about 48% of the solids from the original bean. This is much higher than the 24% solid component conserved by household coffee brewing techniques. In most instances, coffee is decaffeinated by removing the caffeine from the beans before roasting. Hundreds of chemicals have been identified in coffee (1003). Chemical substances in coffee include chlorogenic acid, reducing sugars, other carbohydrates, peptides and potassium. Chlorogenic acid is present in even greater quantities than caffeine (914,1004).

There are substances in coffee which binds to the opiate receptor. Animal studies indicated that this compounds compete with tritiated naloxone for binding to opiate receptors in rat brain and has been characterized as one of several isomeric (iso)feruloylquinic lactone compounds present in coffee (954). Also, a cup of instant coffee contains effectively a third of an ampule of naloxone. Recent data have shown that the regular consumption of 6 to 11 cups of coffee per day may produce persistent small elevations in NE levels and FFA release after caffeine metabolism is saturated (956). Coffee consumption seems to correlate with diagnosis of depression and with various measures of stress and anxiety (1005).

8.6. Importance of Lactalbumin

Lactalbumin is the albumin which is contained in milk and obtained from whey. It has been found in the milk of many mammals. There are α- and ß-lactalbumin in milk. A human study with twenty-three recovered depressed patients and 20 healthy matched controls without a history of depression indicate that α-lactalbumin had no effect on mood, but improved abstract visual memory and impaired simple motor performance. These effects were independent of history of depression (1006).

8.7. Fish

There is a significant negative correlation between worldwide fish consumption and the prevalence of depression (135). Data indicated that frequent fish consumption in the general population is associated with a decreased risk of depression and suicidal ideation (136). A recent cross-sectional study conducted in New Zealand found that fish consumption is significantly associated with higher self-reported mental health status (137). In contrast there are negative correlation between total seafood (including shellfish) consumption and the prevalence of postpartum depression in 22 countries. Also higher concentrations of DHA in mother's milk and greater seafood consumption both predicted lower prevalence of post-partum depression (142). Fish provide varying amounts of omega-3 PUFAs in the form of DHA and EPA.

The brain contains a high concentration of PUFA (approximately 20% of dry weight). In the nervous system one out of every three FAs belong to the PUFA group (88,93). Beneficial effects of omega-3 PUFAs have been linked to AD (126), anxiety (1007), autism (1008), attention deficit hyperactivity disorder (1009), bipolar disorder (128), hostility (1010) and schizophrenia (1011).

9. Feeding behaviour

9.1. Caloric Restriction

The ability of caloric restriction (CR) during adult life to lengthen life span has been observed consistently in many different species of mammals (880). In a study with rhesus monkeys CR (30% reduction in calories) improved the health of the monkeys and their life span increased compared with the monkeys on the control diet (1012). In contrast overeating promotes diseases in multiple organ systems that usually shorten life.

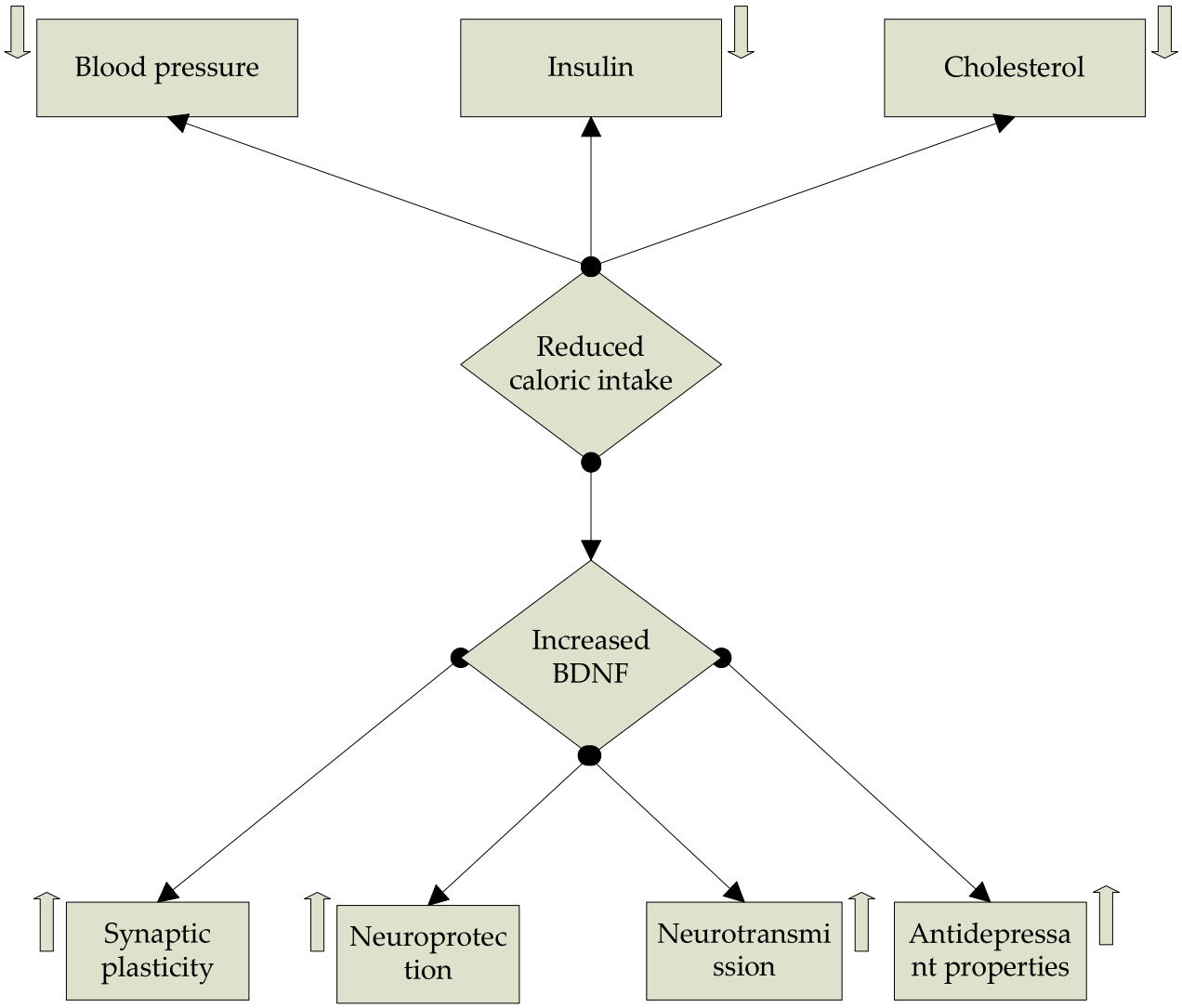

FIG. 14. Positive effects of low caloric intake.

9.2.Meal Frequency

There are data which indicate that reduced meal frequency can increase the resistance of organisms to various types of stress. For example, intermittent fasting increased the resistance of rats to cold stress and resulted in changes in collagen

and bone consistent with an anti-ageing effect (1013). Timing of meal can influence the effects of meals on cognitive behaviour. The effects of an evening meal on cognitive performance and mood indicated that subjects had stronger feeling and were more proficient and interested 1-3 h after meal consumption than subjects who did not consume the meal (1014). Additionally, 90 minutes after intake of the meal, the subjects completed more sentences on a logical-reasoning task than those who had not eaten. Early Studies indicate that stunted and previously malnourished 9- and 10-year-old Jamaicans performed less well on tests of short-term memory and problem-solving ability when they had not eaten breakfast than when they had eaten a morning meal (1015). Also undernourished children's performance on a test of verbal fluency was significantly better when they had consumed a school breakfast than when they had not (1016). Experimental evidence suggests that omitting breakfast negatively affects cognitive functioning (1017). Further, afternoon snacks may also have positive effects on cognitive performance (1018).

9.3. Meal Size

In a study investigating the effects of meal size on attention and mood subjects, who ate a larger than usual lunch, made more errors on attention and search tasks than those who ate a normal-sized lunch or one smaller than usual (1019). Also, there was not any difference in mood as a function of meal size. In other study young men made significantly more errors on a letter-cancellation project after eating a large lunch, but tended to make less error after small lunch. Further the performance improved to a greater degree after the small lunch in subjects who typically ate a heavy lunch than in those who ate a light lunch (1020).

9.4. Meal composition

There is strong suggestion that the proportion of the main dietary components can modulate longevity (1021). For instance, restriction of protein intake significantly increased mean and maximum longevities in different rat strains (1022-1024). Further, when animals were fed a diet restricted in the essential amino acid Met, mean and maximum life spans were enhanced as well (1025). More recently, protein restriction without strong caloric restriction has similar effects on the mitochondrial free radical generation rate and mitochondrial DNA oxidative damage in rat liver as the reduction of the total intake of calories (1026).

9.5. Appetite

Appetitive behaviour is complex and multifaceted. There is much evidence from animal studies that HPA axis function can profoundly influence expression of appetite and regulation of body weight (6). The stress-sensitive adrenal steroids

modulate neurotransmitters which affect appetite, such as B–noradrenergic systems, NPY and galanin (42). Stress reactivity, both physiological and psychological, may distinguish overeaters from under eaters (616). The recently discovered new gut peptide, ghrelin, an endogenous ligand for the growth hormone secretagogue receptor (1027), seems to be involved in the control of food intake and energy balance. In fact, centrally injected ghrelin produces a sustained food intake in rodents and ghrelin blood concentrations and mRNA expression in the stomach are increased by fasting and decreased by feeding (717). Recent data have suggested a possible stimulatory effect of ghrelin on the HPA axis activity in experimental animals (1028). In humans gherlin has a positive effect on glucose levels and negative effects on insulin concentrations (1029). Interestingly ghrelin concentrations are decreased in human obesity (1030).

9.6. Behavioural Decrements

Substantial research indicates that factors such as oxidative stress (1031) and inflammation (1032,1033) may be major contributors to the behavioural decrements seen in ageing. The occurrence of numerous neuronal and behavioural deficits during normal ageing may include decrements in calcium homeostasis (1034) and in the sensitivity of several receptor systems, most notably the dopaminergic (1035,1036), muscarinic (1037,1038), opioid (1039) and adrenergic (1040) receptor systems. These losses in neuronal function may be expressed ultimately as alterations in both cognitive (1041) and motor (1042) behaviours. Alterations in memory appear to occur primarily in secondary memory systems and are reflected in the storage of newly acquired information (1043).

9.7. Ageing and oxidative stress

Different treatments (e.g. heavy-particle irradiation, chemotherapy) that increase oxidative and/or inflammatory stressors may produce behavioural deficits that parallel those seen in ageing (1044-1046). One of the most important factors mediating the deleterious effects of ageing on behaviour and neuronal function is oxidative stress (1047). It has been shown that, not only the CNS particularly is vulnerable to oxidative stress, but also this vulnerability increases during ageing (1048,1049). Age-related changes in the neuronal plasma membrane molecular structure and physical properties (e.g. increased rigidity) may play a role in increasing vulnerability to oxidative stress and inflammation (1048,1050).

9.8. Plant Foods

Antioxidants have been studied for their effectiveness in reducing the deleterious effects of brain ageing and behaviour in many studies (1051-1053). The combinations of antioxidant/anti-inflammatory polyphenolic compounds found in

fruits and vegetables may show efficacy in ageing (1054). Plants, including food plants (fruits and vegetables), synthesize a vast array of secondary chemical compounds that, although not involved in primary metabolism, are important for a variety of ecologic functions that enhance the plant's ability to survive. Interestingly, these compounds may be responsible for the multitude of beneficial effects that have been reported for fruits and vegetables, with an array of health-related bioactivities (1054). In animal studies long-term feeding of rats with diets supplemented with strawberry or spinach extract (1–2% of the diet) or vitamin E (500 IU) retarded age-related decrements in cognitive and neuronal function compared to an AIN-93 diet alone (1054). Also, the supplemented diets could prevent the onset of age-related deficits in several indices (e.g. cognitive behaviour, and Morris water maze performance) (496).

Phytochemicals can selectively regulate multiple signalling pathways at the level of transcription especially signals involving mitogen-activated protein kinase (1055). In this regard there was significant increase in several indices of neuronal signalling (e.g. muscarinic receptor sensitivity) (1056).

10. Oxidation

The high demand for molecular oxygen, the high levels of PUFAs in neural membrane phospholipids and the high iron contents in the brain are important factors rendering cells in the CNS to oxidative stress. Oxidative stress is an important underlying factor for a number of neurodegenerative diseases (1057). Dietary antioxidants are known to influence the antioxidant defence system and dietary antioxidants can influence omega-3 status. Omega-3 PUFAs have been shown to decrease lipid peroxidation in vivo (1058). A diet devoid of antioxidants lowered essential FA levels in the plasma of trained athletes, even though the amount and types of fats were not altered (1059). A recent human study found that depressive symptoms are independently correlated with lipid peroxidation (1058). Patients with obsessive compulsive disorder (OCD) and co-morbid depression have higher levels of lipid peroxidation than those with OCD alone (1060). Animal studies indicated that antioxidant supplementation can prevent the negative influence of saturated fat on BDNF levels and cognitive function (1061).

10.1. Nitric oxide

Nitric oxide (NO) is a free radical that is constantly produced/released throughout the body by diverse tissues, i.e. endothelium (1062,1063). NO is involved in the stress physiology and apparently also takes part in stress-related disease processes (1063-1066). NO seems to be capable of principally exerting either beneficial/ameliorating or deleterious effects (1062,1063,1067-1069). The actual distinction depends on a multitude of factors, such as duration of (an enhanced) NO release, amount of produced NO and type of synthesis of NO molecules (1062-1067). Additionally, NO inhibits the release of other monoamine transmitter molecules, e.g. DA (1070) and here, auto-regulatory pathways that involve different signalling molecules (like opiates, and endocannabinoids) are implicated (1064,1067,1070). NO is produced via two different mechanisms. Immediate release of NO is of constitutive nitric oxide synthase (cNOS) origin (1062). Thereby, cNOS is a calcium-dependent enzyme that is constitutively and permanently expressed, in endothelial (eNOS), neuronal (nNOS) and immune cells and produces NO at a low levels. This 'basal' NO can be increased for a short time via additional cNOS stimulation in response to certain signals (1067). Hence, cNOS-derived NO release is part of acute response mechanisms that occur in many biological states (1062-1065,1067,1071). In contrast, the inducible nitric oxide synthase (iNOS) is a calcium-independent enzyme that is prevalent in many tissues, yet only expressed 'on demand' in specific situations, and under the influence of various signalling molecules, i.e. pro-inflammatory cytokines (1067). Following its induction, iNOS

produces NO at higher levels after a latency period and this NO release lasts for an extended period of time, i.e. days (1067).

11. Antioxidant

Oxidative stress is one of the most important factors mediating the deleterious effects of ageing on behaviour and neuronal function (1047). The CNS appears to be especially vulnerable to the effects of oxidative stress, partially as a result of additional factors such as increases in the ratio of oxidized glutathione to total glutathione (1072), significant lipofuscin accumulation (1073) with bcl-2 increases (1074), increases in the membrane lipid peroxidation (1075), reductions in the glutamine synthetase (1076), reductions in redox-active iron (1073, 1077) and alterations in membrane lipids (1078).

Most dietary agents used to alter behavioural and neuronal effects with ageing included nutritional supplements such as vitamins C and E, garlic (1051) and herbal supplements (e.g. ginseng and Ginkgo biloba) (1052). Long-term (from 6 to 15 months of age) feeding of F344 rats with an AIN-93 diet supplemented with strawberry or spinach extract (1–2% of the diet) or vitamin E (500 IU) retarded age-related decrements in cognitive and neuronal function compared to an AIN-93 diet alone. Results indicated that the supplemented diets could prevent the onset of age-related deficits in several indices (e.g. cognitive behaviour and Morris water maze performance) (496).

There are tens of thousands of natural and synthetic compounds that possess antioxidant activity and a rapidly growing number of these agents have been reported to have beneficial effects in one or more experimental models of age-related disorders. These include vitamin E, coenzyme Q10, lipoic acid, creatine and Ginko biloba extract.

11.1. Vitamin E

Vitamin E (tocopherol) is a lipid-soluble antioxidant that is very effective in suppressing membrane lipid peroxidation. Chronic treatment of rodents with vitamin E can preserve learning and memory function, which otherwise declines during ageing (1079). Treatment of rat hippocampal slices with vitamin E enhanced long-term potentiation of synaptic transmission, a cellular correlate of learning and memory (1080). Clinical trials of vitamin E in AD patients have yielded positive results with patients receiving this antioxidant exhibiting a slowing of disease progression compared with those receiving placebo (1081). As evidence, vitamin E can protect cultured neurons and synaptosomes against dysfunction and death (1082,1083) and can protect against amyloid-induced learning and memory deficits in adult rats (1084). Vitamin E has also been reported

to be effective in animal and cell culture models of PD (1085), although clinical benefit in human patients has not yet been established.

11.2. Coenzyme Q10

Coenzyme Q10 (ubiquinone) is associated with the mitochondrial oxidative phosphorylation enzyme complexes where it serves an antioxidant function. Administration of ubiquinone to rodents can enhance learning and memory (1086). Ubiquinone protected cultured neural cells against insults relevant to the pathogenesis of AD (1087). Dietary supplementation with ubiquinone resulted in increased resistance of midbrain dopaminergic neurons to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced damage in a mouse model of PD (1088).

11.3. Creatine

Creatine increases phosphocreatine levels in muscle and brain cells and may thereby improve cellular energetics and reduce oxy-radical production (1089). Creatine is now widely employed as a dietary supplement by athletes to improve their performance (1090). The possibility that creatine may protect against neurodegenerative conditions has been tested in several animal models. Dietary supplementation with creatine protected dopaminergic neurons against MPTP toxicity in mice (1091) and increased the survival of Purkinje cells in a transgenic mouse model of spinocerebellar ataxia type 1 (1092).

11.4. Gingko biloba

The public has recently been barraged with advertisements touting the health benefits of Gingko biloba with a particular emphasis on its benefits for the brain (1093). Ginkgo biloba extract enhanced performance of aged mice in a learning and memory task (1094). In a rat model of severe diabetes, Gingko biloba was effective in improving learning and memory performance (1095). Ginkgo biloba supplementation in a double-blind and placebo-controlled trial was effective in improving cognitive function in healthy middle-aged subjects (1096). However, other trials of Ginkgo extracts on memory performance in normal adults (1097) and elderly patients with mild cognitive impairment (1098) have not revealed a significant effect of this dietary supplement (1097). Ginkgo extracts reduced damage to dopaminergic neurons caused by MPTP in a mouse model of PD (1099).

11.5. N-acetylcysteine

N-acetylcysteine has proven effective in reducing age-related deficits in learning and memory (1100). Encouraging beneficial effects of N-acetylcysteine supplementation were recently reported in a clinical trial in patients with probable

AD (1101), suggesting that this antioxidant may soon be used as a dietary supplement for patients in the early stages of neurodegenerative disorders.

12. Neurogenesis

The process by which neurons are created is neurogenesis. It is responsible for populating the growing brain. Neurogenesis have been linked to the beneficial actions of certain antidepressant, suggesting a connection between decreased hippocampal neurogenesis and depression (1102,1103).

12.1. Effect of PUFA on neurogenesis

A few weeks of dietary manipulation of LC-PUFA (long chain PUFA) content can increase the numbers of new neurons born in the lobster brain (1104). Specifically, the correlation between levels of neurogenesis and the ratio of omega-3:omega-6 PUFA and α-linolenic acid levels, suggests that one of these two dietary factors is responsible for the increase in neurogenesis (1104). The ratio of omega-3:omega-6 PUFAs is potentially important because undesirable ratios can inhibit the conversion of α-linolenic acid to DHA and EPA (1105). Increased neurogenesis is a result of a favourable omega-3:omega-6 ratio, likely caused by the increase of α-linolenic acid in the enriched Artemia diets. The increases in neuronal proliferation seen with LC-PUFA enrichment imply that the nervous system benefits from this nutritional enhancement (1104).

Omega-3 PUFAs have the potential to influence neurogenesis through at least two distinct mechanisms. First, omega-3 PUFAs are incorporated into neuronal membranes, where they influence the quarternary structure of membrane proteins, some of which act as transporters and receptors (93). They also can alter membrane fluidity (96), which is important for neurotransmitter binding as well as signalling within cells.

Omega-3 PUFAs also influence levels of neurotrophins, molecules that promote neuronal survival and growth. Among the neurotrophins, BDNF levels are altered by dietary intake of omega-3 PUFAs (1106) and BDNF is associated with alterations in neurogenesis and neuronal survival (1107).

12.2. Effects of neurotrophins on neurogenesis

Although the specific effects of cytokines and neurotrophins on neurogenesis, cell fate and survival are still being clarified, the association between omega-3 PUFAs and the regulation these classes of molecules is no longer debatable. These connections between the omega-3 PUFAs, cytokines, neurotrophins and neurogenesis are also intriguing from the clinical perspective. Cytokines appear to play a potentially critical role in depressive illness (1108). Stress can cause an

elevation in cytokines and selective serotonin reuptake inhibitors reduce cytokine levels.

Oxidative stress and inflammation are thought to be major factors in brain ageing and in age-related neurodegenerative disease (1031-1033,1109). Humans and animals show increased motor and cognitive declines with ageing (1110-1112) that are thought to be due to increased susceptibility to the long-term effects of oxidative stress and inflammation (1031). Deficits in brain functions due to oxidative stress may be due in part to a decline in the endogenous antioxidant defence mechanisms and to the vulnerability of the brain to the deleterious effects of oxidative damage (1075,1113).

13. Emotion

Emotional arousal has been associated with both increased or decreased food intake and weight (1114,1115). In humans the effects of variation in workload on food intake and serum lipids has been studied with a small group of female office workers (1116). The workers reported a higher energy intake and a higher percentage of energy as fat, in two high workload periods, compared with the normal work period. Higher energy intakes were reported from a study of dietary habits associated with exam time among university students (1117). The dietary data support modest increases in energy, fat and sugar intake in periods of high work stress compared with low work stress (1116,1118). Psycho-physiological response to stress influences subsequent eating behaviour (41). Self-reported increases in negative mood during the stressor were also significantly positively related to caloric consumption, whereas mood reactivity on the control day was not related to consumption that day. Cortisol reactivity and mood are as two some what independent indices of stress reactivity and found that both were related to eating after stress, but not after rest. It is possible that women more vulnerable to stress, in their mood responses and cortisol reactivity, may be at particular risk of stress-induced eating and weight gain (41). Behavioural factors as one of the psychobiological mechanisms can affect health (1118). Also, either prolonged or frequent work stress could result in increasing the likelihood of weight gain and increased cardiovascular risk (1118).

Individual variability in dietary responses to stress in relation to levels of dietary restraint have been identified in a number of experimental studies (613,1119-1121). Restrained eaters did not just eat more overall, they specifically ate more sweet and fatty foods in the high-work-stress session and the hyperphagic response was greater among those who had a larger increase in perceived stress between the low-and high-workload sessions, implicating emotional reactions in the response (1118).

14. Metabolic Acidosis

The modern Western-type diet in humans, which is rich in animal protein, has been implicated as a cause of lifelong mild chronic metabolic acidosis (CMA) with secondary bone catabolism caused by the induction by this diet of an obligatory daily acid load (endogenous acid production), due largely to endogenous oxidation of cationic and sulphur-containing amino acids (9). CMA is a frequent acid-base disturbance generated by extra-renal loss of base (e.g. diarrhoea), increased acid production (e.g., organic acidosis such as ketoacidosis) or impaired renal acid excretion. CMA has also been shown to cause a significant increase in corticosteroid excretion (1122,1123). In a small human study experimental induced acidosis was also associated with an increase in cortisol excretion (1124). Another similar study in humans did not show any increase in cortisol secretion, although plasma aldosterone levels significantly increased (1125). Animal and human studies suggest that metabolic acidosis stimulates an increase in cortisol production (1122-1124). Also, CMA can increase cortisol production and both acidosis and cortisol induce osteopenia. In muscle, acidosis is known to stimulate protein and essential amino acid breakdown through the ubiquitin-proteasome proteolytic pathway, a mechanism that requires GCs (1122). GCs lead to a dramatic decrease in bone mineral density, either when endogenously in excess or when administered exogenously (1126). The mechanism by which GCs decrease bone density is multifactorial. The osteopenia appears due to a complex combination of direct effects on bone formation (1127-1130) and resorption (1127,1128,1131) and indirect effects on calcium homeostasis, including decreased intestinal calcium absorption (1131). GCs decrease bone formation via suppression of osteoblast maturation and promotion of apoptosis (1130). The net osteopenia observed in-vivo after GC treatment is probably due to a complex combination of direct effects on bone formation and resorption as well as indirect effects to inhibit intestinal calcium absorption and increase renal calcium excretion (1128,1131,1132).

A very mild Western diet-induced CMA results in a state of increased cortisol secretion and plasma concentration and provides several novel findings in humans regarding the possible causality of the Western diet in the aetiology of osteoporosis (1133). In humans CMA results in hyper-secretion of cortisol (1124). Previous studies reported a non-significant 77% increase in urinary cortisol excretion in acid-fed compared with non-acid-fed human subjects (1134). Further, plasma bicarbonate concentration decreases progressively when endogenous acid production is increased by menu changes among normal foodstuffs in normal subjects (1135). Ingestion of neutralizing alkali per se, as exchanged for chloride in the absence of other experimental maneuvers (e.g. concomitant potassium

supplement) can result in urinary calcium retention and suppression of biochemical markers of bone resorption (1133).

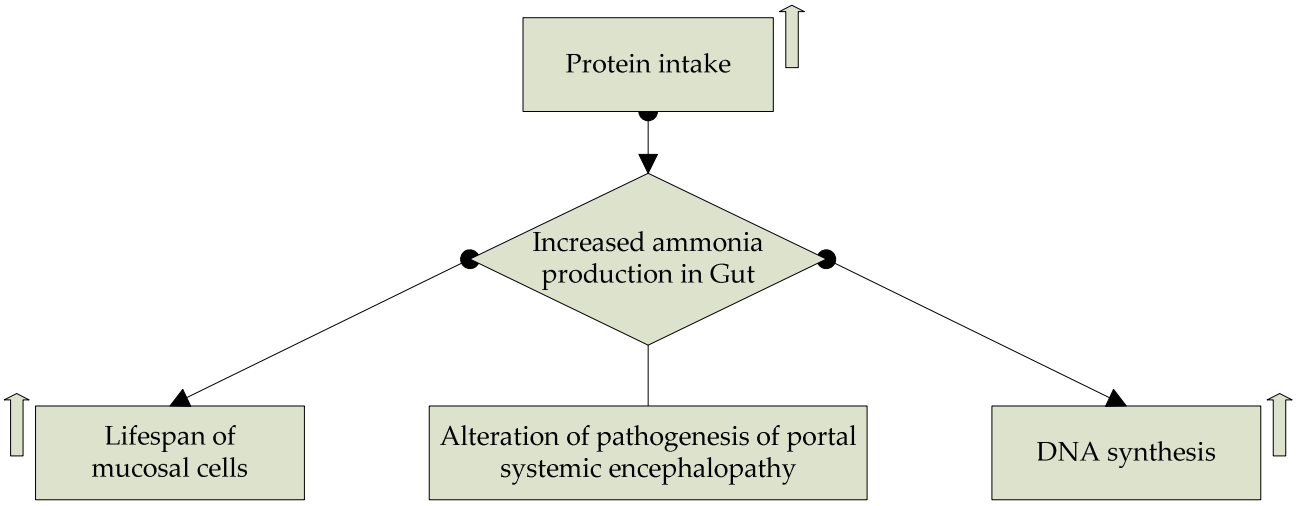

FIG. 15. Negative health effects of CMA

15. Monoamine

Monoamine neurotransmitters are neuro-modulators which are derived e.g. from aromatic amino acids by the action of decarboxylase enzymes. Dietary aromatic amino acids are Phe, Tyr and Trp. Neurotransmitters convey the information to be passed and processed through some 1014 to 1016 interconnections linking approximately 1010 to 1011 neurons in the human brain. Each of the many neurotransmitters (including as yet unidentified ones) acts through a receptor, which in general will have numerous subtypes (1136).

15.1. Histamine

The precursor of histamine is the His an extremely bioactive essential amino acid which has multiple physiological functions. Histamine is synthesized in the brain by the enzymatic decarboxylation of His. Conversion of His to histamine in the hypothalamus is necessary to produce the suppressive effect of His on feeding behaviour. Also, the hypothalamic histamine neurons are an essential component in the regulation of energy intake and energy expenditure. Hypothalamic neuronal histamine suppresses food intake through H1-receptors in the ventromedial hypothalamic nucleus and the para-ventricular nucleus (1137). As for drinking behaviour, activation of hypothalamic histamine neurons showed excitatory but not inhibitory effect on water intake (1138,1139). Further, histamine neurons are involved in the action of leptin on hypothalamic control of feeding behaviour and energy metabolism (1140,1141). Central administration of leptin increased histamine turnover in the hypothalamus (1140).

Increase in hypothalamic histamine concentration has an raising effect on the peripheral glucose concentration (1137,1142), accelerated lipolysis in the adipose tissue (1143,1144) and decreased body temperature (1137,1142). Central exogenous administration of histamine has been found to be effective in reducing body weight and adiposity in leptin resistant obese db/db mice and mice with diet-induced obesity (1145). On the other hand, the concentration and turnover rate of hypothalamic neuronal histamine are increased by neuro-glucoprivation induced by starvation, insulin and 2-deoxy-D-glucose in the brain (1146,1147), elevation of ambient temperature (1137,1142,1148) and cytokines such as IL-1ß (1149).

The hypothalamic histamine neurons are involved as targets for leptin action in the brain (1140,1141). Central administration of leptin increased histamine turnover in the hypothalamus (1140). Depletion of neuronal histamine using α-fluoromethyl-histidine attenuated the suppression of feeding induced by leptin (1140). Exogenously sustained central administration of histamine has proved effective on

reduction in food intake, body weight and adiposity even in leptin resistant db/db mice (1145). This effect could be caused by His role in zinc metabolism acting as the major zinc binding moiety in serum (229,230,231). Normally, zinc is bound to one or two of the available 16 His moieties on albumin (229,230). His administration to animals (231) or humans (232) strips zinc from its albumin binding sites initiating a Zn-His complex which produces significant tissue zinc depletion. It also causes zinc deficiency leading to functional losses of taste, smell, appetite, food intake and other neurological abnormalities (232). These effects are reversed completely by zinc administration while maintaining His intake at any given level, indicating that His induced suppression of appetite relates specifically to this mechanism of zinc depletion (232).

15.2. Serotonin

Serotonin (5-hydroxytryptamine) is a monoamine neurotransmitter which is synthesized in serotonergic neurons in the CNS and in the GIT. It is synthesized from the essential amino acid L-Trp, and the first and rate-limiting step in the biosynthesis of serotonin is the hydroxylation of L-Trp to 5-hydroxyTrp. Since the enzyme Trp-hydroxylase, catalysing the hydroxylation of L-Trp, does not seem to be saturated by L-Trp in-vivo, the rate of this reaction appears to be restricted by L-Trp availability in mammals (1150). Elevated dietary intake of L-Trp has been reported to result in increased brain levels of L-Trp and elevated rates of serotonin synthesis and metabolism (1151,1152). Serotonin is an evolutionarily conserved neurotransmitter that regulates the development and function of the mammalian brain and serves important roles in the regulation of energy metabolism in diverse organisms (1153,1154). Further, it is involved in the regulation of the HPA axis in mammals (1155,1156). An increased activity of serotonergic neurons in the brain is an established consequence of stress and a decline activity of these serotonergic neurons has been demonstrated in disturbances of mood and depressive disorders (1157). Increased brain serotonin activity appears to be a prerequisite for maintaining control over cognitive information processes (1158) and is involved in learning and memory (1159). Levels of serotonin are decreased in the brains of rats during ageing and treatment of the aged rats with the antioxidant α-lipoic acid increased serotonin levels, which suggests that serotonin depletion during ageing may result, at least in part, from oxidative stress (1160). Chronic stress may decrease brain serotonin availability and increase serotonin receptor function by the way of a compensatory mechanism (287,1161). A deficient central serotonin function has been shown in mood disorders like depression (32,1162). Accordingly, changes in serotonin receptor sensitivity are believed to mediate the effect of Trp administration or antidepressant treatment on depression (1163,1164). As serotonin function increases under acute stress, brain serotonin concentrations may be

exhausted under continuous stress exposure. As a consequence the serotonergic system of subjects prone to stress (high stress–vulnerable subjects) may become more sensitive to dietary-induced alterations in L-Trp availability, because of compensatory receptor sensitization (287,1161). Depletion of the precursor of serotonin synthesis, Trp, has been found to increase depressive mood in healthy subjects and subjects with a prior history of depressions (1164).

Brain levels of L-Trp is not only depend on plasma levels of L-Trp, but also on plasma levels of other LNAA (i.e. Tyr, Phe, Leu, Ile and Val) competing for the same carrier (1150,1151). A carbohydrate-rich, protein-poor diet increases the ratio of plasma Trp to the sum of the other LNAAs, giving Trp an advantage in the competition for access into the brain (25,51,291,1165). A carbohydrate-rich, protein-poor food diminished the depressive mood and cortisol response to controllable as well as uncontrollable laboratory-induced stress in highly stress-prone human subjects (1166). Acute stress elevates brain L-Trp concentrations (1167), an effect that appears to be mediated by a stress-induced elevation of sympathetic activity and circulating plasma catecholamines (1168). An activation of the sympathetic system stimulates lipolysis, resulting in elevated plasma levels of non-esterified FAs, competing with L-Trp for binding to albumin and thus elevating the plasma pool of free L-Trp available for uptake into the brain (1155). Sympathetic activation may also increase brain L-Trp uptake by affecting the permeability of the blood—brain barrier (1155).

15.2.1. Serotonin and Cortisol

In several studies the ratio of 5-hydroxyindoleacetic acid (the major serotonin metabolite) to serotonin brain concentrations has been found to correlate with plasma levels of cortisol, suggesting that the action of brain serotonin on the HPA axis is stimulatory (1169,1170). The administration of serotonin precursors is usually found to stimulate cortisol secretion (32). Stress adaptation is associated with a reduction in cortisol concentration and depression (286,1171).

15.3. Dopamine

DA is a neurotransmitter occurring in a wide variety of animals, which is biosynthesized from the amino acid L-Tyr. Further, it can be processed into NE. Tyr administration elevate DA production in the CNS of patients with PD the cause of which is thought to involve a loss of DA neurons and which is typically treated by administering the immediate DA precursor, L-dopa (327).

16. Exercise

Regular physical exercise benefits the nervous system, as well as the musculoskeletal and cardiovascular system. The beneficial role of exercise is evident in many neurodegenerative disorders (1172). In humans exercise may improve mood and cognition (1173) and data suggest that regular exercise can also promote maintenance of cognitive function during ageing (1174). Studies of elderly populations suggest that regular exercise can also promote maintenance of cognitive function during ageing (1175,1176). Other studies have shown that regular exercise in elderly men is particularly effective in improving cognitive performance on tasks that require visuo-spatial processing (1177). Fourteen-month-old rats that exercised regularly (swimming 1 h/day, 5 days/wk for 9 wk) exhibited improved performance in a learning and memory task and reduced levels of membrane lipid peroxidation and oxidative damage to DNA (1178). Exercise results in an increase in the level of BDNF in the hippocampus in rats (1179). The increased levels of BDNF likely play an important role in increased dendritic complexity and improved function in animals maintained in complex environments because BDNF over-expression is sufficient to increase dendritic complexity (1180) and a BDNF-blocking antibody impairs learning and memory (1181). Intravenous administration of IGF-1-blocking antibody abolished the neuroprotective effect of exercise (1182). Research has also provided evidence that circulating IGF-1 plays an important role in the stimulation of hippocampal neurogenesis by physical exercise (1183).

When rats or mice are housed in complex environments or exercised on a regular basis, there are increases in the complexity of dendrites in cortical neurons and increased numbers of synapses (1184,1185). Somato-sensory deprivation reduces dendritic complexity in the neocortex of monkeys (1186) and psychosocial stress and other models of depression result in reduced neuritic and synaptic complexity (1187). Environmental enrichment can also enhance recovery and regeneration of damaged neural circuits. For example, enriched rehabilitative therapy enhances dendritic growth and function recovery after focal ischemic brain injury (1188). Epidemiological studies show that regular vigorous physical activity can reduce risk for ischemic stroke (1189). For example, exercise after brain injury improved functional outcome in rats and the improved outcome was associated with enhanced structural plasticity in the motor cortex (1190).

In response to stressor the autonomic nervous system and HPA axis are known to react and participate in the maintenance of homeostasis and the development of physical fitness. This includes elevation of cortisol and catecholamines in plasma.

However, physical conditioning is associated with a reduction in pituitary-adrenal activation in response to exercise (1191). Excessive and prolonged stress (as in heavy exercise) can lead to depression, mild, and irregular (non-linearly applied, hormetic) stress can actually improve depression (1192). The deleterious behavioural effects of stress were less pronounced in the "exercised and stressed" animals and the beneficial effects became more pronounced with time (more prolonged exercise), as indicated by the results of the behavioural tests (1193-1195). The beneficial effects of regular exercise are partly based on the reactive oxygen species (ROS) generating capacity of exercise, which is in the stimulation range of ROS production (1196). Therefore, exercise-induced ROS production plays a role in the induction of antioxidants, DNA repair and protein degrading enzymes, resulting in decreases in the incidence of oxidative stress-related diseases (1196).

Exercise intensity impacts the affective response during and after exercise, with higher intensity exercise being associated with more negative affect during exercise (1197). Exercise can also influence other brain parameters such as blood flow, antioxidant activities, neuronal apoptosis, receptor sensitization, glutamate secretion and many other unknown factors, which in various combinations can have some effect on depression (1192). Concomitant diet regulation and exercise were shown to reduce muscle sympathetic nerve activity during mental stress (1198).

17. BDNF gene

The BDNF gene is one prominent target of dietary restriction and physical and mental exercise that appears to mediate many of the beneficial effects of these dietary and behavioural stimuli (1199). There is a reciprocal relationship between BDNF and serotonergic signalling, in which BDNF enhances serotonin production and release (1200,1201) and serotonergic signalling stimulates BDNF production (1202). Serotonin can activate receptors coupled to cAMP production and cAMP can induce BDNF expression by a cAMP response element-binding protein mediated mechanism (1202). Collectively, the emerging data suggest that activation of BDNF and serotonergic pathways may provide protection against a variety of neurodegenerative conditions and possibly disorders linked to overeating and obesity, including type 2 diabetes and cardiovascular disease (1203-1206).

Recent studies have shown that BDNF is a very important neurotrophic factor that plays roles in feeding, learning, memory, locomotion, stress responses and affective behaviours (1207). BDNF promotes neuronal differentiation and survival synapto-genesis and synaptic plasticity (152,1208,1209). BDNF may serve in adaptive responses of mammals to a variety of environmental stimuli because BDNF expression in the hippocampus increases in response to cognitive stimulation and EODF (every-other-day fasting), but decreases under conditions of chronic uncontrollable stress (1210,1211). Decreased BDNF levels occur in several neurodegenerative disorders including AD, PD and Huntington's diseases (1212-1214). BDNF suppresses feeding and improves glucose metabolism, as demonstrated in studies of BDNF+/− mice (1204,1215). When BDNF+/− mice are maintained on an EODF diet, levels of BDNF increase in their brains and blood glucose levels and body weights are normalized (1204). The increased level of BDNF in the brain with regular exercise and intermittent fasting may be important in the improved glucose regulation because intra-cerebroventricular infusion of BDNF can increase peripheral insulin sensitivity in normal rodents (1216) and ameliorates diabetes in mice (1217). Moreover, mice in which BDNF was eliminated from the brain after birth were hypersensitive to stress, had elevated plasma glucose and insulin levels and were obese (1218). Thus, EODF and exercise enhance BDNF signalling, which, in turn, may stimulate signalling pathways that improve glucose metabolism and increase cellular stress resistance, thereby protecting against several different diseases.

18. Stress

Stress describes the effects of psychosocial and environmental factors on physical or mental well-being (1219-1221). Also, stress refers to the mental or physical conditions resulting from various disturbing physical, emotional or chemical factors. Stress implies a stimulus that requires behavioural, psychological and physiological changes to be successfully met and a state of hyper-arousal for the initiation of necessary counteracting reactions (1222-1224). The effects of the stressors on the body constitute the "stress response", which may be measured by behavioural, biochemical and genetic modifications. Organism has different factors that play a major role in the allostatic stress response:

- The HPA axis (cortisol),
- The sympatho-adrenal medullary system (NE/epinephrine) (1225-1228) and
- The connection of nitric oxide (1062-1066), melatonin (1229) and anandamide (1064).

The key hormonal pathway that governs the endocrine response to stress is the HPA axis. Elevation of serum corticosterone, the endpoint of stress-induced activation of the HPA system, is frequently used as a stress indicator and a convincing number of studies have found several measures indicative of a hyperactive HPA axis in depressed patients (1230). Cortisol secretion as a response to perceived stress is a powerful factor regulating disease-generating events in the periphery. This seems to be particularly the case when the HPA axis functions with low reactivity and poor feedback control (1063). Most studies have observed that chronic stress over-activates the HPA axis and fuels insulin release, in turn activating abdominal fat storage (1065). Insulin resistance might be followed by both dyslipidemia and elevated blood pressure (1066). In contrast to the tendency of chronic stress to elevate baseline cortisol, it appears to decrease testosterone, both in animals and humans (1231,1232). While psychological stress seems to increase oxidative stress (1233), it decreases DNA repair (1232) and inhibits radiation-induced apoptosis (1234) in human blood cells. This may mean that oxidative damage may persist during psychological stress and may increase the likelihood of a pathological development (1233).

Exaggerated cortisol responses to stress have been observed in women with AN (1234), BN (617) and obesity (620). Eating is thought to be suppressed during stress, due to anorectic effects of CRH and increased during recovery from stress, due to appetite stimulating effects of residual cortisol (41,1235). Cortisol secretion is a major component of the stress response (617) and it has been implicated as a

potential mediator for increased energy intake in healthy males (603) and females (41).

18.1. Effect of stress on food choice

The chronic mild stress in rats decreased sucrose intake per unit body weight, while sucrose intake in a non-stressed control group did not change (1236). There was not any correlation between body weight and sucrose intake. Interestingly the reduction of sucrose intake did not affect body weight. The largest effect was obtained after 2 weeks of the stress protocol, this effect was attenuated afterwards (1236). Overeating has been observed in rats following a stress and a period of caloric restriction (1237) only in those given highly palatable food (1238). In humans dieters are more likely to report stress hyperphagia compared to non-dieters who are more likely to report stress hypophagia (1239). In humans overeating of 'comfort foods' may be stimulated by cortisol in response to stress, which can result in abdominal obesity (612). Stress has been implicated as a primary trigger of overeating (614). Also, the repeated acute stress induces a chronic change in weight independent of stress-induced hypophagia and may represent a change in homeostasis initiated by repeated acute activation of the central CRF system (1240). Delay in gastrointestinal transit time (an indirect measure of gastric emptying and intestinal motility) has been observed in lean participants, but not in the obese, after exposure to both active and passive coping tasks (1241).

Prospective (1116,1118,1242) and self-reported retrospective data (24,1243) suggest that food choice does change under stress, with a tendency toward a relative increase in sugary and fatty (often snack-type) foods. There is a gender difference by food choice after stress. While men and unrestrained eaters show either little difference or a reduction in food intake under stress (40,1244), women and restrained eaters consume more calories and fat under stress (1116,1118) and shift their food choices away from meal-type foods, such as meat and vegetables, toward snack-type foods (1239). Also, stress did increase intake of sweet fatty foods in emotional eaters. In addition, women scored more highly on emotional eating than men (24). These gender differences may have reflected differences in dietary restraint, which is higher in women (1245-1247). There is evidence that snack consumption may be more susceptible to stress than meals (1239,1248). An alternative neuro-hormonal mechanism for stress-induced preferential selection of sweet fatty foods is suggested by evidence that such highly palatable foods can themselves relieve stress through release of endogenous opiates (1249,1250).

18.2. Effects of stress on female reproduction

Secretion of the gonadotrophin hormones LH and FSH from the anterior pituitary is under the control of GnRH (Gonadotropin releasing hormone). These two gonadotrophin hormones (LH and FSH) play a primary role in the regulation of peripheral reproductive tissue function. Stress induces adrenal stimulation and delays or even inhibits the pre-ovulatory GnRH-LH surge. Pulsatile activity is an essential intrinsic property of hypothalamic GnRH neurons and the intricate balance between GnRH synthesis and release is important to ensure that GnRH neurons are in a state of constant readiness to respond to changes in the environment (1251). Also, the pulsatile nature of GnRH secretion is essential for the physiological maintenance of normal gonadotrope function and ultimately for normal reproductive capacity (1252). Slow GnRH pulse input preferentially increases FSH secretion while fast frequency pulses, e.g. hourly, favour LH secretion (1253). It has been shown that circulating insulin can directly regulate GnRH and subsequently LH secretion (1254,1255). Central administration of insulin, as well, has also been shown to directly stimulate GnRH neurons, resulting in LH pulsatile release (1256,1257).

The metabolic status of an animal, dependent on its access to food, controls multiple diverse physiological factors in both males and females (1258). The connectivity between food intake and reproduction is especially evident in the female, where pregnancy and lactation are linked to the considerable energetic drain needed for the nurture of embryos and newborns (1259). One of the most profound alterations that take place with these dietary regimes is disruption of the complex neuroendocrine feedback axes centred the anterior pituitary. Reduced energy intake typically suppresses the reproductive axis and activates the HPA axis and/or somatotropic axes (1260,1261). The maternal adaptations described above, with the significant attenuation of hormonal stress responses in pregnancy and lactation, are important for the healthy prenatal development of the offspring by preventing excessive levels of circulating GCs (1262-1265). For example, it has recently been demonstrated that lactating dams, whose mothers were exposed to stressful stimuli during pregnancy, do not display the normal adaptations observed in pregnancy (1266). In more detail, these dams had elevated CRF and vasopressin mRNA expression within the PVN suggesting a dys-regulation of the stress circuitries, which in turn leads to the elevated HPA axis reactivity found in these rats (1266). Animal and human studies in late pregnancy and lactation showed profound physiological adaptations of neuroendocrine and behavioural stress responses occurring at various brain levels. The adaptations ensure the

healthy development of the offspring by preventing excess prenatal GC exposure and appropriate maternal care in the postpartum period (1267).

18.3. Effects of stress on prenatal life

Animal studies together with retrospective studies in the human have shown that prenatal maternal stress is associated with reduced growth in uterus and can lead to an increased risk for a number of pathologies, including impaired behavioural/emotional development and depression (1268,1269). Studies in non-human primates have demonstrated altered HPA axis activity and stress-related behaviour in offspring of mothers stressed during pregnancy (1270,1271). An early study in the guinea pig demonstrated that exposure to a strobe light for 3 hours on GD60 (gestation day) and GD67 increased maternal and foetal plasma ACTH and cortisol concentrations (1272) and subsequently resulted in decreased plasma ACTH and cortisol responses to stress in juvenile and adult mixed-sex offspring (1273). Moderate prenatal psychological stress has profound effects on growth, behaviour and endocrine function (HPA axis activity and testosterone) in male offspring (1274). Under basal, non-stressed conditions, foetal plasma ACTH levels are rising at GD50, though plasma cortisol concentrations remain low (1275,1276). This suggests that the central drive of the HPA axis is increasing in the foetus, but that the adrenal is relatively insensitive to ACTH at this time in gestation. Maternal food withdrawal (48 h) at GD50 results in significant increases in maternal HPA axis activity and foetal plasma cortisol (2.5-fold), but no change in foetal plasma ACTH levels (1277).

Plasma cortisol responses to ACTH challenge were significantly elevated in PS60 (prenatal stress) offspring and this could reflect a difference in adrenal sensitivity and/or steroidogenesis (1274). Hypercortisolaemia, as observed in the PS50 offspring, is one of the defining features of the metabolic syndrome (1278). This disease is associated with increased central obesity, high blood pressure, glucose intolerance, depression, emotional irritability and cognitive deficits (1278). In a model of chronic prenatal nutrient restriction, male guinea pig offspring exhibited elevated blood pressure (1279). Discreet periods of moderate maternal stress can have a negative impact on adult body weight (1274). Another recent study demonstrated that prenatal stress resulted in aged male rat offspring (24 months) that exhibit hyperglycaemia, glucose intolerance and decreased basal leptin but no difference in the body weight (1280). It is possible that prenatal stress causes male offspring to react more severely to the stress of weaning, inducing temporary hypophagia similar to that reported in models of chronic stress (1240). In humans, low birth weight, which is considered an index of an adverse foetal environment, has been associated with the development of obesity and altered body composition

in later life (1281-1283). Brain sparing is often observed in cases of intrauterine growth restriction in both animals and humans (1284,1285).

Increased anxiety-related behaviour following prenatal stress has been reported in rats and primates (1270,1271,1286-1288). In humans, prenatal stress is a risk factor for the development of major depression and dysregulation of the HPA axis is present in approximately 20–30% of patients experiencing depression (1268). Pregnant rhesus monkeys exposed daily to extended periods of stress delivered offspring that exhibited decreased exploratory behaviour compared with controls (1271,1286). Adult rats exposed to excess endogenous GCs in uterus display decreased grooming and rearing in an open field and increased immobility in a forced swim test (1288).

18.3.1. Effects of stress on early life

HPA axis can be altered prenatally by nutrient restriction, maternal adversity or exposure to synthetic GCs and postnatally by neonatal handling, maternal deprivation or infection (1289). Low birth weight babies have raised cortisol concentrations in umbilical cord blood and raised urinary cortisol excretion in childhood (1290,1291). A number of studies suggest that low birth weight is related to an increased resting pulse rate and fasting plasma cortisol concentrations in adulthood (1292,1293). A study of a subset of 205 men showed that those with lower birth weight had enhanced responses of plasma cortisol to ACTH (1294,1295). Also, plasma cortisol levels in adulthood are correlated with birth weight and risk for glucose intolerance, hypertension and dyslipidaemia (metabolic syndrome) (1295-1297).

In a large cohort of Swedish army recruits there was a continuous relationship between size at birth and stress susceptibility in a psychological assessment of suitability for military combat duties (1298). Also, low birth weight is associated with enhanced blood pressure and heart rate responses to psychological stressors in women but not men (1299). Further, there are marked sex differences in the relationship between birth weight and the stress response, with boys who are small at birth having an enhanced HPA and girls a predominantly sympatho-adrenal response (1300). This observation is supported by increasing animal evidence that foetal programming of the HPA axis differs by sex (1301). Further, birth weight is associated with modulation of both sympathetic and parasympathetic function (1302) and is associated with features of hyperactivity and reduced attention and that this effect was observed across the range of birth weights (1303,1304).

18.4. Effects of stress on sleep

Sleep is commonly considered a restorative process with supportive influences on immune functions. There is considerable circadian rhythm of the immune system, which is likely to be linked with both circadian and sleep dependent hormone release (1305). As a stress hormone cortisol is known to peak in the early morning inducing an influx of neutrophils from the bone marrow and GH is secreted during sleep promoting T-cell function (1306). Sleep deprivation has a negative effect on cognitive and psychomotor performance and mood state, partially because of decreased creatine levels in the brain (1307). A study examining the effect of a single night of sleep deprivation on the antibody response to Hepatitis A vaccination on the previous day showed that subjects who had regular sleep after vaccination displayed nearly a two fold higher antibody titre ($p = 0.18$) after 4 weeks compared to sleep deprived subjects (1308). In addition, the quality and depth of sleep may be a more important determinant of immune function. Increased secretion of IL-6 during sleep was associated with stages 1–2 and "REM sleep"[12] (Rapid eye movement sleep) whereas IL-6 secretion during slow wave sleep was comparable to the levels found whilst awake (1305). In a human study men participating in a 5–7 day military training exercise that involved continuous light physical exercise (35% VO 2max), sleep deprivation (2–3 hrs of sleep during the whole course) and calorie restriction (with a daily intake less than 3,000 kJ) there was a significant reductions in CD4+ T cells, CD8+ T cells, B cells and NK cells. Also, serum levels of immunoglobulin were decreased (IgG 6–7%; IgA 10–20%; IgM 20–35%) (1309).

18.5. Effects of Stress during Exam

The effect of a six week cadet basic training period (a combination of physical and mental stress) followed by academic exams on the reactivation of three latent herpes viruses showed that Epstein-Barr virus antibody titters were significantly higher during the examination week compared with baseline and during the six week basic training (1310). Also academic stress and not basic training modulated the expression of latent Epstein-Barr virus suggests the type of stressor is important in determining the immunological effect.

[12] During a normal night of sleep, humans usually experience about four or five periods of REM sleep. It is characterized by the rapid movement of the eyes. In adult humans REM sleep typically occupies 20–25% of total sleep, about 90–120 minutes of a night's sleep.

19. Food deprivation

19.1. Caloric restriction

The lifespan of all mammals studied to date can be significantly increased by reducing their caloric intake. Also, the lifespan of rats and mice can be increased by up to 50% if dietary restriction (DR) regimens are begun in young adults and maintained throughout the life (880). Studies of tissues from animals on CR and fasting diets have provided evidence for two major mechanisms by which meal size and frequency affect health and disease susceptibility. One mechanism involves the production and removal of free radicals and the second involves stress resistance (880,1311,1312). The vulnerability of cells to being damaged and killed by oxidative insults (radiation, mitochondrial toxins, ischemia, iron, etc.) is decreased in animals maintained on CR or EODF diets (889,890,1313,1314). CR and EODF may suppress oxidative stress by reducing the amount of superoxide anion radicals produced in the mitochondria and by stimulating the expression of genes that encode antioxidant enzymes and protein chaperones (903,1315). Animal studies indicate that DR may prove beneficial in reducing the incidence and/or severity of the corresponding human neurodegenerative disorders. The results of some studies performed in last years suggest that a meal-skipping DR regimen can reduce the risk of each of the major neurodegenerative disorders (e.g. AD, PD, Huntington's disease) (889,890,1316-1318). Rats maintained on DR for 2 to 4 months exhibit increased resistance to kainate-induced damage to hippocampal neurons and associated learning and memory deficits (889). Also, learning and memory is preserved in ageing rodents maintained on DR (886) and that suppression of NPC proliferation can impair learning and memory (1319). Increasing data suggest that the brain may control life span by regulating energy metabolism of the entire organism (1320). Because systems that regulate energy metabolism, such as the insulin signalling pathway, are believed to play major roles in the ageing process (1321), they are likely to have an important influence on brain ageing. It has been hypothesized that the HPA-GC system plays a protective role against the moderate stress of DR (1322) and neuroprotective properties have been described for increased GC in restricted animals (1323). Key signalling pathways involved in the regulation of energy metabolism by the brain include BDNF, IGF and neuropeptides that control feeding behaviour in the brain and insulin in peripheral tissues. Animals maintained on DR exhibit increased levels of GCs consistent with an increased level of stress (1324). In animals fed ad libitum, increased GCs associated with chronic stress have been shown to promote neuronal degeneration (1325) and impair neurogenesis (1326). A different profile of changes in the expression of GC and mineralocorticoid receptors in the hippocampus in response to DR has been seen in animals subjected to psychosocial

stress (1327). Stress and GCs decrease the expression of BDNF in the hippocampus (1328) and BDNF can protect neurons against the adverse effects of GCs (1329).

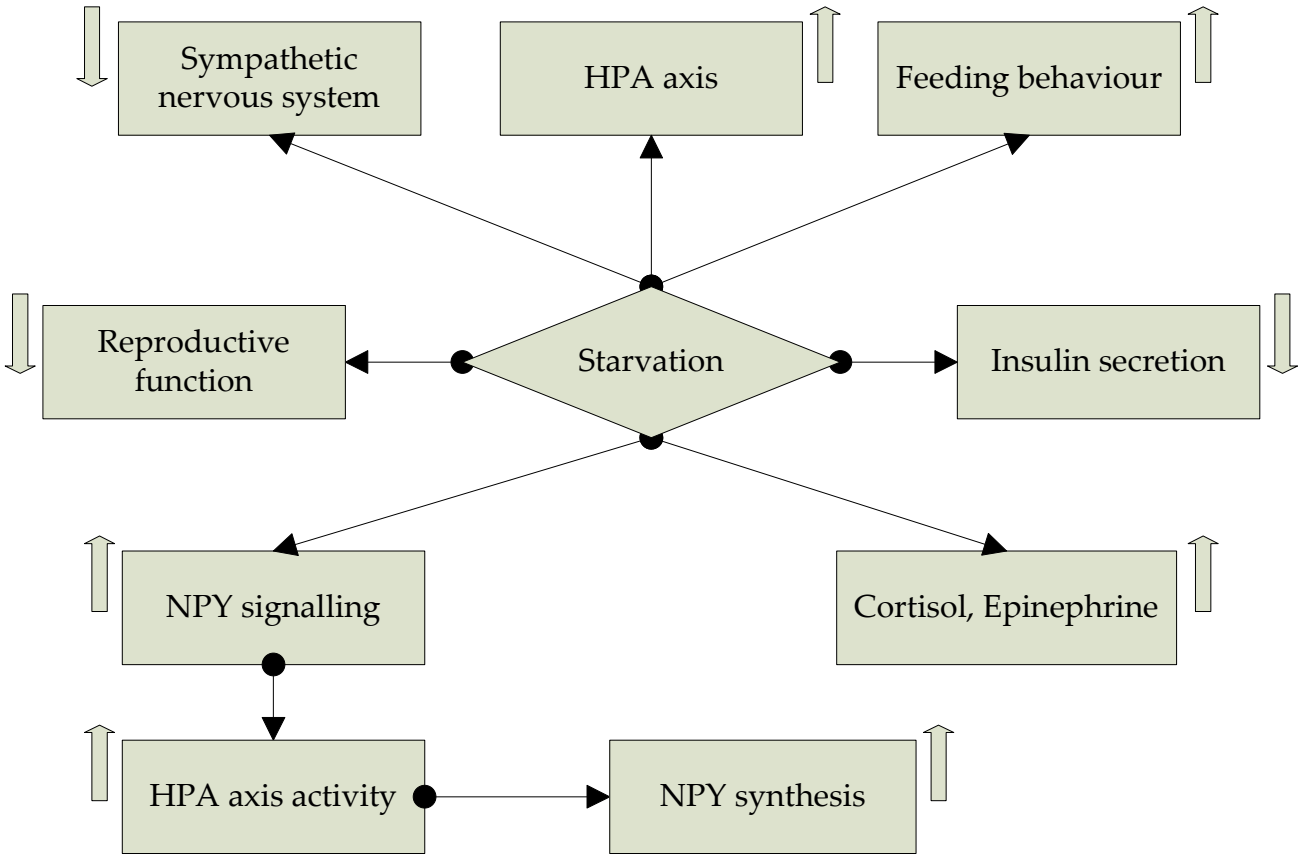

FIG 16. Positive health effects of dietary restriction

In mice maintained on DR food deprivation increases NPY and AgRP mRNA and decreases that of proopiomelanocortin in the arcuate nucleus. These changes are largely reversed 6 h after re-feeding (1330). The adult brain contains populations of cells in the sub-ventricular zone and in the sub-granular layer of the dentate gyrus of the hippocampus that are capable of dividing and then differentiating into neurons or glial cells (1199). Also, DR can increase neurogenesis in the brains of rats and mice (897,1331). It does not affect the proliferation rate of the neural stem cells, but promotes the survival of newly generated neural cells (897,904). Other studies have shown that, in mice, DR can enhance performance of learning and memory tasks (886), which could also be mediated by BDNF (1332). Levels of BDNF are increased in neurons in the cerebral cortex, hippocampus and striatum of rats and mice maintained on DR (896,897,1317,1331). It is known that BDNF can protect neurons in culture and in vivo against excitotoxic, metabolic and apoptotic insults (1333). Neurotrophic factors may protect neurons by stimulating the production of proteins that suppress oxidative stress (antioxidant enzymes, and Bcl-2) and stabilize cellular calcium homeostasis (1334).

In human studies participants who were forced to eat a low-calorie diet over a period of approximately two years exhibited highly significant decreases in blood pressure and insulin and cholesterol levels (1335). Health benefits of smaller and more frequent meals are suggested from survey-based evaluations of the association between meal frequency and obesity, hypercholesterolemia and glucose intolerance (1336) and from the assessment of the effects of short-term (days to weeks) high and low meal-frequency diets on glucose regulation (1337,1338). It has been suggested that skipping breakfast is unhealthy (1338). Further data suggest that both reduced-energy and reduced-meal-frequency diets can reduce inflammatory responses, as indicated by reduced production of TNF by macrophages (1339). T-lymphocyte responses to concanavalin A and responses of B-lymphocytes to pokeweed mitogen were reduced in obese subjects compared with normal weight controls and these impairments in immune responsiveness were reversed by CR (1340). In female mice CR (40%) during their adult life prevented age-related declines in learning and motor coordination (1341). Age-related alterations in neurotransmitter-synthesizing enzymes and neurotransmitter receptors in the brain were suppressed in rats that had been maintained on an EODF diet during their adult life compared with rats fed ad libitum (1342). The adult mammalian brain contains population of self-renewing stem cells that are capable of forming new neurons and glial cells. EODF increases the survival of newly generated neurons in the dentate gyrus of the hippocampus in adult mice (1343). On the other hand, CR did not increase hippocampal neurogenesis, but did enhance glial cell genesis by increasing the survival of newly generated glial cells (1344).

19.1.1. Fasting

Studies of different human populations that periodically fast as part of their religion, suggest health benefits of reduced meal-frequency diets (1345). Consistent with a cardioprotective effect of regular fasting in humans, Moslems who fast during the month of Ramadan have reduced levels of LDL cholesterol and increased levels of HDL cholesterol (1346). In animal studies memory impairment was preserved in the intermittent-fasted rats compared to the control rats fed ad libitum (889). Intermittent fasting results in increased excitability of the CNS (1347). CR may reduce and overeating increases activity of the sympathetic nervous system, which likely contributes the opposite effects of CR and overeating on blood pressure (1348). The increased activity in nerve cell circuits in animals on CR or intermittent fasting likely contributes to several beneficial effects of the reduced meal size and frequency within the brain. It appears that the brain's perception of

CR and intermittent fasting as stressors is central to activation of stress-resistance mechanisms that may protect against disease (1349).

19.1.2. Brain in choosing foods

The brain is evolved as the major regulator of food acquisition and energy metabolism (1320). It is responsible for the behaviours involved in the identification and ingestion of food. Further, it regulates energy allocation and usage in various organs.

19.1.3. Energy balance

Energy homeostasis is regulated through a complex network of central and peripheral signals, including brain neuropeptides and systemic hormones, which provide converging inputs to the CNS (736,1350). The satiating effect of nutrients is strongly dependent on their oxidation and the energy released from this oxidation rather than on their blood concentration (1351,1352).

20. Stress during Pregnancy

Human and animal studies have indicated that many different types of prenatal stressors have significant effects on postnatal behaviour (1353). In the offspring of pregnant animals significant changes have been found in both behaviour and regulation of the HPA axis, regardless of the specific prenatal stressor used. In humans significant effects on postnatal behaviour have been found for prenatal exposure to many different types of maternal stress or anxiety (1354).

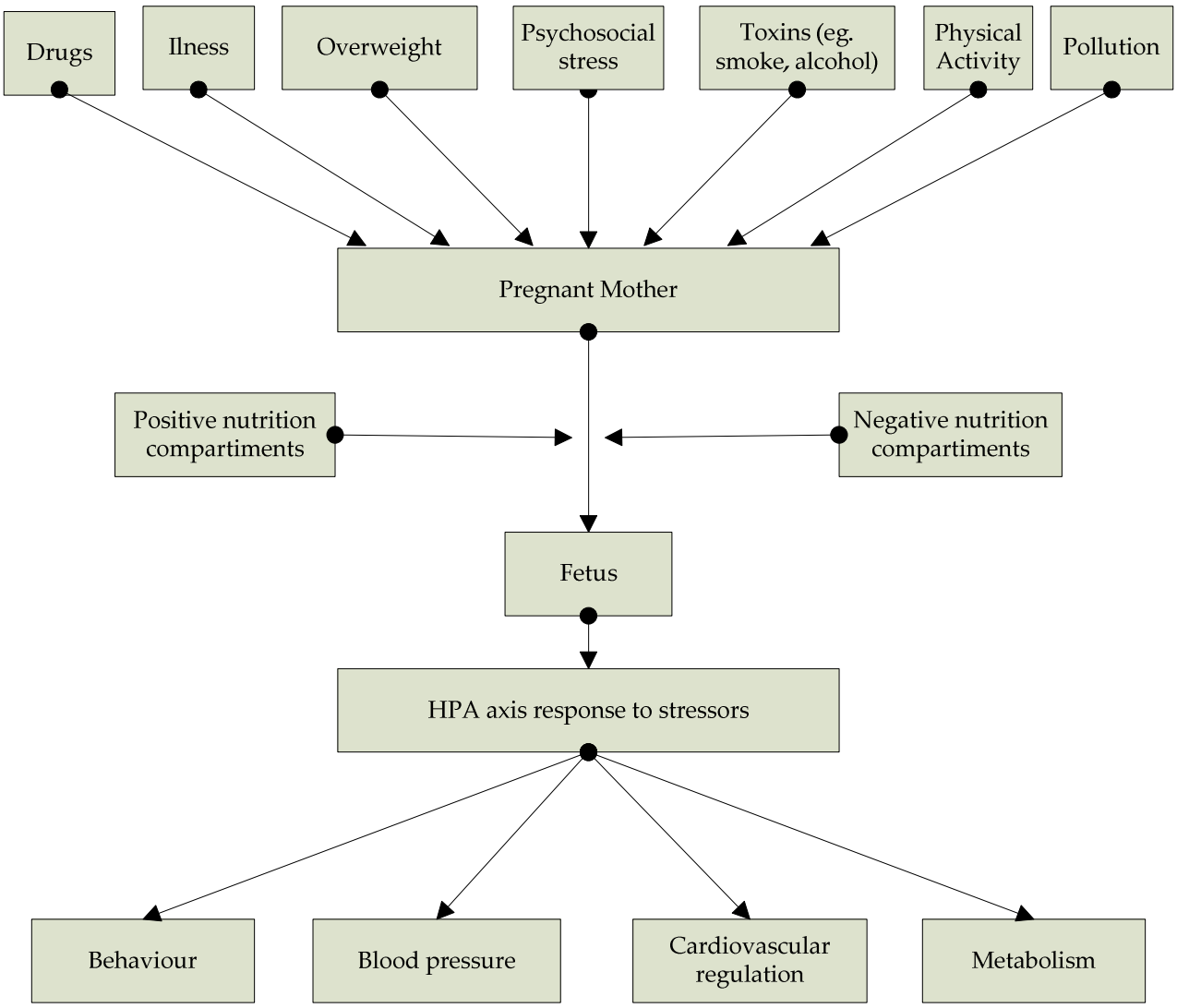

FIG. 17. Factors experienced during pregnancy may results in changing HPA axis activity in the developing fetus

In several studies prenatal exposure to natural disasters significantly increased the risk for a variety of behavioural disorders. Significant relations have been found between prenatal stress and postnatal problems in a variety of behavioural domains, such as attention, language and learning (1355). Also, prenatal stress can

have a variety of effects on brain development including: delayed myelination, elevated sensitivity of the amygdala to GCs and abnormal development of the dopaminergic system (1356-1358). Further, maternal stress and the resultant release of catecholamines can cause uterine vasoconstriction and reduced blood flow to the placenta, resulting in foetal hypoxia and a spectrum of foetal injuries that range from spontaneous abortion to varying degrees of cerebral damage (1356,1359). In the normal gestational environment, the mother transfers GCs to the developing foetus in proportion to the adversity of her environment (1360). The HPA axis is particularly sensitive to effects of prenatal exposure to excess levels of GCs (1361). Prolonged maternal exposure or severe stress can cause the offspring to develop a pathological, life-long hyper-activation of the HPA axis as well as elevation of stress hormone levels (1362). Also, prenatal exposure to environmental stress or GCs can lead to postnatal HPA hyperactivity in response to stress (1363).

21. Food intake

In healthy males exogenous GC administration increased daily food intake compared to placebo (603). Amylin and CCK function as satiety signals to terminate meals, whereas ghrelin has among its actions the stimulation of food intake. The satiety signalling effect of CCK was confirmed in humans. Also, treatment with a CCK type-A receptor antagonist increased caloric intake and sensation of hunger (1364). Antagonist studies in rats provided evidence that CCK is important to postprandial sleeping (1365). Amylin is a pancreatic peptide and is secreted with insulin that has actions similar to those of CCK. Several central sites of amylin signalling were reported including the amygdala (1366) and area postrema (1367). Both dopaminergic (1368) and histaminergic (1369) receptors have been implicated in processing of amylin signals. There is strong evidence that restrained and emotional eaters overeat in response to stress (1370). Restrained eaters consumed more than unrestrained following a reaction time task, while the opposite was observed following a relaxation condition (1371). Following an interpersonal stressor, restrained eaters ate more than did non-restrained eaters (1372). Moreover, the greater the restraint, the more participants ate (1373). Stressed emotional eaters ate more sweet, high-fat foods and a more energy-dense meal than unstressed and non-emotional eaters following a speech preparation task (24). Overeating has been observed in rats following a stress and a period of CR (1237) only in those given highly palatable food (1238). Bulimic patients reported increases in hunger and desires to binge eat compared to restrained eaters and controls following an interpersonal imagery task (1374). Emotional eating has been associated with both increased and decreased food intake (614) and little is known about the mechanisms that underlie the direction of change. In rats, both a single social defeat stressor (1624) and a 2-h immobilization stressor (1375) resulted in a significant reduction of food intake and body weight. More recently, however, incongruent paradigms of stress physiology have emerged (1376).

22. Diseases and Stress

The association between different diseases and stress has been discussed in literature. Some diseases will be discussed here.

22.1. Adiposity

For any given body mass index (BMI), mortality is higher if fat is distributed centrally (visceral adiposity) compared with a more generalized pattern of distribution (1377). This has renewed interest in the factors that control adipose tissue distribution in addition to adipose tissue mass and function (1378). Several studies have indicated positive correlations between high-energy diets and obese animals (1379). It has been suggested that dietary fat is a prime contributor to the development of obesity (70). In rats, a forced high-fat diet increased both basal and stress-induced hormone secretion, it was suggested that chronic dietary fat was itself a stressor (71,1380). In contrast to reports of positive correlations between apparent HPA function and obesity, a number of studies have suggested protective effects of high-energy diets against stress. Rats eating a high-fat diet for 2–3 months had reduced sympathetic responses to stressors, compared with animals eating high carbohydrate diets (70). Most preclinical studies have focused on the effect of stress on ongoing feeding behaviour (612,1238,1381). Humans seem to be vulnerable to maladaptive eating habits of stress and anxiety-like states during dieting (1382,1383). Short-term exposure to high fat diet also reduced anxiety on the elevated plus maze (72). Foods with high simple carbohydrate and fat contents have been reported to be highly palatable, as compared to foods with high fibre content which are less palatable (1384).

In women, visceral fat was associated with high cortisol levels. However, women with low WHR failed to habituate to repeated stress, whereas those with higher WHR habituated (625). Measurements of mesenteric fat weight together with hypothalamic CRF mRNA from either adrenalectomized or from intact rats, showed significant negative correlation between mesenteric fat weight and CRF expression in the PVN (612). Also, mesenteric (but not sc) fat stores serve as a signal of energy stores that feed back to inhibit CRF activity in the HPA axis (612).

Although men tend to progressively increase abdominal fat depots with increasing total adiposity at each age, a tendency to develop different obesity phenotypes throughout the lifespan occurs more clearly in women, particularly after the menopausal age (1385). The response of the HPA axis to a high-lipid/protein meal or high simple carbohydrate meal in obese women depends on their pattern of body fat distribution and that the activation of the HPA following the ingestion of

large amounts of complex carbohydrate may have some patho-physiological relevance, specifically in women with the abdominal obesity phenotype (1386). In obese women, different mechanisms may be responsible for the regulation of the HPA axis following a high-lipid/protein meal or high simple carbohydrate meal, depending on their phenotype (1386). Further, the rate of FA oxidation and its effect on adenylate charge in the liver are involved in regulating food intake (1387). Transport mechanisms (1388) and enzymes for fat oxidation (1389) and fat synthesis (1390) are also present in the brain and administration of inhibitors of fat synthesis produces a centrally mediated inhibition of food intake in rodents (1390,1391). Despite the potential for fat and fat metabolism to inhibit food intake, there is abundant evidence that consumption of diets high in energy from fat leads to increased energy intake, weight gain and obesity in animals and humans (1392-1395).

Local adipose tissue GC levels and intracellular GC availability are controlled by the activity of 11ß-hydroxysteroid dehydrogenase type 1 (11ß-HSD-1), which functions almost exclusively as a high-affinity reductase in vivo, generating active cortisol from inactive cortisone (1396). Obesity increases the expression of 11ß-HSD-1 in human subcutaneous and visceral adipose tissue and both 11ß-HSD-1 transcription and activity are higher in omental versus subcutaneous adipocytes from obese subjects (1397,1398). GCs appear to provide metabolic inhibitory feedback on central networks through redistribution of peripheral energy stores. Removal of GCs by adrenalectomy suppresses food intake and weight gain (679). A major problem in the dietary treatment of obesity is the high rates of relapse to maladaptive eating habits (1399). This relapse is commonly triggered by stress and anxiety-like states (1383,1400).

22.2. Alzheimer Disease

There is a strong correlation between per capita food consumption and risk for AD and stroke (1401,1402). In a population-based longitudinal prospective study of Nigerian families in which some members moved to the United States, it was shown that the incidence of AD among individuals living in the United States was increased compared to their relatives who remained in Nigeria (895). Case-control studies showed that individuals with the lowest daily calorie intakes had the lowest risk of AD and PD (894,1403).

22.3. Anorexia nervosa

Anorexia nervosa (AN) is a complex condition that can lead to death in severe cases. It involves neurobiological, psychological and sociological components. Individuals with anorexia are known to control body weight commonly through

the means of voluntary starvation, purging, vomiting, excessive exercise or other weight control measures. Starvation suppresses sympathetic nervous system activity (1404) and reproductive function (1405) while stimulating the HPA axis (1406,1407) and feeding behaviour (1408). Starvation-induced activation of the HPA axis (1406,1407) appears to involve factors additional to CRH, since hypothalamic synthesis of CRH is reduced (1409,1410) or unchanged (1411) after weight loss induced by starvation or restricted access to food. In contrast, hypothalamic expression of the CRH gene is typically increased during acute stress (1412). Complementing its role as a primary controller of the HPA axis, CRH also acts in the hypothalamus to reduce food intake (1413) and stimulate sympathetic nervous system outflow (686), causing increased energy expenditure and sustained weight loss. After the first few days of starvation, FFAs and ketone bodies, rather than glucose, become the predominant fuels (1414,1415). After depletion of glycogen stores in the liver, plasma glucose is maintained solely by gluconeogenesis, a process that depends in part on catabolism of muscle. Starvation inhibits insulin secretion while increasing the concentrations of glucagon, epinephrine and cortisol. This physiologic combination reduces glucose use while stimulating lipolysis and ketogenesis. Insulin secretion is proportional to both body adiposity and the prevailing energy balance (1416) and insulin enters the CNS through a transport process that appears to be localized to the endothelium of the blood–brain barrier (1417,1418). Insulin provides a negative-feedback signal to the brain (1419). In fasting animals, insulin (1420) and leptin (737,1421) inhibit the expression of the NPY gene, whereas GCs have the opposite effect (684,1422). NPY also activates the HPA axis, but at a hypothalamic site rather than directly in the pituitary (1423-1425). Activation of the HPA axis during starvation, in both animals (1423) and humans (1424) may therefore facilitate the mobilization of fuel in peripheral tissues and CNS responses that promote the restoration of depleted adipose stores. Since the increase in NPY signalling during starvation depends on GCs (1422) the activation of the HPA axis by NPY during starvation may stimulate further hypothalamic synthesis of NPY, creating a positive-feedback loop between NPY and GCs (1426).

22.4. Autoimmune disorders

Stress has been shown to play a major role in autoimmune disorders (1223). NO may be inductor and effector of cellular damage and consequently iNOS has been described to be generally associated with the pathogenesis of chronic inflammation (1427). NO release has also been demonstrated to limit auto-reactive T cell determined spreading and diversification of the antibody repertoire, a process driven by macrophages (1428). NO may be important for silencing auto-reactive T

cells and may further restrict bystander autoimmune reactions following an innate immune response (1428,1429).

22.5. Bulimia

Disordered eating syndromes consist of overeating calories in a bingeing fashion (1430). Persons with disordered eating, whether it is bingeing or ingesting most of the daily calories intake occurs during the night, generally characterize themselves as chronically stressed (1430,1431) and are obese. The foods that are overindulged-in typically have high fat and carbohydrate caloric content and may be characterized as comfort food. GC concentrations in these patients are slightly but not markedly elevated (1432,1433).

22.6. Cancer

Stress is speculated to be part of the cancer aetiology (1228,1434-1436). Already some indications exist from prospective studies that there is no relation between stressful events and cancer. The results of a large scale study in the United Kingdom provide little evidence for an association between bereavement in men or women and later cancer (1437). Longitudinal study of Japanese men living in Hawaii showed no relation between stressful life situations, and later cancer (1438). A growing body of research linking psychological and behavioural factors to the incidence and progression of cancer suggests that psychosocial factors may have an impact on some types of cancer (1439-1444). A characteristic of a certain subset of tumours, particularly virally induced ones, is their ability to grow faster in animals undergoing either somatic or psychogenic stress (1445-1449). Cancers that are induced by chemical carcinogens (e.g. lung cancer) may be less influenced by psychological, behavioural and immunological factors than cancers that are associated with a virus, such as Epstein–Barr Virus, which are immunogenic (1450). Also, stress can accelerate the growth of certain tumours, particularly those that are virally derived (1445-1449). It has often been theorized that stress-induced acceleration of tumour growth is a result of immuno-suppression (1446,1448). Further, it is not clear if stress-related immune changes are of either the type or the magnitude to influence tumour growth and metastases (1441,1451). The mediating mechanisms for such accelerated growth are concentrated on the inhibition of the immune system by GCs during stress because:

- Exogenous GCs, like stress, can accelerate growth of some tumours (1446,1449).
- GCs, as part of their general inhibitory effect upon immunity, inhibit immune constituents known to be tumouricidal, including natural killer cells, antibody-dependent killer cells, macrophages and polymorphonuclear lymphocytes (1452).

- Immuno-suppression can be associated with the enhanced establishment and accelerated growth of tumours (1448).
- Virally derived tumours are most accelerated by stress. Also, the tumour types are most sensitive to immune status (1446,1448).

Psychosocial factors associated with cancer diagnosis include stress, depression, anxiety and distress (1453). In cancer patients cognitive function, defined as higher-order mental processes, may be altered along two distinct and interacting pathways (1454):

- The cancer diagnosis, which can lead to anxiety, stress, distress and depression.
- The direct physiologic effects of cancer treatment.

Changes in cognitive function have been identified as a likely consequence of cancer treatment since the 1980s (1455,1456). A number of known psychological and social effects are related to the challenges of confronting potentially terminal illness. The effects include anxiety, depression and stress. Physiologic and psychosocial factors have been implicated in cognitive function (1457-1460). Despite potentially contributing factors, chemotherapy has long been implicated as the prime suspect in cognitive decline among patients (1456,1461,1462). Further, changes in cognitive function may be dependent on chemotherapy dose or duration (1463-1466). Patients receiving chemotherapy perform only slightly lower on specific cognitive measures compared to age-matched, healthy counterparts (1467-1469). Specific agents are implicated in cognitive changes (1470,1471):

- Chemotherapies associated with CNS neurotoxicity,
- Chemotherapies that cross the blood-brain barrier (e.g., 5-fluorouracil, cytarabine, methotrexate, ifosfamide, cisplatin),
- Concomitant medications used with chemotherapy (e.g., GCs, dexamethasone),

Certain biologic (e.g., interferon) and

- Hormonal therapies (e.g., tamoxifen).

The impact of the drugs on cognitive function may be dose dependent, with patients who are exposed to higher doses or treated for longer periods of time having greater declines in cognitive function (1460,1465,1472,1473). Anaemia can result in reduced brain oxygenation and is a common side effect of chemotherapy treatment (1474). Chemotherapy-induced anaemia has been implicated as a factor contributing to changes in cognitive function (1464,1470,1475). Interventional studies showed that a year of weekly supportive group therapy sessions with self-hypnosis for pain was associated with extended survival time in women with

metastatic breast cancer (1476). In contrast other studies showed no difference in survival for metastatic breast cancer patients who received supportive-expressive group therapy when compared with controls, but the support group did exhibit improved mood and perception of pain compared with controls (1477).

NO is implicated in the control of malignancies. The significance of specific (clinical) NO pathways has been demonstrated in a variety of malignancies. NO is prominently involved in skin cancer (melanoma) (1478), brain tumours (1071,1479,1480), breast tumours (1071,1479-1482), lung tumours (1071,1483,1484), pancreatic cancer (1485) and GIT cancer (1071,1486-1489). The expression of iNOS in tumour cells is generally associated with apoptosis, suppression of tumourigenicity, reduction of tumour growth, abrogation of metastasis and even regression of already established cancer metastases (1478,1490). Stress may alter the DNA repair process (1491). In addition to the effects of stress on DNA repair, additional research has documented the impact of stress on apoptosis, a process of genetically programmed alterations in cell structure that leads to failure of proliferation and differentiation and eventual cell suicide (1234). Stress may also enhance carcinogenesis through alterations in DNA repair and/or apoptosis (1491-1493).

22.7. Cardiovascular diseases

Stress has been shown to be important in vascular hypertension (1222). In part stress may even cause or contribute to the clinical onset of arterial hypertension in certain cases (1494-1496). It may serve as a risk factor (1497), that induces blood pressure spikes or increases an already elevated blood pressure (1228,1498,1499).

22.8. Dementia

Dementia affects about 5% of the elderly population (aged 65 years and older) and has an unexplained predominance in women (1500). The importance of B vitamins and folic acid for the well being and the normal functioning of the brain have been described (1501). Inadequacies of B vitamins can result in hyper-homocysteinemia, a well-known risk factor for atherosclerosis and which recently has been associated with cognitive impairment in old age (1502). Elevated plasma homocysteine levels are, in many cases, indicative of suboptimal B vitamins status (1503). Deficiencies of other essential nutrients, such as the antioxidant vitamins C, E and β-carotene and the subsequent increased risk of oxidative stress, have also been identified as nutrition-related risk factors for cognitive impairment (1504).

22.9. Immunological diseases

It is widely accepted that acute stress tends to enhance immune functioning, whereas chronic stress more likely suppresses it (1434). However, the effects triggered by stress can be beneficial for some types of immune responses and deleterious for others (1498,1505-1507). Inflammation, infection, autoimmune processes and perhaps even the onset and development of malignant tumours may occasionally be associated with the stress phenomenon (1223).

22.10.Immunosuppression

Stress can be immunosuppressive through a variety of humoral and neural mechanisms (1508). Decreased lymphocyte proliferation and reduced NK cell cytotoxicity are consistently observed during stress (1509). Further, NK cell cytotoxicity can be down-regulated by stress, presumably through neuroendocrine mechanisms (1443,1510,1511). NK cells play an important role in a variety of immune functions, including defence against viral infections (1512) and surveillance of tumour cells (1513). Bereaved spouses had elevated cortisol and decreased NK cell activity (1514). Among spouses of cancer patients, those who reported lower levels of social support had lower levels of NK cell cytotoxicity (1515). In rodents social stressors not only decrease NK cell cytotoxicity, but also they enhance metastasis of transplantable tumours (1516,1517). Also, depression and smoking had synergistic effects on reduced NK cell lysis (1518). Several aspects of the cellular immune response are also adversely affected by psychosocial stress (1509,1519). In a study of 45 healthy, older adults who were randomly assigned to one of three protocols (relaxation training, social contact or no intervention), relaxation subjects showed a significant enhancement in NK cell activity at the end of the 1-month intervention, with concomitant decreases in distress-related symptomatology in comparison to non-significant changes in the other two groups (1520). Also, stress-reducing interventions can improve immune function (1521). Further, there is evidence that stress can modulate cytokines synthesis such as INF-α and IL-2 by mitogen treated peripheral blood leukocytes (1522,1523). Also, INF-α, and IL-2 can enhance NK cell and lymphocyte-activated killer cell cytotoxicity (1513).

22.11.Inflammatory bowel disease

Positive associations have been found between inflammatory bowel disease activity with psychiatric diagnoses (1524,1525). Some clinical studies (1526-1528) but not all controlled studies (1524,1529-1531) showed that ulcerative colitis patients recall increased life stress before an exacerbation. The association between

stress and disease activity has been shown to relate not only to subjective symptoms, but also to objective endoscopic measures (1532). Recently, it has been shown that short-term stress does not appear to trigger exacerbations in ulcerative colitis, but that long-term perceived stress increases the risk of exacerbations over a period of months to years (1533). Psychological treatments have been used as a management modality in inflammatory bowel disease. It has been shown that inflammation can develop spontaneously in animals subjected to stressful situations. For example, Gibbon monkeys subjected to social upheaval developed a fatal colitis (1534). In animal studies chronic stress induced primary inflammation in a naive host (1535-1537). Also, rats were exposed to mild repetitive psychological stress in the form of water avoidance stress for 10 consecutive days, as a model of chronic ongoing life stress in humans. A three- to fourfold increase in inflammatory cells was noted in the lamina propria of stressed rats compared with sham stressed controls. Also, longer-term life stresses, at least those that pertain to early maternal deprivation used in animal models may predispose the mucosal barrier to permeability abnormalities when there is an additional acute stressor (1538).

Animal and human studies showed an increase in intestinal permeability in response to stress with acute (1539-1542) and chronic (1536,1537,1543) stress. Changes in permeability as an initial event in inflammatory bowel disease have been described. It has been shown that first degree relatives of patients with Crohn's disease, a sub-group with an increased risk of developing the disease, have an increased intestinal permeability (1544-1548). Also, it seems that relapses in patients with Crohn's disease are preceded by an increase in small intestinal permeability (1549).

Secretion of ions and water is a primary defence mechanism of the epithelial barrier. A change in secretion occurs with acute and chronic stress in animals and humans (1539,1540,1543,1550,1551). In humans stress was induced by dichotomous listening and acute stress resulted in excessive jejunal secretion (1550). In human jejunal water secretion was increased by cold pain stress (1551).

22.12.Insulin resistance

Acute stress is clearly associated with a severe, yet reversible, form of insulin resistance (1552). Also, psychosocial stress might be associated with insulin resistance (804). In Westernized countries 25-35% of the population have a degree of insulin resistance and the health consequences associated with this metabolic derangement (1553). Insulin resistance means that the ability of insulin to dispose of glucose in the liver, skeletal muscle and other peripheral tissues is

compromised. Insulin resistance seems to be a common feature and a possible contributing factor to several frequent health problems, including type 2 diabetes mellitus (1554), cardiovascular disease (1555-1559), certain hormone-sensitive cancers (1554,1560,1561), dyslipidemia (1562), hypertension (1563,1564), polycystic ovary disease (1565,1566), sleep apnoea (1567) and obesity (1568-1571).

TABLE 6

Dietary components with possible increasing effect on insulin resistance

- Low fibre intake
- Low vegetable intake
- High fat intake
- Deficiency of omega-3 FA intake
- Deficiency in Micronutrients
- High intake of refined carbohydrate
- High glycemic meals
- Lack of exercise
- Smoking
- High stress

While both cortisol and the catecholamine stress hormones are capable to elevate blood sugar, chronic elevation of cortisol resulted in increased plasma insulin levels (1572). Also, consistently elevated levels of cortisol greatly inhibit non-hepatic glucose utilization (1572,1573). Further, stress, secondary to cortisol production, may impact insulin resistance directly or indirectly through interaction with leptin. Cortisol might be capable of both increasing leptin levels and inhibiting the action of leptin, thereby promoting a state of leptin resistance (1574-1576). Also, the amount of leptin found in the blood directly correlates with insulin levels and with insulin resistance. In effect, leptin levels decrease in parallel with insulin and leptin resistance decreases as a person becomes more sensitive to insulin (1577-1579). Obesity is commonly characterized by a state of leptin resistance (1580). There is an increased prevalence of insulin resistance in patients with schizophrenia and chronic depression compared with the general population (1581). Overweight and insulin resistance have also been associated with bipolar disorder (1582). Since evidence supports the association between abdominal body fat distribution, insulin resistance and obesity. Also, among obese men loss of weight and a decrease in the WHR are closely associated with improved insulin sensitivity (1583). Epidemiological data suggests that increased consumption of saturated and total fat and decreased intake of fibre is associated with insulin resistance (1584-1586). Further, the macronutrient composition of the diet might

play an important role in fat deposition (1587) and so might consequently influence insulin resistance. Also, low fat, high simple carbohydrate diets might contribute to metabolic problems and certainly do not appear to be capable of reversing insulin resistance, obesity or Syndrome X (1588,1589). In contrast high-carbohydrate, high-fibre diets certainly appear to improve peripheral tissue insulin sensitivity in healthy young and old individuals (1590,1591). Further, exercise can improve insulin resistance. Also, available research demonstrates that postmenopausal women can improve insulin resistance through consistent appropriate exercise (1592).

Dietary micronutrient deficiencies might also promote insulin resistance. Diets higher in vitamin A have shown an inverse relationship with insulin resistance (1593). Deficiencies of minerals including calcium, magnesium, potassium, chromium, vanadium and zinc might also promote insulin resistance (1594-1600). While severe reduction of salt intake may contribute to an increased serum lipid and insulin levels and a deterioration of insulin sensitivity in both healthy volunteers and patients with hypertension (1601-1603). Possibly high sodium intake exacerbates insulin resistance (1604).

22.13.Intestinal Disorders

Intestine is extending from the stomach to the anus. It is an important segment of the GIT. It consists of two segments, the mall and large intestine. Diet has an important role in intestinal pathologies (1605-1607). It is complicated by symptomatic association to psychological disorders (1608-1611). Stress can have negative impact on the intestine. Also, stress and stress-induced anxiety play a major role in functional intestinal disorders (1612). The stimulation of intestinal contraction and colonic transit are the most consistent patterns in the motility response of the intestinal tract to acute stress (1613,1614). Within the cells and neurons of the GIT Trp4 receptors are located (1615,1616). Disturbances in gut and the brain Trp account for the majority of intestinal and psychological illnesses (1617). Both stress-induced anxiety and intestinal disorders are traced, from among other molecular pathologies, to the inappropriate responses of the central and/or peripheral serotonin system (1617,1618). Antagonists on the Trp4 receptor do not affect normal, healthy gut function (1619) but prevent the disturbances caused by stress (1617) or high Trp activity (1620). In addition to their effect on the GIT, Trp4 antagonists block corticosteroid secretion in the adrenal cortex (1621), Trp-induced tachycardia (1622,1623) and stress-induced anxiety (1624).

22.14.Neurodegenerative diseases and mental disorders

In neurodegenerative diseases and mental disorders stress clearly plays a significant role. Also, stress has been shown to be involved in neurodegeneration (1223). It has been demonstrated to cause deficits especially in spatial memory performance (1625-1628). Stress may lead to a loss of neurons, particularly in the hippocampal area (1223,1627). Moreover, the ageing hippocampus apparently is more susceptible to stress and this vulnerability may yet be increased in AD (1629).

Neurodegenerative disorders result from insurmountable cellular stress. In AD, synaptic dysfunction and neuronal degeneration result from the ageing process in combination with increased production and accumulation of neurotoxic forms of amyloid β-peptide and perturbed cellular calcium homeostasis (1630). Membrane lipid peroxidation and engagement of apoptotic cascades may be pivotal events in AD. The degeneration of dopaminergic neurons in PD may result from age-related oxidative stress and impairment of mitochondrial ATP production, perhaps in combination with exposure to environmental toxins (1631). The abilities of antioxidants and drugs that stabilize cellular calcium homeostasis to reduce ischemic brain injury in animal models attest to the involvement of free radicals, energy impairment and perturbed calcium regulation in stroke-induced neuronal death (898). In animal and cell culture models neuronal dysfunction and death have been ameliorated of AD, PD and Huntington's disease by manipulations that reduce levels of oxidative stress and by agents that maintain ATP levels and ion homeostasis (1632).

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