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Chapter 7

Nutrition, Sleep and Sleep Disorders – Relations of Some Food Constituents and Sleep

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Additional information is available at the end of the chapter

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1. Introduction

Many people suffer from excessive sleepiness during the afternoon hours. In all human individuals the alertness level decreases after the noon peak. This afternoon dip or "postprandial dip" is physiological. The alertness level rises again later in the afternoon and early evening, reaching another peak at about 7 to 8 p.m. Obesity is a recognized public health problem. It is a strong risk factor for type 2 diabetes and cardiovascular disease. Obesity is also the strongest risk factor of obstructive sleep apnea. Nutritional factors are important also in many other sleep disorders. Many patients with restless legs syndrome have low blood ferritin levels. [1] Sleepy patients with hypersomnias should avoid rapidly absorbing carbohydrates at daytime to minimize afternoon sleepiness. Adenosine is accumulating in the brain, notably in the basal forebrain, during wake, increasing the sleep pressure. [2] Caffeine, the most commonly used stimulant, is an adenosine receptor antagonist. During deep slow wave sleep glucose is stored in the glial cells. [3, 4] The brain-gut relationship is important also in the sleep-wake regulation, although well-done studies on that topic are still scarce.

Sleep disorders are a large and under-recognised problem in many parts of the world. The international classification of sleep disorders (ICSD), the most frequent and often the most severe are obstructive sleep apnoea (OSA), narcolepsy, restless legs syndrome (RLS), periodic limb movement disorder, insomnia, parasomnias, circadian rhythm disorders including jet lag and shift work, and sudden infant death syndrome. However, the major research focuses on OSA, insomnia and RLS since they are among the most highly prevalent sleep disorders and there are established links between them and other health conditions, which is the area where the majority of costs are incurred. The health system costs of sleep disorders comprise the cost of the sleep disorders themselves and the share of health costs from other conditions attributed

to sleep disorders. The total European cost of brain disorders in 2010 was €798 billion [5], headaches and sleep disorders, meanwhile, only cost 285 and 348 euros respectively [6]. "The human brain is not only the site of our personality, thoughts, feelings and other human characteristics; it is also the seat of many chronic disabling diseases. These diseases have not received the attention that has been devoted to heart disease, cancer or AIDS, but in recent years there has been a growing awareness of their importance" [5]. A growing body of evidence indicates that free radical formation is a mediator of the excessive lipid peroxidation and cell damage seen in neurological disorders [7]. Antioxidant vitamins and trace elements have been shown to have biological activity in acting as scavengers for free radical's delays the onset of defined milestones in the development of a disease. Therefore, micronutrients such as vitamins, minerals or trace elements are supported by evidence that it can delay deterioration of the disease.

Different nutritional factors, and eating, can have an effect on the CNS by different mechanisms: direct nervous connections through the vagus nerve and nucleus tractus solitarius, humoral effects, affecting absorption of different molecules, emotional and cognitive processes.

2. Substances involved in the sleep-wake regulation and food intake

Many different neurotransmitters, neuromodulators and hormones have an important role in regulation of sleep and wakefulness, and in eating behaviour. These substances include (in alphabetical order): acetylcholine, adenosine, alpha-MSH (alpha melanocyte-stimulating hormone), cholecystokinin, dopamine, GABA, ghrelin, glutamate, glycine, insulin, histamine, hypocretin (orexin), leptin, MCH (melanin-concentrating hormone), melatonin, norepinephrine, NPY (neuropeptide Y), prostaglandins, serotonin, somatotrophin and thyrotropin. Little is known about the effect of vitamins and minerals on sleep. They will be discussed shortly later in this review.

3. Neurotransmitters in the Enteric Nervous System (ENS)

The enteric nervous system (ENS) can be considered the body's second brain with more than 100 million neurons of different types. Neural signals may be transmitted from gut to the CNS by neural connection and by humoral mechanisms. The afferent fibers of the gut-brain neural are vagal (parasympathetic) and (ortho)sympathetic. Different sensors respond also to distension of stomach and contractions of the intestine. Chemical stimuli (e.g. spices), gut hormones, neurotransmitters, neuromodulators, cytokines and inflammatory mediators produced by the bacterial flora in the gut-are all important. In the brainstem most afferent vagal fibers terminate on the nucleus tractus solitarius (NTS). There is a viscerotopic representation of different parts of the enteric system in the NTS. The NTS is in connection with hypothalamus and amygdala, which also plays a role in regulation of hunger and satiety. We

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should not forget the emotional aspects of eating (smell, taste, and situational factors during eating).

Cholecystokinin is secreted by duodenal and jejunal cells after eating food. CCK acts on vagal neurons projecting to the brainstem, giving a signal of satiety inhibiting further need for eating.

Ghrelin is secreted when a person is hungry and it increases appetite. It acts on the hypothalamus stimulating feeding, counteracting the inhibitory effects of leptin.

Leptin is manufactured mainly in fat cells in adipose tissue. Leptin counteracts the effects of neuropeptide Y and inhibits secretion of alpha-MSH (alpha melanocyte-stimulating hormone). Leptin decreases appetite and inhibits food intake contrary to ghrelin.

Alpha-MSH is in the arcuate nucleus in the brain where it acts to suppress appetite. Alpha-MSH may have also some function in the sleep-wake regulation.

Serotonin is an important neurotransmitter in the central nervous system (CNS) with important effects on sleep-wake regulation. Serotonin also has an important role in regulation of the gastrointestinal (GI) function through an interaction with the ENS. Up to 60-90 % of the total body amount of serotonin is in the GI tract, and 2-20% of all enteric neurons express serotonin. Stimulatory receptors include β-adrenoceptors, muscarinic and nicotinic Ach receptors and 5-HT3 receptors. Inhibitory receptors include alpha2-adrenceptors, histamine H3, GABA-B, adenosine A2, and 5-HT4 receptors. In the GI tract 5-HT is eliminated mainly by monoamine oxidase metabolism. [8]

Hypocretin (orexin) was originally considered to be important especially in central control of food intake [9, 10] but it is essential also in control of sleep and wakefulness. There are about 70 000 hypocretin neurons in the lateral hypothalamus. Narcolepsy, a central hypersomnia with excessive daytime sleepiness and cataplexy, is characterized by destruction of the hypocretin neurons. [11, 12] Hypocretin is involved also in energy homeostasis, nociception, reward seeking behavior, and drug addiction. [13-19] In addition to brain, hypocretins are also widely present in the gastrointestinal tract12 where they have a role in regulation of peristaltic GI motility, and in gastric, intestinal and pancreatic secretions. The hypothalamic hypocretin cells are intermingled with MCH neurons. Both hypocretin-and MCH-cells are glucose-sensing neurons. Decrease of glucose increases activity of hypocretin neurons and decreases activity of the MCH cells, producing wakefulness. Respectively, increase of glucose decreases activity of hypocretin and increases activity of MCH, producing sleepiness. These interactions explain at least partly the alerting effects of fasting and the observations that eating rapidly absorbing carbohydrates, provoking fast increase of blood glucose, increase sleepiness.

4. Caffeine and sleep

Coffee is the world's most common psychoactive drug. Coffee includes caffeine, which is also present in coffee, tea, cola and chocolate. The stimulant and wake-producing properties of caffeine depend on its ability to reduce adenosine transmission in the brain. Caffeine acts as an antagonist to adenosine A1 and especially to adenosine A2 receptors. [20, 13]

In experimental studies the concentration of adenosine is higher during wakefulness than during sleep, it accumulates in the brain during prolonged wakefulness, and local perfusions as well as systemic administration of adenosine and its agonists induce sleep and decrease wakefulness.2, 18 Supportive findings have been observed in humans. The longer the previous wakefulness period is, the longer and deeper is the following sleep. [22] The increase in extracellular adenosine concentration decreases the activity of the wakefulness-promoting cell groups, especially the cholinergic cells in the basal forebrain. [2, 22]

In addition to coffee caffeine is found in tea (20-100 mg per 3.5 dl cup of tea), Cola-drinks (30-50 mg per 3.3 dl bottle), energy drinks and chocolate. In chocolate also theobromine is present in large quantities. Dark chocolate is stimulating and 100 grams of 70% chocolate corresponds to 1-2 cups of coffee depending on strength of the coffee and size of the cup.

One small cup (30 ml) of espresso contains 30-50 mg of caffeine, and one large cup (2-4 dl) of ordinary coffee contains 75-150 mg of caffeine. Caffeine is absorbed rapidly and the peak of action occurs in 30 to 60 minutes. The duration of action is usually 4 to 6 hours, but in elderly subjects with slower metabolism the duration may last up to more than 16 hours. A large amount of caffeine, usually over 300-500 mg, i.e. more than 4 to 8 cups of coffee, depending on individual sensitivity, causes restlessness, anxiety, trembling, tinnitus and feelings of euphoria / delirium. Everyday use of more than 500 mg caffeine leads to caffeinism with insomnia, fatigue, and different psychosomatic symptoms. Some chronic coffee drinkers have developed tolerance to caffeine, and may drink more than 10 cups of coffee daily. They have withdrawal symptoms if they do not have their coffee.

Coffee is a well-known factor disturbing sleep. [23-31]Two or three cups (or in sensitive persons just one cup of coffee) in the evening is followed by difficulty falling asleep and restless sleep. Insomniacs are usually advised to avoid coffee after 6 p.m. but in some sensitive persons with insomnia coffee at noon or early afternoon may disturb falling asleep in the evening. It is important to recognize that energy drinks such as Battery and Red Bull contain large amounts of caffeine, which is a known cause for insomnia in adolescents. [31] Paradoxically, in some persons one or two cups of coffee may ameliorate quality of sleep. The reason can be behavioral conditioning, but it is also known that caffeine is inotropic and it stimulates respiratory functions.

5. Neurohormetic phytochemicals

Mediterranean diets rich in fibres, vegetables, fruits and olive oils are associated with reduced risk of cardiovascular disease and many neurological diseases. [32-34]Some effects are explained by antioxidative effects of different phytochemicals, but there is also evidence that some effects may be due to subtoxic effects of some neurotoxic molecules in the gut.

Hormesis is the paradoxical, stimulatory or beneficial action of toxins. Hormetic effects explain why, sometimes, low doses of a given toxic substance, or radiation, may induce beneficial effects while larger doses of the same substance or radiation are toxic to cells and organisms.

[35, 36] Examples of endogenous molecules with neurohormetic actions are nitric oxide, carbon monoxide, glutamate and calcium. Examples of neuroprotective substances include alpha-tocopherol, lycopene, resveratrol (red grapes, red wine, peanuts and soy), sul-foraphanes (broccoli), catechins (green tea), allicin and allium (garlic), curcumin (turmeric) and hypericin (St John's Wort).

Hot spices may disturb sleep. Tabasco and mustard in the evening may reduce slow wave and reduce total time awake and increase time to fall asleep. The spicy food in the evening elevated body temperature during the first sleep cycle, which explains probably some of the effects of capsaicin on sleep. [37]

6. Free radicals, oxidative stress and sleep

Increasing evidence associates sleep deprivation and sleep-related disorders with oxidative stress. Oxidative metabolism and energy production in the body generate free radicals and nonradical derivatives of oxygen and of nitrogen [38]. Normally, the mitochondrial respiratory chain generates a low level of free radicals during the process of making ATP. These free radicals, in turn, may cause further damage to the mtDNA creating a vicious cycle of damage and free radical production. It's unclear exactly how large a role the generation of free radicals plays in causing or worsening the symptoms of mitochondrial disease. Antioxidants, usually in the form of vitamins or trace elements, help neutralize free radicals. Although these products are involved in normal cell regulation and signal transduction, an imbalance between their generation and the antioxidant defense system results in oxidative stress. At the cellular level, the stress response can be initiated by external environmental factors that cause damage to biological macromolecules including lipids, proteins, and nucleic acids [39]. Oxidative stress in sleep apnea is thought to be produced by hypoxic events and by hypoxia-reperfusion injury, and in this way it contributes to cardiovascular complications and inflammatory processes [40, 41]. A role for disrupted sleep itself in the metabolic complications of sleep apnea has been implied by some of the evidence but not fully explored [42]. Ramanathan et al. [43] reported a significant decrease in superoxide dismutase (SOD) activity in the hippocampus and brain stem, but not in the cerebral cortex, hypothalamus, or cerebellum in rats sleep deprived for 5–11 days.

7. Prostaglandins and sleep

Prostaglandins (PGs) are synthesized from arachidonic acid by activated cyclo-oxygenase (COX) in response to various stimuli in various types of cells. When synthesized, PGs are immediately released and exert their actions on cells in the vicinity of their synthesis [44]. PGs act in many parts of the body, including the reproductive system, the nervous system, the cardiovascular system, the immune system and gastrointestinal system [45]. Due to their diverse biological activity, there is potential for prostaglandin analogs (prostanoids) to function as effective therapeutic agents.

Sleep, a complex phenomenon, is not merely the result of physical fatigue or decrease in activity; instead it is a complicated behavioural state requiring the integration of several neuronal processes. Prostaglandins (PGs) are ubiquitously distributed in mammalian tissues, exerting a variety of physiological and pathological effects such as disaggregation of blood platelets [46], relaxation of smooth muscle [47] and pain and inflammation [48]. It is generally accepted that PGD2 is one of the major PGs unique to the CNS, when compared to the relatively low concentrations present in peripheral tissue [49]. Studies have revealed a variety of endogenous substances that convincingly induce sleep. Among the multitude of sleep-promoting substances, PGD2 has been described as a somnolence promoting substance in the adult rat by acting on the traditional sleep centres of the VLPO area. PGD2 is produced from PGH2 precursor by enzyme PGDS that is predominately synthesised in the leptomeningeal layers and CP of the brain.

Prostaglandin D2 (PGD2) is a biologically active primary prostaglandin and a common product of arachidonic metabolism in mammals. As a major eicosanoid product of mast cells PGD2 is released in large quantities during allergic and asthmatic anaphylaxis. Several studies have reported a crucial role for the prostaglandin D system in sleep regulation. This PGD2 accumulates in the cerebrospinal fluid (CSF), where it induces physiologic sleep in rats and humans. PGD2 and PGE2 are found in high concentrations in the hypothalamus compared to other regional areas of the brain [50, 51]. In addition, marked elevations of endogenous PGD2 concentrations in CSF occur in patients who suffer African sleeping sickness [52]. Continuous infusion of PGD, into the lateral cerebral ventricle of monkeys during the diurnal period induced a sleep pattern similar to physiological night sleep [53]. It is involved in the regulation of reducing body temperature in sleep [54]. It is also produced in the brain via an alternative pathway involving a soluble, secreted PGD-synthase also known as β-trace [55]. PGD2 acts in the central nervous system in sleep induction and lowering of body temperature [51].Further pharmacological actions include inhibition of platelet aggregation and relaxation of vascular smooth muscle [56].

8. Glutathione and sleep

Glutathione is a tripeptide (gamma-glutamylcysteinylglycine) that performs many vital functions in every cell of the body [57]. It is present in two forms in the body; in a "reduced (GSH)" or an "oxidized (GSSG)" form. The majority of glutathione in the body is present in its reduced form because this is the only way it can perform its critical role. Certain tissues are more susceptible to GSH depletion than others. The reduced form of glutathione is the most active form and is found in healthy cells. GSH plays an important role in the protection of cells against damage from free radicals and other electrophiles. Several steps in the metabolism of arachidonic acid may be normally regulated by GSH-enzymes [58]. It was an early observation that GSH may function as a chemical cofactor or coenzyme in the formation of some PGs, particularly PGEs [59]. Measuring glutathione levels in specific areas of the brain of sleep-deprived animals reveals that the thalamus and hypothalamus are particularly susceptible [60]. It is essential for detoxifying cells and this process is more active during sleep [61]. The

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vulnerability of these tissues may contribute to some of the functional effects of sleep deprivation. The relationship between Glutathione (GSH) and sleep has been shown that it defends the cells from destructive agents such as free radicals, chemical toxins, and heavy metals that constantly assault the cells and inhibit their optimum function, causing disease and accelerating the aging process. Studies have shown that sleep deprived animals have lower glutathione levels in certain parts of the brain. The two brain areas involved in sleep are the thalamus and hypothalamus. These areas are particularly vulnerable to glutathione depletion and can lead to sleeping problems [60]. It has been reported that GSH is the only antioxidant that does not become a free radical itself after donating a free electron [62]. Further research suggested that high blood GSH concentrations correlates with long lifespan both in animals and humans [63]. Mancuso et al [64] observed that GSH levels were lower in patients with OSAS than in controls and suggests that antioxidant defences are impaired in patients with Obstructive sleep apnea syndrome (OSAS). Recently, Ntalapascha et al (2012) reported that overnight changes (%) in plasma biomarkers were significantly different between OSAS and controls for GSH/GSSG, controls had increased GSH levels overnight whereas OSAS did not.

9. Dietary nutrients and sleep

In a recent large survey on more than 4500 people the association of many different nutrients to sleep were studied. [66] The nutrients associated with difficulty falling asleep in order of importance were lack of alpha carotene, lack of selenium, lack of dodecanoic acid, lack of calcium and increased hexadecanoic acid. [66]Difficulty maintaining sleep was associated with increased use of salt, less butanoic acid, less carbohydrates, less dodecanoic acid, less vitamin D, less lycopene, more hexanoic acid and more moisture. Non-restorative sleep was associated with more butaneoic acid less calcium, less vitamin C, less plain water, more moisture and more cholesterol. In the same survey increased daytime sleepiness was associated more moisture, more theobromine (see above for caffeine), less potassium and less plain water. [66]

10. Vitamins and minerals and sleep

Management of sleep disturbances combines nonpharmacologic and pharmacologic approaches individualized for the patient. According to the International Classification of Sleep Disorders (ICSD-2, 2005) [67] there are around 90 distinct sleep disorders. The cumulative effects of sleep loss and sleep disorders have been associated with a wide range of deleterious health consequences including an increased risk of hypertension, diabetes, obesity, depression, heart attack, stroke and nutritional status of an individual could play a major role on sleep quality. Observational studies have shown a link between sleep [68] and vitamins and minerals, whether taken in combination or individually, are the most frequently consumed dietary supplements among people today. Unlike other dietary supplement ingredients, vitamins and certain minerals are considered essential nutrients for which standards of adequacy are needed.

10.1. Vitamins B

B vitamins are essential micronutrients and have many important functions in the body. The B vitamins generally are coenzymes in the energy metabolism in the body. They are needed for the syntheses and release of certain neurotransmitters and neurohormones that are involved in the regulation of sleep and the circadian cycle. B vitamins have been advanced as a preventive for insomnia based on research that suggests deficiencies in vitamin B6 promote psychological distress and ensuing sleep disturbance [69]. Folic acid and vitamin B12 are both B vitamins. Folic acid is often used in combination with other B vitamins [70]. Although the direct link between vitamins and insomnia is unclear, there are studies that show an association between vitamins and sleep disorders.

10.2. Vitamin B12, B6 and Folic Acid

Vitamin B12 deficiency has been linked to various neuropsychiatric disorders including slow cerebration; confusion; memory changes; delirium, with or without hallucinations and/or delusions; depression; acute psychotic states; sleep, and reversible manic and schizophreniform states affective illness [71, 72]. It has been shown that depressed subjects have low serum vitamin B12 levels [73]. It has been reported that high levels of vitamin B12 are associated with good treatment outcome in patients with MDD [74]. However, others did not found any association [75]. It has been reported that both folate and vitamin B12 are essential in several metabolic pathways in the central nervous system, and their metabolism is intimately connected [76]. A deficiency of either vitamin causes impaired methylation in the central nervous system and may result in neurological and psychiatric disease that becomes irreversible if not treated properly [71]. Furthermore, vitamin B12 has been shown to modulate human melatonin secretion [77]. Vitamin B6 is involved in the same metabolic pathways in the central nervous system as vitamin B12 and folate. Earlier studies found a low level of plasma vitamin B6 associated with symptoms of depression [78]. Other reported that vitamin B6 supplementation has positive effects on memory performance, but not on mood [79].

10.3. Vitamin D

Vitamin D is a group of fat-soluble prohormones synthesised in response to sunlight. The major source of vitamin D in humans is exposure to UV radiation. The active form of vitamin D in the body is 1,25-dihydroxyvitamin D, or calcitriol. Vitamin D has received a great deal of attention recently. It has long been recognized as primarily a regulator of calcium and phosphorus, helping to protect bone density. In recent years, however, our understanding of the functions of Vitamin D in the body has expanded with numerous health outcomes. Vitamin D is now understood to play an important role in metabolic and immune system functions. Vitamin D deficiency has been linked to a number of illnesses and chronic conditions, including high blood pressure, diabetes; metabolic syndrome, pulmonary disease, and chronic pain. Vitamin D supplementation during winter improve mood in healthy volunteers [80]. One possible mechanism of action is that serum 1,25-dihydroxyvitamin D levels affect the levels of serotonin in the hypothalamus [81] and thereby enhance the synthesis and transmission of serotonin, leading to improvement in mood. Novel associations between sleep symptoms and

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vitamin D have been reported [82, 83, 84]. Further evidence suggest that low vitamin D levels increase the risk for autoimmune disease, chronic rhinitis, tonsillar hypertrophy, cardiovascular disease, and diabetes [85]. McCarty et al. [86] reported that persistent inadequacy of vitamin D may also increase the risk for obstructive sleep apnea via promotion of adenotonsillar hypertrophy, airway muscle myopathy, and/or chronic rhinitis.

10.4. Vitamin A

Vitamin A is the parent compound of retinoid, which regulate gene transcription by binding to nuclear retinoid receptors. It is involved in immune function, vision, reproduction, and cellular communication. Vitamin A is very important for the mucous membranes as it is needed for the proper production of mucopolysaccharides, which help to protect against infections. Barceló et al. [87], reported that patients with obstructive sleep apnoea syndrome have a decreased antioxidant capacity of vitamin A and E levels. Study of sleep in mouse models of ageing, Ransom et al [88] showed further clues as to the involvement of vitamin A in the regulation of delta oscillations. It has been suggested that retinoid signalling pathways are important for adult neural function in health and disease [89]. A definitive role for vitamin A signalling however is evident in the regulation of delta oscillations. This was first proposed by Maret et al. [90], who observed that the relative contribution of the delta wave to slow move sleep (SWS) is determined by the RA receptor RARb1. Moreover, vitamin A deficiency is known to significantly reduce the power of the delta oscillation in mice [91].

10.5. Vitamin C

Vitamin C prevents some oxidative damage brought on by endurance exercise to the fat and muscle tissue. It is required for the transformation of dopamine into noradrenalin [92], and the function of this vitamin has been suggested to extend to neuromodulation of dopamine, regulation of acetylcholine and catecholamine release, and glutamate and GABA mediated neurotransmission [93]. Sleep symptoms are associated with weight gain and cardio metabolic disease. The potential role of diet including vitamin C that was associated independently with non-restorative sleep has been reported [82, 94], they suggest a novel associations between sleep symptoms and diet/metabolism, potentially explaining associations between sleep and cardiometabolic disease. Singh et al. [95], supplementing OSA patients with vitamins E and C concluded that that antioxidant treatment (oral vitamin E and C) reduced oxidative stress in OSA patients. Furthermore, decreased levels of antioxidants (superoxide dismutase, catalase, glutathione and homocysteine, as well as vitamins E, C, B11 and B12) and lower performance on the neuropsychological tasks were observed in patients with obstructive sleep apnea [96]. The authors suggest that an imbalance between antioxidants and pro-oxidants may contribute to neuropsychological alterations in this patient population. In restless leg syndrome (RLS), vitamins C and E and their combination are used as safe and effective treatments for reducing the severity of RLS in hemodialysis patients [97]. Ascorbic acid and sodium-dependent vitamin C transporters (SVCT) have been shown to have important functions in the peripheral nervous system (PNS) [98].

10.6. Vitamin E

Vitamin E has active ingredients of tocopherols and tocotrienols. It exists in eight different natural forms, all of which have antioxidant properties When supplemented it may reduce damage to cell DNA and cell and it has neuroprotective effect on the brain. Vitamin E may stabilize peripheral blood circulation, suppressing abrupt deformation of vessels [99], acceleration of blood flow in vessels would increase the pressure of blood on the vessel walls, and subtle changes in vessel tension or shape might stimulate nerve fibres that are in anatomical proximity to the vessels [99]. Vitamin E normalized chronic sleep deprivation-induced reduction in the hippocampus GSH/GSSG ratio, and activity of catalase, super oxide dismutase (SOD), and glutathione peroxidase (GPx) [100]. Decreased levels of antioxidants and lower performance on the neuropsychological tasks were observed in patients with obstructive sleep apnea [10][1]. This study suggests that an imbalance between antioxidants and pro-oxidants may contribute to neuropsychological alterations in this patient population.During eight-year follow-up study to investigate the link between vitamin E, namely α-tocopherol, and memory disorders, it was found that higher total serum levels of vitamin E, and higher levels of γ-tocopherol, β-tocotrienol and total tocotrienols in particular, seemed to protect against memory disorders [102]. Their results show that the entire vitamin E family plays a role in memory processes. Accordingly, measuring the levels of vitamin E from serum is the most reliable way to determine whether they are sufficiently high. Limited research indicates that supplemental vitamin E may reduce symptom occurrence in restless leg syndrome [103].

10.7. L-carnitine and Sleep

Acetyl-L-carnitine (ALC) is a naturally occurring compound that facilitates the transport of fatty acids into mitochondria for β-oxidation [104]. Acetyl-L-carnitine can enter the brain, and the acetyl group helps form acetylcholine, an important neurotransmitter. L-carnitine enhances resistance to oxidative stress by reducing DNA damage in Ataxia telangiectasia cells [105]. Positive results were seen in carnitine supplementation in depression, dysthymia, mental and physical energy, with less fatigue, muscle pain, and sleep problems [106,107,108]. Muscle weakness and hepatic dysfunction can also been noted [109]. Supplementation of carnitine has also been shown to be a mood elevator in the elderly [110]. Acetyl L-Carnitine helps the brain form acetylcholine, a neurotransmitter needed for memory and thinking [111].

Evidence for the effectiveness of L-carnitine in attention deficit and hyperactivity disorder (ADHD) has been studied [112]. Other studies in animals and human have shown that a combination of acetyl-L-carnitine and alpha-lipoic acid reversed many of the signs of aging and restored both physical and mental vigor. Low levels of carnitine are associated with a higher frequency of fragmented wakefulness [113].

L-Carnitine has been demonstrated to be therapeutic for individuals with narcolepsy. A recent study investigated the contribution of a gene polymorphism found in narcolepsy called CPT1B, which is important in fatty acid oxidation [114]. They found that individuals with narcolepsy had very low levels of serum acylcarnitine [115]. L-carnitine was given (510 mg/day) to patients with narcolepsy it was revealed that total time for dozing off during daytime in narcolepsy patients, the primary endpoint, was significantly decreased by L-carnitine

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supplementation compared with placebo [114]. Although narcolepsy is a rather rare disorder, daytime sleepiness is not. It is possible that low levels of carnitine could be a cause of fatigue and daytime sleepiness. For example, low serum carnitine levels have been observed in patients with chronic fatigue syndrome (CFS) – a clinically defined condition characterized by severe disabling fatigue and a combination of symptoms, such as musculoskeletal pain, difficulty in concentration and sleep disturbances.

L-carnitine supplementation also increased serum carnitine levels and reduced serum triglycerides concentration indicating improvement in the burning of fat as energy. Other researchers found that ALC treatment reduced symptoms of depression in older people [116]. It also improved dysthymia, a milder form of depression, about as well as a common medication. Several studies show that ALC may help improve certain behaviours in boys with fragile X syndrome (FXS), such as their social skills and hyperactivity. The study has linked ALC with less pain or less-intense pain in people with nerve problems from these causes. ALC is a compound of great interest in various neurological disorders such as in treating Alzheimer's dementia, HIV-infection, diabetic neuropathies and aging [117,118,119,120]. A decrease of sleep disorders, a muscle discomfort, and of the prolonged fatigue after exercise has also been shown [121]. Carnitine supplementation could be helpful in mitochondrial disorders as the sleep problems are commonly reported in patients with mitochondrial myopathies [122,123].

11. Fatty acids

There is a growing consensus that omega-3 fatty acids are essential nutrients for humans. Much of the evidence is based on physiological measurements such as neurological development and visual acuity. To better understand why this class of polyunsaturated fatty acids is required, we must determine the biochemical basis for the essentiality. Of the eight fatty acids that comprise the omega-3 metabolic pathway, the two that are most likely to have essential biochemical functions are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

EPA can be converted to prostaglandins, thromboxanes and lipoxygenase products [124]. However, no essential role for these EPA-metabolites has been reported, and it seems unlikely that the formation of these products is the reason that omega-3 fatty acids are essential. When elevated amounts of EPA are available, the incorporation of arachidonic acid (AA) into cell phospholipids and its conversion to eicosanoid mediators is reduced. Thus, EPA acts as a competitive inhibitor of AA, and this probably accounts for some of the beneficial effects of omega-3 fatty acids in the treatment of cardiovascular and inflammatory diseases. While the possibility that EPA is essential in order to modulate the effects of AA cannot be ruled out, the amounts ordinarily present in the plasma and tissues probably are too low to competitively inhibit the actions of AA. Therefore, modulation of AA metabolism is more likely to be a pharmacological effect of omega-3 fatty acid supplements rather than an essential physiological function.

The basis for considering DHA as the biochemically essential omega-3 component is much more compelling. DHA is the most abundant omega-3 fatty acid in most tissues, and it is

present in large amounts in the brain and retina. DHA is the omega-3 fatty acid required for normal development of the nervous system and optimum visual acuity. Furthermore, when an omega-3 fatty acid deficiency exists, the body compensates by replacing it with the corresponding fatty acid of the omega-6 series, omega-6 docosapentaenoic acid (DPAn-6). These findings strongly suggest that DHA has an essential biochemical function. The most likely possibility is a membrane structural effect involving the packing of phospholipid head groups or the interaction of the lipid domains with membrane proteins. The lipids that contain the highest percentages of DHA are ethanolamine plasmalogen, phosphatidylethanolamine and phosphatidylserine. Therefore, it is likely that the function of DHA involves the metabolism, trafficking or physical properties of these phospholipids. Other possibilities that must be considered include the conversion of DHA to a lipid mediator, binding of DHA to a nuclear receptor that regulates gene expression, or formation of a DHA-centered free radical. It is thought that omega-3 fatty acids in fish oils may reduce inflammation of the brain and play a part in brain development and nerve cell regeneration [125]. However, there has been mixed evidence as to the benefits of omega-3 fish oils on the brain and whether they may protect against memory decline and dementia [126,127]. A combination of omega-3 fatty acid and vitamin B12 enriched diet may exert beneficial effects on synaptic plasticity and cognition, which may prove beneficial for mental health, particularly in preventing neurocognitive disorders [128].

A central question concerning the essentiality of omega-3 fatty acids is why DHA rather than the corresponding member of the omega-6 series, DPAn-6, fulfils this purpose. The usual Western diet contains 10-to 20-times more omega-6 fatty acid, and the same metabolic pathway is utilized by both fatty acid classes. One possibility is that DHA is utilized more efficiently than DPAn-6.

However, studies with neural cells in culture indicate that there is no appreciable difference in the uptake, retention or incorporation into phospholipids of DHA as compared with DPAn-6. While more detailed measurements may reveal a functional difference between DHA and DPAn-6, no such evidence is currently available. This suggests that DHA is utilized rather than DPAn-6 because it is more available to the tissues. Although the absolute amounts of these fatty acids in the plasma lipids are very small, there ordinarily is about five-times more DHA than DPAn-6. Furthermore, the main product formed by cultured astrocytes from omega-3 fatty acid precursors is DHA, whereas the main omega-6 product is AA. Astrocytes are the site where most of the polyunsaturated fatty acid precursors are elongated and desaturated in the brain. Thus, much more DHA than DPAn-6 appears to be available in the central nervous system [129].

11.1. Fish oils and omega-3 fatty acids

Polyunsaturated fatty acids (PUFA) are essential fatty acids in many mammals including humans. Both docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are omega-3 acids and they may also be obtained by eating fish oils. There is some evidence showing that a reduced amount of ingested omega-3 fatty acids is associated with fatigue, depression and problems of attention. [130-136] A sufficient amount of PUFA from food is necessary for health

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and well-being. Fatty fish is the best source of omga-3 acids. One hundred grams of salmon contains about 1000 mg of omega-3 acids and 100 grams of herring contains about 2000 mg. White fish meat contains much less of these essential fatty acids than fish with fatty meat. Omega-3 acids have been tested in the treatment of subjects with attention deficit disorder and in subjects with depression, female subjects with borderline personality, fatigue in multiple sclerosis, memory disturbances, dementia and some other neuropsychiatric diseases. Some randomized controlled studies have shown that omega-3 fatty acids may ameliorate mental functions, but they are also conflicting results. [130 – 137]

There is only little evidence showing that essential fatty acids may modulate sleep. In a small studied eight children. They were fed by total parenteral nutrition without essential lipids and seven other children who received a daily supplement of essential lipids in their parenteral nutrition. Slow wave sleep was significantly decreased in the group of children who did not receive fatty acids as compared to those who did. [138]No randomized clinical trials have been done in primary insomnia or in central hypersomnias.

12. Trace elements and sleep

Certain nutritional imbalances appear to influence sleep quality and play an important role in the maintenance of redox homeostasis:

12.1. Zinc

Zinc is an important cofactor for metabolism relevant to neurotransmitters, prostaglandins, and melatonin, and indirectly affects dopamine metabolism [139]. The role of zinc is thought to transduce oxidative stress and other signals converging at the production of nitric oxide into an specific intracellular response, suggesting an intriguing task of "signal transducer" [140]. It contributes to structure and function of brain [141], and low levels of zinc can cause a range of symptoms including hyperactivity and jitters [142]. Epidemiological studies on the influence of zinc/diet and lifestyle implications on degenerative disease and in particular on autism has been documented. Interestingly, antioxidant and micronutrients in the diet, such as zinc, influence the development and function of immune cells, the activity of stress-related proteins and antioxidant enzymes and help to maintain genomic integrity and stability [143, 144]. Zinc is included in many enzymatic processes. [145, 146] In CNS zinc is abundant in the so-called “zinc containing” synapses of glutamatergic neurons. Such neurons are located mainly in the prefrontal lobe. Frontal dysfunction may follow lack of zinc. On the other hand, bivalent zinc may cause excitotoxic damage. Also other minerals (e.g., magnesium, manganese) are important for proper functioning of the CNS. [145, 147, 148]

Zinc was shown to play a role in inducing the synthesis of metallothionein that acts as a scavenger of metals and free radicals [149]. It is necessary for 100 different metalloenzymes and metal–enzyme complexes [150], many of them in the central nervous system. Zinc supplementation of young children in low income countries improves their neurophy-

siological performance [151], also in combination with iron supplements [152]. Some behavioural abnormalities in adults also seem to respond favourably to zinc supplementation, such as mood changes, emotional lability, anorexia, irritability and depression [153]. All these physiological functions occur through the action of proteins involved in the regulation of zinc homeostasis, such as metallothioneins, which bind zinc with high affinity but, at the same time, release free zinc ions in response to oxidative/nitrosative stress to modulate the expression of zinc-dependent genes and to activate antioxidant enzymes and impact immune response [154].

12.1.1. Antioxidant properties of zinc

Zinc deficiency is difficult to evaluate due to the lack of sensitive and specific biomarkers [155]. Studies observed improved neurophysiologic performance, positive growth response, and significantly reduced mortality and morbidity with zinc supplementation in Chinese children [156]. Zinc effect on immune/inflammation responses has been reported [157]. It has been suggested that the bioavailability of zinc ion regulates the expression of pro-inflammatory cytokines and heat shock proteins such as IL-6, TNF-α and Hsp70 [158], and affects TH1/TH2 balance [159]. Several mechanisms could be involved in antioxidant function of zinc. One, zinc may protect protein sulfhydryl groups from oxidative modification by influencing the conformation and reducing potential of thiol groups. Since the sulfhydryl groups are required for the catalytic activities of several enzymes, zinc protects the enzyme's activity from oxidative inactivation.

Second, zinc may antagonize the activity of transition metals such as iron and copper. A number of studies have linked RLS to deficiencies of dopamine and iron. The disorder may result from inefficient processing of iron in certain brain cells [160]. A decrease in iron levels in the substantia nigra and, to a lesser degree, in idiopathic RLS patients was reported [161]. Ferritin levels were lower in cerebrospinal fluid, whereas transferrin levels were higher in patients with RLS compared to controls [162]. Connor et al. [163] found that receptors which help cells absorb iron are abnormally regulated in cells that produce the nerve-signaling chemical dopamine. Zago and Oteiza [164] showed that zinc may compete with copper and iron ions and prevent transition metal mediated oxidative modifications, and third mechanism for the antioxidant property of zinc is that zinc may reduce oxidative damage indirectly by modulating antioxidant defence including (a) enzymes which catalytically remove free radicals and reactive species, like superoxide dismutase, catalase, and glutathione peroxidase; (b) proteins which minimize the availability of pro-oxidants, like transferrins, ceruloplasmin and metallothioneins; (c) low-molecular-mass ROS and RNS scavengers, like glutathione, ascorbic acid, uric acid and alpha-tocopherol.

Antioxidant enzymes such as CuZn superoxide dismutase (CuZnSOD), glutathione peroxidase (GPX) and catalase are located in different cellular compartments and have different functions. Mice defective in CuZnSOD develop neurological damage and cancer at an accelerated rate as they age [165]. GPX-1 knockout mice are much more sensitive to paraquat toxicity than the wide type mice [166]. One human study done in a European

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population observed that the erythrocyte SOD activities were negatively associated with the plasma zinc concentrations, and positively associated with age. They also observed that the plasma catalase and GPX activities were similar among groups having different plasma zinc concentrations [158].

Zinc is one of the micronutrients involved in behavior, learning and mental functions. Zinc is necessary for proper immune function, and to create protein and DNA. The administration of nightly melatonin, magnesium, and zinc appears to improve the quality of sleep and the quality of life in long-term care facility residents with primary insomnia [167]. micronutrients such as zinc and magnesium may play a role in facilitating sleep. Zinc exhibits an antidepressant-like activity, as stated in a preclinical model of depression [168]. Significant clinical correlates were shown by Sowa-Kućma et al. [169] related to its action as an antagonist of the glutamate/N-methyl-D-aspartate receptor. Magnesium has beneficial effects on mood and is crucial, together with zinc, in the endogenous synthesis of melatonin [170].

Zinc is an essential bio-element, which plays a fundamental role in a wide range of biochemical processes. This metal is a major component of various proteins and is an important modulator of the mammalian immune and nervous systems [171]. Zinc is one of the mineral that has such a wide application in human health. A deficiency may result in sleep disturbances. Most sleeping pills, especially when taken over long periods of time, can have multiple side effects. Alterations of blood zinc homeostasis may accompany mood disturbances as well as affect functions of the immune system [172]. Recent data indicate that alterations in zinc (a natural modulator of amino-acidergic neurotransmission) homeostasis may contribute to mood disorders and may be involved in antidepressant-like actions in laboratory models [171].

12.2. Iron

Iron has an important role in many enzymatic processes. Sufficient iron in the CNS is necessary for normal functioning of the dopamine system. Iron has an effect on functioning of the dopamine receptors. Tyrosine hydroxlase regulates dopamine synthesis. Iron and tetrahydrobiopterin are cofactors of tyrosinehydroxylase. Iron is also linked to functions of GABA, serotonin and opidiod-peptides. In experimental cell cultures dopaminergic cells of the substantia nigra can be destroyed by chelation of iron by desferoxamine. Adding opioids in these cell cultures is protective. Iron also has a catalytic effect in oxidative mechanisms of the CNS and epilepsy [173]. Measuring serum ferritin and soluble transferring receptor from a venous blood sample allows estimation of tissue iron levels. In restless legs syndrome S-ferritin is often low, in which case, giving iron per os, or intravenously in more severe cases, should be part of the treatment.

In patients with RLS 45 μg/L is usually used as a limit when one should consider giving iron supplement even if hemoglobin is normal. Usually the soluble transferrin receptor values are also low. Iron should be gioven as Fe2+(bivalent iron) together with vitamin C to increase absorption of iron from the gut. If ferritin levels do not rise and the symptoms are bothersome

one might consider IV iron. Iron dextrane should be avoided because of potential risks but safe formulations exist, such as Venofer®. Several studies have already shown the benefits of IV iron starting from the early experiences from Sweden in the 1950's. [174, 175]

Yehuda has noted that in young children sleep disturbances, fatigue and possible learning disturbances may be related to iron deficiency early in life. These findings require further studies. [176] To determine if there is a relationship between low serum ferritin and sleep disturbance in children with autism spectrum disorder, an eight-week open-label treatment trial on 33 children with oral iron supplementation has been done. Seventy-seven percent had restless sleep at baseline, which improved significantly with iron therapy, suggesting a relationship between sleep disturbance and iron deficiency in children with autism spectrum disorder. Sixty-nine percent of preschoolers and 35% of school-aged children had insufficient dietary iron intake. Mean ferritin increased significantly (16 μg/L to 29 μg/L). It may be that children with autism spectrum disorder should be screened for iron deficiency. [177]

Kuhn et al. studied the effects of five days of sleep deprivation on the circadian rhythm of serum iron in a group of six healthy male volunteers. The results were compared with a control group of five individuals, whose normal sleep cycle was preserved, but whose daily regimen was otherwise identical with the sleep deprivation group. Their biorhythm was analyzed using cosinor analysis. Sleep deprivation markedly reduced the mean level of iron, diminished the absolute and relative amplitude of oscillations, disturbed the shape of the daily course of serum iron and gradually decreased the computative acrophase, i.e., shortened the period of rhythm. Forty-eight hours of recovery resulted in only a partial normalization of all the observed changes. The potential mechanisms of the observed changes are discussed. [178]

12.3. Copper

Copper acts as a cofactor in many enzymatic processes including ceruloplasmin, monoaminexidases, cytochromoxidase, and superoxide dismutase. The largest part of copper (96%) is binded into cerluloplasmin and ferro-oxidase, which is needed in many phases of iron metabolism. [179] Lack of copper can manifest as neutropenia, microcytic anemia, growth disturbances or slowing of erythropoiesis. Large amount of vitamine C, zinc, iron and cysteine worsen the absorption of copper from the gut. Menkes syndrome is an example of a genetic disturbance of copper metabolism causing deficiency of copper. Wilson's disease is an autosomal recessive disease that causes accumulation of copper in the liver and brain [180]. It is practically impossible to have too much copper from a normal diet. Lack of copper may follow poor diet or excessive consumption of zinc tablets.

12.4. Selenium

Selenium (Se) is a natural antioxidant which delays the oxidation of polyunsaturated fatty acids and preserves the elasticity of tissue [181, 182]. Se is an essential component of thioredoxinreductase and glutathione peroxidases, with strong antioxidative and antiinflam-

matory properties, and there is particular interest in the potential of Se to modulate oxidative stress and induce anticancer activity [183, 184]. Selenium is required for the production of certain prostaglandins which decrease platelet aggregation [185]. Selenium deficiency has been linked to adverse mood states [183]. Several lines of evidence have shown that selenium is crucially important in the maintenance and modulation of different brain functions. [186-189] Selenium may have some role in regulation of sleep and in development of insomnia as lack of selenium was statistically significantly associated with difficulty falling asleep in a recent large survey. [130]

Selenium supplementation together with other vitamins has been found beneficial in the treatment of mood lability [190, 191].In synergy with vitamin E, selenium promotes normal growth and fertility, and improves the function of certain energy producing cells [192, 193]. Also, selenium also plays a role in your immune system and thyroid function and may contribute to sleeping abnormalities. Infusion of selective inhibitors of PGDS, e.g., tetravalent selenium compounds, reversibly, time-and dose-dependently inhibited both non-rapid eye movement (NREM) and rapid eye movement (REM) sleep during the daytime [194], which shows that PGDS plays a crucial role in the regulation of physiological sleep. Selenium deficit may result in severe disorders [195, 196], including mood disorders. Gosney et al [197] reported the effects of micronutrient supplementation on mood in nursing home residents; selenium supplementation was directly correlated with decreases in depression scores and increases in serum levels. Supplementation with selenium resulted in reduced serum thyroid hormone T4 and increased serum thyroid hormone T3, suggesting that the additional selenium helped the rather boring T4 become the metabolically active T3. Effects of sleep deprivation (SD) and selenium (Se) on wound healing were studied [198], the number of fibroblasts and capillary vessels were higher in control and Se groups than in sleep deprivation groups, and the number of PNLs and the radiolabeled polyvalent IgG levels were higher in SD groups than in control and Se groups. OSA patients had lower concentrations of plasma Zn and erythrocyte Se [199]. Furthermore, the effect of selenium on restless leg syndrome treatment was studied [200, 201], selenium supplementation would be an alternative treatment in improvement of RLS symptoms.

13. In summary

Little is still known about the effects of different constituents of meals on sleep. There is evidence that a heavy lunch and rapidly absorbing carbohydrates enhance sleepiness in the afternoon. This may add to daytime sleepiness and for that reason they should be avoided when one wants to avoid fatigue. On the contrary, a light evening meal which is rich in carbohydrates may help one to fall asleep in the evening. The relationships between the enteric nervous system and CNS, and different roles of dietary nutrients and CNS need to be studied much more in the future.

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