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REVIEW

Sleep deprivation: A toxicogenic drive for neurodegenerative diseases and public health issue

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Abstract: Sleep deprivation is gradually becoming a common phenomenon in modern societies, especially among chronic users of social media, night shifts workers, students and some less-privileged populations. The erroneous perception among certain subgroups of the population that time spent to sleep is time wasted is of great concern, because sleep is indeed critical for good health and survival. Of greater concern are the effects of alcohol, beverages like caffeine, and environmental toxicants like heavy metals and pesticides, on normal sleep mechanisms. The consequences of sleep disorder are dire as it alters immune responses and have been reported to increase the risk of some non-communicable diseases. The inter-individual differences in sleep requirements may present a challenge in determining adequate sleep duration. On the average, most adults need about seven to eight hours of sleep each night while teens and children need more. Accumulation of sleep debt for individuals sleeping less than the required sleeping duration may lead to chronic health and behavioural problems. We opine that the mechanisms underlying sleep disruption by some foods and toxicants have toxicogenic link. There is need, therefore, to consider sleep deprivation as a public health issue with a view to ensuring proper advocacy among risk groups in order to improve quality of life and economy of nations. Given the prevalence of alcohol and caffeine consumption, exposures to heavy metals and pesticides, and increasing neurodegenerative disorders, there is need to elucidate the precise mechanisms of sleep disruption and exposures to the aforementioned chemicals.

Keywords: environmental toxicants, neurodegenerative diseases, public health, sleep deprivation, toxicogenic drive

1 Introduction

Sleep is generally defined based on the physiological characteristics observed in mammals including reduced body movement and electromyographic activity, reduced responsiveness to external stimuli, closed eyes, reduced breathing rates, and altered body position and brain wave architecture assessed by polysomnography. Sleep could, therefore, be said to be a complex biological state characterized by behavioural, physiological, and electrophysiological parameters. Two mechanisms have been reported to underlie the sleep regulation: the neurophysiological, and biochemical mechanisms (homeostatic nature of sleep). In this opinion presentation, the indications for sleep deprivation as a toxic-mediated neurodegenerative process and need to consider it as a public health issue are examined. It will also examine the mechanistic interplay between sleep and some foods and toxicants.

Ramon y Cajal first speculated that neurons release signaling molecules that are involved in physiological functions [1]. Excitatory neurotransmitters (examples: acetylcholine, dopamine, norepinephrine, histamine, serotonin, hypocretins [orexin], neuropeptide S and glutamate), typically enhance arousal or wakefulness, and hypocretin is recognized as a sleep regulatory molecule located in the hypothalamus [2, 3]. Hypocretins in the hypothalamus have also been found to regulate feeding behavior [4]. These molecules stimulate and maintain wakefulness, in part, through stimulating the release of wake-promoting neurotransmitters including norepinephrine, dopamine, acetylcholine, and histamine [5]. Hypocretins activate the G-protein coupled receptors: hypocretin receptor 1 and hypocretin receptor 2 (orexin 1 and 2 receptors respectively). The hypocretin receptors are activated, in part, through phospholipase C and Ca^{2+}-dependent and Ca^{2+}independent pathways to activate protein kinase C, protein kinase A, and mitogen-activated protein kinase (MAPK) signaling pathways, all of which are inflammatory and metabolic pathways that affect sleep/wakefulness. Enhanced wakefulness activates the hypocretin 1 receptor, further supporting the role of hypocretins in promoting wakefulness. Moreover, hypocretin antagonists inhibit arousal. Neurons that produce hypocretins also co-express multiple receptors, including glutamatergic receptors [6], adenosinergic A1 receptors [7],

muscarinic M_3 receptors [8], and serotonergic 5-HT_{1A} receptors [9]; thus, allowing hypocretin the ability to induce changes in sleep-wake states.

Gamma amino butyric acid (GABA) is one of the well-characterized neurotransmitters that is known to induce sleep and slow wave activity (SWA), which occurs, in part, through its ability to modulate the neuronal release of excitatory neurotransmitters including glutamate, acetylcholine, norepinephrine, and hypocretin [3]. To produce this effect, GABA functions to largely inhibit the activity of glutamatergic neurons and their respective receptors, thus enhancing non-rapid eye movement (NREM) sleep. Glutamate is present in most neurons and, acting as an excitatory neurotransmitter through either the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) or N-methyl-D-aspartate (NMDA) receptor, predominantly promotes arousal and inhibits sleep. Gamma amino butyric acid acts on both ligand-gated ion channel complex GABA-A receptors, and G protein-coupled GABA-B receptors. Both GABA-A and GABA-B receptor antagonists enhance wakefulness, while GABAergic receptor agonists promote NREM sleep. Moreover, well-known GABA-A receptor agonists, including benzodiazepines, barbiturates, imidazopyridines, and cyclopyrrolones, enhance NREM sleep [10].

Substance P is a neuropeptide that is derived from the preprotachykinin A gene, which is produced by many cell types including neurons and microglia [11]. It acts primarily through the neurokinin-1 (NK-1) receptor (also called tachykinin receptor 1) and is found throughout the body including the central nervous system, peripheral nervous system, pulmonary tissue, and immune and vascular endothelial cells [12]. Substance P regulates SWA and possibly sleep duration [13]. Its release is well-known to induce cytokines like interleukin-1beta (IL-1β) and tumor necrosis factor-alpha (TNF-α), that enhance sleep duration and SWA [14, 15]. Neurokinin-1 receptors have also been found to be co-expressed on cortical sleep-active neurons that express neuronal nitric oxide synthase (nNOS), whose activity is positively correlated with change in SWA [16, 17]. Moreover, injections of substance P fragment 1,7 enhance SWA locally in the cortical hemisphere where the substance was applied, and NK-1 receptor antagonists attenuated SWA locally, indicating that substance P and the NK-1 receptor regulate SWA [13].

2 Sleep deprivation

Sleep deprivation occurs when an individual fail to get enough sleep. The latest guidelines published by the National Sleep Foundation in United States of America recommend that adults (18-64 years) obtain 7-9 h of sleep per night, teenagers (14-17 years) 8-10 h per night and school-aged children (6-13 years) 9-11 h per night [18]. The recommendation also recognizes the inter-individual variability in sleep need and suggested that for some adults, as little as 6 h may suffice, while others may require 10-11 h. Sleep deprivation is known to lead to significant decrements in cognitive function, including lapses of attention, alertness, vigilance, and the speed of cognitive and psychomotor responses [19]. Laboratory studies have shown that a deficit in nocturnal sleep of as little as 90 min for just one night can lead to a reduction of daytime objective alertness by one-third [20]. Sleep deprivation can be caused by voluntary behaviours, personal obligation, work hours and medical problems. Risk groups include male and female of all ages, adolescents, caregivers and individuals having sleep disorders [21]. Of special interest among these risk groups are the occupationally-exposed individuals; a group that cuts across many workers, including the healthcare workers. Beyond the excessive daytime sleepiness that is usually experienced after sleep deprivation, both acute and chronic sleep deprivations have been implicated in neurodegenerative diseases, especially Alzheimer's, and other non-communicable diseases.

For more than 25 years now, sleep disorders have been associated with Alzheimer's disease, with about 25-66% of the patients that exhibit sleep disturbances being considered one of the leading causes of patient institutionalization [22]. With the growing interest in the preclinical stage of Alzheimer's disease, however, the role of sleep in association with Alzheimer's disease has radically changed. Sleep changes occur many years before the appearance of cognitive symptoms, together with the early pathophysiological events. The presence of sleep disturbances, since the preclinical stage of the disease, underlines a possible crucial role of sleep in Alzheimer's disease pathology and progression. This growing interest in the preclinical stage of Alzheimer's disease has led researchers to identify modifiable risk and predictive factors useful to design early intervention strategies [23]. The preclinical stage of Alzheimer's disease has been found to be characterized by β-amyloid (Aβ) aggregation into amyloid plaques and tau phosphorylation, and aggregation into neurofibrillary tangles. Also, evidence has lent support to the notion that sleep-related disorders like insomnia, excessive daytime sleepiness, sleep-disordered breathing, and circadian sleep–wake alterations all seem to increase the risk of Alzheimer's disease. Sleep disorders modify the activity of some neurotransmitters that could cause consequent dysfunction of the "default mode network", which has a crucial role in the pathophysiology of Alzheimer's

disease [24].

3 Interactions between sleep and some foods and toxicants

Generally, toxicants tend to affect normal sleep mechanisms by disrupting sleep initiation or duration. Some of the foods and toxicants that have been shown to affect normal sleep mechanisms include alcohol, caffeine, some heavy metals, pesticides, phthalates, polyaromatic hydrocarbons, polyfluoroalkyl compounds, among others. These toxicants interact with sleep via various mechanisms.

3.1 Alcohol

Preclinical studies have provided some understandings as to how alcohol may mingle with the sleep-wake system. The molecule, adenosine has been reported to be involved in the pathophysiology of both sleep disorders and chronic alcoholism [25]. Administration of alcohol tends to induce an increase in extracellular adenosine level in some regions of the brain, thus leading to increased inhibition [26]. Cell culture studies, on the other hand, indicate that acute alcohol intake inhibits transporter-mediated (equilibrative nucleoside transporter 1, ENT1) reuptake of adenosine. Animal studies with rodents propose that alcohol induces dose-dependent adenosine accumulation in the basal forebrain which inhibits wake-promoting neurons [27]. Downregulation of both ENT1 and adenosine A_1 receptor expression in the basal forebrain has been demonstrated during acute withdrawal following development of alcohol dependency [26, 28, 29]. During alcohol withdrawal, insomnia has been noted to be due, in part, to reduced inhibition of basal forebrain wake-promoting neurons disrupting sleep homeostasis. Thus, acute administration of alcohol enhances inhibition by increasing GABA activity and decreasing glutamate activity possibly mediating some of the sedative properties [30, 31]. It has been proposed, therefore, that inhibition of wake-promoting neurons through activation of $GABA_A$ receptors is the underlying mechanism of increased nonrapid eye movement (NREM) sleep resulting from acute alcohol consumption, while decreased REM sleep may be due to the activation of $GABA_B$ receptors and/or inhibition of kainate receptors on brainstem cholinergic cells [32].

Ingestion of moderate amount of alcohol before bedtime has been found, by laboratory studies, to be usually associated with decreased sleep latency, increased NREM sleep, increased total sleep time, and reduced or fragmented REM sleep, which leads to decreased sleep efficiency [27,30,31,33]. This is followed by rebound increases of REM sleep on the following nights [34]. Likewise, another study that examined associations between daily alcohol use and each night's sleep found a positive association with sleep duration and a negative association with sleep quality [35]. The most common problems of chronic alcohol use include increased sleep latency, poor sleep quality and daytime sleepiness. These problems, often, will persist through withdrawal but resolve after protracted abstinence [36]. In essence, the effects of alcohol on sleep have detrimental socio-economic consequences, as alcohol-related sleep problems have been reported to account for about 10% of the annual costs related to alcohol use disorders [37].

3.2 Caffeine

Caffeine (1,3,7-trimethylxanthine) is a central nervous system stimulant and the most widely consumed psychoactive substance, being consumed by about 80 % of the world's population [38, 39]. It is readily available in coffee and other foods and beverages, and used to mitigate sleepiness and enhance performance. Acute caffeine intake can delay sleep initiation and reduce sleep intensity, particularly when consumed in the evening. The sleep-disrupting effects of caffeine are mainly attributed to its influence on the homeostatic component of sleep-wake regulations. Sleep homeostasis describes the increase in sleep pressure during time awake and its dissipation during the following sleep episode, which has been suggested to be related to rising and decreasing concentrations of adenosine [40]. Caffeine is an adenosine receptor antagonist, blocking the A_1 and A_{2A} adenosine receptors in the central nervous system [41], and may, thus, attenuate the increase in sleep pressure during wakefulness and lead to delayed sleep initiation and more superficial sleep [42]. The effects of caffeine intake on sleep are known to be dependent on the timing of its consumption. Caffeine, taken in the evening hours, tend to prolong sleep latency [43–45], reduces total sleep time (TST) [43, 45, 46], shortens deep sleep [43–46], and decreases electroencephalographically (EEG)-derived slow-wave activity (SWA), while activity in the sigma range is increased [43]. Recent finding has shown that daily caffeine intake in the morning and afternoon hours does not necessarily impair nighttime sleep structure nor subjective sleep quality in healthy good sleepers who regularly consume caffeine.

The reduced EEG power density in the sigma range might represent early signs of overnight withdrawal from the continuous presence of the stimulant during the day [47].

3.3 Heavy metals

3.3.1 Lead

Lead toxicity is one potentially important but understudied biological factor that could be related to sleep disturbance [48]. Exposure to Pb is known to be associated with hyperactivity and insomnia. However, occupational exposure to Pb among workers has been reported to be associated with self-reported sleep disturbances [49]. Kordas *et al.* reported that blood lead levels (BLL) $\geq$ 10 μg/dL were associated with later waking time and decreased sleep duration in 550 Mexican children aged 6–8 years old [48]. According to Liu *et al.*, elevated BLL in early childhood are associated with increased risk for sleep problems and excessive daytime sleepiness in later childhood [50]. The mechanism by which Pb exposure could cause sleep problems is not yet elucidated. However, Pb is a well-known neurotoxin that damages, destroys, or impairs the function of the developing nervous system in multiple ways, including reduction in brain plasticity, disruption of the blood-brain barrier, negative alterations in cellular concentration of calcium, and induction of oxidative stress [51, 52]. Lead exposure can result in disruption and dysregulation of some neurochemicals like serotonin [53], which contributes to negative psychological and physical outcomes with prolonged exposure, including sleep problems [54]. Dysregulation of catecholamines can increase the likelihood of depression and panic disorders which are associated with poor sleep [55]. Also, environmental lead exposure can cause oxidative stress, which has also been linked to sleep disorders such as sleep apnea [53,56]. Excessive daytime sleepiness (EDS) has been characterized in patients exhibiting obstructive sleep apnea syndrome [57]. Thus, Pb exposure-induced oxidative stress could be a mechanism linked to sleep problems such as EDS among children with BLL $\geq$ 10 μg/dL, with other mediating factors including neurobehavioral impairments, which have been found to be both a consequence of Pb toxicity and correlated with sleep quality [58, 59].

3.3.2 Mercury

Joannes Antonius Scopoli first described Hg poisoning in Venice in 1761. He recognized difficulty in sleeping, restless sleep, dream disturbances, and restless leg syndrome, and thus identified sleep disorders as a prominent sign of Hg toxicity [60]. Mercury accumulation has been shown in the pineal gland, which participates in circadian function through the secretion of melatonin and serotonin [61]. Arito and his colleagues showed that methylmercury exposure resulted in circadian sleep-wake disruption in rats [62]. Mercury exposure also results in changes in cytokine production. In children, mercury exposure has been found to be associated with reduced levels of TNF-alpha and shorter sleep duration [63]. One possible mechanism of sleep disruption by Hg is the effect on glutamate, which results in increased extracellular glutamate and a possible excitotoxic effect [64].

3.3.3 Arsenic

Low level of arsenic exposure has been associated with sleep disturbance in copper smelter workers [65]. Also, long-term poisoning with As was later found to cause sleep disorder in children [66]. Shiue recently found that higher levels of urinary arsenic were associated with wake-up at night and leg jerk while sleeping [67]. However, the biological mechanism of As disruption of sleep is not yet confirmed.

3.4 Pesticides

Exposure to pesticides, especially 2,4,5-trichlorophenol, was found to influence idiopathic REM sleep behaviour disorder in older adults [68]. In male mice, pesticides exposure seemed to reduce sleep time [69]. Using the United States National Health and Nutrition Examination Surveys' (2005–2006) national representative human sample, 2,5-dichlorophenol and 2,4-dichlorophenol were shown to have borderline associations with leg cramps in sleeping [67].

The mechanisms linking pesticides and sleep disorders are not yet elucidated.

4 Public health perspectives of sleep deprivation

Xie *et al.* showed that the restorative effect of sleep is as a result of the removal of neurotoxic waste products, especially amyloid protein, during sleep [70]. In line with this observation, Ju *et al.* [71] tested whether β-amyloid deposition in preclinical Alzheimer's disease, prior to the appearance of cognitive impairment is associated with changes in quality and quantity of sleep. The results from 142 cohorts suggest that poor sleep may increase the risk of the Alzheimer's disease. Further studies among 22 healthy participants showed that sleep deprivation increases

amyloid-β, thus suggesting that chronically disrupted sleep may promote amyloid plaques and other downstream Alzheimer's disease pathologies including tauopathy or inflammation, thus making sleep deprivation a public health issue [72]; an observation that has been corroborated by recent study correlating one-night sleep deprivation to amyloid-β burden [73]. Sleep deprivation has also been associated with some chronic conditions like type-2 diabetes, heart diseases, elevated blood pressures, increased metabolic changes and risk for depression. The link between sleep deprivation and these conditions may be due to oxidative stress or other toxicity pathways. Villafuerte *et al*. [74] reviewed 44 research articles and concluded that sleep deprivation promotes oxidative stress in animal models. Recent observation in humans has also implicated oxidative stress in sleep deprivation as Trivedi *et al*. [75] and Jowko *et al*. [76] have shown that acute sleep deprivation results in redox-based global DNA methylation changes in human plasma samples with low level of antioxidant defenses. Also, Teixeira *et al*. [77] confirmed that sleep deprivation in night shift workers lowers antioxidant defenses and increase lipid oxidation and muscle damage. These growing evidences supporting the negative impact of sleep deprivation present a task to public health professionals.

5 Conclusion

Sleep acts as a garbage collector that removes the waste products like β-amyloid and tau proteins, which are left by the brain, by night. These waste products tend to accumulate in the brains of Alzheimer's disease patients, indicating that they play a role in neurodegenerative disorders. It has now been discovered that these toxic by-products are flushed out in waves by cerebrospinal fluid during the slow-wave sleep phase. Sleep deprivation may thus lead to increase in the accumulation of these waste products and consequently contribute to neurodegenerative disorders like Alzheimer's disease and mental illnesses among vulnerable individuals. In the opinion of the authors, the mechanisms underlying the disruption of normal sleep by toxicants have some toxicogenic association. Given the wide range of risk groups involved, it is opined, herein, that sleep deprivation be considered a public health problem, since getting enough sleep is a preventive therapy for many diseases. Mitigating the adverse effects of sleep deprivation is a collective responsibility and should be of public health concern considering the economic importance of its consequences. We recommend, therefore, that efforts be intensified towards reducing exposures to sleep-disrupting chemicals like alcohol, caffeine, lead, mercury and pesticides, among others, as means of improving sleep. Further research into the precise biological mechanisms however, is advocated.

Conflict of interest

The authors declare there is no conflicts of interest.

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