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Neurochemicals and Behavioural Alterations in Sleep Deprivation: A Revisit

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Abstract

Sleep is an invigorative biological process which cannot be defined as such, but is organized through intricate interactions between various brain regions and neurochemistry. Sleep endures physical and cognitive performance, health and well-being; even mild sleep restriction degrades behavioural performance over a few days. Sleep deprivation (SD) leads to an array of disorders such as cognitive dysfunctions, attention deficits including coordination and concentration. A decrease in the cortical sensitivity to an incoming stimuli leads to defect in attention. Also sleep deprivation leads to elevated levels of excitatory neurotransmitters and abnormalities in certain other neuromodulators which ultimately has effects on neuronal and executive functions. Inspite of wide-cut literatures availability on the neurochemical deviations following sleep deprivation, this review focuses on the major neurotransmitters effects leading to behavioural alterations and the concomitant brain region activities.

Keywords: Sleep; Sleep deprivation; Neurotransmitters; Cognition; Behaviour; Neurobiology

Introduction

Sleep comprises almost one-third of human life and is common to all animal species, yet its impact on health and medical conditions remains unknown [1]. Sleep should be viewed in the context of other forms of "adaptive inactivity" and is subdivided into rapid eye movement (REM) sleep, characterized by high-frequency electroencephalogram (EEG) recordings and muscle atonia and non - REM (NREM/slow-wave) sleep, characterized by low frequency EEG recordings and body rest [2,3]. What is most remarkable about sleep is not the impassiveness or vulnerability it creates, but rather its ability to reduce activity and the body and brain metabolism [4]. The quality of life, performance, and mental well-being are all adversely affected by even a single night's loss of sleep. Sustained sleep deprivation (SD) impairs central thermostat, metabolism and immune functions, and leads ultimately to death. Accumulated sleep pressure caused by prolonged wakefulness can impair cognitive function [5]. SD is prevalent in various occupations and individuals including shift workers, medical personnel, military, children who do not have regular sleep cycles, and individuals with sleep disorders. SD in human is broadly classified into three categories: total sleep deprivation (TSD), partial sleep deprivation (PSD) and sleep fragmentation. TSD is the complete lack of sleep for at least one night and often longer. PSD involves restricted sleep for multiple nights, that is, individuals obtaining an inadequate amount of sleep for several consecutive nights. Sleep fragmentation is repeated awakenings from sleep throughout the night. This result in a decreased amount of sleep but a normal time spent in bed [6].

Empirical reports on neurophysiological and biochemical methods explain the fundamental mechanisms underlying sleep regulation. Neurophysiological methods helped in identification of circuits involved in NREMS regulation, such as corticothalamic projections and the hypothalamic ventrolateral preoptic and median preoptic circuits, and the REMS regulation, such as laterodorsal tegmental nucleus. Satisfactory explanations of how these circuits impose sleep on the brain and how they keep track of past sleep–wake activity likely will involve the biochemical mechanisms that interact with these circuits [7]. The control mechanism of sleep are established at every level of biological organization, from genes and intracellular mechanisms to networks of cell populations, and to all central neuronal systems at the organismic level, including those that control movement, arousal, autonomic functions, behaviour and cognition [8]. Experimental data have shown that many brain regions possess specific functions in sleep at its each structural level. Strong evidences suggest that sleep is homeostatically regulate, it possess beneficial effects on cognitive functions and it helps in memory consolidation and desaturate the ability to learn [9-13].

This review focuses on the consequences of chronic sleep restriction on brain vulnerability, with characteristic emphasizing on systems that have been associated in psychopathology. Literatures suggest that deprivation in sleep increases the risk to develop psychopathology, although the mechanisms underlying this effect are largely unknown. Loss of sleep could increase the risk for psychopathology acting on various neurobiological systems. The review focuses on the effects of sleep loss on neuromodulatory effects leading to behavioural alterations and the concomitant brain region activities.

Sleep Deprivation and Neurotransmitters

The most conspicuous changes that occur during sleep loss are the neuromodulatory transitions and effective control of these transitions is critical for fitness and survival. In the brain, activity of neuromodulatory neurons, grouped within nuclei of the midbrain and brainstem, co-varies with the psychological and physiological factors, thereby mediating behavioural state in the central nervous system. This is how cognitive processes, including focused attention, learning,

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memory, and even perception are impacted by the behavioural state [14]. The subcortical neuromodulatory circuits involved in sleep-wake control also play important roles in the regulation of arousal and attention, and malfunctioning of these circuits causes a variety of cognitive impairments.

The ascending activating reticular system (ARAS) projecting to the thalamus, hypothalamus, basal forebrain, and neocortex in the brain are the critical regions in sustaining wakefulness and responsible for cortical activation. This ascending system of brain comprises the major brain neuromodulatory systems – acetylcholine (ACh), dopamine (DA), norepinephrine (NE), and serotonin (5-HT)-all but DA are under strict regulation across the sleep cycle. In waking, these neuromodulators are released at high levels, activating the inositol triphosphate/diacylglycerol (IP_3/DAG) and cyclic AMP second-messenger systems, thereby reducing neuronal K^+, causing neurons to be tonically depolarized [15]. In REM sleep, this same result is achieved by release of acetylcholine alone, as release of serotonin and norepinephrine in REM sleep is minimal [16-18]. In non-REM sleep, these neuromodulators are all released at relatively low levels, and hence neurons are relatively hyperpolarized in this state.

Cholinergic System

Acetylcholine (ACh) is a fast-acting, steeplechase cholinergic neurotransmitter present at the neuromuscular junction and in the autonomic ganglia [19]. Pontomesencephalic tegmentum projection, laterodorsal tegmentum, medial habenula, thalamus, hypothalamus and the basal forebrain (BF) complex including the medial septum contains ACh -containing neurons [20-23]. These cholinergic neurons apart from its role in wakefulness have been included in control of much wake-promoting behaviours such as attention, sensory procession and learning. It was found that behaviourally pertinent signals from the sensory inputs induce a transient increase in the PFC ACh levels and the subsequent activation of cholinergic transmission improves the performance of sustained attention task [24].

ACh changes the neuronal excitability, influences synaptic transmission, induces synaptic plasticity, and coordinates firing of groups of neurons. ACh signals through two classes of receptors: metabotropic muscarinic receptors (mAChRs) and ionotropic nicotinic receptors (nAChRs) [25,26]. Inhibition of cholinergic nuclei resulting in reduced cortical levels of ACh is a major effect caused by SD. SD discharges these Ach-containing neurons which fires at lower rate during slow wave sleep and at higher rates during paradoxical SD [27]. Ninety-six hours of REM sleep deprivation increases acetyl cholinesterase in the pons, thalamus, and medulla oblongata, but not in other brain regions including the hippocampus. It is important to note that the pons contains cholinergic cells involved in the generation of REM, while the thalamus and medulla oblongata receive cholinergic input from the pons. The higher levels of acetyl cholinesterase suggest that there is a higher turnover of acetylcholine in these regions as a consequence of SD [28].

Empirical reports on neurotoxin induced lesions on FB cholinergic neurons further edify the pivotal role of ACh in learning and memory tasks which showed that decrease in ACh leads to certain behavioural deficits. Experimental studies for cognition involving locomotors activation showed correlation between levels of ACh and motor activity. The cholinergic neurons are also highly active during REM sleep [29-31]. The descending projections from cholinergic neurons in the brainstem inhibit motor neurons producing atonia. ACh improves cortical plasticity in adult mammals, and has been suggested that ACh may modulate molecular mechanisms of memory consolidation [32].

The role of ACh in learning and memory has been reviewed by Hasselmo [33]. It was proposed that high ACh biases the system for memory encoding, while low levels bias the system towards recall. ACh levels in the hippocampus are significantly greater during REM than during wake, while neocortical levels are similar in the two states. High levels of ACh release block K^+ channels, depolarizing membrane potential and increasing membrane resistance. Impairment of attention which is vital for almost all the cognitive processes occurs due to SD and this neuromodulator is especially linked to vigilance and attention [34]. Sustained attention otherwise termed as vigilance refers to constant allocation of processing resources for detecting an important event. Diminishment in the process of sustained attention performance is widely thought out to be the most sensitive and simple way of measuring behavioural deficit produced by sleep disruption [35]. Hence, sustained attention impairments are widely used as an indirect measure of sleepiness.

ACh has impact on synaptic plasticity and dynamics of local circuits through astrocytic control of synaptic Ca^{2+} concentration following nAChR stimulation [36]. Astrocytic signalling can lead to LTP as a result of the temporal coincidence of the postsynaptic activity and the astrocyte Ca^{2+} signal simultaneously evoked by cholinergic stimulation [37]. Receptor expression studies have indicated that REM sleep deprivation reduces muscarinic M2 cholinergic receptors in the pons and hippocampus [38]. The prominent role of cholinergic system in selective attention was well shown by the effects of attention and activation of forebrain. The activation of basal forebrain causes decreased interneuronal correlation and increased sensory – driven response dependability in the visual cortex. This decline in the cortex interneuronal correlation was found to be mediated by mAchRs whereas the improved visual response was found to be mediated by nAChRs-dependent amplification of thalamocortical transmission and/ or mAChR-dependent firing rate increase within the cortex [39-41]. Further reports by Parikh et al. suggests that cholinergic transmission can be regulated in a task dependent manner add up the credibility of its involvement in attentional modulation.

Serotonergic System

The Serotonergic system is subtle to sleep loss and serotonin (5-hydroxytryptamine, 5-HT), play a possible role in sleep deprivation. Extracellular 5-HT levels are highest in waking, lower in SWS, and lowest in REM sleep, in all brain regions, including the frontal cortex and the hippocampus [42-44]. Anti-depressant studies showed dysfunction of serotonin and that most antidepressant drug therapies are thought to act by increasing serotonergic neurotransmission [45]. Altered intracellular and extracellular 5-HT concentration during development and adulthood periods lead to increased anxiety and stress-related behaviours. [46,47]

5-HT possess a multifaceted system of different receptor subtypes, through which it is involved in the regulation of emotional, neuroendocrine, cognitive and motor functions in the central nervous system (CNS) [48-50].The localization of serotonin receptors in central motor-related centers also suggest that they are involved in locomotors activity, probably by modulating the release of neurotransmitters such as γ- amino butyric acid (GABA) from striatal neuron terminals [51]. Both depotentiation and habituation to an environment where inhibited by 5-HT agonist application [52]. 5-HT agonist application also improved acquisition but impaired memory consolidation [53].

In a study by Toru et al. it was observed that the tissue concentration of 5-hydroxyindoleacetic acid (5-HIAA), the principal 5-HT metabolite was elevated in the dorsal raphe nucleus and thalamus of rats that were deprived of sleep for 24 h. SD also enhances the serotonin turnover and decreases serotonin transporter binding in some brain areas. Furthermore, total sleep deprivation in cats increases mean firing rates of serotonergic neurons in the dorsal raphe nucleus by 18% [54-57]. The effects of chronic sleep loss on the serotonergic neurons are not well known; however, chronic sleep restriction in animals has been shown to cause a gradually developing desensitization of the Serotonin-1A receptors (5-HT_{1A}) [58,59]. It has been suggested that this effect could be the result of the repeated stimulation of these receptors due to an enhanced serotonin release. The increased serotonin release during SD occurs in a manner independent of stress [60]. The spontaneous activity of serotonergic neurons throughout the brainstem is strongly dependent on the behavioural state. Serotonin also inhibits cholinergic transmission in basal forebrain (BF), thereby creating sleep homeostatic pressure in the BF [61].

Among its different 5-HT receptors, 5-HT_1 and 5-HT_2 types are the ones studied most in relation to vigilance. Reduced serotonergic transmission and reduced sensitivity of the 5-HT_{1A} receptor system represent a potential pathway through which sleep loss may alter neuronal plasticity and enhance the sensitivity to neurodegeneration. Desensitization of 5-HT_{1A} receptor caused due to chronic sleep deprivation leads to neurodegeneration [62]. Literatures show that both metabotropic and ionotropic 5-HT_{1A} receptors are involved in learning and memory as well as in a wide array of cognitive disorders and emotional dysregulation [63-65]. Mice lacking the 5-HT1A receptor have been shown to have increased anxiety, as shown by decreased time in the open arms of the elevated plus maze test [66]. 5-HT_2ARs are found in the cortex and basal ganglia, and mediate certain behavioural syndromes. 5- HT_2 receptors (A, B and C subtypes) activate phospholipase C (PLC), and can be considered excitatory. Out of these three subtypes 5- HT_2C receptor plays an important role in regulation of synaptic plasticity, as it activates the phosphor-inositol signalling pathway thereby leading to L-type Ca^{2+} channels opening following release of calcium stores. These data suggest a role of serotonin in the effect of sleep deprivation. In addition to this, 5 – HT is also implicated in a variety of behaviours including hunger/feeding, aggression, anxiety and mood.

Noradrenergic System

Norepinephrine (NE) is one of the main neurotransmitters involved in arousal. Being an initiator for maintaining sustained periods of alert waking, the noradrenergic system could be a suitable and prospective target in the treatment of sleep-wake disorders. Lateral hypothalamus, basal forebrain and the cerebral cortex comprises noradrenergic neurons. Neurons of the brainstem nucleus locus coeruleus are the sole source of noradrenaline, a neuromodulator that has a key role in all of these forebrain activities such as sleep – wake cycle and other stress responses [67].

NE levels increase early in both total and REM sleep deprivation. NE can enable various forms of activity-dependent synaptic plasticity and can stimulate gene transcription. NE seems to be essential for working memory and focusing of attention [68,69]. Finally, there is a growing body of evidence from rodent, primate, and human studies that the LC-noradrenergic system plays an imperative role in attentional shifting and behavioural flexibility [70-74]. It was shown in a recent study that the LC noradrenergic neurons during NREM sleep possess increased firing rates which in turn enhance synaptic plasticity and facilitate memory consolidation [75,76].

Dopamine β-hydroxylase knockout (Dbh -/-) mice lacking NE showed altered sleep and arousal patterns. They show decreased latency to sleep after stress, require stronger stimuli to wake them after sleep deprivation, and have increased overall sleep, in a 24 h period [77-79]. REM SD exhibited a considerable decline in single – unit activity of noradrenaline in cat and concentration of noradrenaline in rat when measured in locus coeruleus (LC) [80,81]. Noradrenergic neurons are tonically active in all states except REM sleep. They influence synaptic excitability and plasticity and fall uniquely silent during REM sleep.

The decrease or absence of NE due to SD leads to depotentiation, and either stimulation of the noradrenergic cells of the locus coeruleus (LC), or direct intracerebroventricular application of NE enhances and prolongs LTP [82]. A longer REM SD (72 h) led to an elevated noradrenaline concentration and turnover in the rat LC [83,84]. Furthermore, the waking-induced expression of transcription factors and neurotrophins in rat cerebral cortex, which depends on noradrenergic input, is maintained during 3-8 h of total SD [85].

The LC-NE system plays a prominent role in the regulation of immediate early genes (IEGs); genes which is up-regulated selectively during short (3 h) period of wakefulness. Systemic administration of α_2 noradrenergic receptor antagonist or direct infusion of NE increases the NE level with subsequent increase in IEGs such c-fos, nur77, tis-7, tis-21 and zif-268. This suggests that the LC-NE system by regulating the IEGs, plays a perceptible role in the regulation of long-term plasticity and behavioural plasticity of forebrain circuits [86,87]. The correlation between sustained attention (vigilance) and forebrain activity patterns is measured in terms of EEG and it might be drawn to a conclusion that the relationship between EEG and forebrain activity pattern would have curtailed from the modulatory actions of LC-NE [88]. An increased level of NE was found in response to stressors such as alarming, threatening or even noxious. Similarly the crucial role of LC-NE system in behavioural and EEG indices of waking are well documented by suppression of LC neuronal discharge activity and NE activity which is caused by systemic administration of α_2 agonist [89,90].

Dopaminergic System

Dopamine acts as a key neurotransmitter which plays a pivotal role in regulation of motor and limbic functions. Experimental reports show evidence that dopamine (DA) modulates wakefulness exerting a wake promoting action. An increased level of DA was observed during waking as well as in association with behavioural arousal [91]. Empirical reports also suggest that the mesolimbic dopaminergic (ML-DA) reward system is activated during sleep. Neurophysiological studies in animals have revealed that regions of the ML-DA circuit such as the nucleus accumbens and the ventral tegmental area show increased bursting neural activity during rapid-eye movement (REM) sleep and a role of dopamine in the generation of REM sleep has been suggested [92-94]. Also increased levels of DA in the ML – DA system during sleep have been suggested to play a pivotal role in the generation of dreams [95,96].

Several behavioural alterations induced by sleep deprivation are associated with the dopaminergic system [97-100]. The nigrostriatal dopamine (DA) pathway mediates activation of motor activity, including exploration, which may promote waking and inhibit sleep, although the discharge of nigral neurons is not dependent on vigilance

states. DA plays an important role in the control of fine motor actions and higher cognitive functions such as learning, working memory, attention, decision making, and appetitive and consummatory aspects of reward.

Mice lacking dopamine transporter gene and thus having increased synaptic concentrations of dopamine had threefold waking amount [101]. The effect of dopamine on sleep-wakefulness may often be secondary to influences on motor activity and emotions. In 1978, Tufik and colleagues demonstrated an enhancement in DA receptor sensitivity after REM sleep deprivation in rats and also a significant increase in stereotypic behaviours, including biting, rearing and hypothermia in rats. In fact, PSD increased D2 binding in the striatum and nucleus accumbens in rats [102]. Their results were complemented by Dzirasa et al. whose study demonstrated that dopamine play a central role in regulating sleep-wake states and that the action is mediated by the D2 dopamine receptor pathway. Studies using dopamine-receptor-deficient mice or animals injected with an antisense vector demonstrate that dopamine D1 and D2 receptors facilitate behavioural arousal, while D3 receptors mediate the opposite effect. D1 and postsynaptic D2 receptor agonists increase behavioural arousal and waking, and decrease sleep [103].

The down regulation of D2/D3R in ventral striatum under SD conditions, in addition to contributing to reduced wakefulness, could also affect other behaviours. Specifically, DA stimulation of D2/D3R in ventral striatum is implicated in attention and thus D2/D3R down regulation could contribute to the inattentiveness observed with SD [104-106]. Acute sleep deprivation in rats increased goal-directed behaviours toward cocaine. In humans, SD increases the risk of substance abuse and appetitive behaviour [107-109]. This increase in impulsivity and reward seeking post-SD may reflect a compensatory mechanism to adjust for the down regulation of D2 and D3 receptors in the ventral striatum immediately after SD. This down regulation of D2 and D3 receptors might lead to impairment in performance, reward learning and decision making after SD. In line with this interpretation, Hanlon et al. demonstrated that REMSD reduces the rate of responding to the acquisition and maintenance of an operant task for food reward in rats, which might be due to a suppression of dopamine activity in the nucleus accumbens during REMSD [110,111]. In addition, total SD can disrupt the reconsolidation of morphine reward memory [112].

GABAergic System

γ-Amino Butyric acid (GABA) is the most prominent inhibitory neurotransmitter in the brain mediating inhibitory post synaptic potentials [113]. SD induced stress has been reported to alter the content of GABA neurotransmitter in the animals suggesting role of GABAergic mechanism in the sleep deprivation-induced changes in behaviour alterations and oxidative damage in the animals [114,115]. SD causes significant alterations in GABA contents as well as an elevation of L-glutamic acid decarboxylase (GAD) activity [116].

Fast synaptic inhibition in the adult brain is primarily mediated by γ-amino butyric acid receptors (GABArs). Regulation of $GABA_A$ receptor surface expression at synapses is a process that is critical for maintaining the correct level of synaptic inhibition and is important for memory consolidation [117]. Wang et al. reported higher GABA levels in cortex, hypothalamus, and brain stem after 72 h of sleep deprivation in mice. This suggested that sleep deprivation might increase GABA tone, leading to increased GABAergic signalling and a suppression of activity of excitatory neurons [118]. Modirrousta et al. showed that expression of the GABAr β2–3 subunit is enhanced in cholinergic cells in the basal forebrain after sleep deprivation, suggesting that one way through which prolonged wake reduces cholinergic activity is through higher GABAergic activity [119]. Increases in GABABr receptor protein levels in hippocampal lysates after 12 h of sleep deprivation using the gentle handling method have also been reported by others [120-124].

Conclusion

Among the greatest challenges currently facing neuroscientists throughout the world, is the quest for a better understanding of the neurophysiologic factors in the central regulatory mechanisms of sleep and of the mechanism of the transition between one stage of sleep and another. Several reports show that there are presently a growing numbers of neurotransmitter agents, proposed neurotransmitter systems and suspected neurotransmitter agents, in the subject of sleep regulatory mechanism. Meanwhile, this review has helped to highlight a number of the neurotransmitter systems that have featured more prominently and frequently and can be said to be currently the more under study by researchers, as well as highlighted the brain areas in which each neurotransmitter systems appears to have featured more significantly in the subject of the central regulator mechanism of sleep.

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