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EDITORIAL

Drinking during pregnancy: Potential role of endocannabinoid signaling in fetal alcohol effects

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Abstract

Alcohol is a well-recognized teratogen that can cause variable physical and behavioral effects on the fetus. Alcohol use and abuse during pregnancy is one of the major health and societal problems and has been linked to a wide range of birth defects in the offspring collectively termed as fetal alcohol spectrum disorder (FASD). The severity of abnormalities may depend on a number of factors that include the amount, the frequency, the period during gestation and the route of alcohol administration. The current knowledge about the neurobiological basis of FASD is limited. However, recent studies have suggested that the membrane-derived lipids especially bioactive endogenous cannabinoids (eCB) such as arachidonyl ethanolamide and 2-arachidonyl glycerol resulting from alcohol exposure, may play a significant role in modulating neurophysiological and neurobehavioral effects in chronic alcohol exposed adult animals. Based on these findings and on reported studies on the role of eCB signaling in neurodevelopment and behavior, it is speculated that the eCB signaling may play a critical role in fetal alcohol syndrome and FASD-related behavioral effects. The current discussion will touch upon some of the mechanistic explanations about the role of eCB signaling system in FASD and provide further guidance for future direction.

Key words: Lipid; Cannabinoids 1 receptor; Alcohol; γ-aminobutyric acid; Endocannabinoid; Fetal alcohol spectrum disorder

Core tip: Drinking during pregnancy leads to severe neurobiological consequences in the fetus and results in a variety of morphological and neurobehavioral abnormalities including mental retardation. One of the promising neurobiological mechanisms that can explain fetal alcohol spectrum disorder as discussed in this editorial is that of the possible role of alcohol-induced alteration in the levels of bioactive endogenous cannabinoids (eCBs) that are derived from membrane lipids and eCB signaling. Further studies exploring dietary supplementation with

unsaturated fatty acids that can regulate the levels of the eCBs and testing of the drugs targeted against the eCB signaling, may have significant therapeutic value.

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INTRODUCTION

Alcohol use and abuse during pregnancy has been linked to a wide range of birth defects that include anatomical, physiological and behavioral abnormalities in the offspring collectively termed as fetal alcohol spectrum disorder (FASD)[1-3]. Although the risk is much greater with heavy and binge drinking, exposure even to a small amount of alcohol for a shorter period during critical periods of gestation has been shown to be sufficient to produce birth defects in animal models[3-9]. Mental retardation, learning disabilities and craniofacial defects are some of the reported abnormalities that result from alcohol-induced impairment of central nervous system (CNS) development[2]. A key question has been; whether there is a threshold for vulnerability below which alcohol can be consumed safely without harming the developing fetus? What is also not clear is that of molecular mechanisms underlying FASD-related neurophysiological, neuroanatomical and neurobehavioral abnormalities and neurodegeneration. In this editorial I will present evidence for a potential role, the eCB signaling system may play during fetal growth and development and attempt to provide mechanistic explanation, for involvement of the endocannabinoid (eCB) signaling system in FASD resulting from maternal drinking during pregnancy.

DEVELOPMENTAL STAGES DURING NERVOUS SYSTEM DEVELOPMENT AND POSSIBLE DISRUPTION BY INSULT SUCH AS ALCOHOL EXPOSURE

Alcohol can cause alterations in normal growth and development beginning from embryonic stage through fetal stage leading to a range of birth defects. Between third and six weeks of fertilization the CNS begins to form[10]. During this critical period of fetal growth, any insult such as alcohol, may result in accumulation of significant amount of alcohol in maternal placenta and in fetal tissue longer than the maternal tissue because of lack of alcohol metabolizing enzyme in fetal tissue[11]. This may cause disruption in normal development of nervous system machinery. The documented studies suggest that exposure to alcohol during first trimester leads to facial deformations, while exposure during second trimester can disrupt neuronal formation and neuronal connectivity and third trimester exposure interferes with CNS development[10,12-15]. It has also been reported that children of binge drinking pregnant women exhibited rather severe cognitive and behavioral deficits[13]. Adolescence is a critical stage during brain development, which is characterized by neuronal maturation, myelination and synaptic plasticity and any interference by alcohol during this critical period of fetal growth may hamper proper nervous system development[14]. These changes in the brain affect every developmental events that include emerging sexuality, emotionality and judgment in the offspring.

NEUROBIOLOGICAL CONSEQUENCES OF FETAL ALCOHOL EXPOSURE

Although much remains to be understood with regard to neurobiological changes in the offspring due to maternal alcohol use and abuse during pregnancy, recent studies with pre-clinical models provide some intriguing information regarding possible neurobiological mechanisms underlying deleterious effects of *in utero* alcohol exposure in the offspring. The primary focus of studies aimed at defining mechanisms have been placental dysfunction, nutritional deficiency, acetaldehyde toxicity, fetal hypoxia and the role of prostaglandins[12,15]. Other mechanisms discussed in the literature are; alterations in regulation of gene expression, enhancement of free radical formation and excitotoxic neuroinflammatory microglial activation[8,9,16]. Recent studies also suggest that alcohol's effect is mediated *via* several intracellular signal transduction pathways involving many classical transmitters[16]. Alcohol may cause FASD effects by disrupting membrane proteins such as neurotransmitter receptors (*e.g.,* NMDA, GABA and glutamate and ion channels)[17]. However, significant new developments have emerged in recent years, which can provide better mechanistic explanation of the FASD. Major focus of the current discussion will be on one of the alternate mechanisms namely, on the role of membrane-derived bioactive lipids specifically eCBs that act through central cannabinoid (CB) receptors.

ROLE OF ENDOCANNABINOIDS AND ENDOCANNABINOID SIGNALING DURING FETAL GROWTH AND DEVELOPMENT

The eCB system consists of CB1 and 2 receptors, their endogenous ligands, the eCBs, arachidonyl ethanolamide (AEA), 2-Arachidonyl glycerol (2-AG), and the enzymes involved in their synthesis, degradation and transport[18-20]. Besides the well characterized eCBs, AEA and 2-AG, much remains to be understood about the lesser known eCBs such as palmitoyl and oleoyl ethanolamides, which may also have some physiological roles (Figure 1). The eCBs

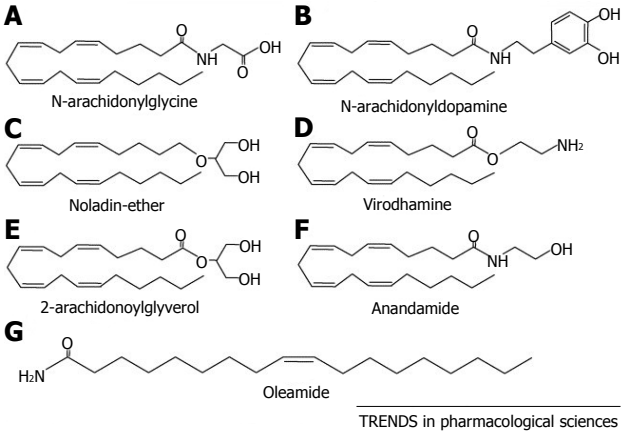

Figure 1 Structure of endogenous cannabinoids. The structures of N-arachidonylglycine (A), N-arachidonyldopamine (B), 2-arachidonoylglyceryl ether (noladin-ether) (C), O-arachidonoyl ethanolamine (virodhamine) (D), 2-arachidonoylglycerol (E), N-arachidonoyl ethanolamide (anandamide) (F) and 9-octadecenoamide (oleamide) are shown (G)[20].

are considered as a new class of neuromodulator and are found abundantly in cerebral cortex, basal ganglia and limbic structures, and exert their effects mainly through the CB receptors[21,22]. Since their discovery, the eCBs and their signaling have gained prominence in recent years and have been implicated in a variety of health and diseases. The CB1 receptor has been found to be the most abundant presynaptic G-protein coupled receptor[23].

The role of the eCB system in alcohol-induced neurotoxicity is complex and much remains to be understood. The eCB system is suggested to play an important role during brain development and is implicated in prenatal wiring of the brain during developmental processes such as neuronal cell proliferation, cell migration and differentiation and stem cell proliferation[24,25]. It has been demonstrated in earlier studies that the eCB system is present in early embryo before neurogenesis suggesting its role in early embryogenesis[26]. It is also of significance to note that the eCBs are reported to be present in placenta and possibly in peripheral fetal tissue[27].

It has also been reported that eCBs and CB1 receptors play critical roles in directional migration of neuroblasts and subsequent synaptogenesis and neuron to neuron communication[28]. The levels of the two eCBs, AEA and 2-AG significantly fluctuate during CNS development[29]. The levels of eCB, AEA increases during embryo implantation and during early phase of organogenesis. On the other hand, 2-AG levels increase gradually and reach peak levels during synaptogenesis[29]. Thus any disruption in eCB signaling due to circumstances such as alcohol exposure may result in a broad array of neurodevelopmental abnormalities. The eCB system plays a crucial role during brain development by modulating neuronal function and neurogenesis[24]. It is demonstrated that the activation of CB1 and CB2 receptors modulates the rate of neurogenesis[24]. The significance of the eCB system during fetal development and growth is further supported by the observation that pharmacological blockade of CB1 receptors in mid-to-late gestational periods adversely affects the progenitor proliferation in subventricle zone, disrupts axonal path finding and results in cortical delamination[30]. Furthermore, *in utero* exposure to tetrahydrocannabinol led to inappropriate interneuron positioning during corticogenesis[31]. The CB1 receptor expression is found to increase dramatically from infancy to young adulthood in regions such as prefrontal cortex (PFC), striatum, and hippocampus[32]. These changes in receptor expression may be both regionally and temporally specific as demonstrated in some specific brain regions such as shell and core, and PFC during adolescence[31]. Similar to CB receptors, developmental changes in eCBs, AEA and 2-AG during adolescence have also been reported[33,34]. The eCB system is one of the major neuromodulatory system and plays a critical role in mediating release of neurotransmitters in the CNS[35,36]. CB1 receptors are present on cells such as astrocytes, microglia and oligodendrocytes[37,38], which may affect the white matter development because of the exposure to teratogen like alcohol[39]. Similarly, effect on grey matter development may result in hippocampal and amygdala volume changes[40-42]. Furthermore, PFC neurons during adolescence may also be affected by in *utero alcohol* exposure and results in functional effect on GABA release by CB1 receptor activation that are co-expressed on GABAergic neurons in PFC. Consequently, this may affect inhibitory inputs to pyramidal neurons in the PFC resulting in impaired cognitive function[43]. Activation of CB1 receptors also results in increased extracellular dopamine thereby enhancing the dopaminergic activity[43].

Further support for a role for eCB signaling system is derived from recent reports, which suggest that pharmacological or genetic manipulation of CB1 receptors reverses alcohol-induced learning and memory, emotion and anxiety, reward, eating, nociception and motor systems, among others in a neonatal alcohol exposure model[16].

ECB SIGNALING AND FETAL ALCOHOL EFFECTS

Although there is considerable amount of literature on the role of eCB signaling system in sensitivity to, tolerance and dependence on alcohol in adult animals[18,19], there have not been any studies directly implicating eCB system in FASD. Except for a handful of studies, where a neonatal model for alcohol exposure on post-natal days 4-10, a period equivalent to third trimester in humans when significant brain development and rapid synaptic growth occurs, a significant effect of alcohol on the eCB system[16,44] and subsequent neurobehavioral deficits, have been demonstrated (for details see the review[16]). The current hypothesis/speculation is based on the existing knowledge of the association of developmental changes in the components of the eCB system with neurophysiological and neurobehavioral status and observed teratogenic effect of alcohol in the developing

fetus. Therefore, I believe that there indeed is sufficient supporting evidence that directly links eCB system to FASD-related neurophysiological and neurobehavioral deficits in the offspring exposed to alcohol *in utero*. However further studies as suggested here will enhance further understanding of the role eCB signaling plays in FASD and future development of therapeutic strategies to treat FASD-related neuroanatomical, neurobehavioral and other neurophysiological deficiencies.

COMMENTARY

As presented here, the existence of eCB synthesizing and metabolizing machinery in placenta and throughout various stages of neurodevelopment beginning from embryogenesis to adolescence and adulthood, strongly support a role for bioactive eCBs in FASD. Furthermore, alcohol-induced production of bioactive lipids may also contribute to dysfunctional/abnormal functioning of the eCB signaling leading to disrupted neuronal wiring, neuronal communication mechanisms and neurotransmitter function. This is evidenced by fluctuating levels of eCBs throughout fetal development and growth. As an example, it is reported that diacyl glycerol lipase, that synthesizes 2-AG, and CB1 receptors are a requirement for axonal growth and guidance and for retrograde synaptic signaling during early development. However, the expression of 2-AG changes from axonal tracts in the embryo to dendritic fields in the adult. This is highlighted in developmental changes in requirement from pre to post - synaptic compartment[45]. Alterations in eCB signaling may lead to improper neuronal connections and communication and thus may lead to many of the neurobehavioral deficits observed in the offspring exposed alcohol *in utero*. It is of great value to explore further and understand the contribution of eCB signaling towards FASD and investigate whether manipulation of the components of the eCB signaling system pharmacologically or genetically could produce beneficial effects in alleviating the alcohol-induced FASD.

The following important conclusions can be drawn based on the evidence presented here that: (1) maternal alcohol use during pregnancy leads to a variety of neuroanatomical, neurobehavioral and neurophysiological abnormalities (FASD), severity of which may depend on the amount and duration of alcohol consumed, route of alcohol administration and gestational period during pregnancy; (2) the abnormalities may be the result of alcohol's interference with normal developmental processes, especially the nervous system development. The alcohol's effect may last longer or even irreversible in the offspring and may translate into neurocognitive, neurobehavioral and neuropsychiatric disorders; and (3) one among the many speculative mechanistic explanations, the proposed role for eCB signaling, may be well equipped to explain many aspects of the consequential events due to alcohol exposure that lead to FASD. Further studies exploring the manipulation of eCB signaling using pharmacological or genetic tools may yield valuable information regarding the neurobiological processes underlying FASD. The investigation of pharmacological agents targeting eCB signaling system may be a worthwhile proposition to find a therapeutic solution to the deleterious effect of *in utero* alcohol exposure that leads to FASD and related abnormalities in the offspring.

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REVIEW

Disciplined sleep for healthy living: Role of noradrenaline

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Abstract

Sleep is essential for maintaining normal physiological processes. It has been broadly divided into rapid eye movement sleep (REMS) and non-REMS (NREMS); one spends the least amount of time in REMS. Sleep (both NREMS and REMS) disturbance is associated with most altered states, disorders and pathological conditions. It is affected by factors within the body as well as the environment, which ultimately modulate lifestyle. Noradrenaline (NA) is one of the key molecules whose level increases upon sleep-loss, REMS-loss in particular and it induces several REMS-loss associated effects and symptoms. The locus coeruleus (LC)-NAergic neurons are primarily responsible for providing NA throughout the brain. As those neurons project to and receive inputs from across the brain, they are modulated by lifestyle changes, which include changes within the body as well as in the environment. We have reviewed the literature showing how various inputs from outside and within the body integrate at the LC neuronal level to modulate sleep (NREMS and REMS) and vice versa. We propose that these changes modulate NA levels in the brain, which in turn is responsible for acute as well as chronic psycho-somatic disorders and pathological conditions.

Key words: Epigenetic changes; Healthy living; Lifestyle; Noradrenaline; Sleep disturbance; Psycho-somatic and metabolomic disorders

Core tip: Sleep is affected by many internal factors as well as lifestyle changes and vice versa. Noradrenaline (NA) is one of the molecules affected by lifestyle as well as sleep-loss; rapid eye movement sleep-loss in particular. Many of the sleep-loss associated cellular-molecular-behavioral and patho-physiological changes are induced by NA. Therefore, we propose that disciplined sleep habit, which would maintain optimum level of NA, is essential for leading healthy life.

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INTRODUCTION

The classical proverb of wisdom…..“health is wealth”….. has been expressed in almost all cultures and ages in

some form or the other. To enjoy life, one needs to be physically and mentally healthy. "Health" constitutes two aspects, the physical body and the mind; the substrate for the latter is the brain. Directly or indirectly the physical substrates, the body and the brain are constantly interacting with their immediate as well as distant surroundings, the environment. The interactions are complex; synthesis of one is often coupled with transformation of another; however they always remain in equilibrium for normal and healthy living. Disturbance or a shift in such equilibrium results in disease or altered state, which if gets rectified, cure or recovery may follow; however, in the absence of recovery, irreversible damage may precipitate/accumulate. In general, waking and sleep are among the fundamental instinct behaviors. Broadly and relative to each other, waking is considered to be energy consuming process (catabolic) while sleep (anabolic) as natural resuscitation. Until about mid-twentieth century sleep was largely considered to be a passive phenomenon; however, consistent research has proven that it is an active process regulated by the brain. Sleep researchers often face questions like why sleep is necessary, how much daily sleep is needed and how sleep loss exerts its effects and so on. In this review we will discuss the role of sleep, rapid eye movement sleep (REMS) in particular, in maintaining the level of a common factor, noradrenaline (NA), disturbance of which induces sleep-loss induced/associated effects.

Sleep is a spontaneous, reversible state of reduced sensitivity when the consciousness remains in a subdued state; during this state the body recuperates by replenishing the exhausted resources. Organisms have faced environmental and physiological challenges through evolution, which have impacted the quality and quantity of sleep-wake behavior in various species[1-4]. Also, the amount of sleep varies among different groups of individuals and populations depending on the lifestyle and environmental conditions. However, the modern lifestyle threatens the sleep behavior and pattern, which affect the health negatively. For example, the circadian misalignment usually seen in shift workers, truck drivers, frequent travelers, health support givers (nurses, *etc.*), those on special operation missions, *etc*., alters the natural sleep durations as well as cycle resulting in patho-physiological changes including fatigue, irritability, anxiety, restlessness, frequent daytime naps, lack of concentration, decreased performance at work[5]. These sleep-disturbances exert a global effect on body physiology leading to short (acute) - and long (chronic)-term pathological conditions. Further, these changes inflict significant hidden costs to the individual as well as to the society at large, which is not worth trading-off against a few hours of apparent immediate wakefulness. However, as we are constantly exposed to various psycho-social-environmental conditions which modulate sleep, with the best of efforts it is almost impossible to completely avoid sleep disturbance; however, we may attempt avoiding the effects if we know the reasons (etiology). Keeping this in mind, here we reviewed how even environmental and psycho-social factors modulate sleep and correlated them with changes in the level of a common physiological factor, NA, which is responsible for sleep-loss related effects.

Sleep is not a homogenous state; the least fraction of sleep time is spent in a unique state when one dreams. Based on electrophysiological signals recorded from the brain, eye- and neck-muscles sleep has been broadly divided into REMS and non-REMS (NREMS). REMS is a unique physiological process expressed in humans and most likely in other higher order vertebrates in evolution possessing evolved brain. Role of REMS has been implicated with several physiological processes including that it maintains brain excitability and thus maintains "house-keeping function of the brain"[6].

REMS disturbance has been reported to be associated with most physiological dysfunctions and pathological conditions including mood, mania, bipolar-disorders, Alzheimer's (AD) and Parkinson's (PD), epilepsy, narcolepsy, cognitive impairment, cardiovascular and respiratory disorders[7-13], infections, fever and trauma[14,15]. REMS is regulated by the interactions of neurons located in different brain regions forming complex neural network. Notably the NA-ergic neurons in brainstem are continuously active during wake as well as NREMS and cease activity during REMS, while they continue firing during REMS deprivation (REMSD). Upon REMS loss, the level of NA increases in the brain, which has been suggested to induce many REMS loss associated acute and chronic effects. Isolated studies have shown that several of the symptoms, *e.g*., hypertension, hyperglycemia, hyper-excitability, lack of concentration, memory loss, psycho-somatic disorders, *etc*., are reported to be modulated by increased NA[16-24]. Thus, there are enough convincing reasons to accept that disciplined sleep, which includes REMS, maintains optimum levels of NA in the brain and therefore, it is necessary for healthy living, which we would elaborate in this review. However, for complete understanding, it is necessary we understand how REMS is regulated by the brain and hence, first, we would discuss in short the essential basic mechanism(s) of REMS regulation.

BRAIN MECHANISM OF REMS REGULATION WITH PARTICULAR REFERENCE TO LC

Localizing the brain structures responsible for REMS

Aserinsky first objectively identified the REMS state in humans as having desynchronized EEG, phasic eye movements in the EOG and complete loss of muscle tone in the EMG recorded from the antigravity muscles[25]. Later, it was identified in rat, cat and many other mammalian species. By the time REMS was identified it was known that rostral brain stem reticular formation is important for EEG desynchronization and waking, while the caudal part is responsible for EEG synchronization and sleep (NREMS and REMS were not classified until

then). Transection and lesion studies identified that the areas responsible for REMS regulation are also located in the brain stem[26,27]. Some studies reported that neurons in the medial[28] and the lateral[29,30] pontine reticular structure were critical for REMS. Transection made rostral or caudal to the pons showed that signs identifying REMS were expressed in the portion of the brain which remained connected with the pons[31,32]. The pons includes two major nuclei, the LC and the laterodorsal and pedunculopontine-tegmentum (LDT/PPT), which have been reported to be important for REMS regulation[33-35]. Non-pontine brain regions like perifornical area[36,37], preoptic area in hypothalamus[38-40], basal ganglia[41], nucleus accumbens, ventral tegmental area, amygdala[42], basal forebrain, prefrontal cortex[43,44], dorsal raphe nucleus[45], substantia nigra[46,47], prepositus hypoglossus[48], *etc*., have been reported to modulate REMS.

Based on the firing patterns of neurons associated with waking-NREMS-REMS, those neurons almost exclusively active during REMS were classified as REM-ON type, while those shut-off during REMS were termed as REM-OFF neurons. The former were identified primarily in the LDT/PPT, while the latter in the LC[49-54]. Interaction between LC-NA-ergic and PPT-acetylcholine (ACh)-ergic neurons has been proposed to regulate REMS and that has been the focus of several reviews[49,55]. Briefly, REM-OFF neurons are inactivated for activation of the REM-ON neurons and initiation of REMS. It has been proposed that cessation of LC neurons is a pre-requisite condition for REMS generation[56]. Therefore, the behavior of the LC neurons, their afferents (inputs) and efferents (outputs) for REMS regulation will be discussed in brief.

LC-NA-ergic system and REMS regulation

The LC neurons are normally silent during REMS and continue to remain active during REMSD[57]. Stimulation and inactivation of the LC neurons had opposite effects on REMS. For instance, inactivation of LC neurons by local cooling, 6-OHDA induced selective loss of NA-ergic neurons in LC or lesion of LC neurons increased REMS[58-61], whereas stimulation of LC neurons decreased REMS[62-64]. Tyrosine hydroxylase (TH) mRNA, TH as well as NA levels in brain were higher in REMS deprived animals[65]. NA concentration has been reported to be lower in brain regions[66,67] and blood[68] during REMS as compared to NREMS and wakefulness, while NA levels were elevated during REMSD[65]. Expression profiles of NA-ergic receptor density have been inversely correlated with ontogenetic development of REMS[69]. Therefore, it has been proposed that one of the functions of REMS is to maintain NA-level in the brain which in turn maintains brain excitability and thus serves house-keeping function of the brain[6].

Neurochemicals modulating LC neurons and REMS

Many studies investigated influence of various neurotransmitters and their diverse effects on LC neurons. Agonist and antagonist of various neurotransmitters injected into the LC modulated REMS. It was observed in cats that infusion of NA into the LC decreased REMS while adrenergic antagonist increased REMS[70]. Administration of ACh into LC decreased REMS[71]. Infusion of GABA and its agonist, muscimol into the LC increased[35,72], while GABA antagonist, picrotoxin[73], bicuculine[74] and baclophen[72] decreased REMS. Orexin (Orx)-ergic agonist injection into the LC has been shown to reduce REMS[75], whereas knockdown of Orx-ergic receptors in the LC increased REMS[76]. Electrical or pharmacological stimulation of Orx-ergic neurons reduced REMS, whereas the effects on REMS were abolished by simultaneously blocking Orx action in LC[75,77,78]. Infusion of a somatostatin antagonist into LC also resulted in marked decrease in REMS[79]. Application of serotonin (5-HT) into LC inhibited basal neuronal discharge rate; however, the effects on REMS was not studied[45,80]. Various studies have shown that although dopamine (DA) may modulate REMS, detailed mechanism and site of action, particularly on the LC neurons, are not known[81]. The projections from the GABA-ergic neurons from substantia nigra onto LC-NA-ergic terminals have been suggested to act pre-synaptically and fine tune NA release over PPT ACh-ergic neurons and initiate REMS[47,55]. Thus, the LC neurons are modulated by many of the neurotransmitters in the brain. Further, LC neurons project to various areas of the brain including on the ACh-ergic and Orx-ergic neurons and modulate physiological processes and behaviors including REMS[42]. Thus, complex communications among various neurons containing different neurotransmitters affect the LC neuronal activities, which would modulate release of NA and regulate REMS (Figure 1).

Therefore, we have sufficient evidence that REMS and NA-level in the brain are closely linked and they modulate each other; also REMS tends to maintain NA-level in the brain. Notwithstanding, it is also known that NA affects many other physiological processes and NA is modulated in many pathological conditions; further, REMS as well as many of the pathophysiological conditions are associated with lifestyle changes[11,22,82-84]. Hence, we propose that environmental and lifestyle processes and its associated changes might affect either NA levels or REMS and thereby may be responsible for many of the acute as well as chronic patho-physiological conditions.

ENVIRONMENTAL FACTORS AND REMS

Modernity and stormy lifestyle have resulted into reduced sleep. Changes in lifestyle which include shorter sleeping hours, electricity and artificial lights at night, long television viewing and low physical activity have precipitated various health disorders/problems. Several studies have reported the effects of changes in lifestyle, ambient as well as body temperature and diet on NREMS and REMS. Therefore, loss of REMS cannot be overlooked and the factors affecting REMS merit attention. Physical fitness, nutritious food, stress reduction, exercises, lifestyle changes motivating positive thinking are essential for maintenance of quality sleep including REMS. Even

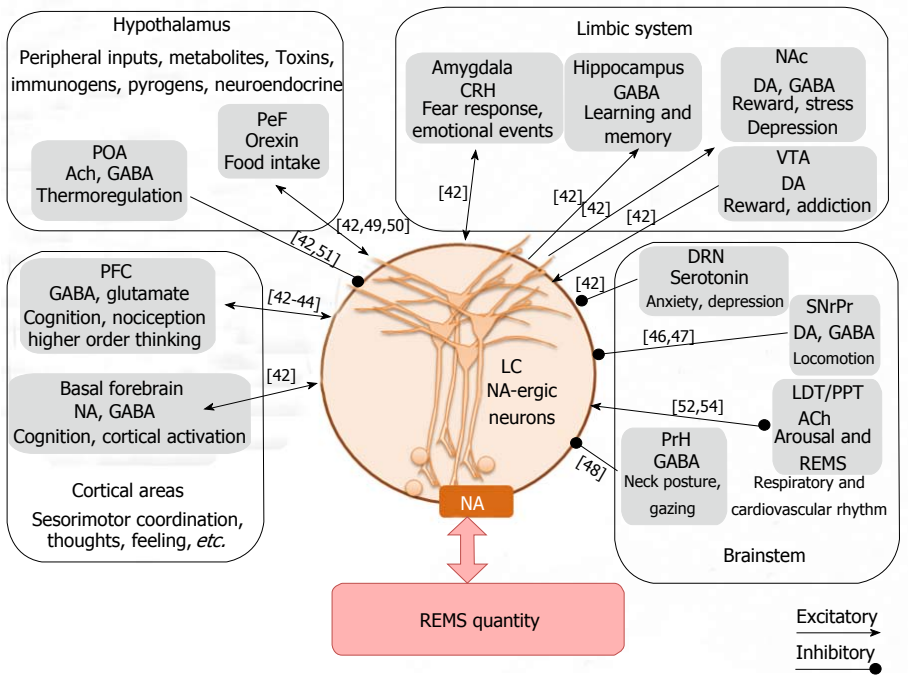

Figure 1 Schematic illustration of inputs to the locus coeruleus neurons from different regions in the brain, some of them are influenced by the environmental changes. The resultant output of the LC neurons is responsible for level of NA in the brain. As those LC-NA-ergic neurons cease activity during REMS, disturbance in the latter keeps those neurons active and thus modulates NA level in the brain. This altered level of NA (mostly elevated level) in turn affects physiological processes regulated by the brain. PFC: Prefrontal cortex; NAc: Nucleus accumbens; VTA: Ventral tagmental area; DRN: Dorsal raphe nucleus; SNrPr: Substantia niagra pars reticulate; PrH: Prepositus hypoglossus; PeF: Perifornical area; POA: Preoptic area; LDT/PPT: Laterodorsal tegmentumpedunculopontine tegmentum; LC: Locus coeruleus; ACh: Acetylcholine; DA: Dopamine; GABA: Gamma-amino butyric acid; NA: Noradrenaline.

excess sleep may be harmful; as the Greek physician Hippocrates wrote "Disease exists if either sleep or watchfulness be excessive". Thus, monitoring quality as well as quantity of sleep for the maintenance of healthy living beckons serious attention. Disturbance/loss of REMS is often associated with multiple symptoms, which might be an influence of complex circuitry involved in REMS regulation, NA being one of them.

Temperature

In mammals sleep is strongly associated with thermoregulation and temperature maintenance is a key determinant of sleep[85]. The core body temperature varies along with the sleep-wake rhythm. In healthy individuals and under normal environmental conditions, sleep propensity and body temperature vary inversely across day and night[86]. As the body and brain temperatures decrease during NREMS, while it tends to increase during REMS, it has been proposed that one of the functions of REMS is to maintain the brain temperature by "warming the CNS"[87].

Among the sleep stages, REMS is more sensitive to changes in ambient temperature; its cycle length significantly decreases with an increase in ambient temperature from 13 ℃ to 25 ℃[88]. In humans, sensitivity to hot or cold stimulation is reduced during REMS compared to NREMS and wakefulness[89,90]; however, it is not completely abolished. It has been observed in animal studies that thermoregulatory response as well as thermo-sensitivity of most of the hypothalamic preoptic neurons decrease during REMS[91], which suggested a causal relationship between them. Medial preoptic area in the brain is responsible for thermoregulation[92,93]; the thermosensitive neurons in the medial preoptic area possess α1-ARs and they are modulated by stimulation of brainstem ascending reticular activating system[94]. NA is involved in the neural regulation of REMS as well as body temperature[69,95]. Increased turnover of NA in specific nerve terminals of hypothalamus was observed in rats upon exposure to mild thermal stress[95]. As NA stimulates metabolic rate[96,97], it could elevate body temperature and trigger heat dissipation for thermoregulation. It has been suggested that one of the reasons for reduced core temperature during sleep is reduced NA-ergic peripheral vasoconstrictor tone resulting in increased peripheral blood flow and dissipation of heat[98,99]. Also, NA has been shown to induce hypothermia by acting on α1-ARs in the medial preoptic area[100,101]. Abnormalities in the body temperature rhythm are associated with insomnia and associated symptoms[102]. In fact, in a study the body temperature was monitored every 24 h during 10 d REMSD in rats. It was found that there was hyperthermia during initial about 4 d of REMSD; thereafter there was hypothermia if the deprivation continued. The authors explained the findings in relation to the REMSD associated elevated levels of NA[103]. Thus, REMS and associated change in NA level play crucial role in thermoregulation and as a corollary their disturbance would affect the body physiology.

Exercise

"The sleep of a laboring man is sweet" is a beautiful phrase from biblical times written in the Holy book

Ecclesiastes. Several research groups have examined the effects of exercise on sleep. Important relationship has been found between sleep and exercise although both the behaviors are mediated by physiologically different mechanisms. Regular physical activity promotes sleep, improves sleep quality and reduces day time sleepiness[104]. It is important to note that moderate amount of exercise is beneficial to health and upon exposure to severe acute exercise a reduction and a delay in REMS onset latency as well as an increase in slow wave sleep was observed[105-108]. These effects could be due to the stress associated with intense exercise. The observed increased latency for the onset of REMS was due to the significant increase in NA[109]. Several other studies have also reported significantly increased concentration of NA after exercise[110,111]. These results support that elevated levels of NA might reduce REMS and vice versa and that in turn might affect physiological processes.

Extensive research towards understanding the effects of exercise has shown that several brain areas receive various feedback inputs from peripheral structures such as muscles and joints which then influence the brain functions[112]. Exercise is beneficial for synaptic plasticity which could be due to molecules like brain derived neurotrophic factor that favors neuronal growth and plasticity[113,114]. It increases long term potentiation[115,116], neurogenesis[117] and thus has beneficial effects on learning and memory[118]. As a mechanism of action it may be said that sleep including REMS and NA[119] have been shown to enhance hippocampus dependent memory[120]. In support, sleep and REMS loss has been reported to reduce learning and memory formation[121,122]. Exercised sleep deprived rats learn and perform normally in comparison to sedentary/control sleep deprived rats in whom the learning and memory were severely impaired[123]. Regular exercise protocol prevents long term potentiation deficits and memory impairment induced by sleep deprivation (SD)[124]. As REMS-loss has been shown to elevate NA level in the brain[65] and that NA has been shown to induce apoptosis and neuronal loss[125,126], it appears that a critical level of NA in the brain is essential for normal healthy brain functioning including memory and plasticity. As REMS plays a critical role in maintenance of brain level of NA to its optimum levels, we propose that optimum REMS is essential for healthy living.

Several epidemiological studies have shown that regular physical activity, such as running, has favorable physiological effects. It reduces the risk of neurodegenerative disorders like AD, dementia which are also associated with REMS disorder; exercise also promotes functional recovery from brain injury[127-129]. Isolated studies in humans have shown exercise in combination with mood stabilizers as an adjunctive therapy improves manic symptoms of bipolar disorder, which is strongly influenced by environmental and genetic factors as well as inappropriate amount of sleep[130-132]. Moderate aerobic exercise also improves sleep quality, anti-depressive response and immune function in patients with chronic insomnia[133]. Thus, one of the possibilities is that the exercise mediates its beneficial effect on the body physiology by maintaining sleep, NREMS and REMS.

Yoga, an ancient Indian practice based knowledge, is apparently a holistic set of mind-body exercise. Of late it has become popular due to its benefits on physical and mental health and for amelioration of symptoms associated with many altered and patho-physiological conditions including insomnia[134,135]. For example, *Yoga* has been shown to reduce the severity of restless leg syndrome; it improved sleep in women with restless leg syndrome[136,137]. *Yogic* exercises have been reported to improve sleep qualitatively in cancer patients[138]. One of the possibilities is that at least some of the benefits of the Yoga could be by modulating the quality of sleep of an individual.

Food

Sleep plays an important role in the metabolic control of the body[139,140]. Recently, a relationship between circadian clock and nutrition has been referred to as "chrono-nutrition"[141]. Not only nutrients quality and quantity, the meal timings are also important and thus affect the biological (circadian) clock.

Amino acids like tryptophan, glutamate, and tyrosine are the precursor molecules for the biosynthesis of neurotransmitters like serotonin, GABA, NA and DA respectively and they all are involved in sleep-wake regulation. Therefore, diet can influence the rate of biosynthesis and functions of these neurotransmitters and affect physiological processes including sleep-wake cycle. Neurotransmitter Orx regulates feeding behavior[142] and also enhances wakefulness which could be by activating the LC-NAergic neurons[77]. GABA promotes sleep and is also a food ingredient[143]. Loss of GABA and other sleep related nutrients from whole grains as in polished grain in diet is considered to be one of the key factors for insomnia[144]. Certain other dietary nutrients like calcium, magnesium and potassium are also associated with improving sleep quality[143].

Body mass index is closely associated with sleep since obese and overweight individuals mostly have shorter sleep duration compared with normal subjects[145]. This association between sleep duration and body mass index has also been reported in patients with sleep disorders like obstructive sleep apnea, narcolepsy, insomnia, restless leg syndrome or periodic limb movements during sleep[146]. Also, habitual short/long sleep duration as well as intervening sleep restriction have been suggested as a risk factor for weight gain, obesity[147], insulin resistance, type 2 diabetes[148,149] and hypertension[150,151]. Obese adults show high amount of NREMS though very low REMS percentage[145]. A low carbohydrate diet with high fat content increases NREMS while REMS is reduced[152,153]. This might be due to higher metabolic demand of REMS[154] because greater glucose utilization occurs during this stage as compared to NREMS[155]. Different studies have shown that consuming food closer to the bed time negatively influences sleep; it increases

REMS latency and decreases REMS percentage in healthy individuals[156]. Dietary constituents influence sleep and adequate sleep protects against several nutritional and metabolic disorders including insulin resistance, diabetes[157-159], obesity[160], dyslipidemia[146]. Thus, maintenance of proper diet and sleep patterns is a necessity for healthy living.

Light

Light is one of the most important external factors for maintaining normal healthy living. Depending on the intensity, light affects sleep directly by preventing us from falling asleep and indirectly by altering the circadian clock. Light not only regulates sleep timing but also elicits acute changes in many behaviors. As night approaches reduced light intensity is detected by the photoreceptors; in higher animals they are primarily located in the retina. The retina projects to the suprachiasmatic nucleus of the hypothalamus, which is the biological master clock and the site for homeostatic regulation of circadian functions[161]. Removal of suprachiasmatic nucleus abolishes the circadian rhythm including that of sleep-waking in individuals[162]. The effects of circadian phase shift and SD were more pronounced on NREMS[163]. The NREMS was selectively enhanced during short light periods while REMS was elevated during short dark periods[164].

Exposure to light in late night hours resets the internal clock and makes it difficult to return to sleep. For example, in shift workers or travelers across time zones, the internal clock adjusts to the altered day-night cycle which mostly predisposes these individuals to insomnia when trying to sleep outside their internal temporal phase. Definitely this is a serious concern for such individuals like pilots, physicians, nurses, public safety workers, police, *etc*. These individuals may fall asleep during work or driving and may cause threat to life in addition to other disorders. Sleep was recorded in humans with morning type and evening type sleep for 3 successive nights and then after shifting sleep during daytime for next 3 d. Although night time sleep was not significantly affected, the day time sleep was shortened; REMS episode was found to be longer without much difference in NREMS[163]. Thus, it appears that a homeostatic mechanism operates to regulate REMS quantity and it suggests that circadian rhythm related periodic appearance of REMS is necessary to avoid sleep related disorders.

Different neurotransmitters are involved to regulate the sleep response to light. For instance, the levels of melatonin, NA, ACh decrease, while serotonin increases under the influence of light[165,166]; NA exhibits a clear circadian variation[5]. NA levels were highest in the brain during night in rat, a nocturnal animal while during the day in rabbit and cat[167]. Notwithstanding, isolated studies have shown that exposure of light to sites other than eyes (extra-ocular light) during sleep also significantly increased REMS[168]. This suggests that light exposed to sites other than eyes may also influence brain functions although the mechanism of such action needs further investigation[169]. Thus, the light-dark is likely to affect the sleep-waking rhythm, affecting various neurotransmitters, or vice versa, which then affect other physiological processes.

ENVIRONMENT INTERACTS WITH GENOME TO MODULATE REMS

As discussed above, the brain modulates various behaviors including waking, NREMS and REMS by releasing biomolecules, the neurotransmitters. The latter are directly or indirectly modulated by gene expression, which are affected by modifications on the DNA per se or at the epigenetic level.

The susceptibility and vulnerability to diseases are strongly influenced by genetic makeup of individual as well as environmental conditions[170-173]. However, it is neither the genetic make-up nor the environment alone but their interactions, which decide the phenotype of an organism and expression of behaviors in health and diseases. Here, we would discuss these events with particular reference to NA and REMS in acute and chronic conditions in health and diseases.

Gene expression

Point mutation of prion protein-gene was possibly the first to be linked to human sleep disorder, fatal familial insomnia[174]. Later in 1999 through genetic studies, Orx was shown to be involved in human narcolepsy[175,176]. Sleep-wakefulness is associated with widespread changes in gene expressions in the mammalian brain[177]. REMS is a complex phenomenon and its regulation is multifactorial, therefore, many genes and their interactions are likely to contribute to its regulation and pathologies associated to REMS disorders, which are increasingly gaining recognition[178]. However, presently most of the studies have correlated gene expressions with loss of total sleep, which includes loss of both NREMS as well as REMS; not many studies have correlated changes in gene expressions upon exclusive loss of REMS. In 1970s and 1980s it was known that transcription is accelerated during sleep[179] and sleep promotes mRNA translation. Microarray experiments have shown that the patterns of gene expressions vary during sleep and wakefulness[180,181]. Subsequently, it has been demonstrated that extended wakefulness, due to SD, hinders the expression of several genes including those required for memory formation and learning[182-185].

During wakefulness, the NA-ergic system induces increased expression of genes encoding BDNF, NGF-1 and phosphorylated cAMP response element binding (pCREB) protein (required for neurogenesis and memory among other functions), c-fos (immediate early gene expression for several proteins), Arc and BiP[181]. Inactivity of NA-ergic system during sleep prevents the expressions of BDNF, Arc and pCREB, thus causing impairment of long-term memory formation during

sleep[180]. Transcriptional regulatory molecule CREB, which is critical for synaptic plasticity and memory consolidation[186], also regulates the expression of TH gene which is essential for biosynthesis of NA and this factor in turn modulates REMS. Also, NA regulates the expression of transcription factors like CREB involved in memory formation and consolidation.

Sleep has been suggested to have an anabolic function by replenishing the wakefulness associated loss of energy (glycogen stores). This has been reported to be achieved by increasing protein targeting to glycogen, decreasing glycogen synthase and glycogen phosphorylase mRNA[187]. Further, this increased protein targeting to glycogen mRNA during wakefulness has been suggested to be due to increased level of NA during wakefulness.

In PD there is reduced expression of TH and dopamine β hydroxylase (required for biosynthesis of NA) resulting in reduced NA synthesis along with the loss of nigro-striatal DA-ergic and some other catecholamine neurons. These have been proposed to be caused by unknown exogenous environmental factors and by endogenous genetic factors suggesting interaction(s) between genes and environment[188]. However, although the role and mechanism of action of NA affecting wakefulness-NREMS-REMS have been investigated, their genetic regulation in health and diseases, particularly in relation to sleep and REMS disturbance needs to be studied.

Epigenetic regulation

Gene expression induces transcription and involves several processes including epigenetic modifications. Some of the important epigenetic changes are DNA methylation and chromatin remodeling through histone modifications. These regulate chromatin uncoiling and thus allow access to transcription factors and activation of the transcriptional machineries. Environmental as well as patho-physiological changes have been reported to modulate epigenetic machineries to regulate the genomic organizations in living organisms[189]. Increasing evidence (mostly indirect though) suggests that epigenetic changes induce chronic disorders including long term sleep-loss associated disorders and associated behavioral changes of sleep-wake states[190]. DNA methylation modulates the transcriptional and synaptic responses of neurons to sleep loss[191]. Genomic imprinting, which is established by epigenetic processes, also extends its effects to sleep-wake regulation[192]. Both REMS and NREMS are regulated by separate sets of imprinted genes which are differentially expressed in brain regions[193]. Maternally expressed imprinted gene, *e.g.*, Gnas, has also been shown to modulate the expression of sleep-wake states[194]. These and similar other studies reinforce the concept of the role of epigenetic changes in sleep-REMS and their-loss associated sustained patho-physiological changes particularly for understanding the associated molecular circuitry underlying behavioral phenomena.

Independent studies have shown that the bio-molecules (factors) regulating levels of NA and molecules affecting NA in the brain, for instance TH[65,195], α1 adrenergic receptor[196,197] and monoamine oxidase[198] are transcriptionally regulated and they are modulated by REMSD[65,199-201]. These factors are encoded by one or more specific genes at the molecular level; however, our understanding about their transcriptional regulation in association with REMS and its loss in particular, are still lacking. Furthermore, many of the neurological disorders, including depression, AD, Schizophrenia, PD, cognition disorders, ageing, attention deficit/hyperactivity disorder, anxiety, post-traumatic stress disorder, *etc.,* are associated with dysregulation of REMS as well as LC-NA-ergic system. As those disorders are generally chronic by nature, the component of those disorders modulated by NA is likely to be modulated directly or indirectly by epigenetic modulation of NA synthesis, or by the factors responsible for modulating the NA level at the synapse. However, direct evidences which can relate the role of epigenetic modifications of the NA-ergic system in these neurological disorders, especially in relation to REMS or its loss or dysfunction, are lacking. Recently we have proposed a model explaining the possible mechanism of REMS-loss associated epigenetic modifications of NA synthesis in LC neurons in the brain leading to sustained (chronic) associated symptoms[202]. The model explains how upon REMS-loss epigenetic modifications would regulate NA levels in the brain which in turn might modulate factors for transcriptional regulation of other bio-molecules in the brain. An understanding of these mechanisms is expected to provide insights into the detailed role of NA mediated regulation of REMS or its loss in health and diseases. Interactions among environment, genome and REMS for the regulation of the common mediator molecule, NA and their effects on physiological processes have been shown in Figure 2.

REMS LOSS ASSOCIATED PATHO-PHYSIOLOGICAL DISORDERS

Cardiovascular system

In humans, mean blood pressure was higher during REMS as compared to the remaining phases of sleep accompanied by progressive decrease in heart and respiratory rates[203,204]. During REMS, both hemispheric and brainstem blood flow increased even higher than during wakefulness[205,206]. REMSD may contribute to arterial hypertension and arthrosclerosis by altering blood parameters associated with cardiovascular disorder risk[207,208]; hypertensive patients have been reported to have significantly reduced REMS[209]. It has been observed that 96 h REMSD in young rats led to decrease in homocystein, an amino acid that is considered an independent risk factor for cardiovascular disease and stress[210]. Neves *et al*[211] reported that REMSD by platform method induced significant and sustained blood pressure elevation in rats with partial predisposition

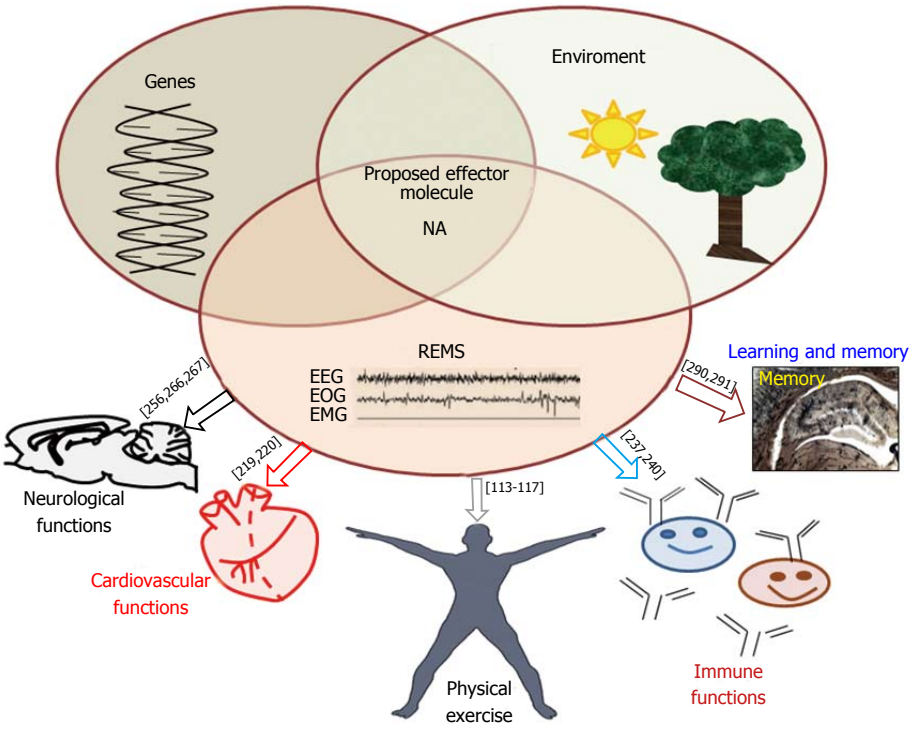

Figure 2 Interactions among environmental factors, rapid eye movement sleep and associated changes in gene expressions for long-term (sustained) modulation of patho-physiological changes have been diagrammatically represented in this figure. NA is at least one of the common mediators to induce the changes, which ultimately affects the overall physiology in health and diseases. REMS: Rapid eye movement sleep; NA: Noradrenaline.

to developing hypertension. Association of REMS with considerable peripheral vasoconstriction has also been reported in humans[212]. Heart rate, cardiac pressure, cardiac output, arterial pressure, and breathing rate become irregular when one goes into REMS. In general, respiratory reflexes such as response to hypoxia diminish during REMS.

The NA is an important and common factor for the regulation of autonomic functions, *e.g.*, cardio-vascular-respiratory systems[213], it increases heart rate, cardiac contractility and vascular tone[214]. Impaired neuronal NA reuptake transporter activity has been reported in hypertension and postural tachycardia syndrome[215]. Also, in common heart diseases, such as congestive heart failure, ischemic heart disease and stress-induced cardiomyopathy, NA transporter function seems to be reduced[214]. Patients with chronic sleep apnea associated with heart failure have been shown to be associated with higher urinary and plasma NA levels along with an increase in sympathetic activity[216,217]. As NA is an important factor to regulate both NREMS as well as REMS, a healthy sleep habit is likely to be very important to maintain overall physiological processes including the autonomic cardio-vascular responses.

Immune functions

Sleep is compromised in most infections and diseased conditions[218-223]. Immune responses also vary in relation to sleep conditions and quantity, while immune challenge alters sleep[220]. Shift workers and students studying overnight compromising sleep time have been seen to have propensity to suffer from cold or flu, suggesting sleep loss possibly enhances susceptibility to infections. A relationship between amount of sleep and number of white blood cells was observed across 26 mammalian species. Those with more sleep had more white blood cell count favoring better immuno-competency[220]. The amount of time spent in NREMS increases while REMS is reduced in cases of several infections[224]. REMSD has been reported to affect several hormones, metabolites[225], interleukins[221,226-228], enzymes[229], neuronal structural proteins and apoptosis[125,126] in the brain. REMS loss possibly initiates acute phase response. REMSD rats increased ceruloplasmin, an acute phase response protein[230,231]. A component of immune system like IL-1β is somnogenic, it has been shown to enhance NREMS[232,233]. The number and activity of phagocytes and natural killer cells, the white blood cells, decreased in the REMS deprived animals suggesting severely weakened immune system. In experimental rats, increased tendency of acquiring infection, lesions in foot paws and gastric mucosa after total SD and REMSD have been reported[234,235].

Supporting the general theme of this review, it has been reported that after REMSD the level of NA increases significantly in the blood[236] and the brain (Mehta *et al*, 2016 MS under revision), and NA is known to modulate the immune system[237]. NA has multiple roles in the body; it acts both as a hormone as well as neurotransmitter. Among the adrenoceptors, β2-

subtypes are mostly expressed on immune cells[16]. NA is essential for the maintenance of normal level of antibody production *in vivo* and thus augments the $CD4^+$-T cell and B-cell activity[237]. NA suppresses the expressions of pro-inflammatory molecules, such as TNF-α and IL-1β, while increasing the expressions of anti-inflammatory molecules, like IκB, by signaling through α1-, α2-, and β-adrenergic receptors on astrocytes and glia[24]. Thus, both NA levels and REMS contribute to optimum immune responses and their deficiencies predispose the body to compromised immunity.

Neurological disorders

Post-traumatic stress disorder: REMS disturbance is a hallmark symptom of post-traumatic stress disorder (PTSD)[238]; in some cases REMS is reduced, while it is increased in other cases[238-240]. NA-ergic involvement in PTSD is supported by the fact that pharmacologic stimulation of NA-ergic neurons evoked PTSD symptoms[241,242] and adrenoreceptors antagonist reduced nightmares and sleep disruption in patients with chronic PTSD[243]. Mellman *et al*[244] found that heart rate (LF/HF ratio) was higher during REMS of PTSD patient than non-PTSD group.

PD: PD is primarily due to loss of DA-ergic neurons. However, NA is also a catecholamine synthesized following the same pathway, and found to be involved in wide range of brain functions. It is important to note that in PD patients there is loss of the enzyme synthesizing NA, decreased NA level and there is some loss of LC-NA-ergic neurons[245,246]. PD patients show sleep disturbance, particularly reduced REMS[247]. In addition, PD patients show increased latency to sleep, fragmented sleep and symptoms like restless legs, daytime sleepiness which are usually associated with REMS disturbance and REMS behavior disorders[83]. Normally, REMS and NA level in brain are inversely related; REMSD induces elevated level of NA in brain. In case of diseases like PD the relationship between REMS and NA level in brain is lost and both are affected.

AD: Like other neurodegenerative diseases, AD patients also suffer from sleep disturbances. Polysomnography indicated the loss of REMS and increased REMS latency in AD patients[7,248,249]. REMS behavior disorder like REMS without atonia are distinguishing feature in AD[250]. Although the brain of the patients suffering from AD shows significant loss of cholinergic population in brain, loss of LC neurons has also been reported with progression of AD[251-253]. The surviving NA-ergic neurons are reported to be highly active possibly for maintenance of high NA level in the brain in aging and AD[254]. Prazosin that blocks the action of NA was found to improve aggression and agitation symptoms in AD[255]. Compensation of NA level in the brain by NA reuptake inhibitor are helpful in early stage of AD, possibly due to its anti- oxidant property[256,257] and neuroprotective role[258,259]. Although both REMS and NA-ergic mediators are affected in AD, the role of NA and REMS in pathogenesis of AD needs further investigation.

Depression: REMS loss is a characteristic symptom of depression; alterations in REMS have been observed in patients with depressive episodes[260]. An increase in total duration and density of REMS and decreased REMS latency have been observed in patients with major depressive disorder[261,262]. Depression is primarily associated with dysregulation of the LC NA-ergic system[263,264]. Also, disruptions in serotonin, NA and DA neurotransmissions are generally observed during major depression. In general, the monoaminergic hypofunction has been traditionally accepted as the cause of depression[265,266]. Anti-depressants inhibit re-uptake of the monoamine neurotransmitters, inhibits monoamine oxidase (which degrades NA), or antagonize the inhibitory presynaptic NA-ergic auto-receptors[23]. These are likely to enhance availability of NA at the synapse resulting in facilitation of NA-mediated neurotransmission and amelioration of the symptoms of depression.

Cognitive dysfunctions: Sleep has been implicated in the neuronal plasticity in the brain that underlie learning and memory[267]. Indications that sleep participates in the consolidation of fresh memory traces come from a wide range of experimental observations[268]. Sleep loss is associated with decreased concentration, attention, vagueness, longer reaction time, lack of coordination, disorientation and making mistakes[269,270]. Also, REMS has a positive effect on memory while its loss adversely affects memory[271,272]. NA is an essential modulator of memory formation because of its ability to regulate synaptic plasticity[119]. It is released during arousal and has a central role to play in the emotional regulation of memory[273]. The memory deficits observed during AD could be due to the loss of NA-ergic system reported during the disorder[251-253]. Thus, NA can be attributed to be a common molecule in most of the neurological disorders where REMS is also disrupted.

Obstructive sleep apnea: There are several sleep disorders where both REMS and NA are affected. Obstructive sleep apnea (OSA) is one such disorder characterized by sporadic collapse of upper airway during sleep leading to arousal. OSA patient suffers sleep loss, complains persistent drowsiness and daytime sleepiness. OSA events have been reported during both NREMS and REMS. During REMS the excitatory input to motoneurons regulating upper airway reduces due to cessation of NA-ergic neurons, consequently in OSA patients the REMS is often associated with higher propensity and frequency of obstructive events[274]. Epidemiologically observed such relationship is also known as "REMS related OSA"[275]. OSA patients show the multitude of the symptoms like hypertension, metabolic dysfunction, vascular irregularities and oxidative stress; these are associated with altered NA level in body. In fact, sympathetic activity and plasma NA is reported to be high in OSA patients[276].

Reduction in the number of catecholaminergic neurons is shown in OSA; there are also reports of activation of hypothalamic pituitary axis that may increase the NA-ergic activity in brain. The remarkable association of REMS and NA with OSA indicates their therapeutic importance of the disease.

CONCLUSION

Both quantity as well as quality of sleep (NREMS and REMS) is essential for healthy living. Interactions among various intracellular and extracellular factors viz. nutrition, light, temperature, exercise, genetic as well as epigenetic mechanisms affect/contribute to the regulation of sleep which affects health in short and long term. The NA system plays a significant role in regulating NREMS as well as REMS. The role of NA in relation to REMS and REMSD has been investigated in more detail; NA level decreases during REMS while it increases during REMSD. Broadly, it has been observed that NA is a key molecule which induces REMSD associated changes from molecule to behavior. As sleep is affected by life-style changes, we propose that many of the lifestyle related pathophysiological conditions could be due to dysregulation of sleep (NREMS and REMS) and the effects are mediated by elevated levels of NA. Thus, sleep discipline plays a key role in maintenance of good health.

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