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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

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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

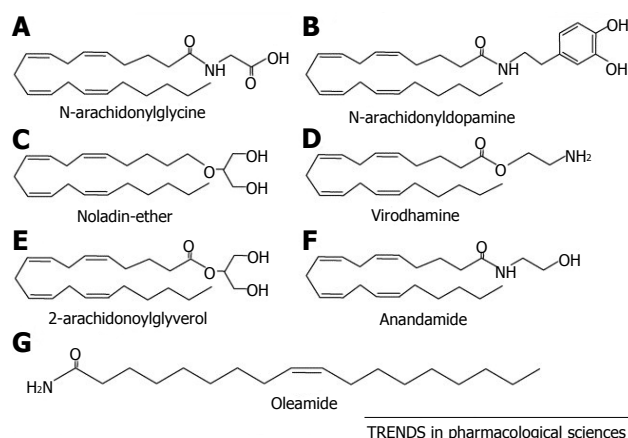


Figure 1 Structure of endogenous cannabinoids. The structures of N-arachidonylglycine (A), N-arachidonyldopamine (B), 2-arachidonoylglycerol ether (noladin-ether) (C), O-arachidonoyl ethanolamine (virodhamine) (D), 2-arachidonoylglycerol (E), N-arachidonoyl ethanolamide (anandamide) (F) and 9-octadecenoamide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

EBC 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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REFERENCES

- 1 Jones KL, Smith DW, Ulleland CN, Streissguth P. Pattern of malformation in offspring of chronic alcoholic mothers. *Lancet* 1973; **1**: 1267-1271 [PMID: 4126070 DOI: 10.1016/S0140-6736(73)91291-9]
- 2 Streissguth AP, Landesman-Dwyer S, Martin JC, Smith DW. Teratogenic effects of alcohol in humans and laboratory animals. *Science* 1980; **209**: 353-361 [PMID: 6992275 DOI: 10.1126/science.6992275]
- 3 Webster WS, Walsh DA, McEwen SE, Lipson AH. Some teratogenic properties of ethanol and acetaldehyde in C57BL/6J mice: implications for the study of the fetal alcohol syndrome. *Teratology* 1983; **27**: 231-243 [PMID: 6867945 DOI: 10.1002/tera.1420270211]
- 4 Sulik KK, Johnston MC. Sequence of developmental alterations following acute ethanol exposure in mice: craniofacial features of the fetal alcohol syndrome. *Am J Anat* 1983; **166**: 257-269 [PMID: 6846205 DOI: 10.1002/aja.1001660303]
- 5 Randall CL. Alcohol as a teratogen: a decade of research in review. *Alcohol Alcohol Suppl* 1987; **1**: 125-132 [PMID: 3322304]
- 6 Hungund BL, Gokhale VS, Cooper T, Mahadik SP. Prenatal Ganglioside GM1 Treatment Protects Ethanol-Induced Sleep Time in Rats Exposed to Ethanol In Utero During Gestation Days 7 and 8. *Drug Devel Res* 1991; **24**: 261-267 [DOI: 10.1002/ddr.430240307]
- 7 Hungund BL, Ross DC, Gokhale VS. Ganglioside GM1 reduces fetal alcohol effects in rat pups exposed to ethanol in utero. *Alcohol Clin Exp Res* 1994; **18**: 1248-1251 [PMID: 7847614 DOI: 10.1111/j.1530-0277.1994.tb00113.x]
- 8 Riley EP, Thomas JD, Goodlett CR, Klintsova AY, Greenough WT, Hungund BL, Zhou F, Sari Y, Powrozek T, Li TK. Fetal alcohol effects: mechanisms and treatment. *Alcohol Clin Exp Res* 2001; **25**: 110S-116S [PMID: 11391059 DOI: 10.1111/j.1530-0277.2001.tb02384.x]
- 9 Charness ME, Riley EP, Sowell ER. Drinking During Pregnancy and the Developing Brain: Is Any Amount Safe? *Trends Cogn Sci* 2016; **20**: 80-82 [PMID: 26801950 DOI: 10.1016/j.tics.2015.09.011]
- 10 O'Neil E. Developmental Timeline of Alcohol-Induced Birth Defects. Embryo Project Encyclopedia. [updated 2011 Apr 24]. Available from: URL: <http://embryo.asu.edu/handle/10776/2101>
- 11 Zorzano A, Herrera E. Disposition of ethanol and acetaldehyde in late pregnant rats and their fetuses. *Pediatr Res* 1989; **25**: 102-106 [PMID: 2919109 DOI: 10.1203/00006450-198901000-00022]
- 12 Chen SY, Periasamy A, Yang B, Herman B, Jacobson K, Sulik KK. Differential sensitivity of mouse neural crest cells to ethanol-induced toxicity. *Alcohol* 2000; **20**: 75-81 [PMID: 10680720 DOI: 10.1016/S0741-8329(99)00058-0]
- 13 Mattson SN, Riley EP. A review of the neurobehavioral deficits in children with fetal alcohol syndrome or prenatal exposure to alcohol. *Alcohol Clin Exp Res* 1998; **22**: 279-294 [PMID: 9581631]
- 14 Streissguth AP, Aase JM, Clarren SK, Randels SP, LaDue RA, Smith DF. Fetal alcohol syndrome in adolescents and adults. *JAMA* 1991; **265**: 1961-1967 [PMID: 2008025 DOI: 10.1001/jama.1991.03460150065025]
- 15 Randall CL, Ekblad U, Anton RF. Perspectives on the pathophysiology of fetal alcohol syndrome. *Alcohol Clin Exp Res* 1990;

- 14: 807-812 [PMID: 2088115]
- 16 **Basavarajappa BS**. Fetal Alcohol Spectrum Disorder: Potential Role of Endocannabinoids Signaling. *Brain Sci* 2015; **5**: 456-493 [PMID: 26529026 DOI: 10.3390/brainsci5040456]
 - 17 **Alfonso-Loeches S**, Guerri C. Molecular and behavioral aspects of the actions of alcohol on the adult and developing brain. *Crit Rev Clin Lab Sci* 2011; **48**: 19-47 [PMID: 21657944 DOI: 10.3109/10408363.2011.580567]
 - 18 **Hungund BL**, Vinod KY. Roles of the Endocannabinoid System in Alcohol-Related Behaviors. *Open Neurop* 2009; **2**: 31-39 [DOI: 10.2174/1876523800902020031]
 - 19 **Vinod KY**, Hungund BL. Endocannabinoid lipids and mediated system: implications for alcoholism and neuropsychiatric disorders. *Life Sci* 2005; **77**: 1569-1583 [PMID: 16005471 DOI: 10.1016/j.lfs.2005.05.041]
 - 20 **Vinod KY**, Hungund BL. Role of the endocannabinoid system in depression and suicide. *Trends Pharmacol Sci* 2006; **27**: 539-545 [PMID: 16919786 DOI: 10.1016/j.tips.2006.08.006]
 - 21 **Devane WA**, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffen G, Gibson D, Mandelbaum A, Etinger A, Mechoulam R. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* 1992; **258**: 1946-1949 [PMID: 1470919 DOI: 10.1126/science.1470919]
 - 22 **Mechoulam R**, Hanus LO, Pertwee R, Howlett AC. Early phytocannabinoid chemistry to endocannabinoids and beyond. *Nat Rev Neurosci* 2014; **15**: 757-764 [PMID: 25315390 DOI: 10.1038/nrn3811]
 - 23 **Herkenham M**, Lynn AB, Little MD, Johnson MR, Melvin LS, de Costa BR, Rice KC. Cannabinoid receptor localization in brain. *Proc Natl Acad Sci USA* 1990; **87**: 1932-1936 [PMID: 2308954 DOI: 10.1073/pnas.87.5.1932]
 - 24 **Maccarrone M**, Guzmán M, Mackie K, Doherty P, Harkany T. Programming of neural cells by (endo)cannabinoids: from physiological rules to emerging therapies. *Nat Rev Neurosci* 2014; **15**: 786-801 [PMID: 25409697 DOI: 10.1038/nrn3846]
 - 25 **Aguado T**, Palazuelos J, Monory K, Stella N, Cravatt B, Lutz B, Marsicano G, Kokaia Z, Guzmán M, Galve-Roperh I. The endocannabinoid system promotes astroglial differentiation by acting on neural progenitor cells. *J Neurosci* 2006; **26**: 1551-1561 [PMID: 16452678 DOI: 10.1523/JNEUROSCI.3101-05.2006]
 - 26 **Psychoyos D**, Vinod KY, Cao J, Xie S, Hyson RL, Wlodarczyk B, He W, Cooper TB, Hungund BL, Finnell RH. Cannabinoid receptor 1 signaling in embryo neurodevelopment. *Birth Defects Res B Dev Reprod Toxicol* 2012; **95**: 137-150 [PMID: 22311661 DOI: 10.1002/bdrb.20348]
 - 27 **Fonseca BM**, Correia-da-Silva G, Taylor AH, Lam PM, Marczylo TH, Bell SC, Konje JC, Teixeira NA. The endocannabinoid 2-arachidonoylglycerol (2-AG) and metabolizing enzymes during rat fetoplacental development: a role in uterine remodelling. *Int J Biochem Cell Biol* 2010; **42**: 1884-1892 [PMID: 20727980 DOI: 10.1016/j.biocel.2010.08.006]
 - 28 **Berghuis P**, Rajniecek AM, Morozov YM, Ross RA, Mulder J, Urbán GM, Monory K, Marsicano G, Matteoli M, Canty A, Irving AJ, Katona I, Yanagawa Y, Rakic P, Lutz B, Mackie K, Harkany T. Hardwiring the brain: endocannabinoids shape neuronal connectivity. *Science* 2007; **316**: 1212-1216 [PMID: 17525344 DOI: 10.1126/science.1137406]
 - 29 **Fernández-Ruiz JJ**, Berrendero F, Hernández ML, Romero J, Ramos JA. Role of endocannabinoids in brain development. *Life Sci* 1999; **65**: 725-736 [PMID: 10462073 DOI: 10.1016/S0024-3205(99)00295-7]
 - 30 **Mulder J**, Aguado T, Keimpema E, Barabás K, Ballester Rosado CJ, Nguyen L, Monory K, Marsicano G, Di Marzo V, Hurd YL, Guillemot F, Mackie K, Lutz B, Guzmán M, Lu HC, Galve-Roperh I, Harkany T. Endocannabinoid signaling controls pyramidal cell specification and long-range axon patterning. *Proc Natl Acad Sci USA* 2008; **105**: 8760-8765 [PMID: 18562289 DOI: 10.1073/pnas.0803545105]
 - 31 **Berghuis P**, Dobszay MB, Wang X, Spano S, Ledda F, Sousa KM, Schulte G, Ernfors P, Mackie K, Paratcha G, Hurd YL, Harkany T. Endocannabinoids regulate interneuron migration and morphogenesis by transactivating the TrkB receptor. *Proc Natl Acad Sci USA* 2005; **102**: 19115-19120 [PMID: 16357196 DOI: 10.1073/pnas.0509494102]
 - 32 **Mato S**, Del Olmo E, Pazos A. Ontogenetic development of cannabinoid receptor expression and signal transduction functionality in the human brain. *Eur J Neurosci* 2003; **17**: 1747-1754 [PMID: 12752773 DOI: 10.1046/j.1460-9568.2003.02599.x]
 - 33 **Wenger T**, Gerendai I, Fezza F, González S, Bisogno T, Fernandez-Ruiz J, Di Marzo V. The hypothalamic levels of the endocannabinoid, anandamide, peak immediately before the onset of puberty in female rats. *Life Sci* 2002; **70**: 1407-1414 [PMID: 11883716 DOI: 10.1016/S0024-3205(01)01516-8]
 - 34 **Ellgren M**, Artmann A, Tkalych O, Gupta A, Hansen HS, Hansen SH, Devi LA, Hurd YL. Dynamic changes of the endogenous cannabinoid and opioid mesocorticolimbic systems during adolescence: THC effects. *Eur Neuropsychopharmacol* 2008; **18**: 826-834 [PMID: 18674887 DOI: 10.1016/j.euroneuro.2008.06.009]
 - 35 **Wilson RI**, Nicoll RA. Endogenous cannabinoids mediate retrograde signalling at hippocampal synapses. *Nature* 2001; **410**: 588-592 [PMID: 11279497 DOI: 10.1038/35069076]
 - 36 **Hillard CJ**. The Endocannabinoid Signaling System in the CNS: A Primer. *Int Rev Neurobiol* 2015; **125**: 1-47 [PMID: 26638763 DOI: 10.1016/bs.irn.2015.10.001]
 - 37 **Bouaboula M**, Bourrié B, Rinaldi-Carmona M, Shire D, Le Fur G, Casellas P. Stimulation of cannabinoid receptor CB1 induces krox-24 expression in human astrocytoma cells. *J Biol Chem* 1995; **270**: 13973-13980 [PMID: 7775459 DOI: 10.1074/jbc.270.23.13973]
 - 38 **Sánchez C**, Galve-Roperh I, Canova C, Brachet P, Guzmán M. Delta9-tetrahydrocannabinol induces apoptosis in C6 glioma cells. *FEBS Lett* 1998; **436**: 6-10 [PMID: 9771884 DOI: 10.1016/S0014-5793(98)01085-0]
 - 39 **Bava S**, Frank LR, McQueeney T, Schweinsburg BC, Schweinsburg AD, Tapert SF. Altered white matter microstructure in adolescent substance users. *Psychiatry Res* 2009; **173**: 228-237 [PMID: 19699064 DOI: 10.1016/j.psychres.2009.04.005]
 - 40 **Bangalore SS**, Prasad KM, Montrose DM, Goradia DD, Diwadkar VA, Keshavan MS. Cannabis use and brain structural alterations in first episode schizophrenia--a region of interest, voxel based morphometric study. *Schizophr Res* 2008; **99**: 1-6 [PMID: 18248793 DOI: 10.1016/j.schres.2007.11.029]
 - 41 **Yücel M**, Solowij N, Respondek C, Whittle S, Fornito A, Pantelis C, Lubman DI. Regional brain abnormalities associated with long-term heavy cannabis use. *Arch Gen Psychiatry* 2008; **65**: 694-701 [PMID: 18519827 DOI: 10.1001/archpsyc.65.6.694]
 - 42 **Eggan SM**, Hashimoto T, Lewis DA. Reduced cortical cannabinoid 1 receptor messenger RNA and protein expression in schizophrenia. *Arch Gen Psychiatry* 2008; **65**: 772-784 [PMID: 18606950 DOI: 10.1001/archpsyc.65.7.772]
 - 43 **Malone DT**, Hill MN, Rubino T. Adolescent cannabis use and psychosis: epidemiology and neurodevelopmental models. *Br J Pharmacol* 2010; **160**: 511-522 [PMID: 20590561 DOI: 10.1111/j.1476-5381.2010.00721.x]
 - 44 **Subbanna S**, Psychoyos D, Xie S, Basavarajappa BS. Postnatal ethanol exposure alters levels of 2-arachidonoylglycerol-metabolizing enzymes and pharmacological inhibition of monoacylglycerol lipase does not cause neurodegeneration in neonatal mice. *J Neurochem* 2015; **134**: 276-287 [PMID: 25857698 DOI: 10.1111/jnc.13120]
 - 45 **Bisogno T**, Howell F, Williams G, Minassi A, Cascio MG, Ligresti A, Matias I, Schiano-Moriello A, Paul P, Williams EJ, Gangadharan U, Hobbs C, Di Marzo V, Doherty P. Cloning of the first sn1-DAG lipases points to the spatial and temporal regulation of endocannabinoid signaling in the brain. *J Cell Biol* 2003; **163**: 463-468 [PMID: 14610053]

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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 psychosomatic disorders and pathological conditions.

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

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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

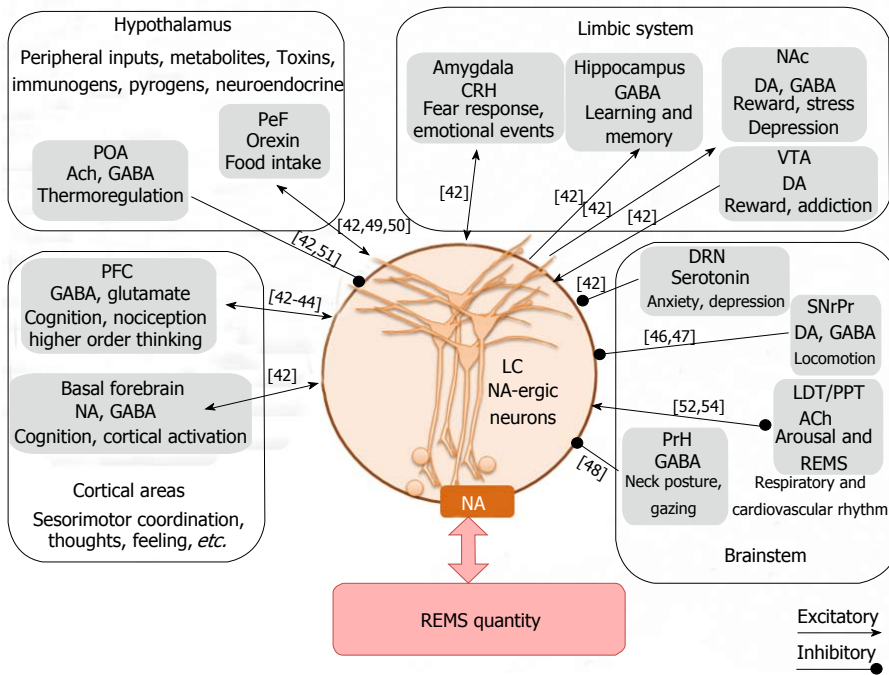


Figure 1 Schematic illustration of inputs to the locus coeruleus neurons from different regions in the brain, some of them are influenced by the environmental changes. The resultant output of the LC neurons is responsible for level of NA in the brain. As those LC-NA-ergic neurons cease activity during 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 nigra pars reticulata; PrH: Prepositus hypoglossus; PeF: Perifornical area; POA: Preoptic area; LDT/PPT: Laterodorsal 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 °C to 25 °C^[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 $\alpha 1$ -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 $\alpha 1$ -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 "chrononutrition"^[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], $\alpha 1$ 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 atherosclerosis 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

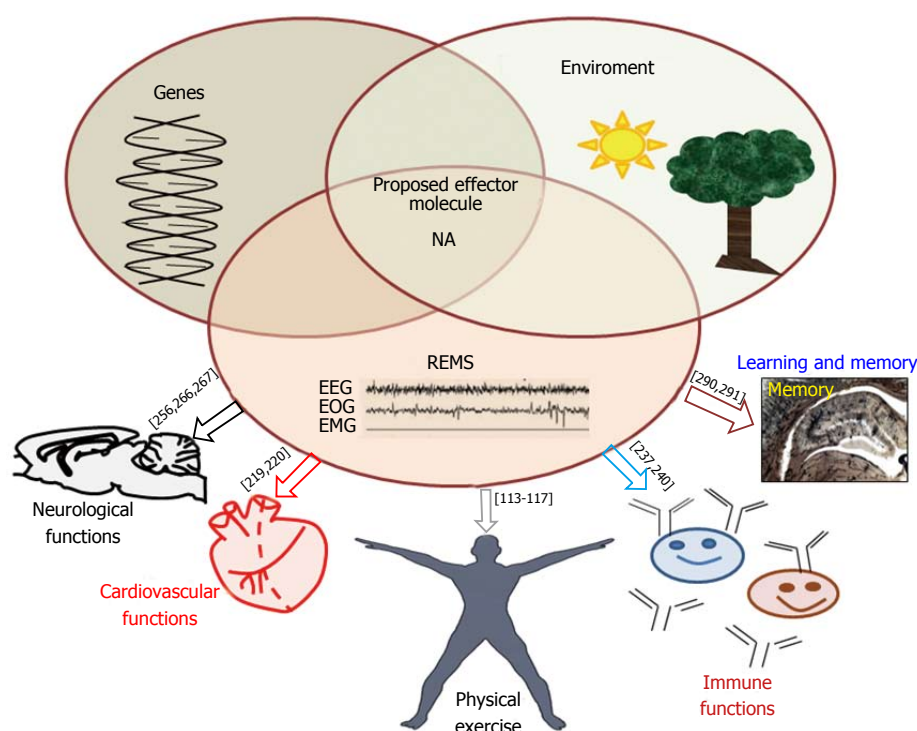


Figure 2 Interactions among environmental factors, rapid eye movement sleep and associated changes in gene expressions for long-term (sustained) modulation of patho-physiological changes have been diagrammatically represented in this figure. NA is at least one of the common mediators to induce the changes, 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-1 β 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, β 2-

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-1 β , while increasing the expressions of anti-inflammatory molecules, like I κ B, by signaling through α 1-, α 2-, 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 adrenoceptors 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 hypo-function 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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REFERENCES

- 1 **Tobler I.** Is sleep fundamentally different between mammalian species? *Behav Brain Res* 1995; **69**: 35-41 [PMID: 7546316 DOI: 10.1016/0166-4328(95)00025-O]
- 2 **Capellini I, Barton RA, McNamara P, Preston BT, Nunn CL.** Phylogenetic analysis of the ecology and evolution of mammalian sleep. *Evolution* 2008; **62**: 1764-1776 [PMID: 18384657 DOI: 10.1111/j.1558-5646.2008.00392.x]
- 3 **Cirelli C, Tononi G.** Is sleep essential? *PLoS Biol* 2008; **6**: e216 [PMID: 18752355 DOI: 10.1371/journal.pbio.0060216]
- 4 **Siegel JM.** Clues to the functions of mammalian sleep. *Nature* 2005; **437**: 1264-1271 [PMID: 16251951 DOI: 10.1038/nature04285]
- 5 **Akerstedt T.** Psychological and psychophysiological effects of shift work. *Scand J Work Environ Health* 1990; **16** Suppl 1: 67-73 [PMID: 2189223 DOI: 10.5271/sjweh.1819]
- 6 **Mallick BN, Singh A.** REM sleep loss increases brain excitability: role of noradrenaline and its mechanism of action. *Sleep Med Rev* 2011; **15**: 165-178 [PMID: 21482157 DOI: 10.1016/j.smrv.2010.11.001]
- 7 **Bliwise DL.** Sleep disorders in Alzheimer's disease and other dementias. *Clin Cornerstone* 2004; **6** Suppl 1A: S16-S28 [PMID: 15259536 DOI: 10.1016/S1098-3597(04)90014-2]
- 8 **Petit D, Lorrain D, Gauthier S, Montplaisir J.** Regional spectral analysis of the REM sleep EEG in mild to moderate Alzheimer's disease. *Neurobiol Aging* 1993; **14**: 141-145 [PMID: 8487916 DOI: 10.1016/0197-4580(93)90089-T]
- 9 **Boeve BF, Silber MH, Ferman TJ, Lucas JA, Parisi JE.** Association of REM sleep behavior disorder and neurodegenerative disease may reflect an underlying synucleinopathy. *Mov Disord* 2001; **16**: 622-630 [PMID: 11481685 DOI: 10.1002/mds.1120]
- 10 **Malik S, Boeve BF, Krahn LE, Silber MH.** Narcolepsy associated with other central nervous system disorders. *Neurology* 2001; **57**: 539-541 [PMID: 11502932 DOI: 10.1212/WNL.57.3.539]
- 11 **Boeve BF, Silber MH, Saper CB, Ferman TJ, Dickson DW, Parisi JE, Benarroch EE, Ahlskog JE, Smith GE, Caselli RC, Tippman-Peikert M, Olson EJ, Lin SC, Young T, Wszolek Z, Schenck CH, Mahowald MW, Castillo PR, Del Tredici K, Braak H.** Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. *Brain* 2007; **130**: 2770-2788 [PMID: 17412731 DOI: 10.1093/brain/awm056]
- 12 **Postuma RB, Gagnon JF, Vendette M, Charland K, Montplaisir J.** REM sleep behaviour disorder in Parkinson's disease is associated with specific motor features. *J Neurol Neurosurg Psychiatry* 2008; **79**: 1117-1121 [PMID: 18682443 DOI: 10.1136/jnnp.2008.149195]
- 13 **Poryazova RG, Zachariev ZI.** REM sleep behavior disorder in patients with Parkinson's disease. *Folia Med (Plovdiv)* 2005; **47**: 5-10 [PMID: 16152765]
- 14 **Pawlyk AC, Jha SK, Brennan FX, Morrison AR, Ross RJ.** A rodent model of sleep disturbances in posttraumatic stress disorder: the role of context after fear conditioning. *Biol Psychiatry* 2005; **57**: 268-277 [PMID: 15691528 DOI: 10.1016/j.biopsych.2004.11.008]
- 15 **Breslau N.** Neurobiological research on sleep and stress hormones in epidemiological samples. *Ann N Y Acad Sci* 2006; **1071**: 221-230 [PMID: 16891573 DOI: 10.1196/annals.1364.017]
- 16 **Cosentino M, Marino F.** Nerve Driven Immunity: Noradrenaline and Adrenaline. In: Levite M, editor *Nerve Driven Immunity: Neurotransmitters and Neuropeptides in the Immune System*: Springer Vienna, 2012: 47-96
- 17 **Francis BM, Yang J, Hajderi E, Brown ME, Michalski B, McLaurin J, Fahnestock M, Mount HT.** Reduced tissue levels of noradrenaline are associated with behavioral phenotypes of the TgCRND8 mouse model of Alzheimer's disease. *Neuropsychopharmacology* 2012; **37**: 1934-1944 [PMID: 22491352 DOI: 10.1038/npp.2012.40]
- 18 **González MM, Debilly G, Valatx JL.** Noradrenaline neurotoxin DSP-4 effects on sleep and brain temperature in the rat. *Neurosci Lett* 1998; **248**: 93-96 [PMID: 9654350 DOI: 10.1016/S0304-3940(98)00333-4]
- 19 **Iimori K, Tanaka M, Kohnno Y, Ida Y, Nakagawa R, Hoaki Y, Tsuda A, Nagasaki N.** Psychological stress enhances noradrenaline turnover in specific brain regions in rats. *Pharmacol Biochem Behav* 1982; **16**: 637-640 [PMID: 7200246 DOI: 10.1016/0091-3057(82)90429-4]
- 20 **Adolfsson R, Gottfries CG, Roos BE, Winblad B.** Changes in the brain catecholamines in patients with dementia of Alzheimer type. *Br J Psychiatry* 1979; **135**: 216-223 [PMID: 486847 DOI: 10.1192/bjp.135.3.216]
- 21 **Berridge CW, Arnsten AF, Foote SL.** Noradrenergic modulation of cognitive function: clinical implications of anatomical, electrophysiological and behavioural studies in animal models. *Psychol Med* 1993; **23**: 557-564 [PMID: 8234565 DOI: 10.1017/S0033291700025332]
- 22 **Bryson G.** Biogenic amines in normal and abnormal behavioral states. *Clin Chem* 1971; **17**: 5-26 [PMID: 4321003]
- 23 **Moret C, Briley M.** The importance of norepinephrine in depression. *Neuropsychiatr Dis Treat* 2011; **7**: 9-13 [PMID: 21750623 DOI: 10.2147/NDT.S19619]
- 24 **Rommelfanger KS, Weinshenker D.** Norepinephrine: The redheaded stepchild of Parkinson's disease. *Biochem Pharmacol* 2007; **74**: 177-190 [PMID: 17416354 DOI: 10.1016/j.bcp.2007.01.036]
- 25 **Aserinsky E, Kleitman N.** Regularly occurring periods of eye

- motility, and concomitant phenomena, during sleep. *Science* 1953; **118**: 273-274 [PMID: 13089671 DOI: 10.1126/science.118.3062.273]
- 26 **Moruzzi G.** The sleep-waking cycle. *Ergeb Physiol* 1972; **64**: 1-165 [PMID: 4340664]
- 27 **Siegel J.** Brainstem mechanisms generating REM sleep. In: Kryger M, Roth T, dement W, editors. Principles and practice of sleep medicine. Philadelphia: Saunders, 1989: 104-120
- 28 **Jones BE.** Elimination of paradoxical sleep by lesions of the pontine gigantocellular tegmental field in the cat. *Neurosci Lett* 1979; **13**: 285-293 [PMID: 231225 DOI: 10.1016/0304-3940(79)91508-8]
- 29 **Drucker-Colin R, Pedraza JG.** Kainic acid lesions of gigantocellular tegmental field (FTG) neurons does not abolish REM sleep. *Brain Res* 1983; **272**: 387-391 [PMID: 6311343 DOI: 10.1016/0006-8993(83)90590-5]
- 30 **Friedman L, Jones BE.** Computer graphics analysis of sleep-wakefulness state changes after pontine lesions. *Brain Res Bull* 1984; **13**: 53-68 [PMID: 6478271 DOI: 10.1016/0361-9230(84)90008-X]
- 31 **Siegel JM, Tomaszewski KS, Nienhuis R.** Behavioral states in the chronic medullary and midpontine cat. *Electroencephalogr Clin Neurophysiol* 1986; **63**: 274-288 [PMID: 2419085 DOI: 10.1016/0013-4694(86)90095-7]
- 32 **Siegel JM, Nienhuis R, Tomaszewski KS.** Rostral brainstem contributes to medullary inhibition of muscle tone. *Brain Res* 1983; **268**: 344-348 [PMID: 6871687]
- 33 **Jones BE.** The role of noradrenergic locus coeruleus neurons and neighboring cholinergic neurons of the pontomesencephalic tegmentum in sleep-wake states. *Prog Brain Res* 1991; **88**: 533-543 [PMID: 1813933 DOI: 10.1016/S0079-6123(08)63832-7]
- 34 **Mallick BN, Kaur S, Jha SK, Siegel JM.** Possible role of GABA in the regulation of REM sleep with special reference to REM-OFF neurons. In: Mallick BN, Inoue S, editors. Rapid Eye Movement Sleep New York: Marcel Dekker, 1999: 153-166
- 35 **Mallick BN, Kaur S, Saxena RN.** Interactions between cholinergic and GABAergic neurotransmitters in and around the locus coeruleus for the induction and maintenance of rapid eye movement sleep in rats. *Neuroscience* 2001; **104**: 467-485 [PMID: 11377848 DOI: 10.1016/S0306-4522(01)00062-8]
- 36 **de Lecea L, Kilduff TS, Peyron C, Gao X, Foye PE, Danielson PE, Fukuhara C, Battenberg EL, Gautvik VT, Bartlett FS, Frankel WN, van den Pol AN, Bloom FE, Gautvik KM, Sutcliffe JG.** The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. *Proc Natl Acad Sci USA* 1998; **95**: 322-327 [PMID: 9419374 DOI: 10.1073/pnas.95.1.322]
- 37 **Hagan JJ, Leslie RA, Patel S, Evans ML, Wattam TA, Holmes S, Benham CD, Taylor SG, Routledge C, Hemmati P, Munton RP, Ashmeade TE, Shah AS, Hatcher JP, Hatcher PD, Jones DN, Smith MI, Piper DC, Hunter AJ, Porter RA, Upton N.** Orexin A activates locus coeruleus cell firing and increases arousal in the rat. *Proc Natl Acad Sci USA* 1999; **96**: 10911-10916 [PMID: 10485925 DOI: 10.1073/pnas.96.19.10911]
- 38 **Alam MN, Gong H, Alam T, Jaganath R, McGinty D, Szymusiak R.** Sleep-waking discharge patterns of neurons recorded in the rat perifornical lateral hypothalamic area. *J Physiol* 2002; **538**: 619-631 [PMID: 11790824 DOI: 10.1113/jphysiol.2001.012888]
- 39 **Lin JS, Sakai K, Jouvet M.** [Role of hypothalamic histaminergic systems in the regulation of vigilance states in cats]. *C R Acad Sci III* 1986; **303**: 469-474 [PMID: 2877720]
- 40 **Mallick BN, Thankachan S, Islam F.** Influence of hypnogenic brain areas on wakefulness- and rapid-eye-movement sleep-related neurons in the brainstem of freely moving cats. *J Neurosci Res* 2004; **75**: 133-142 [PMID: 14689456 DOI: 10.1002/jnr.10827]
- 41 **Takakusaki K, Saitoh K, Harada H, Okumura T, Sakamoto T.** Evidence for a role of basal ganglia in the regulation of rapid eye movement sleep by electrical and chemical stimulation for the pedunculo pontine tegmental nucleus and the substantia nigra pars reticulata in decerebrate cats. *Neuroscience* 2004; **124**: 207-220 [PMID: 14960352 DOI: 10.1016/j.neuroscience.2003.10.028]
- 42 **Samuels ER, Szabadi E.** Functional neuroanatomy of the noradrenergic locus coeruleus: its roles in the regulation of arousal and autonomic function part II: physiological and pharmacological manipulations and pathological alterations of locus coeruleus activity in humans. *Curr Neuropsychopharmacol* 2008; **6**: 254-285 [PMID: 19506724 DOI: 10.2174/157015908785777193]
- 43 **Andrews GD, Lavin A.** Methylphenidate increases cortical excitability via activation of alpha-2 noradrenergic receptors. *Neuropsychopharmacology* 2006; **31**: 594-601 [PMID: 15999146 DOI: 10.1038/sj.npp.1300818]
- 44 **Jodo E, Chiang C, Aston-Jones G.** Potent excitatory influence of prefrontal cortex activity on noradrenergic locus coeruleus neurons. *Neuroscience* 1998; **83**: 63-79 [PMID: 9466399 DOI: 10.1016/S0306-4522(97)00372-2]
- 45 **Aston-Jones G, Akaoka H, Charléty P, Chouvet G.** Serotonin selectively attenuates glutamate-evoked activation of noradrenergic locus coeruleus neurons. *J Neurosci* 1991; **11**: 760-769 [PMID: 1672153]
- 46 **Pal D, Mallick BN.** Role of noradrenergic and GABA-ergic inputs in pedunculo pontine tegmentum for regulation of rapid eye movement sleep in rats. *Neuropharmacology* 2006; **51**: 1-11 [PMID: 16616214 DOI: 10.1016/j.neuropharm.2006.02.006]
- 47 **Pal D, Mallick BN.** GABA in pedunculo pontine tegmentum increases rapid eye movement sleep in freely moving rats: possible role of GABA-ergic inputs from substantia nigra pars reticulata. *Neuroscience* 2009; **164**: 404-414 [PMID: 19698764 DOI: 10.1016/j.neuroscience.2009.08.025]
- 48 **Kaur S, Saxena RN, Mallick BN.** GABAergic neurons in prepositus hypoglossi regulate REM sleep by its action on locus coeruleus in freely moving rats. *Synapse* 2001; **42**: 141-150 [PMID: 11746711 DOI: 10.1002/syn.1109]
- 49 **McCarley RW, Hobson JA.** Discharge patterns of cat pontine brain stem neurons during desynchronized sleep. *J Neurophysiol* 1975; **38**: 751-766 [PMID: 1159463 DOI: 10.1016/0006-8993(77)90925-8]
- 50 **Hobson JA, McCarley RW, Wyzinski PW.** Sleep cycle oscillation: reciprocal discharge by two brainstem neuronal groups. *Science* 1975; **189**: 55-58 [PMID: 1094539 DOI: 10.1126/science.1094539]
- 51 **Rasmussen K, Morilak DA, Jacobs BL.** Single unit activity of locus coeruleus neurons in the freely moving cat. I. During naturalistic behaviors and in response to simple and complex stimuli. *Brain Res* 1986; **371**: 324-334 [PMID: 3697761 DOI: 10.1016/0006-8993(86)90370-7]
- 52 **Chu NS, Bloom FE.** Activity patterns of catecholamine-containing pontine neurons in the dorso-lateral tegmentum of unrestrained cats. *J Neurobiol* 1974; **5**: 527-544 [PMID: 4373534 DOI: 10.1002/neu.480050605]
- 53 **Sakai K, Jouvet M.** Brain stem PGO-on cells projecting directly to the cat dorsal lateral geniculate nucleus. *Brain Res* 1980; **194**: 500-505 [PMID: 7388627 DOI: 10.1016/0006-8993(80)91231-7]
- 54 **Steriade M, McCarley RW.** Brain control of wakefulness and sleep. first ed. New York: Kluwer Academic/Plenum, 2005
- 55 **Kumar R, Bose A, Mallick BN.** A mathematical model towards understanding the mechanism of neuronal regulation of wake-NREMS-REMS states. *PLoS One* 2012; **7**: e42059 [PMID: 22905114 DOI: 10.1371/journal.pone.0042059]
- 56 **Pal D, Madan V, Mallick BN.** Neural mechanism of rapid eye movement sleep generation: Cessation of locus coeruleus neurons is a necessity. *Shengli Xuebao* 2005; **57**: 401-413 [PMID: 16094486]
- 57 **Mallick BN, Siegel JM, Fahringer H.** Changes in pontine unit activity with REM sleep deprivation. *Brain Res* 1990; **515**: 94-98 [PMID: 2357583 DOI: 10.1016/0006-8993(90)90581-U]
- 58 **Cesputio R, Gomez ME, Faradj H, Jouvet M.** Alterations in the sleep-waking cycle induced by cooling of the locus coeruleus area. *Electroencephalogr Clin Neurophysiol* 1982; **54**: 570-578 [PMID: 6181980 DOI: 10.1016/0013-4694(82)90042-6]
- 59 **Caballero A, De Andrés I.** Unilateral lesions in locus coeruleus area enhance paradoxical sleep. *Electroencephalogr Clin Neurophysiol* 1986; **64**: 339-346 [PMID: 2428582 DOI: 10.1016/0013-4694(86)90158-6]

- 60 **Laguzzi RF**, Adrien J, Bourgoin S, Hamon M. Effects of intraventricular injection of 6-hydroxydopamine in the developing kitten. I. On the sleepwaking cycles. *Brain Res* 1979; **160**: 445-459 [PMID: 217478 DOI: 10.1016/0006-8993(79)91072-2]
- 61 **Farber J**, Miller JD, Crawford KA, McMillen BA. Dopamine metabolism and receptor sensitivity in rat brain after REM sleep deprivation. *Pharmacol Biochem Behav* 1983; **18**: 509-513 [PMID: 6135227 DOI: 10.1016/0091-3057(83)90272-1]
- 62 **Singh S**, Mallick BN. Mild electrical stimulation of pontine tegmentum around locus coeruleus reduces rapid eye movement sleep in rats. *Neurosci Res* 1996; **24**: 227-235 [PMID: 8815443 DOI: 10.1016/0168-0102(95)00998-1]
- 63 **Kaitin KI**, Bliwise DL, Gleason C, Nino-Murcia G, Dement WC, Libet B. Sleep disturbance produced by electrical stimulation of the locus coeruleus in a human subject. *Biol Psychiatry* 1986; **21**: 710-716 [PMID: 3730455 DOI: 10.1016/0006-3223(86)90235-0]
- 64 **Carter ME**, Yizhar O, Chikahisa S, Nguyen H, Adamantidis A, Nishino S, Deisseroth K, de Lecea L. Tuning arousal with optogenetic modulation of locus coeruleus neurons. *Nat Neurosci* 2010; **13**: 1526-1533 [PMID: 21037585 DOI: 10.1038/nn.2682]
- 65 **Porkka-Heiskanen T**, Smith SE, Taira T, Urban JH, Levine JE, Turek FW, Stenberg D. Noradrenergic activity in rat brain during rapid eye movement sleep deprivation and rebound sleep. *Am J Physiol* 1995; **268**: R1456-R1463 [PMID: 7611522]
- 66 **Léna I**, Parrot S, Deschaux O, Muffat-Joly S, Sauvinet V, Renaud B, Suaud-Chagny MF, Gottesmann C. Variations in extracellular levels of dopamine, noradrenaline, glutamate, and aspartate across the sleep-wake cycle in the medial prefrontal cortex and nucleus accumbens of freely moving rats. *J Neurosci Res* 2005; **81**: 891-899 [PMID: 16041801 DOI: 10.1002/jnr.20602]
- 67 **Nitz D**, Siegel JM. GABA release in the locus coeruleus as a function of sleep/wake state. *Neuroscience* 1997; **78**: 795-801 [PMID: 9153658 DOI: 10.1016/S0306-4522(96)00549-0]
- 68 **Dodt C**, Breckling U, Derad I, Fehm HL, Born J. Plasma epinephrine and norepinephrine concentrations of healthy humans associated with nighttime sleep and morning arousal. *Hypertension* 1997; **30**: 71-76 [PMID: 9231823 DOI: 10.1161/01.HYP.30.1.71]
- 69 **Mallick BN**, Singh A, Khanday MA. Activation of inactivation process initiates rapid eye movement sleep. *Prog Neurobiol* 2012; **97**: 259-276 [PMID: 22521402 DOI: 10.1016/j.pneurobio.2012.04.001]
- 70 **Masserano JM**, King C. Effects on sleep of phentolamine and epinephrine infused into the locus coeruleus of cats. *Eur J Pharmacol* 1982; **84**: 199-204 [PMID: 7173319 DOI: 10.1016/0014-2999(82)90202-3]
- 71 **Masserano JM**, King C. Effects on sleep of acetylcholine perfusion of the locus coeruleus of cats. *Neuropharmacology* 1982; **21**: 1163-1167 [PMID: 7177340 DOI: 10.1016/0028-3908(82)90174-5]
- 72 **Kawahara Y**, Kawahara H, Westerink BH. Tonic regulation of the activity of noradrenergic neurons in the locus coeruleus of the conscious rat studied by dual-probe microdialysis. *Brain Res* 1999; **823**: 42-48 [PMID: 10095010 DOI: 10.1016/S0006-8993(99)01062-8]
- 73 **Kaur S**, Saxena RN, Mallick BN. GABA in locus coeruleus regulates spontaneous rapid eye movement sleep by acting on GABAA receptors in freely moving rats. *Neurosci Lett* 1997; **223**: 105-108 [PMID: 9089684 DOI: 10.1016/S0304-3940(97)13410-3]
- 74 **Pollock MS**, Mislberger RE. Rapid eye movement sleep induction by microinjection of the GABA-A antagonist bicuculline into the dorsal subcoeruleus area of the rat. *Brain Res* 2003; **962**: 68-77 [PMID: 12543457 DOI: 10.1016/S0006-8993(02)03956-2]
- 75 **Bourgin P**, Huitrón-Réndiz S, Spier AD, Fabre V, Morte B, Criado JR, Sutcliffe JG, Henriksen SJ, de Lecea L. Hypocretin-1 modulates rapid eye movement sleep through activation of locus coeruleus neurons. *J Neurosci* 2000; **20**: 7760-7765 [PMID: 11027239]
- 76 **Chen L**, McKenna JT, Bolortuya Y, Winston S, Thakkar MM, Basheer R, Brown RE, McCarley RW. Knockdown of orexin type 1 receptor in rat locus coeruleus increases REM sleep during the dark period. *Eur J Neurosci* 2010; **32**: 1528-1536 [PMID: 21089218 DOI: 10.1111/j.1460-9568.2010.07401.x]
- 77 **Choudhary RC**, Khanday MA, Mitra A, Mallick BN. Perifornical orexinergic neurons modulate REM sleep by influencing locus coeruleus neurons in rats. *Neuroscience* 2014; **279**: 33-43 [PMID: 25168734 DOI: 10.1016/j.neuroscience.2014.08.017]
- 78 **Alam MA**, Mallick BN. Glutamic acid stimulation of the perifornical-lateral hypothalamic area promotes arousal and inhibits non-REM/REM sleep. *Neurosci Lett* 2008; **439**: 281-286 [PMID: 18534750 DOI: 10.1016/j.neulet.2008.05.042]
- 79 **Toppila J**, Niittymäki P, Porkka-Heiskanen T, Stenberg D. Intracerebroventricular and locus coeruleus microinjections of somatostatin antagonist decrease REM sleep in rats. *Pharmacol Biochem Behav* 2000; **66**: 721-727 [PMID: 10973509 DOI: 10.1016/S0091-3057(00)00242-2]
- 80 **Segal M**. Serotonergic innervation of the locus coeruleus from the dorsal raphe and its action on responses to noxious stimuli. *J Physiol* 1979; **286**: 401-415 [PMID: 439032 DOI: 10.1113/jphysiol.1979.sp012628]
- 81 **Monti JM**, Monti D. The involvement of dopamine in the modulation of sleep and waking. *Sleep Med Rev* 2007; **11**: 113-133 [PMID: 17275369 DOI: 10.1016/j.smrv.2006.08.003]
- 82 **Cuturic M**, Abramson RK, Vallini D, Frank EM, Shamsnia M. Sleep patterns in patients with Huntington's disease and their unaffected first-degree relatives: a brief report. *Behav Sleep Med* 2009; **7**: 245-254 [PMID: 19787493 DOI: 10.1080/15402000903190215]
- 83 **Factor SA**, McAlarney T, Sanchez-Ramos JR, Weiner WJ. Sleep disorders and sleep effect in Parkinson's disease. *Mov Disord* 1990; **5**: 280-285 [PMID: 2259351 DOI: 10.1002/mds.870050404]
- 84 **Montplaisir J**, Petit D, Lorrain D, Gauthier S, Nielsen T. Sleep in Alzheimer's disease: further considerations on the role of brainstem and forebrain cholinergic populations in sleep-wake mechanisms. *Sleep* 1995; **18**: 145-148 [PMID: 7610309]
- 85 **Okamoto-Mizuno K**, Mizuno K. Effects of thermal environment on sleep and circadian rhythm. *J Physiol Anthropol* 2012; **31**: 14 [PMID: 22738673 DOI: 10.1186/1880-6805-31-14]
- 86 **Gilbert SS**, van den Heuvel CJ, Ferguson SA, Dawson D. Thermoregulation as a sleep signalling system. *Sleep Med Rev* 2004; **8**: 81-93 [PMID: 15033148 DOI: 10.1016/S1087-0792(03)00023-6]
- 87 **Wehr TA**. A brain-warming function for REM sleep. *Neurosci Biobehav Rev* 1992; **16**: 379-397 [PMID: 1528526 DOI: 10.1016/S0149-7634(05)80208-8]
- 88 **Muzet A**, Ehrhart J, Candas V, Libert JP, Vogt JJ. REM sleep and ambient temperature in man. *Int J Neurosci* 1983; **18**: 117-126 [PMID: 6840976]
- 89 **Jennings JR**, Reynolds CF, Bryant DS, Berman SR, Buysse DJ, Dahl RE, Hoch CC, Monk TH. Peripheral thermal responsivity to facial cooling during sleep. *Psychophysiology* 1993; **30**: 374-382 [PMID: 8327623 DOI: 10.1111/j.1469-8986.1993.tb02059.x]
- 90 **Candas V**, Libert JP, Muzet A. Heating and cooling stimulations during SWS and REM sleep in man. *J Thermal Biol* 1982; **7**: 155-158 [DOI: 10.1016/0306-4565(82)90005-5]
- 91 **Parmeggiani PL**. Interaction between sleep and thermoregulation: an aspect of the control of behavioral states. *Sleep* 1987; **10**: 426-435 [PMID: 3317725]
- 92 **Boulant JA**, Demieville HN. Responses of thermosensitive preoptic and septal neurons to hippocampal and brain stem stimulation. *J Neurophysiol* 1977; **40**: 1356-1368 [PMID: 925734 DOI: 10.1111/j.1749-6632.1998.tb08319.x]
- 93 **Boulant JA**, Hardy JD. The effect of spinal and skin temperatures on the firing rate and thermosensitivity of preoptic neurones. *J Physiol* 1974; **240**: 639-660 [PMID: 4416218 DOI: 10.1113/jphysiol.1974.sp010627]
- 94 **Jha SK**, Mallick BN. Presence of alpha-1 norepinephrinergic and GABA-A receptors on medial preoptic hypothalamus thermosensitive neurons and their role in integrating brainstem ascending reticular activating system inputs in thermoregulation in rats. *Neuroscience* 2009; **158**: 833-844 [PMID: 19015008 DOI: 10.1016/j.neuroscience.2008.10.038]
- 95 **Simmonds MA**. Effect of environmental temperature on the

- turnover of noradrenaline in hypothalamus and other areas of rat brain. *J Physiol* 1969; **203**: 199-210 [PMID: 5821872 DOI: 10.1113/jphysiol.1969.sp008859]
- 96 **Nemoto EM**, Klementavicius R, Melick JA, Yonas H. Norepinephrine activation of basal cerebral metabolic rate for oxygen (CMRO₂) during hypothermia in rats. *Anesth Analg* 1996; **83**: 1262-1267 [PMID: 8942597]
- 97 **Ratheiser KM**, Brillion DJ, Campbell RG, Matthews DE. Epinephrine produces a prolonged elevation in metabolic rate in humans. *Am J Clin Nutr* 1998; **68**: 1046-1052 [PMID: 9808221]
- 98 **Kräuchi K**, Cajochen C, Werth E, Wirz-Justice A. Functional link between distal vasodilation and sleep-onset latency? *Am J Physiol Regul Integr Comp Physiol* 2000; **278**: R741-R748 [PMID: 10712296]
- 99 **Lack L**, Gradisar M. Acute finger temperature changes preceding sleep onsets over a 45-h period. *J Sleep Res* 2002; **11**: 275-282 [PMID: 12464094 DOI: 10.1046/j.1365-2869.2002.00312.x]
- 100 **Mallick BN**, Alam MN. Different types of norepinephrine receptors are involved in preoptic area mediated independent modulation of sleep-wakefulness and body temperature. *Brain Res* 1992; **591**: 8-19 [PMID: 1332801 DOI: 10.1016/0006-8993(92)90972-C]
- 101 **Poole S**, Stephenson JD. Effects of noradrenaline and carbachol on temperature regulation of rats. *Br J Pharmacol* 1979; **65**: 43-51 [PMID: 760890 DOI: 10.1111/j.1476-5381.1979.tb17332.x]
- 102 **Lack LC**, Gradisar M, Van Someren EJ, Wright HR, Lushington K. The relationship between insomnia and body temperatures. *Sleep Med Rev* 2008; **12**: 307-317 [PMID: 18603220 DOI: 10.1016/j.smrv.2008.02.003]
- 103 **Jaiswal MK**, Mallick BN. Prazosin modulates rapid eye movement sleep deprivation-induced changes in body temperature in rats. *J Sleep Res* 2009; **18**: 349-356 [PMID: 19552734 DOI: 10.1111/j.1365-2869.2008.00731.x]
- 104 **O'Connor PJ**, Youngstedt SD. Influence of exercise on human sleep. *Exerc Sport Sci Rev* 1995; **23**: 105-134 [PMID: 7556348]
- 105 **Youngstedt SD**. Effects of exercise on sleep. *Clin Sports Med* 2005; **24**: 355-365, xi [PMID: 15892929 DOI: 10.1016/j.csm.2004.12.003]
- 106 **Horne JA**, Moore VJ. Sleep EEG effects of exercise with and without additional body cooling. *Electroencephalogr Clin Neurophysiol* 1985; **60**: 33-38 [PMID: 2578352 DOI: 10.1016/0013-4694(85)90948-4]
- 107 **Kubitz KA**, Landers DM, Petruzzello SJ, Han M. The effects of acute and chronic exercise on sleep. A meta-analytic review. *Sports Med* 1996; **21**: 277-291 [PMID: 8726346 DOI: 10.2165/00007256-199621040-00004]
- 108 **Youngstedt SD**, Kline CE. Epidemiology of exercise and sleep. *Sleep Biol Rhythms* 2006; **4**: 215-221 [PMID: 25374476 DOI: 10.1111/j.1479-8425.2006.00235.x]
- 109 **Netzer NC**, Kristo D, Steinle H, Lehmann M, Strohl KP. REM sleep and catecholamine excretion: a study in elite athletes. *Eur J Appl Physiol* 2001; **84**: 521-526 [PMID: 11482546 DOI: 10.1007/s004210100383]
- 110 **Hagberg JM**, Seals DR, Yerg JE, Gavin J, Gingerich R, Premachandra B, Holloszy JO. Metabolic responses to exercise in young and older athletes and sedentary men. *J Appl Physiol* (1985) 1988; **65**: 900-908 [PMID: 3170436]
- 111 **Greiwe JS**, Hickner RC, Shah SD, Cryer PE, Holloszy JO. Norepinephrine response to exercise at the same relative intensity before and after endurance exercise training. *J Appl Physiol* (1985) 1999; **86**: 531-535 [PMID: 9931187]
- 112 **Lista I**, Sorrentino G. Biological mechanisms of physical activity in preventing cognitive decline. *Cell Mol Neurobiol* 2010; **30**: 493-503 [PMID: 20041290 DOI: 10.1007/s10571-009-9488-x]
- 113 **Griffin EW**, Bechara RG, Birch AM, Kelly AM. Exercise enhances hippocampal-dependent learning in the rat: evidence for a BDNF-related mechanism. *Hippocampus* 2009; **19**: 973-980 [PMID: 19437410 DOI: 10.1002/hipo.20631]
- 114 **Shen H**, Tong L, Balazs R, Cotman CW. Physical activity elicits sustained activation of the cyclic AMP response element-binding protein and mitogen-activated protein kinase in the rat hippocampus. *Neuroscience* 2001; **107**: 219-229 [PMID: 11731096 DOI: 10.1016/S0306-4522(01)00315-3]
- 115 **O'Callaghan RM**, Ohle R, Kelly AM. The effects of forced exercise on hippocampal plasticity in the rat: A comparison of LTP, spatial- and non-spatial learning. *Behav Brain Res* 2007; **176**: 362-366 [PMID: 17113656 DOI: 10.1016/j.bbr.2006.10.018]
- 116 **Farmer J**, Zhao X, van Praag H, Wodtke K, Gage FH, Christie BR. Effects of voluntary exercise on synaptic plasticity and gene expression in the dentate gyrus of adult male Sprague-Dawley rats in vivo. *Neuroscience* 2004; **124**: 71-79 [PMID: 14960340 DOI: 10.1016/j.neuroscience.2003.09.029]
- 117 **van Praag H**, Kempermann G, Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat Neurosci* 1999; **2**: 266-270 [PMID: 10195220 DOI: 10.1038/6368]
- 118 **Xu WP**, Shan LD, Gong S, Chen L, Zhang YJ, Yin QZ, Hisamitsu T, Jiang XH, Guo SY. Forced running enhances neurogenesis in the hippocampal dentate gyrus of adult rats and improves learning ability. *Sheng Li Xue Bao* 2006; **58**: 415-420 [PMID: 17041724]
- 119 **Tully K**, Bolshakov VY. Emotional enhancement of memory: how norepinephrine enables synaptic plasticity. *Mol Brain* 2010; **3**: 15 [PMID: 20465834 DOI: 10.1186/1756-6606-3-15]
- 120 **Cai DJ**, Shuman T, Gorman MR, Sage JR, Anagnostaras SG. Sleep selectively enhances hippocampus-dependent memory in mice. *Behav Neurosci* 2009; **123**: 713-719 [PMID: 19634928 DOI: 10.1037/a0016415]
- 121 **Harrison Y**, Horne JA. The impact of sleep deprivation on decision making: a review. *J Exp Psychol Appl* 2000; **6**: 236-249 [PMID: 11014055 DOI: 10.1037/1076-898X.6.3.236]
- 122 **Alhaider IA**, Aleisa AM, Tran TT, Alkadhi KA. Sleep deprivation prevents stimulation-induced increases of levels of P-CREB and BDNF: protection by caffeine. *Mol Cell Neurosci* 2011; **46**: 742-751 [PMID: 21338685 DOI: 10.1016/j.mcn.2011.02.006]
- 123 **Zagaar M**, Alhaider I, Dao A, Levine A, Alkarawi A, Alzubaidy M, Alkadhi K. The beneficial effects of regular exercise on cognition in REM sleep deprivation: behavioral, electrophysiological and molecular evidence. *Neurobiol Dis* 2012; **45**: 1153-1162 [PMID: 22227452 DOI: 10.1016/j.nbd.2011.12.039]
- 124 **Zagaar MA**, Dao AT, Alhaider IA, Alkadhi KA. Prevention by Regular Exercise of Acute Sleep Deprivation-Induced Impairment of Late Phase LTP and Related Signaling Molecules in the Dentate Gyrus. *Mol Neurobiol* 2016; **53**: 2900-2910 [PMID: 25902862 DOI: 10.1007/s12035-015-9176-4]
- 125 **Somarajan BI**, Khanday MA, Mallick BN. Rapid Eye Movement Sleep Deprivation Induces Neuronal Apoptosis by Noradrenaline Acting on Alpha1 Adrenoceptor and by Triggering Mitochondrial Intrinsic Pathway. *Front Neurol* 2016; **7**: 25 [PMID: 27014180 DOI: 10.3389/fneur.2016.00025]
- 126 **Biswas S**, Mishra P, Mallick BN. Increased apoptosis in rat brain after rapid eye movement sleep loss. *Neuroscience* 2006; **142**: 315-331 [PMID: 16887278 DOI: 10.1016/j.neuroscience.2006.06.026]
- 127 **Bohannon RW**. Physical rehabilitation in neurologic diseases. *Curr Opin Neurol* 1993; **6**: 765-772 [PMID: 8293149 DOI: 10.1097/00019052-199310000-00015]
- 128 **Cotman CW**, Berchtold NC, Christie LA. Exercise builds brain health: key roles of growth factor cascades and inflammation. *Trends Neurosci* 2007; **30**: 464-472 [PMID: 17765329 DOI: 10.1016/j.tins.2007.06.011]
- 129 **Kramer AF**, Hahn S, Cohen NJ, Banich MT, McAuley E, Harrison CR, Chason J, Vakil E, Bardell L, Boileau RA, Colcombe A. Ageing, fitness and neurocognitive function. *Nature* 1999; **400**: 418-419 [PMID: 10440369 DOI: 10.1038/22682]
- 130 **Ng F**, Dodd S, Berk M. The effects of physical activity in the acute treatment of bipolar disorder: a pilot study. *J Affect Disord* 2007; **101**: 259-262 [PMID: 17182104 DOI: 10.1016/j.jad.2006.11.014]
- 131 **Kucyi A**, Alsuwaidan MT, Liauw SS, McIntyre RS. Aerobic physical exercise as a possible treatment for neurocognitive dysfunction in bipolar disorder. *Postgrad Med* 2010; **122**: 107-116 [PMID: 21084787 DOI: 10.3810/pgm.2010.11.2228]
- 132 **Anderson IM**, Haddad PM, Scott J. Bipolar disorder. *BMJ* 2012;

- 345: e8508 [PMID: 23271744 DOI: 10.1136/Bmj.E8508]
- 133 **Passos GS**, Poyares D, Santana MG, Teixeira AA, Lira FS, Youngstedt SD, dos Santos RV, Tufik S, de Mello MT. Exercise improves immune function, antidepressive response, and sleep quality in patients with chronic primary insomnia. *Biomed Res Int* 2014; **2014**: 498961 [PMID: 25328886 DOI: 10.1155/2014/498961]
 - 134 **Chen KM**, Chen MH, Lin MH, Fan JT, Lin HS, Li CH. Effects of yoga on sleep quality and depression in elders in assisted living facilities. *J Nurs Res* 2010; **18**: 53-61 [PMID: 20220611 DOI: 10.1097/JNR.0b013e3181ce5189]
 - 135 **Halpern J**, Cohen M, Kennedy G, Reece J, Cahan C, Baharav A. Yoga for improving sleep quality and quality of life for older adults. *Altern Ther Health Med* 2014; **20**: 37-46 [PMID: 24755569]
 - 136 **Innes KE**, Selfe TK. The Effects of a Gentle Yoga Program on Sleep, Mood, and Blood Pressure in Older Women with Restless Legs Syndrome (RLS): A Preliminary Randomized Controlled Trial. *Evid Based Complement Alternat Med* 2012; **2012**: 294058 [PMID: 22474497 DOI: 10.1155/2012/294058]
 - 137 **Innes KE**, Selfe TK, Agarwal P, Williams K, Flack KL. Efficacy of an eight-week yoga intervention on symptoms of restless legs syndrome (RLS): a pilot study. *J Altern Complement Med* 2013; **19**: 527-535 [PMID: 23270319 DOI: 10.1089/acm.2012.0330]
 - 138 **Mustian KM**, Janelins M, Peppone LJ, Kamen C. Yoga for the Treatment of Insomnia among Cancer Patients: Evidence, Mechanisms of Action, and Clinical Recommendations. *Oncol Hematol Rev* 2014; **10**: 164-168 [PMID: 25861453 DOI: 10.17925/OHR.2014.10.2.164]
 - 139 **Spiegel K**, Tasali E, Penev P, Van Cauter E. Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann Intern Med* 2004; **141**: 846-850 [PMID: 15583226 DOI: 10.7326/0003-4819-141-11-200412070-00008]
 - 140 **Taheri S**, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. *PLoS Med* 2004; **1**: e62 [PMID: 15602591 DOI: 10.1371/journal.pmed.0010062]
 - 141 **Tahara Y**, Shibata S. Chrono-biology, chrono-pharmacology, and chrono-nutrition. *J Pharmacol Sci* 2014; **124**: 320-335 [PMID: 24572815 DOI: 10.1254/jphs.13R06CR]
 - 142 **Belanger-Willoughby N**, Linehan V, Hirasawa M. Thermosensing mechanisms and their impairment by high-fat diet in orexin neurons. *Neuroscience* 2016; **324**: 82-91 [PMID: 26964685 DOI: 10.1016/j.neuroscience.2016.03.003]
 - 143 **Grandner MA**, Jackson N, Gerstner JR, Knutson KL. Sleep symptoms associated with intake of specific dietary nutrients. *J Sleep Res* 2014; **23**: 22-34 [PMID: 23992533 DOI: 10.1111/jsr.12084]
 - 144 **Zeng Y**, Yang J, Du J, Pu X, Yang X, Yang S, Yang T. Strategies of Functional Foods Promote Sleep in Human Being. *Curr Signal Transduct Ther* 2014; **9**: 148-155 [PMID: 26005400 DOI: 10.2174/1574362410666150205165504]
 - 145 **Afaghi A**, O'Connor H, Chow CM. Acute effects of the very low carbohydrate diet on sleep indices. *Nutr Neurosci* 2008; **11**: 146-154 [PMID: 18681982 DOI: 10.1179/147683008X301540]
 - 146 **Vorona RD**, Winn MP, Babineau TW, Eng BP, Feldman HR, Ware JC. Overweight and obese patients in a primary care population report less sleep than patients with a normal body mass index. *Arch Intern Med* 2005; **165**: 25-30 [PMID: 15642870 DOI: 10.1001/archinte.165.1.25]
 - 147 **Stern JH**, Grant AS, Thomson CA, Tinker L, Hale L, Brennan KM, Woods NF, Chen Z. Short sleep duration is associated with decreased serum leptin, increased energy intake and decreased diet quality in postmenopausal women. *Obesity* (Silver Spring) 2014; **22**: E55-E61 [PMID: 24347344 DOI: 10.1002/oby.20683]
 - 148 **Spiegel K**, Knutson K, Leproult R, Tasali E, Van Cauter E. Sleep loss: a novel risk factor for insulin resistance and Type 2 diabetes. *J Appl Physiol* (1985) 2005; **99**: 2008-2019 [PMID: 16227462 DOI: 10.1152/japplphysiol.00660.2005]
 - 149 **Yaggi HK**, Araujo AB, McKinlay JB. Sleep duration as a risk factor for the development of type 2 diabetes. *Diabetes Care* 2006; **29**: 657-661 [PMID: 16505522 DOI: 10.2337/diacare.29.03.06.dc05-0879]
 - 150 **Gangwisch JE**, Heymsfield SB, Boden-Albala B, Buijs RM, Kreier F, Pickering TG, Rundle AG, Zammit GK, Malaspina D. Short sleep duration as a risk factor for hypertension: analyses of the first National Health and Nutrition Examination Survey. *Hypertension* 2006; **47**: 833-839 [PMID: 16585410 DOI: 10.1161/01.Hyp.0000217362.34748.E0]
 - 151 **Moreno CR**, Louzada FM, Teixeira LR, Borges F, Lorenzi-Filho G. Short sleep is associated with obesity among truck drivers. *Chronobiol Int* 2006; **23**: 1295-1303 [PMID: 17190714 DOI: 10.1080/07420520601089521]
 - 152 **Phillips F**, Chen CN, Crisp AH, Koval J, McGuinness B, Kalucy RS, Kalucy EC, Lacey JH. Isocaloric diet changes and electroencephalographic sleep. *Lancet* 1975; **2**: 723-725 [PMID: 52766 DOI: 10.1016/S0140-6736(75)90718-7]
 - 153 **Porter JM**, Horne JA. Bed-time food supplements and sleep: effects of different carbohydrate levels. *Electroencephalogr Clin Neurophysiol* 1981; **51**: 426-433 [PMID: 6164541 DOI: 10.1016/013-4694(81)90106-1]
 - 154 **Howorka K**, Heger G, Schabmann A, Anderer P, Tribl G, Zeitlhofer J. Severe hypoglycaemia unawareness is associated with an early decrease in vigilance during hypoglycaemia. *Psychoneuroendocrinology* 1996; **21**: 295-312 [PMID: 8817728 DOI: 10.1016/0306-4530(95)00034-8]
 - 155 **Boyle PJ**, Scott JC, Krentz AJ, Nagy RJ, Comstock E, Hoffman C. Diminished brain glucose metabolism is a significant determinant for falling rates of systemic glucose utilization during sleep in normal humans. *J Clin Invest* 1994; **93**: 529-535 [PMID: 8113391 DOI: 10.1172/Jci117003]
 - 156 **Crispim CA**, Zimberg IZ, dos Reis BG, Diniz RM, Tufik S, de Mello MT. Relationship between food intake and sleep pattern in healthy individuals. *J Clin Sleep Med* 2011; **7**: 659-664 [PMID: 22171206 DOI: 10.5664/jcsm.1476]
 - 157 **Mikuni E**, Ohoshi T, Hayashi K, Miyamura K. Glucose intolerance in an employed population. *Tohoku J Exp Med* 1983; **141** Suppl: 251-256 [PMID: 6680494 DOI: 10.3109/07420528.2010.489883]
 - 158 **Padilha HG**, Crispim CA, Zimberg IZ, Folkard S, Tufik S, de Mello MT. Metabolic responses on the early shift. *Chronobiol Int* 2010; **27**: 1080-1092 [PMID: 20636217]
 - 159 **Knutson A**. Relationships between serum triglycerides and gamma-glutamyltransferase among shift and day workers. *J Intern Med* 1989; **226**: 337-339 [PMID: 2572667 DOI: 10.1111/j.1365-2796.1989.tb01405.x]
 - 160 **Hasler G**, Buysse DJ, Klaghofer R, Gamma A, Ajdacic V, Eich D, Rössler W, Angst J. The association between short sleep duration and obesity in young adults: a 13-year prospective study. *Sleep* 2004; **27**: 661-666 [PMID: 15283000]
 - 161 **Mitchell HA**, Weinshenker D. Good night and good luck: norepinephrine in sleep pharmacology. *Biochem Pharmacol* 2010; **79**: 801-809 [PMID: 19833104 DOI: 10.1016/j.bcp.2009.10.004]
 - 162 **Satinoff E**, Prosser RA. Suprachiasmatic nuclear lesions eliminate circadian rhythms of drinking and activity, but not of body temperature, in male rats. *J Biol Rhythms* 1988; **3**: 1-22 [PMID: 2979628 DOI: 10.1177/074873048800300101]
 - 163 **Lancel M**, van Riezen H, Glatt A. Effects of circadian phase and duration of sleep deprivation on sleep and EEG power spectra in the cat. *Brain Res* 1991; **548**: 206-214 [PMID: 1868336]
 - 164 **Alföldi P**, Franken P, Tobler I, Borbély AA. Short light-dark cycles influence sleep stages and EEG power spectra in the rat. *Behav Brain Res* 1991; **43**: 125-131 [PMID: 1867754 DOI: 10.1016/S0166-4328(05)80062-2]
 - 165 **Héry F**, Rouer E, Glowinski J. Daily variations of serotonin metabolism in the rat brain. *Brain Res* 1972; **43**: 445-465 [PMID: 5053284 DOI: 10.1016/0006-8993(72)90400-3]
 - 166 **Roberts JE**. Light and immunomodulation. *Ann NY Acad Sci* 2000; **917**: 435-445 [PMID: 11268371 DOI: 10.1111/j.1749-6632.2000.tb05408.x]
 - 167 **Ziegler MC**, Lake CR, Wood JH, Ebert MH. Circadian rhythm in cerebrospinal fluid noradrenaline of man and monkey. *Nature*

- 1976; **264**: 656-658 [PMID: 826835 DOI: 10.1038/264656a0]
- 168 **Murphy PJ**, Campbell SS. Enhancement of REM sleep during extraocular light exposure in humans. *Am J Physiol Regul Integr Comp Physiol* 2001; **280**: R1606-R1612 [PMID: 11353661]
- 169 **Campbell SS**, Murphy PJ. Extraocular circadian phototransduction in humans. *Science* 1998; **279**: 396-399 [PMID: 9430592 DOI: 10.1126/science.279.5349.396]
- 170 **Coplan JD**, Andrews MW, Rosenblum LA, Owens MJ, Friedman S, Gorman JM, Nemeroff CB. Persistent elevations of cerebrospinal fluid concentrations of corticotropin-releasing factor in adult nonhuman primates exposed to early-life stressors: implications for the pathophysiology of mood and anxiety disorders. *Proc Natl Acad Sci USA* 1996; **93**: 1619-1623 [PMID: 8643680 DOI: 10.1073/pnas.93.4.161]
- 171 **Liu D**, Diorio J, Tannenbaum B, Caldji C, Francis D, Freedman A, Sharma S, Pearson D, Plotsky PM, Meaney MJ. Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. *Science* 1997; **277**: 1659-1662 [PMID: 9287218 DOI: 10.1126/science.277.5332.1659]
- 172 **Plotsky PM**, Meaney MJ. Early, postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats. *Brain Res Mol Brain Res* 1993; **18**: 195-200 [PMID: 8497182 DOI: 10.1016/0169-328X(93)90189-V]
- 173 **Seckl JR**, Meaney MJ. Early life events and later development of ischaemic heart disease. *Lancet* 1993; **342**: 1236 [PMID: 7901549 DOI: 10.1016/0140-6736(93)92215-F]
- 174 **Medori R**, Tritschler HJ, LeBlanc A, Villare F, Manetto V, Chen HY, Xue R, Leal S, Montagna P, Cortelli P. Fatal familial insomnia, a prion disease with a mutation at codon 178 of the prion protein gene. *N Engl J Med* 1992; **326**: 444-449 [PMID: 1346338 DOI: 10.1056/Nejm199202133260704]
- 175 **Lin L**, Faraco J, Li R, Kadotani H, Rogers W, Lin X, Qiu X, de Jong PJ, Nishino S, Mignot E. The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. *Cell* 1999; **98**: 365-376 [PMID: 10458611 DOI: 10.1016/S0092-8674(00)81965-0]
- 176 **Chemelli RM**, Willie JT, Sinton CM, Elmquist JK, Scammell T, Lee C, Richardson JA, Williams SC, Xiong Y, Kisanuki Y, Fitch TE, Nakazato M, Hammer RE, Saper CB, Yanagisawa M. Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. *Cell* 1999; **98**: 437-451 [PMID: 10481909 DOI: 10.1016/S0092-8674(00)81973-X]
- 177 **Jones S**, Pfister-Genskow M, Benca RM, Cirelli C. Molecular correlates of sleep and wakefulness in the brain of the white-crowned sparrow. *J Neurochem* 2008; **105**: 46-62 [PMID: 18028333 DOI: 10.1111/j.1471-4159.2007.05089.x]
- 178 **Dauvilliers Y**, Maret S, Tafti M. Genetics of normal and pathological sleep in humans. *Sleep Med Rev* 2005; **9**: 91-100 [PMID: 15737788 DOI: 10.1016/j.smrv.2004.06.001]
- 179 **Giuditta A**, Rutigliano B, Vitale-Neugebauer A. Influence of synchronized sleep on the biosynthesis of RNA in neuronal and mixed fractions isolated from rabbit cerebral cortex. *J Neurochem* 1980; **35**: 1267-1272 [PMID: 6160205 DOI: 10.1111/j.1471-4159.1980.tb08997.x]
- 180 **Cirelli C**, Tononi G. Differential expression of plasticity-related genes in waking and sleep and their regulation by the noradrenergic system. *J Neurosci* 2000; **20**: 9187-9194 [PMID: 11124996]
- 181 **Cirelli C**, Tononi G. Gene expression in the brain across the sleep-waking cycle. *Brain Res* 2000; **885**: 303-321 [PMID: 11102586 DOI: 10.1016/S0006-8993(00)03008-0]
- 182 **Cirelli C**, Gutierrez CM, Tononi G. Extensive and divergent effects of sleep and wakefulness on brain gene expression. *Neuron* 2004; **41**: 35-43 [PMID: 14715133 DOI: 10.1016/S0896-6273(03)00814-6]
- 183 **Mackiewicz M**, Shockley KR, Romer MA, Galante RJ, Zimmerman JE, Naidoo N, Baldwin DA, Jensen ST, Churchill GA, Pack AI. Macromolecule biosynthesis: a key function of sleep. *Physiol Genomics* 2007; **31**: 441-457 [PMID: 17698924 DOI: 10.1152/physiolgenomics.00275.2006]
- 184 **Vecsey CG**, Peixoto L, Choi JH, Wimmer M, Jaganath D, Hernandez PJ, Blackwell J, Meda K, Park AJ, Hannehalli S, Abel T. Genomic analysis of sleep deprivation reveals translational regulation in the hippocampus. *Physiol Genomics* 2012; **44**: 981-991 [PMID: 22930738 DOI: 10.1152/physiolgenomics.00084.2012]
- 185 **Naidoo N**, Giang W, Galante RJ, Pack AI. Sleep deprivation induces the unfolded protein response in mouse cerebral cortex. *J Neurochem* 2005; **92**: 1150-1157 [PMID: 15715665 DOI: 10.1111/j.1471-4159.2004.02952.x]
- 186 **Abel T**, Havekes R, Saletin JM, Walker MP. Sleep, plasticity and memory from molecules to whole-brain networks. *Curr Biol* 2013; **23**: R774-R788 [PMID: 24028961 DOI: 10.1016/j.cub.2013.07.025]
- 187 **Petit JM**, Tobler I, Allaman I, Borbély AA, Magistretti PJ. Sleep deprivation modulates brain mRNAs encoding genes of glycogen metabolism. *Eur J Neurosci* 2002; **16**: 1163-1167 [PMID: 12383246 DOI: 10.1046/j.1460-9568.2002.02145.x]
- 188 **Nagatsu T**, Ichinose H. Molecular Biology of Catecholamine Systems: Multiple Tyrosine Hydroxylases in Different Simian Species, and in Humans in Relation to Parkinson's Disease. In: Hanin I, Yoshida M, Fisher A, editors. *Alzheimer's and Parkinson's Diseases: Recent Developments*. New York: Plenum Press, 1995: 655-659
- 189 **Powlledge TM**. Behavioral Epigenetics: How Nurture Shapes Nature. *Bioscience* 2011; **61**: 588-592 [DOI: 10.1525/bio.2011.61.8.4]
- 190 **Qureshi IA**, Mehler MF. Epigenetics of sleep and chronobiology. *Curr Neurol Neurosci Rep* 2014; **14**: 432 [PMID: 24477387 DOI: 10.1007/s11910-013-0432-6]
- 191 **Massart R**, Freyburger M, Suderman M, Paquet J, El Helou J, Belanger-Nelson E, Rachalski A, Koumar OC, Carrier J, Szyf M, Mongrain V. The genome-wide landscape of DNA methylation and hydroxymethylation in response to sleep deprivation impacts on synaptic plasticity genes. *Transl Psychiatry* 2014; **4**: e347 [PMID: 24448209 DOI: 10.1038/tp.2013.120]
- 192 **McNamara P**. Genomic Imprinting and Neurodevelopmental Disorders of Sleep. *Sleep and Hypnosis*, 2004: 82-90
- 193 **Tucci V**, Nolan PM. Toward an understanding of the function of sleep: New insights from mouse genetics. *Evolution of Sleep: Phylogenetic and Functional Perspectives*: Cambridge University Press, 2009: 218-237
- 194 **Lassi G**, Ball ST, Maggi S, Colonna G, Nieuw T, Cero C, Bartolomucci A, Peters J, Tucci V. Loss of Gnas imprinting differentially affects REM/NREM sleep and cognition in mice. *PLoS Genet* 2012; **8**: e1002706 [PMID: 22589743 DOI: 10.1371/journal.pgen.1002706]
- 195 **Kumer SC**, Vrana KE. Intricate regulation of tyrosine hydroxylase activity and gene expression. *J Neurochem* 1996; **67**: 443-462 [PMID: 8764568 DOI: 10.1046/j.1471-4159.1996.67020443.x]
- 196 **Michelotti GA**, Brinkley DM, Morris DP, Smith MP, Louie RJ, Schwinn DA. Epigenetic regulation of human alpha1d-adrenergic receptor gene expression: a role for DNA methylation in Sp1-dependent regulation. *FASEB J* 2007; **21**: 1979-1993 [PMID: 17384146 DOI: 10.1096/fj.06-7118com]
- 197 **Razik MA**, Lee K, Price RR, Williams MR, Ongjoco RR, Dole MK, Rudner XL, Kwatra MM, Schwinn DA. Transcriptional regulation of the human alpha1a-adrenergic receptor gene. Characterization Of the 5'-regulatory and promoter region. *J Biol Chem* 1997; **272**: 28237-28246 [PMID: 9353275 DOI: 10.1074/jbc.272.45.28237]
- 198 **Zhu QS**, Chen K, Shih JC. Bidirectional promoter of human monoamine oxidase A (MAO A) controlled by transcription factor Sp1. *J Neurosci* 1994; **14**: 7393-7403 [PMID: 7996184]
- 199 **Thakkar M**, Mallick BN. Effect of rapid eye movement sleep deprivation on rat brain monoamine oxidases. *Neuroscience* 1993; **55**: 677-683 [PMID: 8413930]
- 200 **Majumdar S**, Mallick BN. Increased levels of tyrosine hydroxylase and glutamic acid decarboxylase in locus coeruleus neurons after rapid eye movement sleep deprivation in rats. *Neurosci Lett* 2003; **338**: 193-196 [PMID: 12581829 DOI: 10.1016/S0304-3940(02)01404-0]

- 201 **Basheer R**, Magner M, McCarley RW, Shiromani PJ. REM sleep deprivation increases the levels of tyrosine hydroxylase and norepinephrine transporter mRNA in the locus coeruleus. *Brain Res Mol Brain Res* 1998; **57**: 235-240 [PMID: 9675421 DOI: 10.1016/S0169-328X(98)00088-6]
- 202 **Mehta R**, Singh A, Bókkon I, Nath Mallick B. REM sleep and its Loss-Associated Epigenetic Regulation with Reference to Noradrenaline in Particular. *Curr Neuropsychopharmacol* 2016; **14**: 28-40 [PMID: 26813120 DOI: 10.2174/1570159x13666150414185737]
- 203 **Snyder F**, Hobson JA, Goldfrank F. Blood pressure changes during human sleep. *Science* 1963; **142**: 1313-1314 [PMID: 14074846 DOI: 10.1097/00132586-196502000-00011]
- 204 **Snyder F**, Hobson JA, Morrison DF, Goldfrank F. Changes in respiration, heart rate, and systolic blood pressure in human sleep. *J Appl Physiol* 1964; **19**: 417-422 [PMID: 14174589 DOI: 10.1097/00132586-196508000-00005]
- 205 **Sakai F**, Meyer JS, Karacan I, Derman S, Yamamoto M. Normal human sleep: regional cerebral hemodynamics. *Ann Neurol* 1980; **7**: 471-478 [PMID: 7396425 DOI: 10.1002/ana.410070514]
- 206 **Xie L**, Kang H, Xu Q, Chen MJ, Liao Y, Thiagarajan M, O'Donnell J, Christensen DJ, Nicholson C, Iliff JJ, Takano T, Deane R, Nedergaard M. Sleep drives metabolite clearance from the adult brain. *Science* 2013; **342**: 373-377 [PMID: 24136970 DOI: 10.1126/science.1241224]
- 207 **Martín B**, Fernández B, Domínguez FJ. [Sleep apnea-hypopnea syndrome and cardiovascular diseases]. *An Sist Sanit Navar* 2007; **30** Suppl 1: 89-95 [PMID: 17486149]
- 208 **Andersen ML**, Martins PJ, D'Almeida V, Santos RF, Bignotto M, Tufik S. Effects of paradoxical sleep deprivation on blood parameters associated with cardiovascular risk in aged rats. *Exp Gerontol* 2004; **39**: 817-824 [PMID: 15130676 DOI: 10.1016/j.exger.2004.02.007]
- 209 **Friedman O**, Bradley TD, Ruttanaumpawan P, Logan AG. Independent association of drug-resistant hypertension to reduced sleep duration and efficiency. *Am J Hypertens* 2010; **23**: 174-179 [PMID: 19927130 DOI: 10.1038/ajh.2009.220]
- 210 **de Oliveira AC**, D'Almeida V, Hipólido DC, Nobrega JN, Tufik S. Sleep deprivation reduces total plasma homocysteine levels in rats. *Can J Physiol Pharmacol* 2002; **80**: 193-197 [PMID: 11991229]
- 211 **Neves FA**, Marson O, Baumgratz RP, Bossolan D, Ginosa M, Ribeiro AB, Kohlmann O, Ramos OL. Rapid eye movement sleep deprivation and hypertension. Genetic influence. *Hypertension* 1992; **19**: II202-II206 [PMID: 1735579]
- 212 **Lavie P**, Schnall RP, Sheffy J, Shlitner A. Peripheral vasoconstriction during REM sleep detected by a new plethysmographic method. *Nat Med* 2000; **6**: 606 [PMID: 10835649 DOI: 10.1038/76135]
- 213 **El Fazaa S**, Somody L, Gharbi N, Kamoun A, Gharib C, Gauquelin-Koch G. Effects of acute and chronic starvation on central and peripheral noradrenaline turnover, blood pressure and heart rate in the rat. *Exp Physiol* 1999; **84**: 357-368 [PMID: 10226176 DOI: 10.1111/j.1469-445X.1999.01818.x]
- 214 **Schroeder C**, Jordan J. Norepinephrine transporter function and human cardiovascular disease. *Am J Physiol Heart Circ Physiol* 2012; **303**: H1273-H1282 [PMID: 23023867 DOI: 10.1152/ajpheart.00492.2012]
- 215 **Esler M**, Alvarenga M, Pier C, Richards J, El-Osta A, Barton D, Haikerwal D, Kaye D, Schlaich M, Guo L, Jennings G, Socratous F, Lambert G. The neuronal noradrenaline transporter, anxiety and cardiovascular disease. *J Psychopharmacol* 2006; **20**: 60-66 [PMID: 16785272 DOI: 10.1177/1359786806060605]
- 216 **van de Borne P**, Oren R, Abouassaly C, Anderson E, Somers VK. Effect of Cheyne-Stokes respiration on muscle sympathetic nerve activity in severe congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1998; **81**: 432-436 [PMID: 9485132 DOI: 10.1016/S0002-9149(97)00936-3]
- 217 **Naughton MT**, Benard DC, Liu PP, Rutherford R, Rankin F, Bradley TD. Effects of nasal CPAP on sympathetic activity in patients with heart failure and central sleep apnea. *Am J Respir Crit Care Med* 1995; **152**: 473-479 [PMID: 7633695 DOI: 10.1164/ajrccm.152.2.7633695]
- 218 **Krueger JM**, Karnovsky ML. Sleep and the immune response. *Ann N Y Acad Sci* 1987; **496**: 510-516 [PMID: 2440372 DOI: 10.1007/s00424-011-1044-0]
- 219 **Moldofsky H**, Lue FA, Davidson JR, Gorczynski R. Effects of sleep deprivation on human immune functions. *FASEB J* 1989; **3**: 1972-1977 [PMID: 2785942]
- 220 **Opp MR**. Sleeping to fuel the immune system: mammalian sleep and resistance to parasites. *BMC Evol Biol* 2009; **9**: 8 [PMID: 19134176 DOI: 10.1186/1471-2148-9-8]
- 221 **Redwine L**, Hauger RL, Gillin JC, Irwin M. Effects of sleep and sleep deprivation on interleukin-6, growth hormone, cortisol, and melatonin levels in humans. *J Clin Endocrinol Metab* 2000; **85**: 3597-3603 [PMID: 11061508 DOI: 10.1210/jcem.85.10.6871]
- 222 **Ruiz FS**, Andersen ML, Martins RC, Zager A, Lopes JD, Tufik S. Immune alterations after selective rapid eye movement or total sleep deprivation in healthy male volunteers. *Innate Immun* 2012; **18**: 44-54 [PMID: 21088046 DOI: 10.1177/1753425910385962]
- 223 **Schiffelholz T**, Lancel M. Sleep changes induced by lipopolysaccharide in the rat are influenced by age. *Am J Physiol Regul Integr Comp Physiol* 2001; **280**: R398-R403 [PMID: 11208567]
- 224 **Imeri L**, Opp MR. How (and why) the immune system makes us sleep. *Nat Rev Neurosci* 2009; **10**: 199-210 [PMID: 19209176 DOI: 10.1038/nrn2576]
- 225 **Spiegel K**, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet* 1999; **354**: 1435-1439 [PMID: 10543671 DOI: 10.1016/S0140-6736(99)01376-8]
- 226 **Irwin M**, Thompson J, Miller C, Gillin JC, Ziegler M. Effects of sleep and sleep deprivation on catecholamine and interleukin-2 levels in humans: clinical implications. *J Clin Endocrinol Metab* 1999; **84**: 1979-1985 [PMID: 10372697 DOI: 10.1210/jcem.84.6.5788]
- 227 **Yehuda S**, Sredni B, Carasso RL, Kenigsbuch-Sredni D. REM sleep deprivation in rats results in inflammation and interleukin-17 elevation. *J Interferon Cytokine Res* 2009; **29**: 393-398 [PMID: 19450150 DOI: 10.1089/jir.2008.0080]
- 228 **Kang WS**, Park HJ, Chung JH, Kim JW. REM sleep deprivation increases the expression of interleukin genes in mice hypothalamus. *Neurosci Lett* 2013; **556**: 73-78 [PMID: 24080377 DOI: 10.1016/j.neulet.2013.09.050]
- 229 **Mallick BN**, Madan V, Faisal M. Biochemical Change In: Kushida CA, editor Sleep deprivation Basic Science, Physiology and behavior. New York: Marcel Dekker, 2005: 339-357
- 230 **Andersen M**, Guindalini C, Alvarenga TA, Egydio F, Tufik S. Expression of ceruloplasmin in cavernosal tissue of paradoxical sleep deprived rats. *Sleep Sci* 2012; **5**: 40-44
- 231 **Pandey AK**, Kar SK. REM sleep deprivation of rats induces acute phase response in liver. *Biochem Biophys Res Commun* 2011; **410**: 242-246 [PMID: 21651899]
- 232 **Tobler I**, Borbély AA, Schwyzler M, Fontana A. Interleukin-1 derived from astrocytes enhances slow wave activity in sleep EEG of the rat. *Eur J Pharmacol* 1984; **104**: 191-192 [PMID: 6333990]
- 233 **Opp MR**, Krueger JM. Anti-interleukin-1 beta reduces sleep and sleep rebound after sleep deprivation in rats. *Am J Physiol* 1994; **266**: R688-R695 [PMID: 8160860]
- 234 **Kushida CA**. Sleep Deprivation; basic science, physiology and behavior. newyork: marcel-dekker. *Marcel Dekker* 2005
- 235 **Rechtschaffen A**, Bergmann BM, Everson CA, Kushida CA, Gilliland MA. Sleep deprivation in the rat: X. Integration and discussion of the findings. 1989. *Sleep* 2002; **25**: 68-87 [PMID: 11833857]
- 236 **Bergmann BM**, Seiden LS, Landis CA, Gilliland MA, Rechtschaffen A. Sleep deprivation in the rat: XVIII. Regional brain levels of monoamines and their metabolites. *Sleep* 1994; **17**: 583-589 [PMID: 7531362]
- 237 **Kohm AP**, Sanders VM. Norepinephrine: a messenger from the brain to the immune system. *Immunol Today* 2000; **21**: 539-542 [PMID: 11094255 DOI: 10.1016/S0167-5699(00)01747-3]
- 238 **Ross RJ**, Ball WA, Sullivan KA, Caroff SN. Sleep disturbance as the hallmark of posttraumatic stress disorder. *Am J Psychiatry*

- 1989; **146**: 697-707 [PMID: 2658624 DOI: 10.1176/ajp.146.6.697]
- 239 **Mellman TA**. Psychobiology of sleep disturbances in posttraumatic stress disorder. *Ann N Y Acad Sci* 1997; **821**: 142-149 [PMID: 9238200 DOI: 10.1111/j.1749-6632.1997.tb48275.x]
- 240 **Mellman TA**, Bustamante V, Fins AI, Pigeon WR, Nolan B. REM sleep and the early development of posttraumatic stress disorder. *Am J Psychiatry* 2002; **159**: 1696-1701 [PMID: 12359675 DOI: 10.1176/appi.ajp.159.10.1696]
- 241 **Southwick SM**, Bremner JD, Rasmusson A, Morgan CA, Arnsten A, Charney DS. Role of norepinephrine in the pathophysiology and treatment of posttraumatic stress disorder. *Biol Psychiatry* 1999; **46**: 1192-1204 [PMID: 10560025 DOI: 10.1016/S0006-3223(99)00107-9]
- 242 **Southwick SM**, Morgan CA, Charney DS, High JR. Yohimbine use in a natural setting: effects on posttraumatic stress disorder. *Biol Psychiatry* 1999; **46**: 442-444 [PMID: 10435213]
- 243 **Raskind MA**, Peskind ER, Kanter ED, Petrie EC, Radant A, Thompson CE, Dobie DJ, Hoff D, Rein RJ, Straits-Tröster K, Thomas RG, McFall MM. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. *Am J Psychiatry* 2003; **160**: 371-373 [PMID: 12562588 DOI: 10.1176/appi.ajp.160.2.371]
- 244 **Mellman TA**, Knorr BR, Pigeon WR, Leiter JC, Akay M. Heart rate variability during sleep and the early development of posttraumatic stress disorder. *Biol Psychiatry* 2004; **55**: 953-956 [PMID: 15110740 DOI: 10.1016/j.biopsych.2003.12.018]
- 245 **Hurst JH**, LeWitt PA, Burns RS, Foster NL, Lovenberg W. CSF dopamine-beta-hydroxylase activity in Parkinson's disease. *Neurology* 1985; **35**: 565-568 [PMID: 3982644]
- 246 **Greenfield JG**, Bosanquet FD. The brain-stem lesions in Parkinsonism. *J Neurol Neurosurg Psychiatry* 1953; **16**: 213-226 [PMID: 13109537]
- 247 **Friedman A**. Sleep pattern in Parkinson's disease. *Acta Med Pol* 1980; **21**: 193-199 [PMID: 7211468]
- 248 **Christos GA**. Is Alzheimer's disease related to a deficit or malfunction of rapid eye movement (REM) sleep? *Med Hypotheses* 1993; **41**: 435-439 [PMID: 8145655 DOI: 10.1016/0306-9877(93)90121-6]
- 249 **Kundermann B**, Thum A, Rocamora R, Haag A, Krieg JC, Hemmeter U. Comparison of polysomnographic variables and their relationship to cognitive impairment in patients with Alzheimer's disease and frontotemporal dementia. *J Psychiatr Res* 2011; **45**: 1585-1592 [PMID: 21803373 DOI: 10.1016/j.jpsychires.2011.07.008]
- 250 **Gagnon JF**, Petit D, Fantini ML, Rompré S, Gauthier S, Panisset M, Robillard A, Montplaisir J. REM sleep behavior disorder and REM sleep without atonia in probable Alzheimer disease. *Sleep* 2006; **29**: 1321-1325 [PMID: 17068986]
- 251 **Bondareff W**, Mountjoy CQ, Roth M. Loss of neurons of origin of the adrenergic projection to cerebral cortex (nucleus locus ceruleus) in senile dementia. *Neurology* 1982; **32**: 164-168 [PMID: 7198741 DOI: 10.1212/WNL.32.2.164]
- 252 **Zweig RM**, Ross CA, Hedreen JC, Steele C, Cardillo JE, Whitehouse PJ, Folstein MF, Price DL. Neuropathology of aminergic nuclei in Alzheimer's disease. *Prog Clin Biol Res* 1989; **317**: 353-365 [PMID: 2602423 DOI: 10.1002/ana.410240210]
- 253 **Heneka MT**, Nadrigny F, Regen T, Martinez-Hernandez A, Dumitrescu-Ozimek L, Terwel D, Jandanhazi-Kurutz D, Walter J, Kirchhoff F, Hanisch UK, Kummer MP. Locus ceruleus controls Alzheimer's disease pathology by modulating microglial functions through norepinephrine. *Proc Natl Acad Sci USA* 2010; **107**: 6058-6063 [PMID: 20231476 DOI: 10.1073/pnas.0909586107]
- 254 **Raskind MA**, Peskind ER, Holmes C, Goldstein DS. Patterns of cerebrospinal fluid catechols support increased central noreadrenergic responsiveness in aging and Alzheimer's disease. *Biol Psychiatry* 1999; **46**: 756-765 [PMID: 10494443 DOI: 10.1016/S0006-3223(99)00008-6]
- 255 **Wang LY**, Shofer JB, Rohde K, Hart KL, Hoff DJ, McFall YH, Raskind MA, Peskind ER. Prazosin for the treatment of behavioral symptoms in patients with Alzheimer disease with agitation and aggression. *Am J Geriatr Psychiatry* 2009; **17**: 744-751 [PMID: 19700947 DOI: 10.1097/JGP.0b013e3181ab8c61]
- 256 **Traver S**, Salthun-Lassalle B, Marien M, Hirsch EC, Colpaert F, Michel PP. The neurotransmitter noradrenaline rescues septal cholinergic neurons in culture from degeneration caused by low-level oxidative stress. *Mol Pharmacol* 2005; **67**: 1882-1891 [PMID: 15784847 DOI: 10.1124/mol.104.007864]
- 257 **García CR**, Angelé-Martínez C, Wilkes JA, Wang HC, Battin EE, Brumaghim JL. Prevention of iron- and copper-mediated DNA damage by catecholamine and amino acid neurotransmitters, L-DOPA, and curcumin: metal binding as a general antioxidant mechanism. *Dalton Trans* 2012; **41**: 6458-6467 [PMID: 22450660 DOI: 10.1039/c2dt30060e]
- 258 **Troadec JD**, Marien M, Darios F, Hartmann A, Ruberg M, Colpaert F, Michel PP. Noradrenaline provides long-term protection to dopaminergic neurons by reducing oxidative stress. *J Neurochem* 2001; **79**: 200-210 [PMID: 11595772 DOI: 10.1046/j.1471-4159.2001.00556.x]
- 259 **Patri M**, Singh A, Mallick BN. Protective role of noradrenaline in benzo[a]pyrene-induced learning impairment in developing rat. *J Neurosci Res* 2013; **91**: 1450-1462 [PMID: 23996611 DOI: 10.1002/jnr.23265]
- 260 **Steiger A**, Kimura M. Wake and sleep EEG provide biomarkers in depression. *J Psychiatr Res* 2010; **44**: 242-252 [PMID: 19762038 DOI: 10.1016/j.jpsychires.2009.08.013]
- 261 **Tsuno N**, Besset A, Ritchie K. Sleep and depression. *J Clin Psychiatry* 2005; **66**: 1254-1269 [PMID: 16259539 DOI: 10.4088/JCP.v66n1008]
- 262 **Pillai V**, Kalmbach DA, Ciesla JA. A meta-analysis of electroencephalographic sleep in depression: evidence for genetic biomarkers. *Biol Psychiatry* 2011; **70**: 912-919 [PMID: 21937023 DOI: 10.1016/j.biopsych.2011.07.016]
- 263 **Aston-Jones G**, Gonzalez M, Doran S. Role of the locus coeruleus-norepinephrine system in arousal and circadian regulation of the sleep-wake cycle. Cambridge Cambridge University Press, 2007: 157-195
- 264 **Varghese FP**, Brown ES. The Hypothalamic-Pituitary-Adrenal Axis in Major Depressive Disorder: A Brief Primer for Primary Care Physicians. *Prim Care Companion J Clin Psychiatry* 2001; **3**: 151-155 [PMID: 15014598 DOI: 10.4088/PCC.v03n0401]
- 265 **Hensler JG**, Artigas F, Bortolozzi A, Daws LC, De Deurwaerdère P, Milan L, Navailles S, Koek W. Catecholamine/Serotonin interactions: systems thinking for brain function and disease. *Adv Pharmacol* 2013; **68**: 167-197 [PMID: 24054145 DOI: 10.1016/B978-0-12-411512-5.00009-9]
- 266 **Nestler EJ**, Hyman SE. Animal models of neuropsychiatric disorders. *Nat Neurosci* 2010; **13**: 1161-1169 [PMID: 20877280 DOI: 10.1038/nn.2647]
- 267 **Stickgold R**, Hobson JA, Fosse R, Fosse M. Sleep, learning, and dreams: off-line memory reprocessing. *Science* 2001; **294**: 1052-1057 [PMID: 11691983 DOI: 10.1126/science.1063530]
- 268 **Maquet P**. The role of sleep in learning and memory. *Science* 2001; **294**: 1048-1052 [PMID: 11691982 DOI: 10.1126/science.1062856]
- 269 **Orzel-Gryglewska J**. Consequences of sleep deprivation. *Int J Occup Med Environ Health* 2010; **23**: 95-114 [PMID: 20442067 DOI: 10.2478/v10001-010-0004-9]
- 270 **Killgore WD**. Effects of sleep deprivation on cognition. *Prog Brain Res* 2010; **185**: 105-129 [PMID: 21075236 DOI: 10.1016/B978-0-444-53702-7.00007-5]
- 271 **Rasch B**, Born J. About sleep's role in memory. *Physiol Rev* 2013; **93**: 681-766 [PMID: 23589831 DOI: 10.1152/physrev.00032.2012]
- 272 **Smith C**. Sleep states and learning: a review of the animal literature. *Neurosci Biobehav Rev* 1985; **9**: 157-168 [PMID: 3892377 DOI: 10.1016/0149-7634(85)90042-9]
- 273 **Hu H**, Real E, Takamiya K, Kang MG, Ledoux J, Huguier RL, Malinow R. Emotion enhances learning via norepinephrine regulation of AMPA-receptor trafficking. *Cell* 2007; **131**: 160-173 [PMID: 17923095 DOI: 10.1016/j.cell.2007.09.017]
- 274 **Conwell W**, Patel B, Doeing D, Pamidi S, Knutson KL, Ghods F, Mokhlesi B. Prevalence, clinical features, and CPAP adherence in REM-related sleep-disordered breathing: a cross-sectional analysis

- of a large clinical population. *Sleep Breath* 2012; **16**: 519-526 [PMID: 21614575 DOI: 10.1007/s11325-011-0537-6]
- 275 **Mokhlesi B**, Punjabi NM. "REM-related" obstructive sleep apnea: an epiphenomenon or a clinically important entity? *Sleep* 2012; **35**: 5-7 [PMID: 22215911 DOI: 10.5665/sleep.1570]
- 276 **Marrone O**, Riccobono L, Salvaggio A, Mirabella A, Bonanno A, Bonsignore MR. Catecholamines and blood pressure in obstructive sleep apnea syndrome. *Chest* 1993; **103**: 722-727 [PMID: 8449058]

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**CASE REPORT**

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Periodontal surgery in a stage II Parkinson's disease patient: Report of a case with special considerations

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Abstract

Parkinson's disease (PD) is an idiopathic progressive neurological disorder characterised by resting tremor, restrictions in mobility and muscular rigidity that can lead to problems in maintaining oral health. Here we report a case where crown lengthening surgeries were successfully performed in a PD patient for complete oral rehabilitation. Certain special considerations that are required before and during periodontal surgery in such patients are also elucidated. Often dentists and PD patients are reluctant to embark on complex dental procedures resulting in a compromised outcome. However, early intervention along with proper education and motivation of these patients can aid in achieving satisfactory results.

Key words: Parkinson's disease; Overdenture; Crown lengthening

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Core tip: Parkinson's disease (PD) is a degenerative disorder of the central nervous system. Diagnosis of PD is often made after careful history taking, physical examination and observing a positive continued response to dopaminergic medications. Laboratory tests and imaging studies are not used routinely. The problems encountered during the dental treatment of a PD patient include the patient's inability to keep his mouth open, uncontrolled movements of head and tongue and excessive salivation. This case report lays emphasis on various considerations that are required while doing periodontal

surgery in these patients.

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INTRODUCTION

Parkinson's disease (PD) is an advanced neurodegenerative disorder in which patient experiences resting tremor, bradykinesia, constrained mobility and lack of postural stability which have deleterious effects on patient's quality of life^[1]. Patients with PD may require dental treatment for root caries, periodontitis, fractured or attrited teeth and complete oral rehabilitation. Due to the progressive nature of the disease, it is prudent to perform major dental procedures early in the course of the disease; a conservative approach is considered more appropriate in later stages of PD^[2]. Restorations with well-defined margins may not be obtainable in the presence of subgingival decay, short clinical crowns, traumatic injury or endodontic perforation, which may hence require crown lengthening surgeries (CLS)^[3].

The literature regarding intraoral surgical procedures in PD patients is very limited and mainly includes isolated reports of implant placement^[4]. Periodontal surgery in such patients can be performed in routine practice if certain guidelines are followed at the time of surgery. Here we present a case of successful management of an early PD patient in which CLS were performed for oral rehabilitation.

CASE REPORT

A 68-year-old male patient was referred to the Department of Periodontics, Government Dental College, Rohtak for CLS on certain teeth. Patient gave a history of two years of PD and was taking medications for the same. His medical reports indicated that he was having early PD (stage 2 on Hoehn and Yahr scale)^[5] with right side more affected. The patient was taking a combination of Levodopa (100 mg) and Carbidopa (10 mg) thrice daily for the past one year. Patient had a slightly stooped posture with bradykinesia and resting tremor. Parkinsonian tremors were also observed in lips. Past dental history included root canal treatment in 13, 23, 31, 32, 33, 41, 42 and 43; and extractions of 12, 14, 15, 25, 26 and 34.

Intraoral examination revealed eleven teeth in mandibular and six in maxillary arch with an average gingival and plaque index score of two (Figure 1). The lower incisors were severely attrited. These along with upper and lower left canines exhibited insufficient supragingival sound tooth structure for crown margin preparation. An

orthopantomograph and intra oral periapical radiographs were obtained. Crown lengthening surgery was planned in 13, 23 and 33. Mandibular incisors, due to their short clinical root lengths were not suitable for undergoing this procedure. However they were retained for prosthodontic reasons. Patient's physician was consulted for evaluation of patient's medical status before undergoing periodontal surgical procedure. A written informed consent was acquired from the patient after explaining him the procedure.

Beginning with oral prophylaxis, the patient was scheduled for an early morning appointment for CLS. He was asked to take his medication 60-90 min before the procedure so that peak effectiveness of the medication could be attained at the time of surgery. He was assisted in sitting on the dental chair and the chair was slowly raised to a 45° position to make him comfortable. After administration of local anaesthesia, internal bevel incisions along buccal and palatal aspects of 23 were given which continued as a distal wedge on the adjacent edentulous region. Full thickness buccal and palatal flaps were then reflected. Osteotomy and osteoplasty were carried out with hand and rotary instruments under copious irrigation. Vacuum suction was used throughout the procedure.

A periodontal probe was used to confirm the presence of at least 5 mm of sound tooth structure coronal to the crest of bone all around the tooth. The flaps were then adjusted and sutured (Figures 2 and 3). Post operative instructions were given and the patient was asked to report after a week for suture removal. Similar procedure was carried out for tooth numbers 13 and 33. Healing at the end of 1, 2 and 4 wk was found to be good and there were no post surgical concerns. Oral hygiene maintenance was reinforced at each visit. Oral rehabilitation was completed in another six weeks (Figure 4).

DISCUSSION

PD is a progressive disorder of the central nervous system which results from the degeneration of dopamine-containing cells in the substantia nigra, a region of the midbrain. Most people with PD first experience non motor symptoms like constipation, mood changes, anosmia and orthostatic hypotension which are then followed by motor symptoms. The initial symptoms in the course of the disease are movement-related, comprising shaking, rigidity, sluggishness of movement and difficulty in walking. In due course of time, cognitive and behavioural complications may arise. Dementia has also been seen to occur in the later stages of the disease.

A diagnosis of PD is often made after careful history taking, physical examination and observing a positive continued response to dopaminergic medications. Laboratory tests and imaging studies are not used routinely. The problems encountered during the dental treatment of a PD patient include the patient's inability to keep his mouth open, uncontrolled movements of head and tongue and excessive salivation. Weakened ability to swallow can



Figure 1 Intraoral picture at the time of presentation, also note the inability to maintain oral hygiene.



Figure 2 Right maxillary canine after crown lengthening surgery.

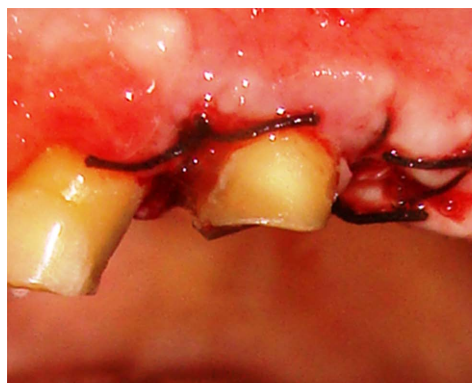


Figure 3 Left maxillary canine after crown lengthening surgery.



Figure 4 Patient after complete oral rehabilitation.

increase the risk of aspiration. PD patients who have been on medications like levodopa may begin to develop dyskinesias after several years, which can affect the jaw as well as lead to teeth grinding. The present patient had sufficient mouth opening, not requiring a mouth prop or bite block, minimal orofacial tremors and normal salivary flow inspite of levodopa medication. Tremor and rigour of the orofacial muscles may bring pain, temporomandibular joint discomfort and attrition^[6].

Restoration of oral health is best completed as early as possible in PD, as was done in the present case. Treatment plan for these patients should be devised taking care of patient's long term dental needs. Retaining teeth can be a means of preserving bone when planning a partial or complete tooth supported overdenture. Teeth, which are periodontally compromised or decayed may serve as overdenture abutments after root canal treatment and/or CLS. PD patients often have difficulty in retaining their dentures due to tremors, rigidity and drooling saliva^[7]. Overdentures can provide better masticatory efficiency as compared to conventional complete dentures and were therefore planned for this patient.

As PD is commonly associated with urinary urgency and incontinence, these patients should be asked to empty their bladders before beginning with any dental procedure^[8]. The dental chair should be raised slowly, allowing the patient to adjust to the upright sitting position to accommodate PD-associated autonomic dysfunction^[9]. Depending on the patient's physical disability, intravenous

sedation, local or general anesthesia can be administered. Appointments should be kept short, not longer than 45 min and should begin about one to one and half hour after administration of PD medication^[6]. The periodontist needs to be extremely patient while giving incisions or performing osseous reduction which require utmost precision. PD patients require certain special instructions as they may face difficulty in maintaining oral hygiene^[10]. Use of toothbrush with specially designed handle for better grasp or an electric toothbrush is recommended as was done in the present case. Mouthwashes are generally not advised for people with PD because they present the risk of choking, but in cases where they are required, it is best to prescribe those which are non-alcohol based.

This report demonstrates that CLS with osseous resection can be successfully performed in a PD patient and PD is no contraindication to periodontal surgery as is generally believed.

COMMENTS

Case characteristics

A 68-year-old male patient having difficulty in chewing was referred for crown lengthening surgeries (CLS) in certain teeth.

Clinical diagnosis

Patient had severely attrited maxillary and mandibular teeth which required

crown lengthening for the placement of an overdenture. Patient was found to have stage II Parkinson's disease (PD).

Laboratory diagnosis

Complete blood counts were within normal limits.

Pathological diagnosis

Insufficient crown lengths in maxillary and mandibular teeth and stage II PD.

Treatment

CLS with special considerations were performed.

Experiences and lessons

Often dentists and PD patients are reluctant to embark on complex dental procedures resulting in a compromised outcome. However, early intervention along with proper education and motivation of PD patients can aid in achieving satisfactory results.

Peer-review

Arora *et al* report periodontal surgery in a patient with PD and discuss potential Parkinson-specific problems, obstacles and caveats when performing dental procedures. The manuscript is concise and well-written.

REFERENCES

- 1 Bhat V, Weiner WJ. Parkinson's disease. Diagnosis and the initiation of therapy. *Minerva Med* 2005; **96**: 145-154 [PMID: 16175158]
- 2 Lobbezoo F, Naeije M. Dental implications of some common movement disorders: a concise review. *Arch Oral Biol* 2007; **52**: 395-398 [PMID: 17125732 DOI: 10.1016/j.archoralbio.2006.09.005]
- 3 Arora R, Narula SC, Sharma RK, Tewari S. Evaluation of supracrestal gingival tissue after surgical crown lengthening: a 6-month clinical study. *J Periodontol* 2013; **84**: 934-940 [PMID: 23088528 DOI: 10.1902/jop.2012.120162]
- 4 Packer M, Nikitin V, Coward T, Davis DM, Fiske J. The potential benefits of dental implants on the oral health quality of life of people with Parkinson's disease. *Gerodontology* 2009; **26**: 11-18 [PMID: 19278520 DOI: 10.1111/j.1741-2358.2008.00233.x]
- 5 Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. 1967. *Neurology* 1998; **50**: 318 and 16 pages following [PMID: 9484345 DOI: 10.1212/WNL.50.2.318]
- 6 Friedlander AH, Mahler M, Norman KM, Ettinger RL. Parkinson disease: systemic and orofacial manifestations, medical and dental management. *J Am Dent Assoc* 2009; **140**: 658-669 [PMID: 19491161 DOI: 10.14219/jada.archive.2009.0251]
- 7 Rajeswari CL. Prosthodontic considerations in Parkinson's disease. *PJSR* 2010; **3**: 45-47
- 8 Winge K, Skau AM, Stimpel H, Nielsen KK, Werdelin L. Prevalence of bladder dysfunction in Parkinson's disease. *Neurol Urodyn* 2016; **25**: 116-122 [DOI: 10.1002/nau.20193]
- 9 Alexander RE, Gage TW. Parkinson's disease: an update for dentists. *Gen Dent* 2000; **48**: 572-580; quiz 581-582 [PMID: 11199638]
- 10 Collins R. Special considerations for the dental patient with Parkinson's disease. *Tex Dent J* 1990; **107**: 31-32 [PMID: 2142341]

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