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Sleep: Implicating Interleukin-1

Vivek Sharma*[1], Sapna Sharma[1], Archana Kashyap[1], Harish Verma[1], Ranjit Singh[1]

1.Govt. College of Pharmacy, Rohru, Distt Shimla-171207, Himachal Pradesh, India

ABSTRACT

Men spend about one-third of their lives asleep and sleep is responsible for memory, emotion, perception, thought, judgement and even consciousness. Sleep is not only responsible for maintenance of healthy life but also for establishment of homeostasis in biological system. Sleep deprivation is a stressor affecting the brain as well as many body systems and researchers are continuously working to understand the sleep architecture and various substances which affect sleep. Wakefulness and sleep-wake-regulation are complex states, a lot of different components and regulatory mechanisms contribute to these functions. One of the factors involved in sleep wake regulation is the immune system particularly cytokines. Interleukin-1 is a pleotrophic cytokine, serving both physiological and pathological functions including modulation of memory, mood, inflammation, appetite, brain development and sleep. This article reviews and try to elaborate various downstream pathways and mediators involved in influence of cytokines on sleep architecture.

Keywords: Sleep, cytokines, Interleukin-1, REM and NREM

*Corresponding Author E-mail: vivesharma_phama@yahoo.co.in

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INTRODUCTION

Intense investigations over the years although could not find the exact answer for question that why do we sleep but there is no second thought that brain is organized to produce sleep and sleep have important role in important brain outputs such as memory, emotion, perception, thought, and even consciousness.

Sleep is responsible for maintenance of healthy life and establishment of homeostasis in biological system and disturbance in sleep cause hazardous changes in our system. Chronic insomnia affects approximately 9% to12% of the population[1,2] and is more prevalent than heart disease, cancer, AIDS, neurologic disease, breathing problems, urinary problems, diabetes, and gastrointestinal problems.[3]

Sleep is a complex behavioral state and one of the great mysteries of modern neuroscience[4] which began to be understood when it was associated with rapid eye movement (REM) by Aserinsky and Kleitman[5] in 1953. In 1998, the discovery of the hypothalamic peptides known as orexins (orhypocretins), together with the identification of their role in the sleep-wake cycle and in the physiopathology of narcolepsy cataplexy, contradicted conventional wisdom regarding the hypothalamus and the sleep-wake cycle, the control of which had previously been exclusively attributed to structures located in the brain stem and thalamus.[6,7] Control of this cycle is now attributed to the hypothalamic systems and to their respective functional interactions with the circadian timing system.[7]

Sleep is more than the absence of wakefulness, since both are regulated and active processes that occur at particular times within the 24-hour period. The timing of sleep and waking is regulated by two processes: (i) a circadian pacemaker located in the suprachiasmatic nuclei of the anterior hypothalamus, which is entrained to the light-dark cycle and promotes wake during an active phase of the cycle and permits sleep during a rest phase of the cycle, and (ii) a homeostatic process in which a need for sleep accumulates during waking and is dissipated or satisfied during sleep.[8]

Mammalian sleep is generally characterized by two major components, rapid-eye-movement (REM) and non–rapid-eye-movement (NREM) states, which alternate in a “sleep cycle” that is repeated one or more times during a sleep bout. An adult sleep cycle typically starts with an episode of NREM, characterized by physical quiescence and high-amplitude, synchronized, slow waves in electroencephalographic (EEG) measurements of brain activity. REM sleep follows and can be distinguished by eye movements, muscle twitches, and low voltage fast waves in the

brain.[9-11] The physiological distinctiveness of these two sleep states is thought to reflect functional differences.[10,11]

In mammals, the amount of time sleep varies greatly, from 3 h in the donkey (*Equus asinus*)[12] to 20 h in the armadillo (*Chaetophractus villous*)[13] as does the amount of time devoted to NREM and REM sleep, referred to as "sleepquotas."[10,11] These great inter specific differences could reflect either variation in the need for specific functional benefits of sleep[11,14] or variation in constraints on sleep time.[15] Allison and Cicchetti (1976), for example, found that species under higher risk of predation spend less time in this relatively vulnerable state.

Sleep is an active, repetitive and reversible behavior that is proposed to serve several different functions. Many of the hypotheses on the function of sleep focus on several aspects of homeostasis, such as energy balance, thermoregulation, tissue restoration, detoxification and immune function[16,17] beside these sleep makes an important contribution to brain plasticity and learning and memory processes.[18,19]

There are no direct measures of sleep; it is inferred from variations in physiological parameters such as the electroencephalogram (EEG), the electromyogram, changes in brain temperature, and eye movements. Sleep is divided into two main states, non-rapid eye movement sleep(NREMS) and rapid eye movement sleep (REMS).The EEG during NREMS exhibits sleep spindles and large slow waves, whereas the EEG during REMS is similar to that in wakefulness.[20]

A major role of NREM sleep is to conserve energy and help balance the costs of endothermy[21] and REM sleep is believed to be beneficial to the brain, because EEG patterns during REM sleep indicate that the brain is in a highly activated state.[22] Specifically, REM sleep might play a role in memory consolidation and learning, suggesting that species with greater cognitive abilities would require more REM sleep.[9,11] More recently, different studies have suggested that memory consolidation and learning may also require some involvement of NREM sleep.[23,24] REM sleep might also be involved in brain maturation.[11,25]

Although our understanding of sleep remains limited much has been accomplished over the past 20 years especially within the context of cytokine regulation of sleep and related physiological and patho-physiological processes.[26]

The evidence that cytokines are involved in physiological sleep regulation particularly interleukin-1β (IL-1) and tumor necrosis factor α (TNF) and their involvement has been proven in physiological sleep regulation and they are currently the best characterized sleep regulatory substances (SRS) and many of their downstream biochemical mechanisms are also implicated in sleep regulation, e.g., adenosine, nitric oxide, prostaglandins, and others.[27]

Sleep Regulatory Substance (SRS) Criteria

For a substance to be classified as a putative SRS several criteria need to be met. These include: 1) the substance and/or its receptor oscillates with sleep propensity; 2) sleep is increased or decreased with administration of the substance; 3) blocking the action or inhibiting the production of the substance changes sleep; 4) disease states, e.g., infection, associated with altered sleep also change levels of the putative SRS; and finally 5) the substance acts on known sleep regulatory circuits. While many substances meet some of these criteria including microRNAs, metabolites, hormones, growth factors, transcription factors, and various proteins and their receptors, only a few meet all the required characteristics to be considered an SRS. These include IL1, TNF and growth hormone releasing hormone (GHRH) for non-rapid eye move ment sleep (NREMS) and prolactin and nitric oxide (NO) for rapid eye movement sleep (REMS). These SRSs act within complex biochemical cascades to form the sleep homeostat, a network of molecules that regulate sleep over different time scales.[27,28]

INERLEUKIN-1

Wakefulness and sleep-wake-regulation are complex states, a lot of different components and regulatory mechanisms contribute to these functions. One of the factors involved in sleep wake regulation is the immune system, itself being highly complex, consisting of humoral and cellular components. Molecules that transport the information are, beside others, the "immunotransmitters", the cytokines.[29]

Sleep-wake-regulation is one example of a CNS function that is influenced by cytokines.[30] In turn, length and quality of sleep as well as sleep deprivation influence the activity of the immune system and cytokine release.[31]

Cytokines such as IL-1 have long evolutionary histories; they date to jawless vertebrates 500 million years ago and related cytokines date to invertebrates occurring at least 850million years ago. Cytokines are well-known for their roles in host defense but may have initially evolved for other purposes.[32] IL1 was first implicated in sleep regulation about 25 years ago by the finding that it has the capacity to enhance non rapid eye movement sleep (NREMS).[33]

Cytokines are low molecular weight soluble glycoproteins that are secreted mainly, but not exclusively, by immunological cells such as T-cells, macrophages, and neutrophils. Other cells that secrete cytokines include keratinocytes and dendritic cells of the skin and Schwann cells and glial cells of the CNS. The first cytokine was discovered by Beeson in 1948[34] as a pyrogenic compound extracted from polymorphonuclear leucocytes and was later known as IL-1β. Since then, many other cytokines have been discovered, and these fall into five main categories:

interleukins, interferons, tumor necrosis factors, growth factors, and chemokines.[35]

IL- 1 has been the most extensively studied cytokine with regard to the regulation of sleep.[36] Interleukin-1. IL-1 is a 17-kDa polypeptide with autocrine, paracrine, and endocrine roles. IL-1 seems to play physiological roles in the regulation of sleep, appetite, brain development, gastrointestinal function, and several endocrine systems, such as the GH-GHRH-insulin-like growth factor axis and the corticotropin-releasing hormone-adreno-corticotropin hormone-glucocorticoid axis. There are now numerous reports indicating that IL-1, IL-1 receptors, and other members of the IL-1 family of molecules are constitutively expressed in normal brain.

IL-1 cerebrospinal levels vary in phase with the sleep wake cycle, with highest levels occurring at sleep onset. Furthermore, there is a diurnal rhythm of IL-1 mRNA in the hypothalamus, hippocampus, and cortex of rats, with the highest levels corresponding to peak sleep periods. In humans, plasma levels of IL-1 peak at the onset of sleep. Finally, after sleep deprivation, brain stem and hypothalamic levels of IL-1 mRNA increase as well as circulating levels of IL-1.[37]

IL-1 has been somnogenic in every species thus far tested: these include rats, mice, monkeys, cats, and rabbits. IL-1 also induce an enhancement of electroencephalographic (EEG) slow waves[37] and indistinguishable enhancements of EEG slow waves occur during the deep sleep following prolonged wakefulness and are thought to reflect the intensity of sleep.[38]

IL-1 thus appears, by a variety of measures, to induce physiological sleep. However, high doses of IL-1 inhibit sleep rather than promote it. This action could result from the upregulation of negative feedback pathways such as the corticotropin-releasing hormone (CRH)–glucocorticoid axis. IL-1 stimulates CRH production and CRH promotes wakefulness.[37]

Injection of exogenous low doses of IL1 enhances NREMS. Conditions that enhance endogenous production of IL1 e.g., excessive food intake[39] or infectious disease, promote NREMS. Conversely, inhibition of endogenous IL1 or TNF, using antibodies or endogenous inhibitors such as their soluble receptors or the IL1RA, inhibits spontaneous sleep.[40]

IL-1 has brain receptors that are widely distributed and they are located in brain structures that are linked to sleep regulation. Likewise, IL-1 is interacting with classical neurotransmitters that are involved in sleep regulation.[36]

INTERLEUKIN-1B (IL-1b) is one of the best characterized sleep-promoting substances.[41] IL-1 induces the up regulation and down regulation of many substances thought to be stimuli for the sleep-wake cycle. IL-1 induce activation of the gene transcription factor, nuclear factor kappa B (NFκB).[42]

To sum up, pro-inflammatory cytokines are more likely to induce sleep, whereas anti-inflammatory cytokines show anti-somnogenic effects or does not affect sleep wake-regulation. Pro-inflammatory cytokines such asIL-1ß, IL-6, and TNF-α augment the immune response to help speed the elimination of pathogens and the resolution of the inflammatory challenge. Antiinflammatory cytokines, in contrast, serve to dampen the immune response to prevent an overreaction of the organism against allergens or pathogens. Examples of anti-inflammatory cytokines are IL-4, IL-10, and IL-13.[43]

Adenosine, NO, NF-κB, PGD2, the neurotransmitters γ-aminobutyric acid (GABA), glutamate and norepinephrine, as well as hormones such as GHRH and CRH are important signaling molecules involved in sleep-wake-regulation. They form part of a complex biochemical cascade, initiated for example bypro-inflammatory cytokines such as TNF-α and IL-1ß.[44]

Nuclear transcription factor κB (NF-κB) was identified by David Baltimore in 1986 as a factor in the nucleus that binds the promoter of the kappa chain of immunoglobulins in B cells.[45] NFkB is a transcription factor usually acting as an enhancer element for a wide array of genes, including other cytokines, such as TNF, NGF and EGF, and other SRSs such as the adenosineA1 receptor, the gluR1 component of AMPA receptors, cyclooxygenase and NO synthase. There may be some degree of specificity for NFkB activation to sleep. Sleep loss enhances hypothalamic and cortical NFkB activation.[46] Adenosine also elicits NFkB nuclear translocation in basal forebrain *via* the adenosine A1 receptor.[47] Finally, an inhibitor of NFkB inhibits duration of NREMS.[48] Thus *via* the actions of IL1 on NFkB and the NFkB-enhanced enzymes and receptors, shorter lived molecules known to be involved in sleep regulation are recruited into the sleep regulatory biochemical cascade including adenosine, NO, and prostaglandins and these mechanisms are also very likely involved in the regulation of local cerebral blood flow which highlights the relationships between cellular metabolism, sleep and blood flow.[49] Overall. NFκB is activated within the hypothalamus and cortex by sleep deprivation and inhibitor of NFκB inhibits NREMS.[42]

Beside this COX-2, which catalyzes the conversion of arachidonic acid to prostaglandin H2, the initial step in the formation of PGs of which PGD2 has been shown to be a sleep inducing factor.[50]

GHRH is also implicated in the regulation of two behavioural activities, food intake (9) and sleep.[51,52] IL-1 also induces release of GHRH which is somnogenic and this pathway may be somewhat independent of NFκB mechanisms, thereby forming a parallel somnogenic pathway.[53] GHRH stimulates and somatostatin suppresses GH secretion. Somatostatin is involved in various

endocrine, autonomic, and behavioural processes unrelated to the inhibition of GH.

Furthermore, IL also works through NO pathway. IL-1ß could be shown to induce sleep by enhanced production of NO due to activation of NO synthetases.[54] There is also evidence that one of the functions of IL-1ß is to increase the endogenous production of adenosine. In rat brain slices, application of IL-1ß caused a profound decrease of glutamate transmission, but not GABAergic inhibition which could be prevented by pharmacological blockade of A1 adenosine receptors (A1AR). Further, it was concluded that IL-1ß can effectively modulate glutamate excitation via an adenosine-dependent mechanism.[55] In other studies, however,IL-1ß was reported to enhance GABA inhibitory effects acting at both pre- and post-synaptic levels.[56] IL-1ß enhances GABA release in preoptic and anterior hypothalamic neurons and it also enhances GABA-induced postsynaptic responses in different in vivo and in vitro experimental models.[55,56] The role of cytokines on other wakefulness-regulating neurotransmitters such as NE [57] and serotonin (5-HT)[58] may also be of clinical and scientific interest, but the physiological and clinical significance is not clear.[59] Beside this, IL- 1 and other cytokines induce the synthesis secretion of multiple neurotransmitters, neuropeptides and hormones that have been implicated in sleep regulation.

CONCLUSION

Cytokines seems to play a crucial role at least in modulating major systems responsible for wakefulness regulation. Several pathways like NFKB, NO, Prostaglandins, Growth hormones and neurotransmitters like GABA and 5HT are implicated and involved as mediators of cytokine influenced sleep, yet the exact pathway is not clear of any of them. Scientific community should try to explain and understand these mechanisms which may prove beneficial clinically, in field of sleep (insomnia).

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