International Journal of Medical and Health Sciences

Journal Home Page: http://www.ijmhs.net ISSN:2277-4505

Review article

Understanding Sleep: A Paradigm Shift

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ABSTRACT

Sleep has fascinated since time immorial people across the spectrum of society and is continued even to the present day. It was considered as a passive phenomenon which rejuvenates the whole organism. However, a great change in understanding of sleep started after discovery of REM sleep and is it is well recognized that it is an active process. Thalamocortical interaction brings about various stages of NREM sleep, where, the sleep deepens as the thalamocortical network progressively hyperpolarizes. This brings about total functional deaffrentiation of cortex to the stimuli and builds an environment where in cortico-cortical interaction takes place, which forms the basis for spectrum of plasticity changes to take place during sleep. However, the emerging evidences have shown that sleep can be in a circumscribed region of the brain. The activity of a cortical column will drive it into sleep mode. This use dependent local sleep at various cortical columns also has a greater functional significance like that of whole organism sleep. However, the sleep is understood, either as a phenomenon of whole organism or a local use dependent, both primarily subserve role of energy conservation at their level. Understanding of sleep from cellular to organism level is discussed in this review.

KEYWORDS: Sleep, Local sleep, Function

The phenomenon of 'sleep' exists across animal kingdom. It is a heterogeneous state comprising of two distinct states, NREM and REM sleep with specific EEG signatures. Phylogenetically, these two states are observed in birds and mammals, whereas, in lower vertebrates only NREM sleep is present. This is to infer that REM sleep is introduced late in the phylogeny, and is proportionate with the development of brain and associated cognition [1]. Hence, it is thought that the emergent of these distinct sleep states at various periods during evolution should subserve specific functions. There are many evidences to show that sleep may have some role in energy conservation, immune function, memory consolidation, neural maintenance, homeostasis and many more. Large body of data shows that sleep play a critical role in somatic, cognitive and psychological processes as well [2].Yet, more fundamental question of why we sleep remains a mystery.

Sleep, as an experience, we are aware that it is an important and critical behavioral state. There are many experimental evidences showing that moderate sleep deprivation results in an adverse impact on various functions like neurogenesis, immunity, cognition, behavior and so on. Extreme

sleep deprivation is known to even cause death [3]. Yet, sleep is the least understood behavior. Behaviourally, sleep is defined as a physiological state of rapidly reversible period of immobility associated with characteristic posture, reduced motor activity, increased response threshold for external sensory stimulation. During sleep, awareness about outside world is lost and brain engages in an offline mode of functioning. But, Dolphins are known to engage in mutually exclusive behaviours simultaneously with one hemisphere in wake and the other in SWS sleep [1]. The fact that these animals engage their one hemisphere in sleep inspite of having a high risk of predators should account that SWS sleep has an important function for brain itself.

It is believed that primarily sleep is essential for energy conservation. During waking hours adenosine gets accumulated in various areas of the brain more so in basal forebrain. Adenosine accumulation reflects the metabolic alterations taking place and is proportional to the amount of energy depletion. This metabolic activity determines the amount and quality of sleep. Adenosine accumulation increases the homeostatic drive for sleep and the brain response to this drive by increasing the amount of SWS and slow wave activity (SWA), a measure of sleep homeostasis. However, sleep homeostasis is known to vary in individuals according to allele that are expressed for adenosine deaminase [4]. Recovery sleep following sleep deprivation shows enhanced SWS and SWA. Fore brain regions shows more SWA during recovery sleep which is propotional to the adenosine accumulation during sleep deprivation [5]. Thus, it is considered that the depleted energy during waking state gets repleted during sleep especially during SWS. There are now emerging evidences that not only adenosine [6], but, even other pathways in cellular energetic like glycogen, electron transport, astrocyte to neuron lactate shuttle, uncoupling of proteins, clock transcription proteins gets modulated during sleep wake cycle. It is proposed that these metabolic pathways help brain to transit from an energy attenuated catabolic wake state to sleep state which is anabolic in nature where energy gets repleted [7].

If sleep be the only way to conserve energy, then nature would have exclusively provided only this behavioral state. However, animals generally enter into hypothermic state either by torpor or hibernation as a mode of energy conservation which forms the basis of their survival. Therefore, energy conservation may not be the exclusive function of sleep, should also subserve other important functions. Increase in SWS is observed in animals after arousal from these hypothermic conditions. It is suggested that increase in SWA after hibernation or topor may not be the result of sleep debt, but an essential and most needed state for neural repair and regeneration, and to maintain synaptic homeostasis. Extremely low temperatures are known to limit synaptic transmission, lose synapses or change in their structure thereby reducing the synaptic efficiency. Post hibernation increase in SWS seems to restore the neural connections between various regions of the brain. Therefore, SWS is important for adaptive neuronal plasticity which plays an important role for survival along with energy conservation [1].

The tight regulation of synaptic strength is the basis to bring about efficient plasticity changes and is of great importance in functioning and energy dynamics of the brain. It has been hypothesized that quality of wakefulness and sleep determines the total synaptic strength of the brain [8]. During wake synaptic strength increases, reaches maximum before sleep and the strength decreases during sleep which reaches its baseline level when sleep is terminated. Thereby, synaptic homeostasis is maintained and is correlated with SWA. During wake, the process of learning and interaction with environment increases the strength of existing synapse and forms new ones. The price that is payed for this waking plasticity is the energy and space requirements, and also this plateaus the learning capabilities. Whereas, during sleep, there is no adaption of synapses due environmental stimuli and the neurochemical profile is altered. These two factors inhibits the strengthening of synapses during sleep. Average synaptic strength peaks at the end of wake hours, therefore, SWA during early sleep will be high. During the period of SWA, the repeated sequence of depolarization and hyperpolarisation impinges on neuron to down scale its strength. Therefore, as the synaptic strength reduces the SWA also decreases during later sleep period. This sleep dependent down scaling of neurons seems to play an important role

in learning and memory, neuronal development and growth [9]. Reduction of SWA during adolescent age is a tell tale sign of maturational changes of sleep during this developmental period of life. This attenuation of SWA is associated with extensive pruning and reorganization of synapses, thereby, strengthening of relevant over irrelevant synapses. These events help in development of cognition and behavior during adolescent period; which otherwise, is known to be linked to many somatic and psychiatric disorders in adolescent age [2]. Therefore, SWA during sleep is the most crucial that brings about greater beneficial effects ranging from cellular to behavioral level.

Presently, understanding of sleep is undergoing a great paradigm shift. The classical EEG change that aids in defining various sleep stages represents the overall global cortical changes in electrophysiological properties. There are now emerging evidences that SWA can be local use dependent i.e SWA in a specific region of the brain after being active [10]. High density EEG recordings after learning rotation adaptation task showed higher SWA corresponding to right parietal region of broadmann area 40 and 7 which are associated with coordination of spatial task. This local sleep (SWA), induced by learning task brings about local plastic changes which aids in enhancing the performance. Further, these down scaling events globally or locally play an important role in increasing the signal to noise ratio in neuronal circuits [8]. These energy efficient events during sleep brings about great beneficial effect on brain per se so the cognition and performance.

Sleep either understood as a global or local phenomenon, it doesn't answer the another most basic question, where sleep is located in brain?. Inspite of large brain lesions, stroke and many insults to the brain no complete absence of sleep is observed either in animal models or in human beings. This speaks of the fact that sleep is a self organizing fundamental property of viable neurons and glia and an auto regulated phenomenon [11, 12]. Practices like exercise and meditation which are known to regulate various factors affecting sleep exerts not only beneficial effect on sleep but also prevents age associated attenuation of sleep architecture [13, 14]. Therefore, the two aspects of sleep, one as a global behavioral and another as a local use dependent phenomenon combined brings about understanding of sleep from behavioral to cellular level. The fact that nature has retained phenomenon called sleep at all levels from systemic to cellular speaks that it is an critical state and should subserve the function that cannot be undertaken during waking state. In spite of all these evidences, to single out and say *'the function of sleep is….' is the most challenging*.

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