

Neurotransmitter Systems in the Central Regulatory Mechanism of Sleep-A Review

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Abstract: The fact remains that neurophysiologic factors in the central regulatory mechanism of sleep is still far from full understanding. Most of the postulations by various workers on the subject of sleep still appear to be more of speculative; there is no clear evidence to suggest that a particular neurotransmitter agent may mediate the proposed mechanism attribute to it in the mechanism of the transition between one stage of sleep and another. It was the aim of this review to identify the neurotransmitter systems variously implicated in the subject of sleep regulation and have featured more prominently in the reports of various researchers in recent past. The method of information gathering was adopted in this review and the sources of information included, published works of past and present researchers, articles on sleep in seminars, conference articles on sleep physiology, textbooks of current editions in neuroscience, lecture notes on neurophysiology and reports accessed from the Internet using search engines such as Google were also among the sources of information consulted etc. In conclusion, this review study have clearly highlighted the major neurotransmitter systems that have gained more prominent mention and featured more frequently in the works of most researchers and therefore can be said to be currently the more under study.

Keywords: Neurotransmitter systems, sleep, regulatory mechanism

INTRODUCTION

In man and all other animals, sleep is believed to be essentially a behavioural state. In man, it was noted that an individual spends approximately one third of his lifetime in sleep. Very few of our behaviours or indeed, the behaviours of all other animals is as mysterious as sleep. One of the greatest challenges that have occupied the attention of most neuroscientists throughout the world today is ascertaining a full understanding of the neurophysiologic factors involved in the central regulatory mechanisms of sleep. One other challenge is ascertaining clearly the neural principles governing the transition between one sleep stage and another. We often claim to have knowledge that sleep is part of the daily routine in everyone, even when the normal sleep and awake pattern (or cycle) is disrupted by outside factors. Sleep is observed in all species of animals, including foetuses, reptiles, amphibians, fish, birds etc. In humans, sleep is often taken very much for granted and is regarded commonly as the natural state of bodily rest in the individual.

The importance of sleep in our daily lives cannot be over emphasized. For example, in one recent report, it was observed that sleep is essential for survival (Addicott *et al.*, 2009) and other group of workers have earlier noted that sleep is a condition specifically required by the body as part of its homeostatic regulatory and repair mechanisms (Bagley, 1989). It is noteworthy that lack of adequate sleep, inability falling asleep, or inability staying asleep etc, are presently fast

becoming some of the commonest problems in our modern society.

A full discussion on the subject of sleep will require adequate introductory clarification. Thus, one of such earliest definitions of the subject regarded sleep as the state of natural unconsciousness from which an individual can be aroused. Notably also, one other earlier definitions put forward by a group of researchers underscored sleep as purely a passive state in which the brain is resting. However, for the purpose of this review, one other explanation regards sleep as a naturally recurring state of relatively suspended sensory and motor activity in the animal, characterized by total or partial unconsciousness and nearly complete inactivity of voluntary muscles. This later definition appears even more scientific and can be said to be more current explanation.

A lot of efforts have been made by most researchers in the quest for a better understanding of the neural factors in the central regulatory mechanisms of sleep. Most of the earlier research works were of the opinion that sleep is purely a passive state. Thus, the workers in that period came up with the proposal that sleep was mainly the product of activities in the neural systems in phylogenetically old reticular core of the brain. Nevertheless, with the advances in research in later years, workers have now come to learn that, on the contrary, sleep is not simply a passive or static state in which the brain is resting. It is now known that sleep is a dynamic and complicated condition during which the brain is quite active. Neuroscientists in recent years

have mapped out the normal sleep as made up of complex series of stages that repeat itself in a characteristic pattern. Thus, more recent research works have established that sleep is not simply a state of neural inactivity. For example, not very long ago, a group of workers were surprised to learn that regions of the frontal cortex show more activity in direct correlation with a person's sleepiness; the sleepier the person, the more active the frontal cortex (Gillin *et al.*, 2002). Thus, recent reports have further established the fact that sleep is not merely a state of neural quiescence; some workers have noted that brain activity are visibly altered following a period of lack of adequate sleep in that certain patterns of chemical activity that occur during sleep are interrupted (Gillin *et al.*, 2002).

A number of earlier concepts concluded that the preoptic and posterior hypothalamic areas are deeply involved in the central regulatory mechanisms of sleep. The lateral hypothalamic area and the mammillary bodies were also linked with sleep regulatory functions. Subsequently, earlier workers proposed that sleep was initiated through withdrawal of sensory input, since it was mainly a passive process. However, as time progressed and with advances in neuroscience, workers have come to recognise an active initiation mechanism which facilitates the brain withdrawal of the sensory input that trigger off sleep. Furthermore, some homeostatic factors (factor S) and circadian factors (factor C) are now believed to interact, not only to determine the timing of sleep, but also its quality (Siegel, 2005).

SYSTEMS IN BRAIN AREAS INVOLVED IN SLEEP

Areas in hypothalamus: Among the present day concepts as proposed by past workers is the sleep model advocated by Siegel *et al.* (2001) and McDonald (2010). In their sleep model, these workers proposed the presence of a 'switch' factor for sleep, considered to have their origin in Ventrolateral Preoptic Nucleus (VLPA) of the anterior hypothalamus. The sleep factor is believed to become active during sleep, using an inhibitory neurotransmitter GABA and Galanin to initiate sleep by inhibiting the arousal regions of the brain (Siegel *et al.*, 2001; McDonald, 2010). The workers further noted that the VLPA area innervates and can inhibit the awake-promoting regions of the brain, including the tuberomammillary nucleus, lateral hypothalamus, locus coeruleus, dorsal raphe and laterodorsal tegmental nuclei and pedunculopontine tegmental nucleus. Thus, in this proposal, the hypocretin (orexin) elements in the lateral hypothalamus are believed to help stabilize the 'switch'; thus, when the hypocretin neurons are lost, narcolepsy can result (Siegel, 2005).

The reticular formation: The characteristics of sleep are functions of different brain activities and circuits. The brain stem houses an extremely complex and interconnecting web of neuronal network that when stimulated provoke arousal. This area termed, Reticular Formation, is shown by experimentation to induce arousal and EEG desynchronization when stimulated. Cells from reticular formation project directly to the neocortex and activity in these cells produce wakefulness. This implies that one of the functions of reticular formation is to maintain (or sustain) the state of wakefulness (Addicott *et al.*, 2009).

The peribrachial area: Specific clusters of cholinergic neurons known as peribrachial area have been mapped out in the pons. This region in the pons is characteristically believed to play important role in the activation of the rapid-eye-movement sleep stage (Addicott *et al.*, 2009). Through experimental evidence it was shown that these cells become quite active during rapid-eye-movement sleep and clinical evidence also confirmed that lesions in the peribrachial area drastically reduced rapid-eye-movement sleep in man. Research experimentation by several workers revealed that cells in peribrachial area start firing 80 seconds just before the onset of rapid-eye-movement sleep. Thus, for reasons of this and other observations, most workers now refer to the peribrachial area as 'REM-On cells'.

Cells of the peribrachial area are known to connect directly to the brain stem regions that control eye movements, as well as have connections with the areas of the higher brain centers involved with emotions, learning and memory (probably the Limbic System). Thus, it is now suggested that the REM-on cells may be the very stuff responsible for the initiation of the fast scanning eye movement's characteristic of rapid-eye-movement sleep and, possibly, the emotional aspect of dreams (Stevens, 2008).

The Medial Pontine Reticular Formation (MPRF): In direct connection with the peribrachial area is the Medial Pontine Reticular Formation (MPRF). This area activates cells in the basal forebrain and is also known to become heavily activated during rapid-eye-movement sleep (Wrong Diagnosis: Statistics about Insomnia, 2007). Thus, the MPRF stimulates cortical activity characteristic of REM sleep and it is possible that this is in direct correlation with the cells of peribrachial area. It is reported that lesions in the MPRF similarly greatly reduces REM sleep (Addicott *et al.*, 2009).

The Ventrolateral Preoptic Area (VLPA): The ventrolateral preoptic area located in the basal forebrain, has been noted to be essential for the initiation of sleep. It was observed that damage to the VLPA produces total insomnia in the animal and that

cells in this area are highly active during all stages of sleep and inactive during wakefulness (Addicott *et al.*, 2009). There are evidence that VLPA cells are GABA secreting neurons and their axons project to areas such as the locus coeruleus, the raphe nuclei and the tuberomammillary nucleus. It has been shown that these are also areas where nor epinephrine, serotonin and histamine are produced and these neurotransmitters are known to be associated with cortical activation, wakefulness and vigilance. In other words, the VLPA cells are known to have inhibitory effects on these aforementioned areas or centers and abolish wakefulness and mental activation while stimulating drowsiness and sleep (Addicott *et al.*, 2009).

OTHER NEUROTRANSMITTERS IMPLICATED IN SLEEP

So far, the neurotransmitter systems involved in sleep regulation are subject still riddled with controversy. Regrettably also, the actual or specific central roles of the individual neurotransmitters implicated in sleep regulation are largely, still subject of much speculation, since none of the systems have been mapped out with certainty. Attempts have been made hereunder to similarly identify the other neurotransmitter systems that have also featured prominently in the subject of sleep in the past decade.

Acetylcholine, glutamine, aspartate, dopamine, serotonin, histamine: The reticular formation, an area most significantly noted as responsible for the production of sleep and wakefulness (Ganong, 2005), is also known to feature prominent cholinergic cells that project to the forebrain and cerebral cortex. Stimulation of the reticular cholinergic cells is shown to result to behavioural arousal. This explains the fact that acetylcholine antagonists decrease cortical activation, while acetylcholine agonists increased them. Also, observations show that when the reticular cholinergic cells are sedated through the application of anaesthetics, the cortical arousal effects of reticular formation is eliminated (Ganong, 2005).

A number of workers have shown that acetylcholine is released in high levels as a result of wakefulness and is found in high levels during REM sleep (España and Scammell, 2004). The lowest levels of acetylcholine have been found in slow wave sleep when there was no cortical arousal, but relaxation. Furthermore, other group of workers have noted that people exposed to acetylcholine agonists spend more time in REM sleep, than individuals that are not exposed to these toxins (Addicott *et al.*, 2009). Thus, these reports and similar observations clearly suggest that acetylcholine may be very significant in the central regulatory mechanisms of REM sleep and arousal.

A number of reports have shown that glutamine and a separate are both excitatory neurotransmitters and they are released more in wakefulness similar to dopamine, which also appear to play important role in wakefulness and alertness. There are suggestions that dopamine that play important role in wakefulness also originate in the cells of substantia nigra (Gumuetekin *et al.*, 2004) and compounds such as cocaine and amphetamines act as dopamine agonists by enhancing its release and inhibiting dopamine uptake, thus, increasing wakefulness and alertness dramatically (McDonald, 2010). This report parallels those of the blocking of receptor sites for histamine (receptors H1) as in antihistamines, a procedure which causes sleepiness and drowsiness (Inoue, 1985). Histaminergic cells are shown to be located in the hypothalamus, specifically, in the tuberomammillary nucleus (Wikipedia Free Encyclopedia, 2010) and they project to areas involved in emotion, memory and sleep. It was also reported that serotonin secreting cells, located mostly in the raphe nuclei in the reticular formation, have projections which target the same areas as histamine. Thus, it was noted that serotonergic cells are activated when we are awake and alert and during slow wave sleep the firing activity of serotonin cells decrease (Siegel *et al.*, 2001).

CONCLUSION

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

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