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Review Article

Neurophysiologic Mechanisms and the Functional Significance of Homeostatic and Circadian Regulation of Sleep

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Abstract

Sleep is regulated through Homeostatic (S) and Circadian (C) processes. Significant literature is available on individual processes. In the current paper, coordination mechanism between the Homeostatic (S) and Circadian (C) Regulatory processes are with reference to Sleep/Wake Cycle is being reviewed. In the current article multiple original contributions were reviewed and a coordination process between the processes S and C is being explained. For the regulatory process S key components were found to be Orexin neuronal system, VLPO (Ventrolateral preoptic nucleus) and GABA neurons, monoaminergic neurons and Adenosine are involved. The process C involves the SCN (Suprachiasmatic -Nucleus), melatonin secretion, pRGCs (Retinal ganglionic cells) and peripheral organ clocks activation. Increased levels of adenosine in the forebrain are linked to induce sleep by virtue of activation of VLPO through GABA neurons. The GABA neurons also give feedback to the Orexin neurons at lateral hypothalamus which in turn leads to sleep induction. In the reciprocal process VLPO system gets deactivated leading to activation of Orexin system and through the Monoaminergic neurons wake state is brought. The process C involves the activation of the SCN by specific wavelength light. SCN which has direct connection with retina of the eye and the former initiates the secretion of Melatonin in the pineal gland and subsequent to which the peripheral organs clocks are activated leading to sleep state (Refer Figure 1). Findings: During the literature review it was observed that the process S and C are proposed to coordinate by interaction of Retina of the eye involving pRGCs (Retinal ganglionic cells) with VLPO (Homeostatic part) and controls Sleep/Wakefulness. Current review focussed to investigate the linkage between the process C and S. It was found that another cells of retinal origin Retinal ganglionic cells (other than rods and cones)were responsible for the link between the two processes. This may lead to innovations in the field of diagnosis and management of Sleep disorders.

Keywords: *Muscle Hypotonia; Pediatric; Hypotonic Infant; Syndrome; Hypotonia*

Abbreviations

AR: Adenosine Receptor; GIRK: G Protein-Coupled Inwardly Rectifying K^+ Channels; GRC: Ganglionic Retinal Cells; LC: Locus Coeruleus; LDT: Laterodorsal Tegmental Nucleus; OXR: Orexin Receptor; NON-REM: Non-Rapid Eye Movement; PPT: Pedunculopontine; REM: Rapid Eye Movement; SCN: Suprachiasmatic Nuclei; TMN: Tuberomammillary Nucleus; VLPO: Ventrolateral Preoptic Nucleus

Introduction

Sleep is one the basic requirement for Humans and other animals. There are multiple factors which influence the sleep patterns, quality and quantum. Here we would like to put emphasis on the Neurophysiological aspects which regulate Sleep. We would also like to highlight the functional significance of the homeostatic and circadian systems and explain how these two systems work in an opposite model and help maintain the balance in Sleep pattern.

Multiple pathways have been proposed which are thought to be responsible for the Sleep wake patterns. Couple of these have been associated with basal forebrain and thalamocortical neurons. "The ascending arousal pathway" (Refer Figure A) comprise of group of neurons which are cholinergic, serotonin neurons, non-adrenergic and histamine secreting in nature. These neurons are primarily found in the areas: pedunculopontine and laterodorsal tegmental nucleus locus coeruleus, dorsal and median raphe nucleus and tubero-mammillary nucleus [1,2].

The inhibitory pathway (Refer figure B) the "GABA-ergic" and "galaninergic neurons" are responsible for the Sleep induction and these neurons are located at the "VLPO (Ventrolateral preoptic nucleus)".

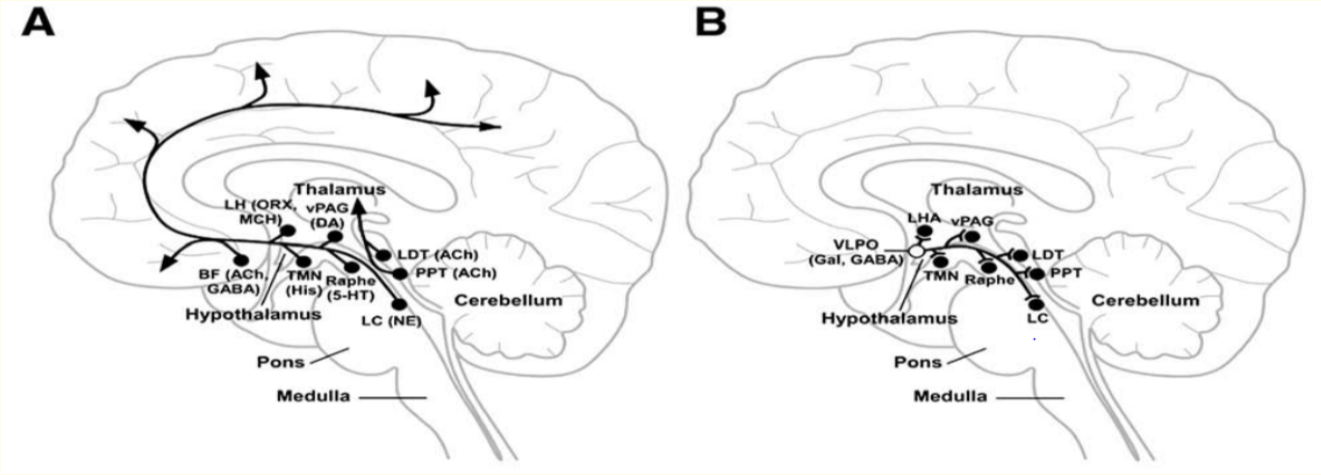


Figure A: *Arousal Pathway [2].*

Figures B: *Inhibitory Pathway [2].*

Sleep is proposed to be regulated by Homeostatic and Circadian pathways. Derangement in any of these regulatory processes can have serious health impacts. Sleep deprivation either partial or complete may have serious pathological implications. There can also be associated Sleep debt related errors which can be fatal like drowsy driving, night shift related errors in the hospital which can sometime prove lethal. Here we discuss the both Homeostatic and Circadian processes in details along with their functional importance in day to day life in Humans.

Neurophysiologic mechanisms of homeostatic regulation of sleep.

Homeostatic regulation of Sleep can be defined as a compensatory mechanism by which Sleep deprivation either acute or chronic can be restored by the body [3]. An example of the same is additional Sleep hours in the weekend taken up by the working population.

One of the proposed mechanism for the same is Adenosine expenditure and its relative availability in the basal forebrain which is directly related with the induction of Sleep. During the day when we are awake the Glycogen is broken down to the production of nucleoside Adenosine. Concentration of this nucleoside is increased in the extracellular fluid of the basal forebrain and this ultimately leads to the urge for Sleep [4].

Multiple studies have highlighted the role of the Adenosine receptors in the regulation of Sleep patterns and results of these studies gave an indication that Adenosine agnostics promoted sleep and antagonists of the same decreased Sleep. Multiple Adenosine receptors

have been postulated namely: A_1R, $A_{2a}R$, $A_{2b}R$ and A_3R out of which A_1Rs and $A_{2a}Rs$ are considered to be responsible for the Sleep Homeostasis [4].

A_1Rs receptor has been postulated to be involved in Thalamocortical pathway deactivation and leading to the slow wave activity [4]. This has been termed as indirect pathway. Figure 1 illustrates the Thalamocortical activation and inactivation during wake stage/REM stage of Sleep and Slow wave sleep respectively. During the wake and the REM sleep stage the Cholinergic activity is on the higher side and there is relative low levels of Adenosine in the extracellular fluid which tend to give an excitatory stimulus though the Thalamocortical neurons of the basal forebrain and the brain stem innervating the cortical region (Refer figure 1A). The same can be observed in the Cortical EEG pattern in the figure 1A [4].

In figure 1B, there is relative increased level of Adenosine and Thalamocortical deactivation again involving the same brainstem and basal forebrain Cholinergic arousal centres. The corresponding Cortical EEG imparts the slow wave type pattern indicative of the deactivation of the arousal centres [4].

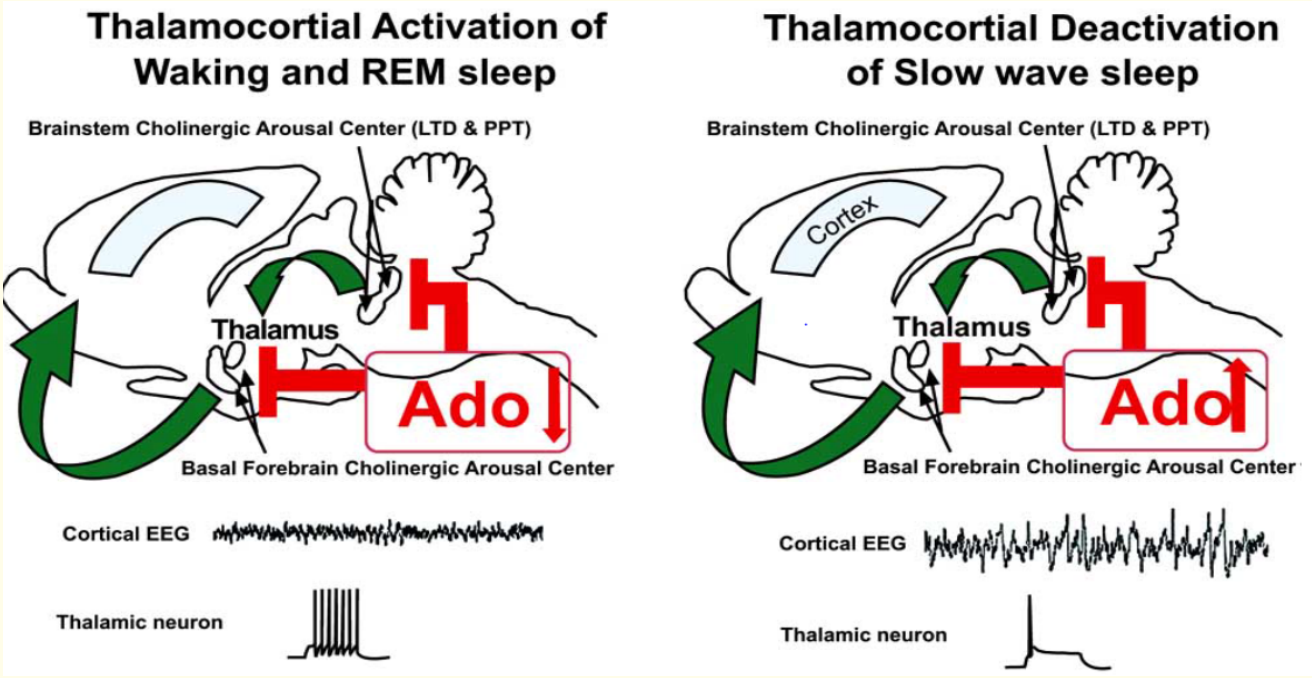


Figure 1A ***Figure 1B***

Figure 1: *Illustrates A1R receptor (Adenosine)role in the Thalamocortical Activation during Wake and REM Stage(1A) versus the Deactivation during the Slow wave Sleep (1B) [4].*

Another pathway proposed is the direct pathway in which direct activation of the A_1Rs activations can lead to slow wave activity by virtue of increased Adenosine levels (Refer Figure 2) [4,5].

"G protein-coupled inwardly rectifying K^+ channels" (GIRK) play a significant role at the level of cortical and thalamic neuronal sites. As a result of this there is relative increase in the Adenosine levels which further augments the flow of the Potassium ions and decrease in the I_h current ultimately resulting in the slow wave activity similar to what is found during Sleep [4,5].

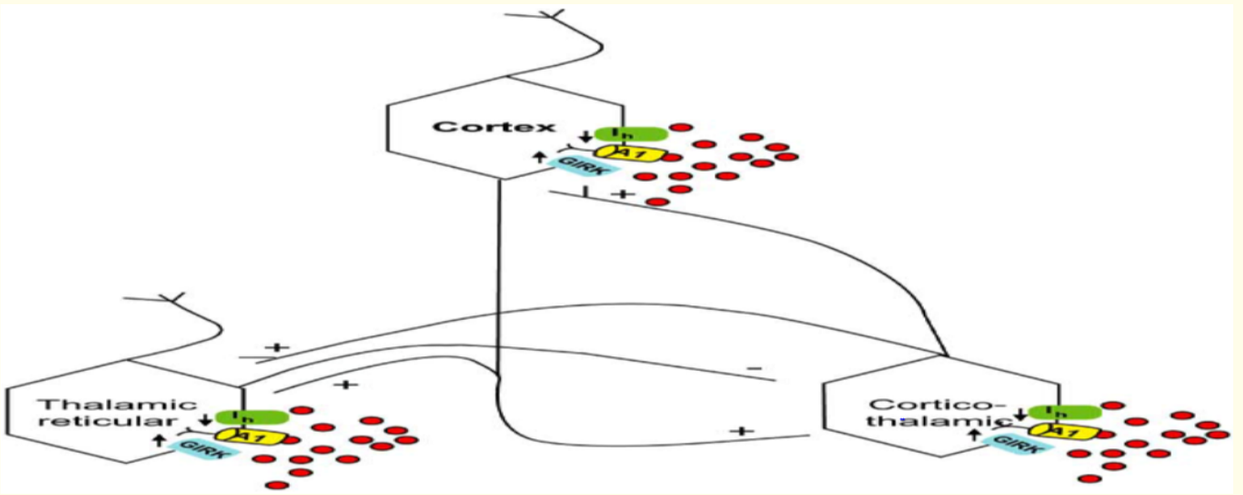


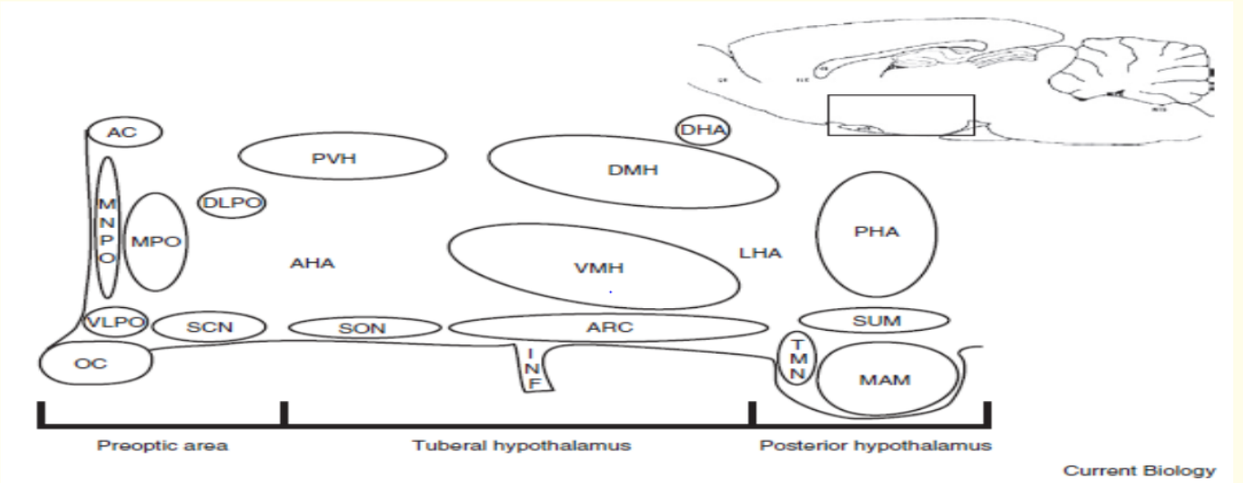
Figure 2: *"G protein-coupled inwardly rectifying K^+ channels" (GIRK) related Direct pathway [4].*

In multiple experiments it has been observed that Adenosine and Adenosine receptor agonists may play an important role in the Sleep induction in Humans and mammals [1,2,6,7].

It has been postulated that Adenosine may trigger the VLPO (Ventrolateral preoptic nucleus) which is responsible for Sleep induction through the inhibitory pathways comprising of the GABA neurons. Hence Adenosine inhibits the arousal ascending pathway and also activates the VLPO leading to Sleep induction and thus maintain the balance between the Sleep debt and the requirement [4,5].

Role of Hypothalamus: Orexin/Hypocretin in Sleep Regulation

Hypothalamus plays a significant role in controlling the Sleep Wake pattern. It has been postulated that the posterior hypothalamus neurons might be associated with the wake stage and those in the anterior part with the Sleep [8]. The posterior hypothalamus comprise of histamine secreting neurons, orexin neurons and glutamatergic neurons in tuberomammillary, lateral hypothalamus and supramammilary regions respectively. All these excitatory neurons project into the basal forebrain cortex and maintain the wake state (Refer figure 3B). In contrast the inhibitory neurons located in the anterior parts of the hypothalamus namely: ventrolateral preoptic nuclei (GABA and the galanin inhibitory neurons)and median preoptic nuclei which are postulated to be responsible for the Sleep state (Refer figure 3B).



This figure and the ones that follow are enlargements of the area shown by the box in the inset at the upper right, projected against a midsagittal section of a rat brain. The relative locations of the hypothalamus and its nuclei shown here are very similar in other mammals, including humans. The most rostral part of the hypothalamus, overlaying the optic chiasm, is the preoptic area (left). The tuberal portion (center) overlays the pituitary stalk (infundibulum, INF). The posterior hypothalamus (right) overlays the mammillary bodies. AC, anterior commissure; AHA, anterior hypothalamic area; ARC, arcuate nucleus; DHA, dorsal hypothalamic area; DLPO, dorsolateral preoptic area; DMH, dorsomedial nucleus; LHA, lateral hypothalamic area; MAM, mammillary nuclei; MNPO, median preoptic nucleus; MPO, medial preoptic area; OC, optic chiasm; PHA, posterior hypothalamic area; PVH, paraventricular hypothalamic nucleus; SCN, suprachiasmatic nucleus; SON, supraoptic nucleus; SUM, supramammillary nucleus; TMN, tuberomammillary nucleus; VLPO, ventrolateral preoptic nucleus; VMH, ventromedial nucleus.

Figure 3A: *Structural Representation of the Hypothalamus [8].*

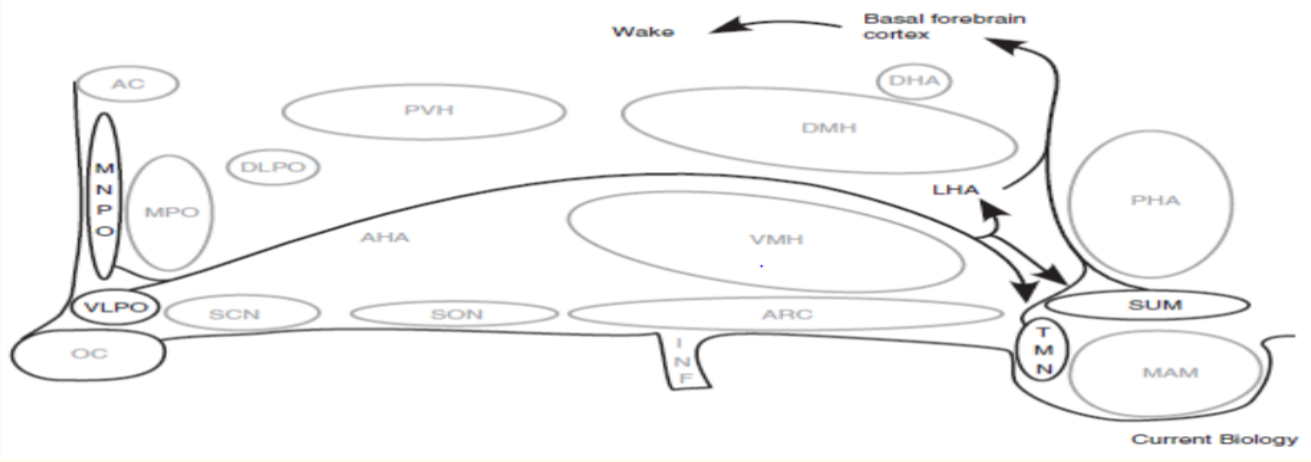


Figure 3B: *Black arrows showing the Hippocampal pathways involved in the Sleep regulation [8].*

Orexin has been historically considered as one of the important factor to regulate the feeding behaviour [9]. Of late role of Orexin/ Hypocretin in maintaining the wake condition has been studied and reviewed [9,10].

Orexin neurons are primarily in the hypothalamus specifically in the perifornical area, lateral and posterior hypothalamus. Figure 3A and 3B depict the distribution of the of the Orexin neurons in various parts of the Hypothalamus and its involvement in the Sleep regulation respectively [8]. The Orexin neurons comprise of two receptors OX_1R and OX_2R which are responsible for the regulation of sleep pattern (Refer figure 4). Various animal and human studies have proposed the role of Orexin is secondary to the activation of hypothalamus and brain stem located monoaminergic and cholinergic neurons.

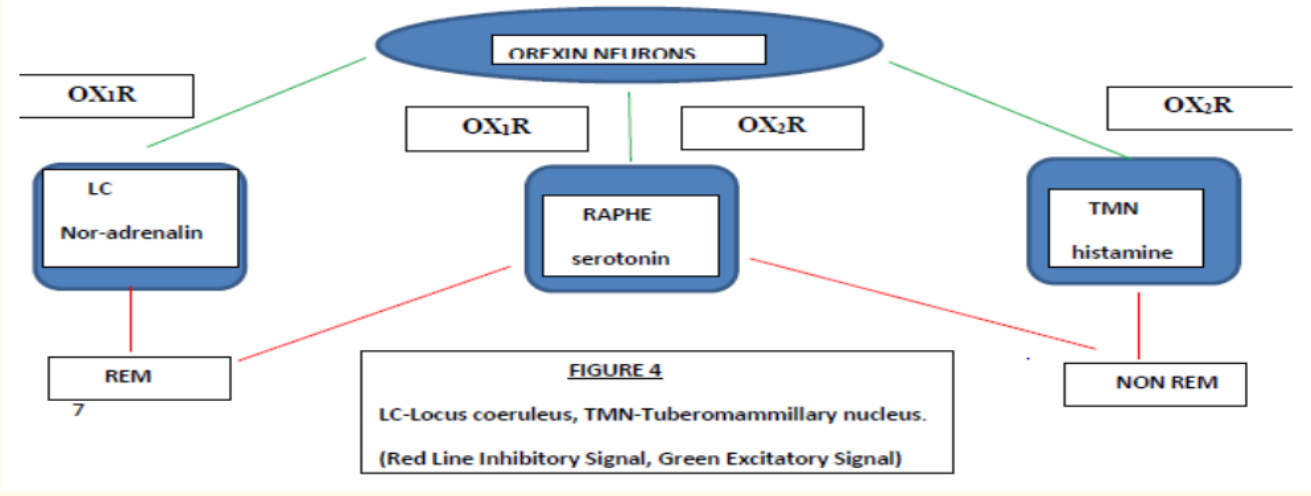


Figure 4: *Neurophysiological Mechanism behind the Sleep Wake Flip Flop Switching and Role of Orexin Neurons [3,8].*

Figure 5A and 5B describe the how different neuronal projections lead to a on and off switch mechanism with respect to the Sleep and Wake patterns. Orexin neurons are primarily responsible for the excitatory action and hence forth responsible for the Wake pattern. Orexin neurons give excitatory inputs to the "monoaminergic neurons" (NA, 5-HT and HA) which in turn give inhibitory signal to the VLPO located GABA neurons and wake stage is maintained [9].

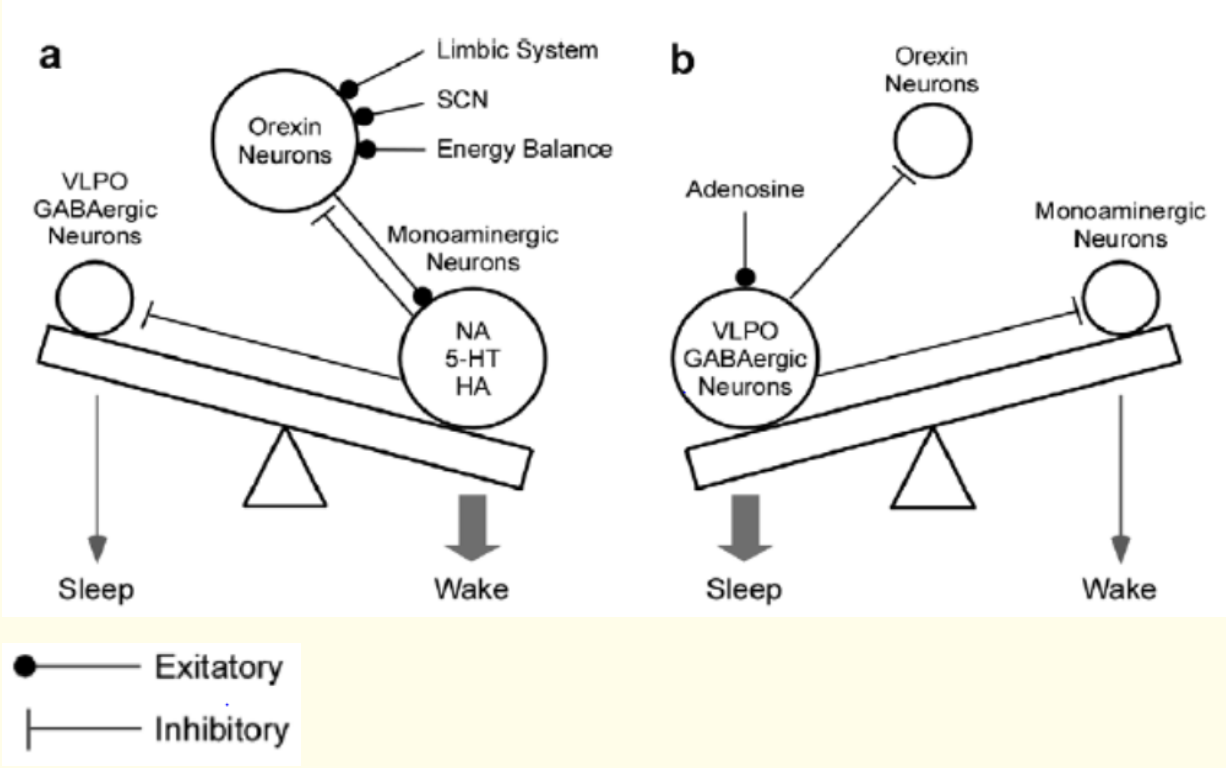


Figure 5A and 5B [9].

As the Adenosine concentration increases in the forebrain extra cellular fluid, the VLPO located GABA neurons are activated which sends an inhibitory signal to the Orexin neurons and thus the monoaminergic neurons leading to Sleep stage.

Neurophysiologic mechanisms of circadian regulation of sleep

Twenty four hours dark and light cycle plays a significant role in our day to day activities. It is worth noting that this alternation in light pattern during day and night also impacts our Sleep cycle [11]. One of the primary function of light is to help making the images at the retina of the eye, along with this specific frequencies of the light also impact the master Circadian clock situated in the brain. This central Circadian clock is postulated to work in close coordination with the peripheral clocks at the cellular level in different parts of the body [11-15].

Almost four decades ago it was proposed that the 24 hour day and night rhythms is managed by set of multiple neurons in "Suprachi-asmatic Nuclei-SCN". The same is located at the anterior part of the hypothalamus. SCN has direct connect with the Retina [11].

Sleep wake cycle regulation is a complex phenomenon comprising of both Circadian and Homeostatic systems. The induction, quantum and the structure of Sleep are dependent upon multiple factors the SCN receipt and transmission of signals being the one of the important aspects to be taken into consideration [11].

Role of Melanopsin and other cells of the retina [11,16]

Retinal Image formation physiology in the eye is known for over hundreds of years now. Rods and cones in the retina have been associated with the image forming cellular structure and the same set of cells were thought to be part of the physiology responsible for the Circadian cycle as well.

Figure 6 demonstrates detection of light process in the retina of the vertebrate. This figure signifies the importance of the photopigment Melanopsin which throws emphasis of the fact that the light detection is a process which not only occurs at the outer retinal level but also the inner retinal level. As a process the light signals are received from the outer retina by the Rods (R) and Cone (C) cells. These signals are then transmitted to the inner retina by the bipolar cells (B) and subsequently to the ganglion cells (G). Axons from the ganglion cells together lead to the formation of the optic nerve (Refer figure 6).

Studies on rodents and fish now suggest that there is another subset of ganglionic cells (pRGcs) which have the ability to detect the light directly bypassing the rods and cone cells and associated structures in the retina [11,16]. These cells require a photopigment called the Melanopsin for their activity. Once the specific frequency light (Blue light in particular) is received by the pRGcs, the Melanopsin leads to the activation of the G-protein mediated activity leading to the conduction of the signal. There have been certain studies in which the genetic mutations were induced in the mice leading to the destruction of rods and cones, however the Circadian rhythm was still maintained which explains the role and importance of the Melanopsin mediated signal conduction in the inner retinal layer of the eye [11,16] (Refer figure 6 and 7).

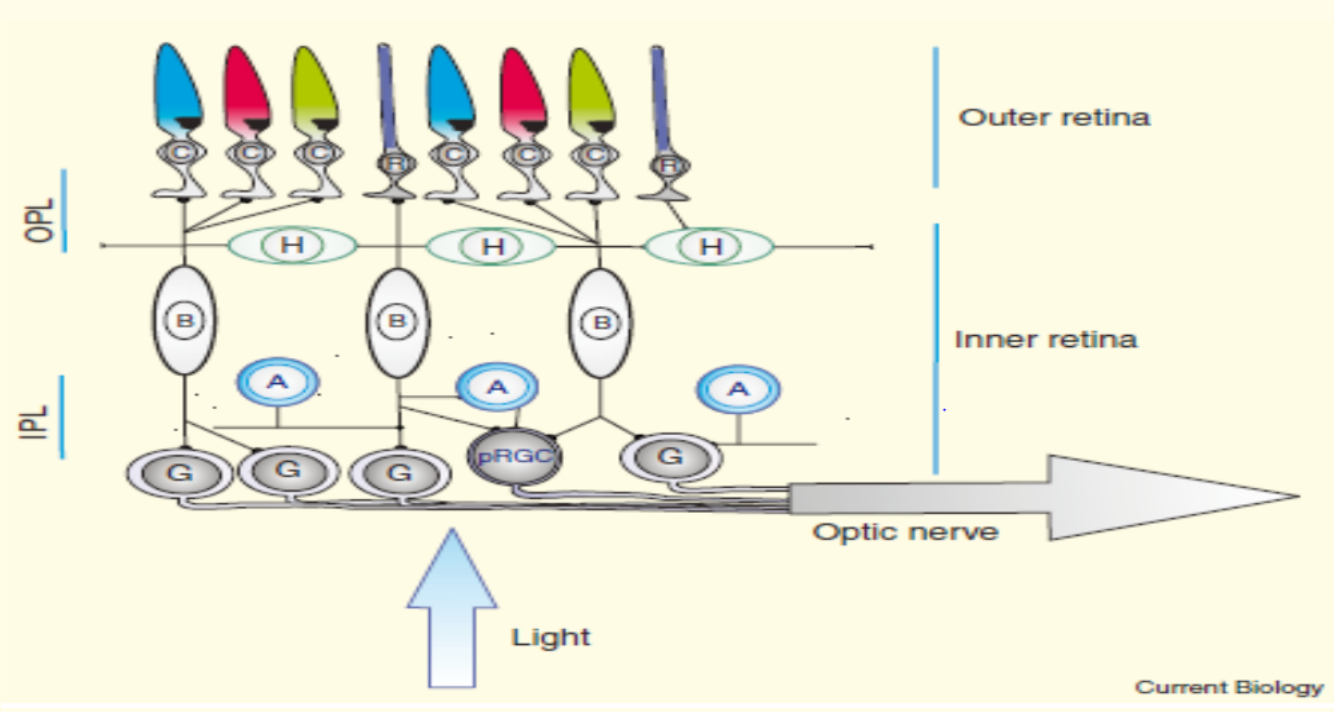


Figure 6: *Detection of light process in the retina of the vertebrate [16].*

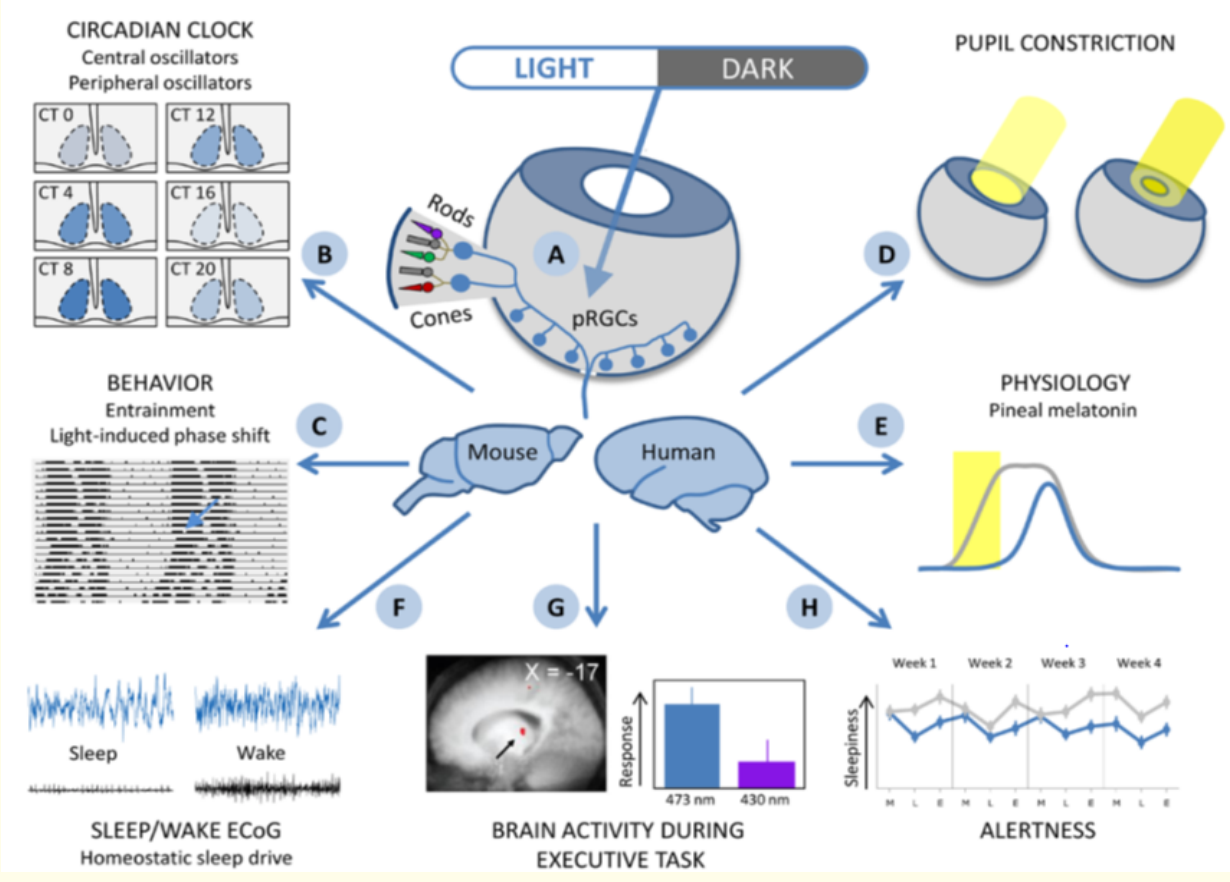


Figure 7: Persistent Impact of Light in the Circadian Clock [11].

Process A:pRGcs receive the Blue wavelength (470 - 480 nm) and the process activation starts.

Process B: pRGCs interact with the SCN and gene expression is initiated at the peripheral organ level.

Process C: The process B can lead to the process C i.e. light induced shift of the phase.

Process D: Followed by the constriction of the pupils.

Process E:pRGCs by stimulating SCN induces the secretion of melatonin by the pineal gland.

Process F: pRGCs also interact with the Homeostatic Regulatory system through VLPO and controls Sleep/ Wakefulness.

Process G: Functional MRI suggestive of Blue light based brain activity.

Process H: Impact of alertness.

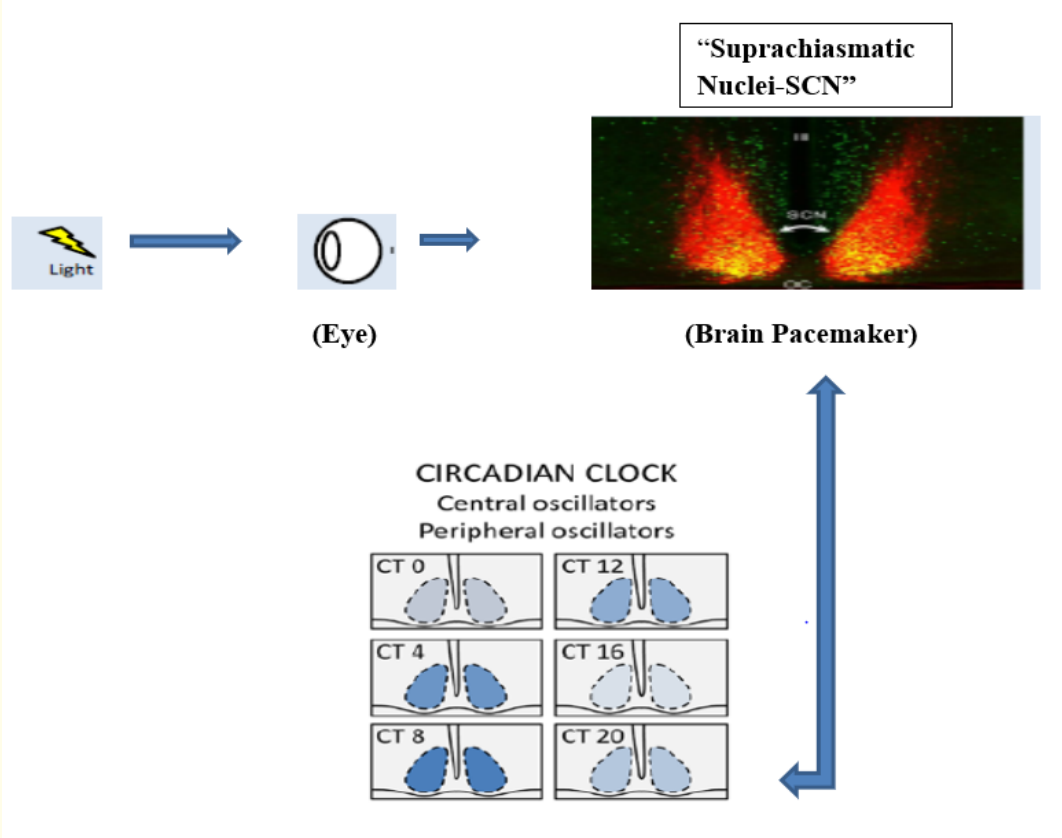


Figure 8: *SCN as a Central Pacemaker and its interaction with the Peripheral Pacemakers [11,13].*

Eye receives the specific frequency light and the SCN as as brain pacemaker which further interacts with the peripheral organs which comprise of peripheral oscillators.The genes associated with transcription of the CRY and PER proteins in mammals are Per 1, Per 2 and Per 3. CRY and PER proteins are responsible the feedback mechanics at the cellular level [11,13].

Above described two process Circardian (Process C) and Homeostatic (Process S) work in oscillatory mode and regulate the Sleep/Wake cycle. Homeostatic process keeps on building the sleep requriement based as the hours pass by in a day. However, the Circadian process which is primarily driven by the light sensitivity tends to oppose the Sleep drive during the day time in humans.As the day passess on, the sleep debt keep on acumulating and by the ned of the day significant debt has been created. This will lead to the induction if sleep [13].

Functional significance of homeostatic regulation of sleep

Currently there are multiple aspects which are very important with respect to the development of Sleep disorders related pathophysiology. These factors can be characterised into neurobiological, social and psychological. Both Homeostatic and the Circadian process work within the framework of these factors and derangement of any of these can lead to pathological conditions.

The Homeostatic and the Circadian regulatory processes are quite complex and each of the process involves multiple loci which can have direct or indirect functional impact not only on the Sleep/Wake but also on some other aspects as well. These processes have significant functional impact on the Sleep wake cycle.

The Homeostatic process involve two significant systems which comprise of Orexin neurons and other is Adenosine based process [6,9,10].

Studies suggest that Orexin deficiency may lead to Nacrolepsy [9]. Nacrolepsy is associated with excessive day time sleepiness which is clinically presented as sleeping in the day at inappropriate time which may be multiple times a day. In this condition the Sleep cycle is disturbed as the after the REM sleep stage wakefulness follows. Nacrolepsy patients may exhibit a stage called "Cataplexy" in which there is remarkable muscle tone decrease and clinical presentation can be of slurred speech, jaw drop and remarkable reduction in the postural muscular tone [9].

Orexin neuronal system also plays significant role in the central motor control [17]. The loss of the Orexin neurons has been found to lead multiple motor deficits. The Orexin neurons innervate multiple structure, however the ascending fibres innervating the basal ganglia and the motor cortex are key structures with respect to the regulation of the motor activity. This excitatory set of neurons functionally may lead to voluntary movements. This concept is in alignment with the finding that Orexin deficiency in the motor cortical area can lead to increase in the threshold pertaining to resting and activity. Overall the lower levels of Orexin may be responsible for the decreased motor activity [17]. Orexin system also plays role in the energy balance [3].

Another major component in Homeostatic process which is of key importance is Adenosine dependent slow wave activity [5]. It has been observed that the Adenosine receptors loss may trigger the relative decrease in the slow wave activity and the later can lead to derangement of the compensatory Sleep debt process. Along with this slow wave activity can have detrimental impact on the working memory and consolidation [5].

As discussed earlier the adenosine levels is of key importance for the induction of sleep. Excess caffeine [3] consumption can reduce the relative levels of the adenosine in the forebrain and the other related areas and hence leading to alertness [3].

Other drugs whihc are usually given for raising alertness levels like "methamphetamine" are directly or indirectly connected with the ascending arousal neuronal fibers [3]. This again signifies the importance of the Homestatic regulatory process. Similarly, another drug "modafinil" seems to have mechanism based on the VLPO and Orexin Neurons systems and leads to the alretness by alteration in the Homeostaic regulatory process [3].

Functional significance of Circadian regulation of sleep

The Circadian process also plays a significant functional role in the sleep wake cycle and disruption in the same can lead to significant consequences. There is a specific class of disorder termed as "Circadian rhythm Sleep disorders". As per the International Classification of Sleep Disorders ISCD 3, the circadian rhythm sleep disorders can be classified as following.

Delayed sleep phase disorder (DSPD): In this particular case, in contrary to the required sleep or wake time there is delay in getting to sleep as compared to the routine time. Secondary to this there is increase day time impairment of work schedule as this process leads to symptoms of chronic insomnia and excessive desire to sleep [18].

Advanced Sleep Phase Disorder (ASPD): In this case the sleep cycle is advanced and stable majorly leading to the very early morning waking up. This early rising up is very unconventional in the current disorder [18].

Irregular sleep-wake rhythm Disorder (ISWRD): In this case there are multiple episodes of short duration sleep and wake within the 24 hours period. These are thought to be secondary to the temporal disorientation of the cycle of sleep and wake [18].

Non-24 Hour Sleep Wake Disorder (N24HSWD): This disorder is characterized by the unstable repetitive pattern of sleep/wake episodes over a period of 24 hours [18].

Shift Work Disorder (SWD): Is classified as the disorder which occurs secondary to the work schedule which is non-conventional like the population working in the night. This is also companied by the day time sleepiness [18]. Night shift workers have been associated with multiple metabolic challenges in later part of their life. Medical errors post 24 hours or longer duration shifts haven been reported in the United states of America. As per the study conducted such Physicians were found to be making 36% serious medical errors [13].

Jet lag: is secondary to travel on fast track leading to time zone differences and further causing derangement in the circadian clock and the external environment. This is probably one of the most commonly known Circadian rhythm disorder across the frequent travellers. This is also associated with the day time sleepiness and finding it difficult to fall asleep or being sleep [18].

Melatonin and Circadian Process: Melatonin release during the night time in humans has been found to induce sleep [11,13]. Earlier in this write up role of pRGCs by stimulating SCN induce the secretion of melatonin by the pineal gland was discussed.

Exogenous administration of melatonin has been found to improve the sleep duration and efficiency. One of the major aspect to be noticed here is that the melatonin administration efficacy is dependent upon the Circadian rhythm i.e. when melatonin was given out of the Circadian phase (in the day time no impact was seen) no impact on the sleep was observed [13]. Further the dose response of the melatonin administered is also dependent on the Circadian regulation.

Management of the "Circadian rhythm Sleep disorders: Treatment of these disorders is linked to the assessments based on the Sleep diaries, actigraphy and other questionnaire etc. It also involves the behavioural aspects as well. Further, phase shifting management along with the timed light exposure or the exogenous melatonin may also be used. This is accompanied with the subsequent insomnia/ excessive sleeping which ever may be the case [19].

Conclusion

To sum up both Homeostatic and Circadian processes comprise of complex neurophysiological mechanisms which do have critical implications in the day to day life of humans. Orexin neuronal system, VLPO and GABA neurons, monoaminergic neurons and Adenosine along with other structures form the Homeostatic regulatory process [3,20]. On the other hand the, Circadian regulatory process is primarily specific wavelength based process which involves Retina of the eye and SCN. The SCN comprises of set of neurons and is located in the anterior part of the hypothalamus. SCN has direct connect with the Retina [11].

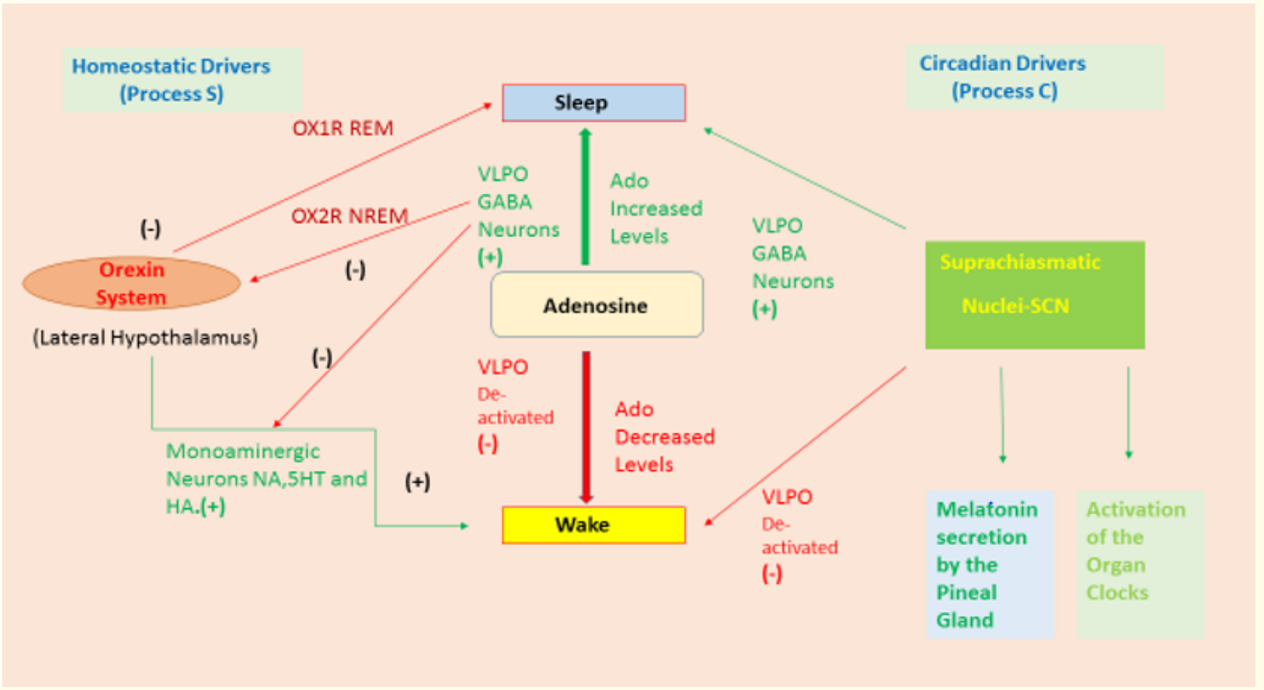


Figure 9: *Schematic Diagram of Homeostatic and Circadian Systems taken together. (Compilation done based on the references [4,9,11,13].*

Figure 9 illustrates the overall Homeostatic and the Circadian process when taken together and how they regulate the sleep/wake patterns.

Derangement in any of these regulatory processes can have serious impact on the metabolic activities which can lead to development of pathological conditions and multiple disorders Shift worker disorder, Insomnia, Narcolepsy, Jet lag disorder a few to name. Another crisis which can be associated is day time drowsiness which can lead to fatal road side accidents. Iatrogenic Medical errors are again very much prominent as the at residency level, where more than 24 hours continuous night duties are being carried out. It is also important to diagnose the basic cause of the Sleep disorders based on which accurate treatment can be done.

With the better understanding of the physiology of these two regulatory processes, scientists and sleep Medicine specialists have been able to diagnose and manage the sleep disorders in a better way, exogenous use of Melatonin is a good example of the same as it is dependent on the timing of the day when it is administered [13].

Further, both these process have been studied in details till now, however still number of questions remain unanswered. Development of newer diagnostic techniques and subsequent treatments based on the better understanding of these two regulatory processes should be the future goal.

Bibliography

1. Scammell TE., *et al*. "Hypothalamic arousal regions are activated during modafinil-induced wakefulness". *The Journal of Neuroscience* 20.22 (2000): 8620-8628.

2. Fuller PM., *et al*. "Neurobiology of the sleep-wake cycle: Sleep architecture, circadian regulation, and regulatory feedback". *Journal of Biological Rhythms* 21.6 (2006): 482-493.

3. Schwartz JRL and Roth T. "Neurophysiology of Sleep and Wakefulness: Basic Science and Clinical Implications". *Current Neuropharmacology* 6.4 (2008): 367-378.

4. Bjorness TE and Greene RW. "Adenosine and Sleep". *Current Neuropharmacology* 7.3 (2009): 238-245.

5. Pape BYH. "Adenosine promotes burst activity in guinea-pig geniculocortical neurones through two different ionic mechanisms". *Journal of Physiology* 447 (1992): 729-753.

6. Strecker RE., *et al*. "Adenosinergic modulation of basal forebrain and preoptic/anterior hypothalamic neuronal activity in the control of behavioral state". *Behavioural Brain Research* 115.2 (2000): 183-204.

7. Chamberlin NL., *et al*. "Effects of adenosine on GABAergic synaptic inputs to identified ventrolateral preoptic neurons". *Neuroscience* 119.4 (2003): 913-918.

8. Saper CB and Lowell BB. "The hypothalamus". *Current Biology* 24.23 (2014): R111-R1116.

9. Ohno K and Sakurai T. "Orexin neuronal circuitry: Role in the regulation of sleep and wakefulness". *Frontiers in Neuroendocrinology* 29.1 (2008): 70-87.

10. Sakurai T. "Roles of orexin/hypocretin in regulation of sleep/wakefulness and energy homeostasis". *Sleep Medicine Reviews* 9.4 (2005): 231-241.

11. Dijk DJ and Archer SN. "Light, Sleep, and Circadian Rhythms: Together Again". *PLoS Biology* 7.6 (2009): e1000145.

12. Panda S., *et al*. "Circadian rhythms from flies to human". *Nature* 417.6886 (2002): 329-335.

13. Czeisler CA and Gooley J. "Sleep and circadian rhythms in humans". *Cold Spring Harbor Symposia on Quantitative Biology* 72 (2007): 579-597.

14. Czeisler JFD and CA. "Effect of Light on Human Cicardian Physiology". *Sleep Medicine Clinics* 4.2 (2009): 165-177.

15. Huang W., *et al*. "Circadian rhythms Sleep and metabolism". *Journal of Clinical Investigation* 121.6 (2011): 2133-2141.

16. Foster RG and Hankins MW. "Circadian vision". *Current Biology* 17.17 (2007): R746-R751.

17. Hu B., *et al*. "Roles of the orexin system in central motor control". *Neuroscience and Biobehavioral Reviews* 49 (2015): 43-54.

18. Sateia MJ. "International classification of sleep disorders-third edition highlights and modifications". *Chest* 146.5 (2014): 1387-1394.

19. Sack RL., *et al*. "Circadian rhythm sleep disorders: part I, basic principles, shift work and jet lag disorders. An American Academy of Sleep Medicine review". *Sleep* 30.11 (2007): 1460-1483.

20. Saper CB., *et al*. "Sleep State Switching". *Neuron* 68.6 (2011): 1023-1042.

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