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Neurophysiological foundations of sleep, arousal, awareness and consciousness phenomena. Part 2

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Abstract

Second section of the paper contains description of hypothalamic centres involved in regulation of circadian rhythms. Connections between these neurons and activating reticular system are described. Transition from arousal to sleep, promoted by substances called somnogens, is discussed. Lastly, function of suprachiasmatic nucleus as circadian oscillator is presented.

Key words: consciousness, awareness, sleep, arousal, reticular system, thalamus, hypothalamus

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HYPOTHALAMUS AND REGULATION OF CIRCADIAN RHYTHM

The hypothalamus is uniformly perceived as the main structure responsible for the regulation of sleep-wakefulness states [1]. Mention of hypothalamic significance in circadian rhythm dates back to the 1930s. An Austrian scientist, Constantin von Economo, performed autopsies on brains from patients who died during viral encephalitis (*encephalitis lethargica*) epidemics and noted that the occurrence of coma in those patients was related to injury of the posterior hypothalamus and anterior midbrain. In some patients, disease-related damage could be found in the anterior hypothalamus, and those subjects presented quite a different symptomatology, as they remained in a state of constant wakefulness. Von Economo suggested that the anterior hypothalamus contains neurons responsible for falling asleep, while the posterior part of the organ contains neurons generating a state of wakefulness. Von Economo published his observations and conclusions in 1931 [2].

In the 1950s Moruzzi and Mogoun presented the notion of an activating reticular system of the brainstem, and in the 1960s the role of the hypothalamus and basal part of the forebrain in the generation of awareness was acknowledged [3]. Further milestones in the neurophysiology of awareness included the theory of the thalamic system of modulating sensory information, the discovery of reciprocal relationships between different neuronal systems in the state of dynamic equilibrium as well as the discovery of the stabiliser, which regulates oscillations of neuronal networks having opposing effects on the state of awareness.

The main centres involved in the generation and regulation of sleep and wakefulness include:

— basal forebrain (BF),
— reticular formation (RF) of the pons and midbrain,
— pedunculopontine tegmental nuclei (PPT) and laterodorsal tegmental nuclei (LDT) of the pons,
— ventrolateral preoptic nucleus (VLPO) of the hypothalamus,
— median preoptic area (MNPO),
— tubero-mammillary nucleus (TMN) of the hypothalamus,
— dorsal and median raphe nuclei (DR) of the brainstem,
— locus coeruleus (LC) of the pons and midbrain,
— orexinergic lateral part of hypothalamus (ORXN),
— suprachiasmatic nucleus (SCN) (Fig. 1).

Synaptic mediators involved in the generation of sleep and wakefulness states include noradrenaline, serotonin, acetylcholine, histamine, melanin-concentrating hormone (MCH), dopamine, γ-aminobutyric acid (GABA), glutamine, glycine and orexins.

Homeostatic regulation of this system depends on the global metabolic state of the organism. This can be approximately reflected by the cerebral concentration of adenosine,

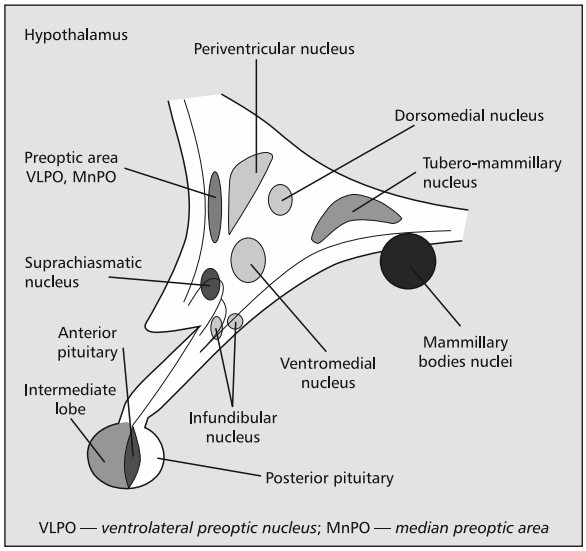


Figure 1. Hypothalamus, sagittal section

a product of ATP breakdown, which increases in the state of activity [4, 5]. Exceeding the critical level of adenosine concentration activates neurons in the ventrolateral and medial preoptic areas (VLPO, MnPO) of the hypothalamus, which are responsible for the transition into sleep [6–8]. Adenosine is therefore the main somnogen of the body, whereas other substances having the same effect include proinflammatory factors TNF-α, IL-1β, and elements of bacterial cells (lipopolysaccharides, muramic acid), released during cell damage, which stimulate production of the aforementioned molecules [7–9]. Presence of these substances regulates the amount and quality of sleep, and thus modifies the function of the immune system. Clinical observations confirm that sleep deprivation markedly increases the incidence of infections. Prostaglandin PGD-2 is another somnogen [10], the concentration of which was observed to increase in the neurological phase of African sleeping sickness [11].

The two main hypothalamic structures with opposing function that take part in the regulation of sleep and wakefulness are the tuberomamillary nucleus and ventrolateral preoptic area [12–14]. The tuberomammillary nucleus contains relatively few neurons, which are the main cerebral source of histamine, and play a major role in the generation of the state of wakefulness. This group of neurons can be simplistically called the hypothalamic "arousal centre". Their axons join axons of cells located in the raphe nuclei, locus coeruleus nuclei and substantia nigra nuclei, together forming the lateral ventral pathway of the reticular activating system. They also have numerous cortical connections; the inhibition of their activity induces sleep [12, 13].

Hypothalamic neurons located in the ventrolateral preoptic nucleus (VLPO) and median preoptic nucleus (MnPO) are referred to as the hypothalamic "sleep centre", as they are active mainly during NREM sleep and, to a lesser extent, during the REM phase. The ventrolateral preoptic nucleus (VLPO) is crucial for sustained sleep, whereas the median preoptic nucleus (MnPO) shows the greatest activity before falling asleep and initiates transition into sleep [12, 13].

Axons of VLPO neurons have numerous synaptic connections to nuclei of the activating system, with particularly strong projection of the histaminergic cells of the tuberomammillary nucleus. These neurons contain inhibitory mediators, γ-aminobutyric acid and galanin peptide [13]. Neurons of the hypothalamic VLPO become stimulated by adenosine via A1 receptors and send indirect signals to the above-mentioned histaminergic neurons, which then become inhibited, thus leading to a transition from wakefulness to NREM sleep. This process is increased by simultaneous inhibition of other centres that are normally active during states of arousal, including the locus coeruleus (LC), dorsal nucleus raphe (DR), laterodorsal tegmental nucleus of pons and midbrain (LDT) and pedunculopontinetegmental nucleus of pons and midbrain (LDT/PPT) as well as groups of orexinergic neurons that form the so-called Meynert nucleus [5, 6].

Neurons in the VLPO and MnPO have receptors for hypothalamus-produced growth hormone releasing hormone (GHRH); their activity is correlated to the circadian rhythm of GHRH release. Pharmacologic agents used for treating sleeplessness promote GABA-ergic activity; benzodiazepines, barbiturates and non-benzodiazepine agents such as zolpidem are GABA A-receptor agonists [5].

The system described above is a negative feedback loop. The activating part of the system includes cholinergic, monoaminoergic and histaminergic projections, with lesser participation of dopaminergic projection, whereas the inhibitory part includes GABA and galaninergic projections. Neurons in the VLPO are active during sleep and have inhibitory effects on monoaminoergic (TMN, NC, DR) and cholinergic (PPT, LTD) neurons, which in turn have activator effects. When the threshold is passed, the dominant monoaminoergic and cholinergic stimulation causes an abrupt inhibition of VLPO neuron activity, thus leading to the state of wakefulness. The negative feedback loop mechanism functions according to the "all or nothing" principle or, to borrow from cybernetic terminology, has a "flip-flop" construction [14–17]. The hypothalamic switch system is based on negative feedback between the activating cholinergic and monoaminoergic networks, and the medial and lateral preoptic areas of hypothalamus, which have inhibitory effects. Neurons in the VLPO are active during sleep, and inhibit monoaminoergic neurons. In doing this, they simultaneously escape the inhibitory effect of monoaminoergic neurons, thereby further increasing their own activity.

The transition from NREM to REM sleep is regulated by a feedback mechanism involving cholinergic neurons (*REM-on*), and noradrenergic and serotoninergic neurons (*REM-off*). Cholinergic neurons are located in the pedunculopontine and lateral tegmental nuclei (Ach 5 and Ach 6), whereas serotoninergic and noradrenergic neurons can be found in the raphe and locus coeruleus nuclei [18–20].

Recent observations suggest that regulation of the NREM-to-REM transition can be much more complex than initially thought. REM-on neurons may be represented by cells located under the sublaterodorsal (SLD) tegmental nucleus, while REM-off neurons — by ventrolateral periaqueductal grey matter nuclei of the midbrain (vlPAG) and lateral pontine tegmental nuclei (LPT) [21, 22]. During REM sleep, vlPAG/LPT nuclei can be inhibited by GABA and glycinoergic neurons, which are activated by the SLD nucleus. Similarly, inhibition of SLD nuclei could occur during NREM through increased melatonin concentration and the production of transmitters (mainly dopamine) by vlPAG/LPT nuclei [23]. This hypothesis is currently the topic of vigorous discussion and investigation. Moreover, neurons of the ventrolateral tegmental nucleus are thought to cause striated muscle atony in the trunk and limbs during REM sleep, as mediated by intercalated spinal neurons [21].

In the state of wakefulness, maximal activity can be observed in cholinergic, noradrenergic, serotoninergic and histaminergic neurons, which become much less active during NREM sleep. Conversely, during the REM phase, the activity of noradrenergic, serotoninergic and histaminergic neurons is inhibited, whereas cholinergic neurons become more active, similar to the wakefulness state [5, 6, 22].

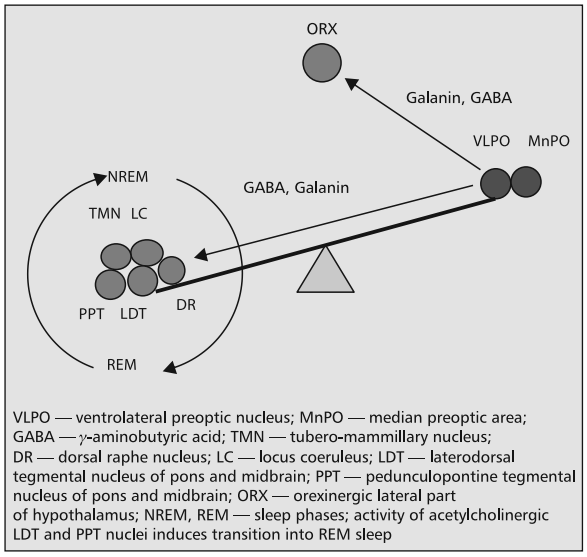
The hypocretin (orexin) system provides stabilisation of the sleep-wake system, and facilitates transitions between the states. These peptides were discovered in 1998 by two independent scientific groups [23, 24]. The first group is called the peptides hypocretins because they were detected in the hypothalamus and had a chemical structure similar to secretin. The other group is called the transmitters orexins, as they were observed to stimulate appetite [24, 25]. Two peptides, called hypocretin/orexin A and B, were identified. These have, respectively, 33 and 28 amino acids, and show different levels of biological activity; orexin A is almost 100 times more powerful than orexin B [23].

Hypocretin-producing neurons are located mostly in the posterior hypothalamus but are also found in the medulla, some nuclei of cranial nerves and in vegetative neurons of the gastrointestinal tract [23, 24]. Orexins exert their action via G protein-coupled metabotropic receptors, where ligand binding causes an intracellular flux of Ca^{2+} ions. Two types of receptors (Ox1R and Ox2R) were identified [23] and could be found in all structures controlling states of wakefulness and regulating sleep [26, 27].

Hypocretin neurons send their axons to different areas involved in sleep-wakefulness regulation, including locus coeruleus nuclei, raphe nuclei, tuberomammillary nuclei as well as cholinergic and dopaminergic nuclei [5]. Significant hypocretin projection from the posterior and lateral hypothalamus involves locus coeruleus nuclei (OX1), tuberomammillary nuclei (OX2) and raphe nuclei (OX1 and OX2). Blockage of OX2 receptors in the tuberomammillary nuclei produces symptoms of narcolepsy. Patients affected by narcolepsy have been found to have increased concentrations of orexin A in their cerebrospinal fluid, possibly as an effect of autoimmune damage to orexinergic neurons [4].

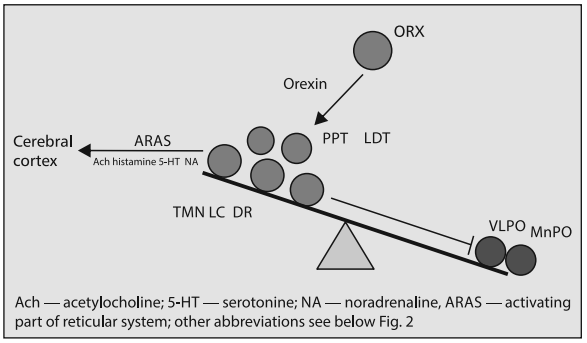
Hypocretins regulate circadian rhythms mainly by influencing the activating part of the sleep-wake system through a complex mechanism. Orexins synchronise the release of monoamines from locus coeruleus nuclei, raphe nuclei, tuberomammillary nuclei, and ventral tegmental area, release acetylcholine from peduncular and tegmental nuclei of the pons and midbrain, and thus cause a sustained wakefulness state. Apart from stimulation of wakefulness-inducing neurons, hypocretins also have inhibitory effects exerted through activation of GABA-ergic neurons [5]. Transition between sleep and awake states seems to depend on an equilibrium between a direct stimulatory effect of hypocretins and the inhibitory effect of GABA-ergic neurons [4]. This relationship is asymmetrical from an anatomical point of view because ORXN neurons do not have a direct inhibitory pathway to VLPO nuclei, whereas negative feedback in the opposite direction does exist. This system is believed to stabilise the "*flip-flop*" switch off, and thus consolidates states of wakefulness and sleep. The phenomenon is also referred to as a "finger on a switch", which explains the physiological inability to abruptly and for no reason change between these states, as this could be dangerous for the organism [18, 19] (Fig. 2, 3).

The role of neurons producing melanin-concentrating hormone (MCH) needs to be mentioned here. MCH neurons are located in the lateral hypothalamus, interspersed between perikaryons of orexinergic neurons, and as postsynaptic targets are identical for both types of neurons [28]. These cells can be found in LC, DR, LDT, PPT, TMN, ORXN and VLPO nuclei. Orexins have a stimulatory effect on these areas, whereas MCH has an inhibitory effect. MCH is a 19 amino acid-long peptide that is synthesised both inside and outside of hypothalamus (in the zona incerta of the subthalamus) [29]. MCH receptors (MCHR1 and MCHR2) are part of the superfamily of G protein-coupled receptors, and ligand interaction causes inhibition of both activating and inhibitory signals. The highest level of MCH-ergic neuron activity is observed during REM sleep, with a decrease during NREM, and complete inactivity during states of arousal [28]. Studies in mice deprived of MCH-containing



VLPO — ventrolateral preoptic nucleus; MnPO — median preoptic area; GABA — γ-aminobutyric acid; TMN — tubero-mammillary nucleus; DR — dorsal raphe nucleus; LC — locus coeruleus; LDT — laterodorsal tegmental nucleus of pons and midbrain; PPT — pedunculopontine tegmental nucleus of pons and midbrain; ORX — orexinergic lateral part of hypothalamus; NREM, REM — sleep phases; activity of acetylcholinergic LDT and PPT nuclei induces transition into REM sleep

Figure 2. Activity of reticular system and hypothalamic nuclei during sleep



Ach — acetylocholine; 5-HT — serotonine; NA — noradrenaline, ARAS — activating part of reticular system; other abbreviations see below Fig. 2

Figure 3. Activity of reticular system nuclei and hypothalamic nuclei during arousal

neurons showed a marked reduction of slow wave EEG activity, with extended wakefulness states in both daytime and night time. Intraventricular administration of MCH has an opposite effect, with a significant prolongation of REM sleep [29]. Immunoneutralisation of MCH in raphe nuclei in rats shortened the duration of the awake state and suppressed REM sleep. Similar effects were observed following the administration of MCH1 receptor antagonists. These studies can hopefully have an impact on the development of medications to combat sleeplessness [28]. In addition to its regulation of sleep-awake states, MCH-ergic projection seems to have an effect on the hunger-satiety centres and circadian metabolism fluctuation. MCH has also been observed to indirectly affect the memory consolidation that occurs during REM sleep. Neurohistochemical studies showed that MCH-ergic neurons project through the medial septal nucleus to the hippocampus. Intraventricular administration of the peptide not only causes extended REM sleep and shortens its latency but also stimulates acetylcholine release from the hippocampus, with no effect on acetylcholine release in the neocortex [30].

SUPRACHIASMATIC NUCLEUS AS A CIRCADIAN OSCILLATOR

The suprachiasmatic nucleus (SCN) is located in the anterior hypothalamus and is referred to as a circadian oscillator [31]. Its neurons are sites of constant transcription and translation, regulated in a feedback loop by the cyclical activity of transcription factors CLOCK and BMAL1 [30, 31, 32]. Even isolated cells in vitro retain these capacities [4]. Cyclical changes in ion channel activity and transmembrane potential transfer molecular signals outside of the cell cytoplasm [33].

Molecules of transcription factors CLOCK and BMAL1 are helix-shaped. The *Bmal1* gene is most actively transcribed during night time. CLOCK and BMAL1 undergo transformation into heterodimers, which permits them to exert their biological activity upon interaction with Period (1–3) and Cryptochrome (1–2) gene promoters. Products of these genes, PERs and CRYs, have inhibitory effects on the transcription of the *Bmal-1* gene, thus self-limiting their own concentrations. Proteins are then phosphorylated by protein kinases and undergo degradation, which occurs mostly during daytime [34].

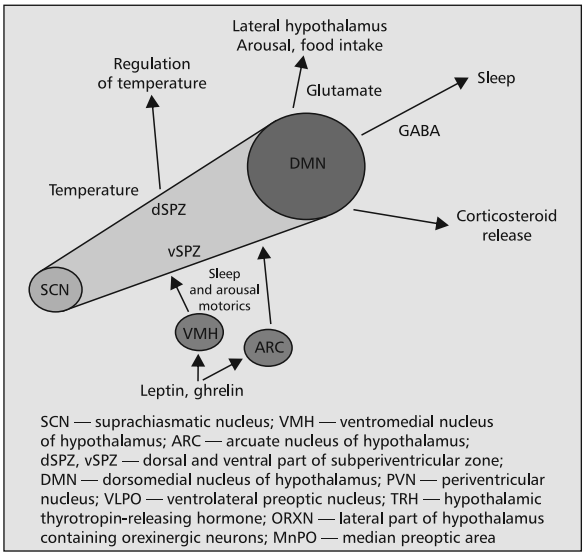
Another feedback loop involves nuclear receptors for retinoic acid, RAR-related orphan receptor α and REV-ERB α, transcription of which is stimulated by the CLOCK- BMAL1 complex. REV-ERB αprotein becomes attached to *Bmal1* gene promoter, inhibiting the process of gene transcription. These phenomena occur cyclically, corresponding to light and dark phases, with increased stimulation from SCN during daytime and inhibition during the night [34]. Circadian oscillator neurons receive afferent signals from melanopsin-containing cells of the retina, which are the anatomical link between sinusoidal SCN activity and environmental stimuli (light). Rhodopsin is activated by photons in receptor cells, causing G-protein-mediated activation of phosphodiesterase. This causes low intracellular concentration of cGMP and hyperpolarises receptor cell membranes during the day. At night, increased cGMP concentration and low activity of lytic enzymes opens Na^+ and Ca2+ ion channels. Depolarisation opens further ion channels (L- VGCCs, L-type voltage- gated calcium channels), causing intracellular calcium flux. This in turn activates the cAMP-related pathway, stimulates the synthesis and release of melatonin as well as the recruitment of presynaptic vesicle neurotransmitters contained in receptor cells [34]. In turn, neurons in the SCN have twice the Ca2+ concentration in daytime compared to the night [35]. Their maximal activity is observed for 4 hours during

the light phase. The circadian oscillator is therefore synchronised with the external environment by light, whereas internal synchronisation occurs due to a nocturnal peak of melatonin release from the pineal gland [4].

The aforementioned loops of transcription and translation in the SCN are biochemically regulated by circadian rhythms of promoter gene methylation and histone spatial transformation. Up to 10% of transcription products are believed to undergo such transitions during day and night, along with constant chromatin remodelling [36].

Only a small fraction of neuronal impulse from the SCN directly affects the VLPO and ORXN. More axons of the circadian oscillator provide signals to the subparaventricular zone (SPZ) and dorsomedial nucleus of the hypothalamus (DMH). The subparaventricular zone is divided into a ventral part (vSPZ), located below the SCN, and a dorsal part (dSPZ), which is adjacent to the periventricular nucleus (PVN). Damage to vSPZ neurons manifests by disruption of the circadian sleep-arousal cycle and motor disturbances, whereas damage to dSPZ cells causes alterations to the circadian pattern of core temperature changes. Impulses from the subparaventricular nucleus are transferred to the dorsomedial nucleus (DMN). Experimental destruction of DMH neurons caused an extended sleep phase, decreased motor activity, decreased corticosteroid concentration , and a decrease in mean body temperature by 0.5oC [3]. Afferent signals to VLPO and orexinergic neurons are provided mostly from DMH, which is an anatomical link between the circadian oscillator activity in response to external environmental signals and the homeostatic regulator of the activating reticular system, which responds mostly to the organism's need for sleep. It can therefore be stated that SPZ and DMH are amplifiers of signals coming from the SCN to the regulatory system of sleep and arousal. Moreover, DMH axons reaching the ventrolateralpreoptical area are GABA-ergic, and axons supplying the lateral hypothalamus contain mostly glutamate and thyrotropin-releasing hormone (TRH). Therefore, the hypothalamic ventromedial nucleus promotes alertness and is active during daytime. This structure also affects the circadian rhythms of corticosteroid secretion, thermoregulation, and feeding-related behaviour (Fig. 4) [4].

The neuronal network of the hypothalamus described above integrates internal and external signals with the sleep-alertness cycle, awareness, cognitive processes and motor phenomena. It facilitates adaptation to constantly changing environmental conditions to increase the organism's chances of survival. As was proven experimentally and on animal (mammal) models, the sleep-alertness cycle was gradually modified and adapted to the circadian rhythm of food availability. Daily activity was adapted to times of feeding or the times when most food was available [4].



SCN — suprachiasmatic nucleus; VMH — ventromedial nucleus of hypothalamus; ARC — arcuate nucleus of hypothalamus; dSPZ, vSPZ — dorsal and ventral part of subperiventricular zone; DMN — dorsomedial nucleus of hypothalamus; PVN — periventricular nucleus; VLPO — ventrolateral preoptic nucleus; TRH — hypothalamic thyrotropin-releasing hormone; ORXN — lateral part of hypothalamus containing orexinergic neurons; MnPO — median preoptic area

Figure 4. Amplification of circadian rhythms from suprachiasmatic nucleus

Signalling from splanchnic receptors, cognitive aspects and the effect of emotions on circadian activity have been described recently. Leptin and ghrelin affect the ventromedial nucleus of the hypothalamus (VMH) and arcuate nucleus (ARC), and thus also affect impulses from the SPZ and DMH. Contraction of smooth muscles in the stomach due to efferent impulses from solitary tract nucleus follows the circadian rhythm. Pathways from the prefrontal cortex and limbic system to the SCN, SPZ, DMH, VLPO and ORXN nuclei have also been described [4].

PROCESS S AND PROCESS C

In the 1980s, Alexander Borbely presented a hypothesis of dual regulation of sleep and alertness. Process S is a network of reticular formation nuclei dispersed within the brainstem. Interactions between these nuclei generate sleep or alertness. Process S constantly reacts to the changing need for sleep. Somnogen accumulation during a state of alertness causes a transition into NREM sleep and gradually discharges Process S. Process C represents SCN, the circadian oscillator, and its amplifiers. The sinusoidal activity of those is synchronised to periods of light or dark and regulates transitions from and into awareness based on cyclical changes in the chromatin molecular structure. This is also the target of signals coming from splanchnic receptors and from higher cortical centres. These structures make up a complex system aimed to provide enough sleep, the importance of which is only being discovered, and to provide adequate reactions to changes in external and internal environments to achieve optimal sleep and alertness circadian activity and enable survival [37] (Fig. 5).

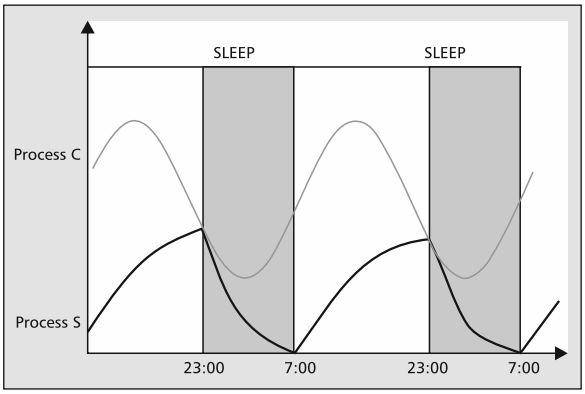


Figure 5. Systems regulating sleep and alertness according to Borbely [37]

SUMMARY

To sum up, the above-described neuronal stimulatory and inhibitory loops, with the agonist action of multiple neurotransmitters, neuromodulators and somnogens have evolved to prevent the organism from being in an "intermediate" phase. Homeostatic regulation of circadian rhythms is aimed to consolidate state of alertness as well as of NREM and REM sleep. Rapid and complete transition between these two states is an obvious survival benefit. Disturbances of cognitive functions during the wakefulness state could be dangerous for the organism, while interrupted sleep is ineffective. Mathematical models demonstrate that disturbances to either side of the flip- flop loop cause accelerated transition between two states. Interactions between the VLPO and activating reticular system constitute a form of a flip-flop loop, whereas orexinergic neurons stabilise the transition between the states.

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2. The authors declare do conflict of interest.

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