Basic Sleep Mechanisms: An Integrative Review

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Abstract: Regulation of the sleep-waking cycle is complex and involves diverse brain circuits and molecules. On one hand, an interplay among many neuroanatomical and neurochemical systems including acetylcholine, dopamine, noradrenaline, serotonin, histamine, and hypocretin has been shown to control the waking state. On the other hand the sleep-onset is governed by the activity of sleep-promoting neurons placed in the anterior hypothalamus that utilize GABA to inhibit wake-promoting regions. Moreover, brainstem regions inhibited during wakefulness (W) and slow wave sleeps (SWS) become active during rapid eye movement (REM) sleep. Further complexity has been introduced by the recognition of sleep-promoting molecules that accumulate in the brain in prolonged W as well as the physiological role of gene expression during sleep. The sleep-wake cycle is currently undergoing intense research with many new findings leading to new paradigms concerning sleep regulation, brain organization and sleep function. This review provides a broader understanding of our present knowledge in the field of sleep research.

Keywords: Anandamide, brainstem, cortex, lateral hypothalamus, neurotransmitter, sleep-wake cycle.

1. INTRODUCTION

Previous studies have shown that different brain structures and neurotransmitters play a key role in the regulation of the sleep-wakefulness states. Stimulation, lesion and unit recording experiments showed that different brain regions, including brainstem, hypothalamus, thalamus and basal forebrain, are involved in the regulation of the vigilance states. For instance, chemical lesions in the preoptic basal forebrain zone of cats and rats cause insomnia [1,2], whereas the stimulation of the preoptic area/anterior hypothalamus (POAH) increases sleep [3]. Inasmuch as the studies of the mechanisms related with the control of the sleep and waking increased during the last years, the purpose of this review is to examine the current stage of our knowledge regarding the sleep/wakefulness-promoting structures and neurochemical-inducing factors associated to these physiological functions.

2. THE NEUROANATOMICAL MECHANISMS OF WAKEFULNESS

2.1. Basal Forebrain

Neuroanatomical structures related with the promotion of waking involve several nuclei of the central nervous system (CNS). In this regard, the input to the cerebral cortex is augmented by lateral hypothalamus and acetylcholine (ACh)-containing neurons of the basal forebrain which are electrophysiological active during alertness and they are referred as "wake-on neurons" [4]; Fig. (**1**).

Lesions in basal forebrain area produce severe loss of sleep [5]. For example, Kalinchuk *et al.* [6] have shown that after injections of the immunotoxin 192 immunoglobulin G (IgG)-saporin (saporin) in rats, there was an 88% cholinergic cell loss, coupled with an enhancement in waking.

2.2. Lateral Hypothalamus

It has been described that lateral hypothalamic neurons start to fire before the transition from sleep to W whereas several studies have indicated that specific neurons send excitatory projections to diverse wake-promoting areas such as adrenergic, histaminergic, dopaminergic, and cholinergic nuclei [7]; Fig. (**1**). Different pieces of evidence have shown that lesions of lateral hypothalamus enhance waking [8-11]. For instance, injection of the neurotoxin hypocretin-2-saporin (490ng/0.5μL), directly to the lateral hypothalamus produced an increase in waking [5], suggesting that lateral hypothalamus has an active role to activate wake-inducing systems.

Hypocretin (HCRT) neurons are located between the fornix and the mammillothalamic tracts in the lateral hypothalamus from where HCRT fibers project throughout the brain and spinal cord, including several areas implicated in the regulation of the sleep-wake cycle [12-18]. Those projections excite the main arousal systems, including the

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cholinergic neurons placed in the laterodorsal tegmental nucleus [15] or basal forebrain [19], histaminergic [20], noradrenergic [21], and serotoninergic [22, 23]. Activation of the thalamocortical neurons [21] and the projections to the basal forebrain regions, including the medial preoptic area, the medial septal area and the substantia innominata [24], has been demonstrated as well.

2.3. Tuberomammillary Nucleus

Histaminergic neurons have been identified in the posterior hypothalamus in the region of the tuberomammillary nucleus (TMN) [25-27]. These neurons project throughout the CNS sending afferents towards the cerebral cortex, the amygdala, and the substantia nigra. Additionally, TMN receives input from the hypocretinergic neurons in the lateral hypothalamus as well as from GABAergic neurons in the ventrolateral preoptic area (VLPO), which strongly contribute to the firing rate of these histaminergic neurons in relation to sleep [28]. TMN firing pattern has been linked to wake since histaminergic neurons display an increase in the electrophysiological firing rate during alertness compared to sleep [25, 29, 30]. In concordance with these findings, lesions in the TMN neurons induce changes in the sleep-wake cycle, including sleep deficits and enhancements in waking [31]. This data suggest that histaminergic neurons of the TMN have an active role in promoting alertness.

2.4. Brainstem

The regions in the rostral reticular formation send projections to the forebrain through two main pathways critical for the regulation of the sleep-wake cycle. The first pathway ascends dorsally through the lateral hypothalamus to the basal forebrain. The dorsal ascending pathway projects to multiple thalamic nuclei, which in turn have widespread projections to the cortex [33-35]. The neurons in the rostral pons and caudal midbrain area are the primary source of ascending projections to the dorsal thalamic nuclei. These neurons fire rapidly during W, but their rate becomes slower during SWS and resume rapid firing again during REM sleep (classified as "wake-on/REM-on neurons").

The second pathway that involves the ventral descending pathway of the brainstem projects rostrally through the lateral hypothalamus, terminating on the magnocellular neurons in the substantia innominata, medial septum, and the diagonal band [32, 33, 35, 36]. This pathway originates in the noradrenergic nucleus, the locus coeruleus, the serotoninergic dorsal and the median raphe nuclei. These cells fire actively during W and become inactive during SWS and REM sleep Fig. (**1**).

On the other hand, the locus coeruleus (LC) contains the majority of noradrenaline (NA) neurons in the brain [38]. This nucleus modulates cortical activation and behavioural arousal by diffuse projections through the forebrain, brainstem and spinal cord [24, 38]. Electrophysiological studies have shown that the firing pattern of LC neurons is highest during W than during sleep [39-41] suggesting that LC has an important neurobiological role in the modulation of alertness.

The role on the modulation of alertness by serotoninergic (5-HT)-containing neurons placed in the brainstem, specifically the raphe nuclei [42], has been described. These neurons display a higher burst discharge during waking whereas its activity is decreased during SWS and cease firing during REM sleep. The phenotype of these cells has been defined as "wake-on neurons" [43-48].

Finally, an additional element modulating W is the pontomesencephalic tegmentum which also contains ACh neurons [49]. This area projects to the thalamocortical system where ACh cells stimulate cortical neurons [38, 50, 51]. Besides, the electrophysiological studies have reported that the ACh-containing pontomesencephalic neurons in the laterodorsal and pedunculopontine tegmental nucleus discharge at higher rates during W and decrease their activity during SWS increasing once again their activity through REM sleep. These cells have been named "wake/REM-on neurons" [52, 51].

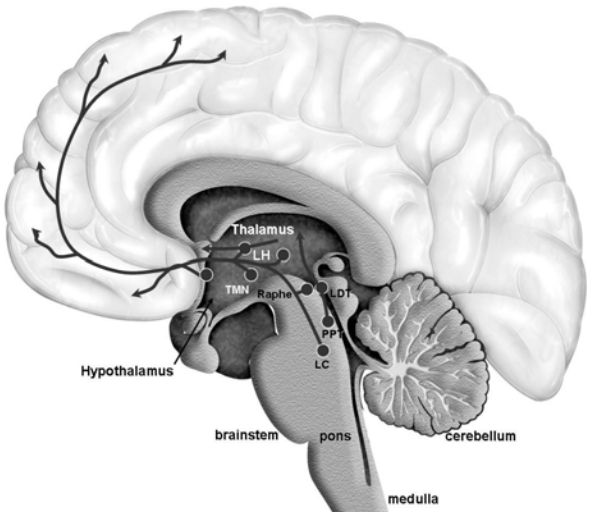

Fig. (1). The brain distribution of the wake-related nuclei. The presence of the neuroanatomical and neurochemical elements that participate in the promotion of alertess are represented as follows: Tuberomammillary nucleus (TMN, histamine), lateral hypothalamus (LH, hypocretin), locus coeruleus (LC, noradrenaline), raphe dorsal (serotonin), and basal forebrain and PPT/LDT nuclei (cholinergic). Laterodorsal tegmental nucleus (LDTg)/pedunculopontine tegmental nucleus (PPTg) send projections to the thalamus, additionally LC, raphe nuclei, TMN, LH and thalamus project to cortex to induce alertness. *Abbreviations:* LC, locus coeruleus; LDT, laterodorsal tegmental nucleus; LH, lateral hypothalamus; TMN, tubermammillary nucleus; PPT, pedunculopontine tegmental nucleus.

3. THE NEUROCHEMICAL MECHANISMS OF WAKEFULNESS

3.1. Glutamate

As stablished by Moruzzi and Magoun [53], the brainstem reticular formation (RF) is critical for maintaining cortical activation and behavioural arousal of the waking state. Projections from neurons concentred gathered in the

oral pontine and mesencephalic RF ascend into the forebrain where they stimulate cortical activation via a dorsal relay in the thalamus and a ventral relay through the hypothalamus and basal forebrain. It is known that neurons concentrated in the caudal pontine and medullary RF facilitate postural muscle activity. On the other hand, the neurons of the diffuse thalamocortical projections relay which project to the cerebral cortex to stimulate cortical activation use glutamate. We can assume that glutamate-containing neurons represent the backbone of the W-activating and behavioural-arousal systems [38, 54]. Furthermore, extracellular levels of glutamate have been found higher during waking than during sleep [55-57].

Pharmacological studies have shown that infusions of glutamatergic agonists, such as NMDA elicit alertness [58-60]. These results suggest that glutamate has an active physiological role in cortical activation that underlies the behavioral arousal.

3.2. Noradrenaline

The wake-promoting properties of noradrenaline (NA) involves α_1-adrenoreceptors that are associated with a depolarization through closing K^+ channels whereas the α_2-adrenoreceptors are linked with a hyperpolarization by the opening K^+ channels. Drugs that antagonize α_1-adrenoreceptors facilitate sleep onset, probably by blocking the postsynaptic action of NA on different target neurons. By contrast, α_2-adrenoreceptor antagonists delay sleep. Opposite to the effects described above, the α_2-adreno-receptors agonists inhibit the NA release and decrease W [61]. Importantly, drugs that block the uptake of NA enhance or prolong waking [62-64]. Regarding this, NA activates other wake-promoting systems and inhibits those involved in the sleep modulation [65].

Additionally, microdialysis experiments have shown that the extracellular contents of NA decline progressively from W to sleep [57, 66, 67] whereas the lesion of the neurons in LC induces a decrease in waking [68-70].

3.3. Dopamine

Dopamine (DA)-containing neurons are placed in the substantia nigra and ventral tegmental area which are important for arousal [38, 71]. The neurons in these areas project to the striatum, basal forebrain and cerebral cortex. It has been reported that higher electrophysiological activity of these neurons is associated with arousal [72-75].

On the other hand, pharmacological experiments have demonstrated that drugs that block the uptake (such as cocaine) or stimulate the release of DA (including amphetamine or modafinil) have arousing effects [76, 77]. Moreover, lesions in ventral tegmental area or substantia innominata induce an enhancement in waking [78, 79]. The role of NA modulating W has been also supported from biochemical studies. In this regard, evidence from microdialysis experiments has shown that extracellular contents of NA are enhanced during W whereas its levels are decreased across sleep [57, 80, 81].

3.4. Serotonin

The relationship between serotonin (5-HT) and the sleep-wake cycle modulation has been described through different experimental approaches. 5-HT-containing neurons have been localized in the raphe nuclei [42] and the lesion of these cells induces an increase in W and diminishes SWS [82, 83].

Furthermore, the extracellular levels of 5-HT have been determined with microdialysis and measured by high performance liquid chromatography in several brain structures, including preoptic area, hippocampus, and medullary reticular formation. Results have shown that 5-HT levels are enhanced during natural or prolonged waking when compared to levels during natural sleep [84, 80-87].

3.5. Acetylcholine

Acetylcholine (ACh)-containing neurons of the basal forebrain have been linked with cortical activation [88]. Molecular studies have described the role of ACh on sleep-wake modulation. For example, Fos protein encoded by the immediate early gene *c*-Fos is often used as a marker of neural activation. Using this experimental approach, it was described that ACh-containing neurons are active during W as a result from a sleep deprivation period [89]. Supporting these findings, Lee *et al.* [4] reported that ACh-containing neurons are electrophysiologically active during W since their firing pattern was found higher during the active period than during the resting phase in rats.

Pharmacological studies have shown the neurobiological modulating role of ACh on the sleep-wake cycle. Early studies using acetylcholinesterase inhibitors showed that when administered alone, REM sleep was increased [88]. Moreover, it has been described that ACh acts on nicotinic and muscarinic receptors to induce waking [90, 50].

The role of ACh in the modulation of waking has been strenghted with microdialisys experiments. Thus, the extracellular concentration of ACh displays dependent-state variations. Diverse studies have shown that levels of ACh are higher during W compared to SWS [55, 91, 92].

3.6. Histamine

The main source of histamine is the cluster of neurons placed in the TMN of the posterior hypothalamus [93, 94]. The wake-inducing properties of histamine involve the activation of several elements of the arousal system through H_1 and H_2 receptors [95]. The hypothesis that the activation of the histaminergic system promotes waking [25, 96-98] is currently accepted since its pharmacological inhibition induces sleep. Regarding this, Tashiro *et al.* [95] showed that antihistamine drugs that act on H_1 receptors induce somnolence.

Different experimental approaches to examine the role of the histaminergic system include gene-manipulated mice [99], lesioned rats [35] as well as microdialysis, which show wake-dependent variations in histamine contents [101]. Taken collectively, the evidence indicates the active neurobiological role of histamine modultaing alertness.

3.7. Hypocretin

The hypocretins (HCRT; 1 and 2, also named as orexin A and B, respectively) are two neuropeptides derived from the same precursor whose expression is restricted to a few thousand neurons of the lateral hypothalamus [13, 18, 101, 102].

At the present time, it has been established that the HCRT system is associated to both canine and humans narcolepsy [103]. Diverse evidence supports this idea. For instance, in a study of post-mortem brains of human narcoleptics, a massive reduction in the number of HCRT-containing cells (85-98%) compared with healthy controls was discovered [104, 105]. On the other hand, it was reported that narcoleptic patients present reduced levels of HCRT in cerebrospinal fluid (CSF) [106-111]. The CSF measurements of levels of HCRT provide a valuable diagnostic tool for narcolepsy, separating narcolepsy from other sleep and neurological disorders [111, 112].

The treatment of narcolepsy includes pharmacological approaches. However, an alternative therapeutical option has been suggested. Regarding this, the transplants of HCRT neurons could be considered as a new experimental approach to treat narcolepsy [113]. For instance, time-course of survival of grafted HCRT neurons into the pons of adult rats was analyzed at 1, 3, 6, 9, 12, 24, or 36 days after grafting. Immunohistochemistry results showed that HCRT neurons were present in the graft zone at day 1 post-grafting and there was a steady decline in the number of HCRT neurons. Finally, on day 36, HCRT neurons that survived in the pons had morphological features that were similar to mature HCRT neurons in the adult lateral hypothalamus, suggesting that these neurons might be functionally active [114, 115].

3.8. Neuropeptide S

Neuropetide S (NPS) is a recently described neuropeptide of 20 amino acid residues which bears no similarity with other neuropeptide families [116]. NPS precursor protein mRNA is strongly expressed in a few hundred neurons in the locus coeruleus area. NPS binds with nanomolar affinity to a G-protein coupled receptor, NPSR, in transfected cells and increases the intracellular calcium levels with high potency [117]. NPSR mRNA is widely distributed throughout the brain and significant expression can be detected in multiple arousal systems, including the midline thalamic nuclei, which relay extensive input from the brainstem reticular formation to cortical regions and are thus important in regulation of arousal [117, 118]. In addition, high level of NPSR expression is localized in the lateral and posterior hypothalamus, regions well known to influence states of vigilance, whereas high levels of NPS mRNA have been also reported in the laterodorsal tegmental nucleus (LDTg) in the mouse brain, region which contains cholinergic neurons and is critical to the maintenance of REM sleep and arousal [117].

In icv infussions of 0.1 and 1.0 nmol of NPS in mice, this peptide stimulates spontaneous locomotor activity and consistently induces anxiolytic-like effects in a battery of behavioral tests (open field, light-dark, elevated plus maze, marble burying). In addition, a significant dose-dependent increase of W was observed one hour after treatment with NPS, whereas the amounts of SWS and REM sleep were decreased during the same period of time compared to their respective controls. In contrast, two and four hours after NPS administration, the amount of SWS increased significantly, compared to control animals, probably due to a rebound process. The increase in W was due to a significant increase in the number of episodes, whereas the increase in SWS was due to an increase in the duration of SWS episodes [117].

Other studies where the activity of NPS as a wake-promoting factor was tested, showed that icv infusion of the peptide in rats increased W even in conditions of high sleep demand, as it was demonstrated in sleep deprivation studies. Infusion of NPS in the lateral ventricles induces c-fos activation in a variety of arousal-promoting nuclei, including the lateral hypothalamus. Due to the fact that NPS receptors are localized in HCRT-containing neurons in the lateral hypothalamus, the posibility that NPS can modulate alertness at least in part through activation of the HCRT system, results interesting altought additional studies are need to probe such hypothesis.

4. THE NEUROANATOMICAL MECHANISMS OF SLEEP

4.1. Suprachiasmatic Nucleus

Two basic mechanisms in sleep modulation have been recognized: The homeostatic and a circadian mechanism. The first one dictates that a given quota of sleep duration and intensity needs to be obtained over a short term and that current needs depend on the individual's immediate history of sleep-wake. For example, sleep deprivation as defined by the interruption of sleep, measured by both behavioural and EEG/EMG means, causes a "rebound" effect where, at the nearest available opportunity, an individual will sleep with a significant increase in the duration and intensity to compensate for lost sleep [119-121].

On the other hand, the circadian mechanism presumably located into the suprachiasmatic nucleus (SCN) of the hypothalamus, sets the time frame for sleep during each cycle. For instance, in diurnal species, the SCN promotes arousal during the day whereas the loss of input from this nucleus to hypothalamus causes a decrease in sleep [122-124]. Neuroanatomical studies have shown that most of the SCN neurons project to the dorsomedial hypothalamus, which in turn projects to the VLPO nucleus suggesting the presence of a neuroanatomical network which may reflect the basis of the sleep promotion.

4.2. Basal Forebrain

The pioneer experiments showed that electrical stimulation of the basal forebrain in cats produced sleep [125, 126]. The idea that the sleep-inducing effect of basal forebrain stimulation could be due to the inhibition of the activity of the TMN is currently accepted, since this structure sends inhibitory projections to the TMN Fig. (**2**), thus it makes reliable this hypothesis [94, 96, 127].

4.3. Lateral Preoptic Nucleus and Median Preoptic Nucleus

The neuronal discharge of the wake-promoting systems declines rapidly at sleep onset. A key element of sleep-

related inhibition of waking lies at the neurons located in the lateral and median preoptic nucleus. Diverse pieces of evidence have shown that preoptic neurons are strongly activated during sleep. For instance, these cells exhibits sleep-wake state-dependent discharge patterns that are the reciprocal of that observed in the arousal systems [96, 127-129]. Besides, it has been demonstrated that the median preoptic nucleus (MnPN) neurons displays 76% cells that exhibits elevated discharge firing rates during sleep compared to W [129, 130].

The majority of preoptic sleep regulatory neurons synthesize the inhibitory neurotransmitter GABA [131, 132]. In addition, anatomical evidence supports the hypothesis that GABAergic neurons in the MnPN and lateral preoptic nucleus (LPO) exert inhibitory control over the wake-promoting systems during sleep [129, 133-135].

4.4. Ventrolateral Preoptic Nucleus

This nucleus is located in the preoptic area of the anterior hypothalamus. According to current evidence, this nucleus represents a "sleep-generating" centre, which opposes the arousing effect of the posterior hypothalamus [136, 137]; Fig. (**2**). Up to date, two major sleep-related nuclei have been described –the first one located in the ventrolateral preoptical nucleus (VLPO) is associated with SWS and the second one, located dorsal and medial to the VLPO nucleus named the extended VLPO, which has been linked with REM sleep generation [138, 139]. The neurons placed in the VLPO contain the inhibitory transmitter GABA and galanin and these cells project to the arousal neurons in the hypothalamus and the brainstem.

4.5. Brainstem

Ach-containing neurons are the major source of upper brainstem input to the thalamic-relay nuclei, as well as to the reticular nucleus of the thalamus. These clusters of neurons are known as the pedunculopontine tegmental and the laterodorsal tegmental nuclei (PPTg and LDTg, respectively) [140, 141]; Fig. (**2**). Stimulation of the PPTg nucleus promotes REM sleep [142, 143] whereas its lesion diminishes it [144, 145].

Considerable experimental evidence has suggested that cholinergic PPTg neurons are critically involved in the regulation of both waking and REM sleep. Besides, the wake-on/REM-on cells that display a pattern of firing exclusively during REM sleep have been described and named "REM-on neurons" [144-150].

Finally, REM sleep is induced by the action of 5-HT, NA, GABA, nitric oxide or HCRT which activates cholinergic neurons within the PPTg [146, 143, 151]. Furthermore, microinjections of 5-HT, NA and adenosine into the PPTg modulate sleep [152].

5. THE NEUROCHEMICAL MECHANISMS OF SLEEP

5.1. Gamma-Aminobutyric Acid

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the brain. Hypnotic drugs (such as fluorazepam) and anaesthetics promote sleep due their binding to the benzodiazepine-recognition site in the $GABA_A$ receptors [153, 156]. Thus the activity of the $GABA_A$ receptor has been proposed as enhancer of SWS [153, 157].

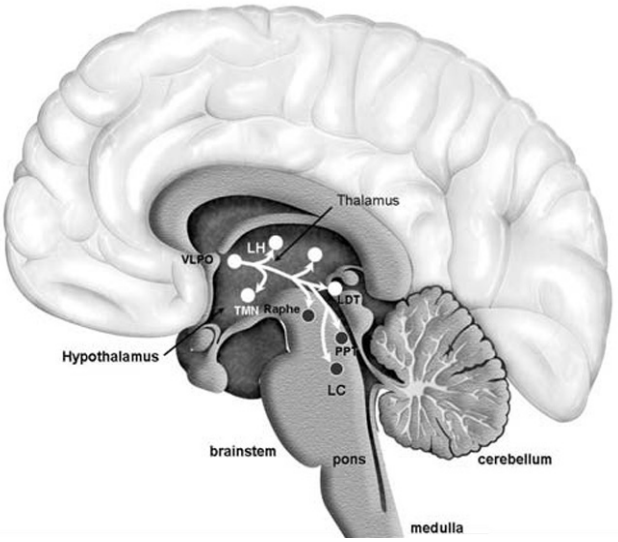

Fig. (2). The sleep-inducing centres in the central nervous system. Ventrolateral preoptic nucleus (VLPO) activity induces sleep, which is the result of the inhibition of the wake-promoting areas. Additionally, VLPO send projections to LH, TMN, raphe nuclei, PPT/LDT and LC. *Abbreviations:* LC, locus coeruleus; LDT, laterodorsal tegmental nucleus; LH, lateral hypothalamus; TMN, tubermammillary nucleus; PPT, pedunculopontine tegmental nucleus; VLPO, ventrolateral preoptic nucleus.

Evidence suggesting the active role of the basal forebrain modulating sleep is provided from pharmacological studies. Basal forebrain encloses neurons, then the administration into the posterior hypothalamus of GABA agonists such as muscimol increase sleep [1, 159].

GABAergic neurons placed in the basal forebrain and preoptic area have been electrophysiologically recorded during the sleep-wake cycle and display a higher firing pattern during SWS than during waking [128, 129, 159-161]. This result has been supported by studies showing that GABA-containing neurons in the preoptic area display an increase Fos expression during sleep [89].

The modulation of sleep via GABA has been described as follows: GABAergic neurons from the basal forebrain and preoptic area project to the posterior lateral hypothalamus where they appear to innervate many groups of wake-modulating neurons, such as HCRT [162, 163]. An alternate pathway involves the projections from basal forebrain and preoptic area to the TMN nucleus or directly to the LC nuclei [96, 164]. Moreover, GABA is also present in other regions such as thalamus inhibiting the thalamocortical relay neurons [165]. Finally, the extracellular levels of GABA are also related with sleep generation. Microdialysis experiments have shown that levels of GABA are increased during sleep in comparison to waking [166-168].

5.2. Acetylcholine

The pioneer studies demonstrating the active role of ACh in the modulation of REM sleep were conducted by Raúl Hernández-Peón [169-171]. Since then, it has been accepted that REM sleep is generated by the activity of specific cholinergic nuclei [172, 173]. Microinjection of carbachol into the rostral pontine tegmentum of the cat induces a state that is comparable to REM sleep. Additionally, muscarinic receptors have been related with REM sleep generation, as shown in diverse pharmacological studies [174-177].

The role of ACh in sleep modulation has been studied from different experimental approaches, including microdialysis. Extracellular contents of ACh have been found to be higher during REM sleep compared to W and SWS [55, 178].

In addition, the mechanism of sleep modulation via ACh suggests that the brainstem GABAergic neurons may control REM sleep. Recently, Brown *et al.* [179] reported that mice expressing green fluorescent protein (GFP) under the control of the GAD67 promoter (GAD67-GFP knock-in mice) exhibit numerous GFP-positive neurons in the central gray and reticular formation. They found that neurons were GABAergic. GFP-positive neurons were tested with pharmacological agents known to promote or inhibit REM sleep, finding that GFP-positive neurons were excited by a cholinergic agonist (carbachol). Supporting these findings, Marks *et al.* [180] found that the injection into the rat nucleus pontis oralis of the reticular formation of the antagonist of $GABA_A$ receptors (bicuculline methiodide) as well as gabazine (GBZ) increased REM sleep. Pre-injection of the muscarinic antagonist atropine completely blocked the REM sleep-increase by GBZ. These results suggest that GABA modulates REM sleep and involves the cholinergic system.

6. SLEEP-INDUCING FACTORS

6.1. Cytokines and Hormones

Several growth factors (GFs) are implicated in sleep modulation, among these molecules are interleukin-1beta (IL-1β), tumor necrosis factor-alpha (TNFα) and growth hormone-releasing hormone (GHRH). Pharmacological studies have shown that systemic or central administration of GHRH enhances SWS. Conversely, antibodies against GHRH (Obál *et al.*, 1991, 1992) or injecting somatostatin [181] or its analog [182] decreases SWS. Regarding this, Szentirmai *et al.* [183] showed that unilateral microinjection of GHRH decreased EEG delta wave power, while the application of a higher dose enhanced it. These effects on EEG delta wave power occurred during SWS but not during REM sleep. Additionally, it was described that cortical GHRH mRNA increased with sleep deprivation whereas the administration of GRHR fails to reduce the SWS observed in mutant and transgenic animals with a defect in GHRHergic activity. The neuroanatomical mechanism of sleep-inducing effects of GHRH suggests that neurons placed in the anterior hypothalamus/preoptic region could be the responsible of modulating sleep [184]. Taken together these results suggest that GHRH modulates sleep.

GFs involved in the sleep modulation are tumor necrosis factor (TNF) and interleukins, which are a group of cytokines related with the immflamation response. The function of the immune system depends on the interleukins, however there is also evidence showing the active role of the interleukins modulating the sleep-wake cycle. For example, IL-1β and TNF-α has been linked with sleep promotion. Pharmacological studies have shown that administration of exogenous IL-1β or TNF-α increases SWS and their inhibition significantly reduces the sleep amount. On the other hand, brain levels of IL-1 and TNF correlate with sleep propensity. Regarding this last issue, it has been observed that after sleep deprivation, their levels are increased compared to control animals. Moreover, the diurnal variation of TNF-α mRNA and IL-1β mRNA in brain shows its highest levels during sleep periods.

Genetic studies show that mice lacking either the TNF 55-kD receptor or the IL-1 type I receptor present a diminution in sleep amounts [185]. Recently, Kapás *et al.* [186] assessed the spontaneous and influenza virus-induced sleep profiles in mice deficient both 55-kDa and 75-kDa TNF-α receptors [TNF-2R KO]. During the nighttime, TNF-2R KO mice had a decrease of SWS compared to wild type animals whereas during the nighttime, KO animals showed a significant enhancement of REM sleep. Furthermore, viral challenge (mouse-adapted influenza X-31) enhanced SWS and decreased REM sleep in both strains.

It has been proposed that IL-1 and TNF are part of a complex biochemical cascade regulating sleep, which includes nitric oxide, GHGH, nerve growth factor, among other biological elements. Endogenous substances moderating the effects of IL-1 and TNF include anti-inflammatory cytokines such as IL-4, IL-10, and IL-13. Clinical conditions, such as infectious disease, alter IL-1 or TNF activity which has been associated with changes in sleep [187] http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22KruegerJM%22%5BAuthor%5D&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pu-bmed_DiscoveryPanel.Pubmed_RVAbstractPlus. Regarding this, sleepiness is a common perception during most infectious diseases, including viral infections.

6.2. Adenosine

Adenosine (AD) is a product of natural metabolism which has been linked with sleep modulation Fig. (**4**). Microdialysis studies have confirmed that cholinergic cells in the basal forebrain are presumably responsible for the accumulation of AD during natural or prolonged waking [188-192]. The mechanism proposed suggests that AD is released from cholinergic neurons in basal forebrain and then acts on AD-1 autoreceptors [193, 194]. The release of AD decreases the activity of the cholinergic neurons blocking the inhibition of the GABAergic neurons in the VLPO to induce sleep [148, 190, 192]. However, our group has described that cholinergic neurons placed in the basal forebrain are not necessary for the accumulation of AD in the basal forebrain [195].

AD may act via A_1 receptors to promote sleep, but an A_{2a} receptor antagonist can block it. Scammell *et al.* [196]

showed that the infusion of the A_{2a} receptor agonist CGS21680 increased SWS as well as the expression of Fos in the VLPO whereas the administration of the A_1 receptor agonist N(6)-cyclopentyladenosine decreased REM sleep. These findings suggest that an adenosine A_{2a} receptor agonist may increase the activity of VLPO neurons and then, modulate the inhibition of multiple wake-promoting regions. Additional evidence supports the findings described above. Methippara *et al.* [197] showed that A1 receptor stimulation or inhibition of AD transport by NBTI induced waking whereas A_{2a} receptor stimulation induced sleep whereas CGS21680 applied to the subarachnoid space underlying the rostral basal forebrain increased sleep but decreased the extracellulr levels of histamine [198].

6.3. Prostaglandins

Derived from arachidonic acid, prostaglandins (PGs) are sleep-inducing lipids Fig. (**4**) as shown by different approaches. The infusion of PG, type D_2, or PGD_2 receptor agonists promotes sleep [199-204]. The role of PGD_2 on sleep has been supported from microdialysis evidence showing that its extracellular concentration is higher during sleep than during waking [205]. The molecular action of PGD_2 modulating sleep involves PGD_2 synthase activity gene expression, activation of AD_{2a} receptors, as well as the inhibition of the histaminergic system [200, 2004, 206-208].

6.4. Anandamide

During the 1970s-1980s several experiments were carried out in order to evaluate the effects of the cannabinoids on sleep. The main conclusion of these studies was that cannabinoids increase both SWS and REM sleep [209-215].

Since anandamide (ANA) was the very first endocannabinoid described [216] the interest about its potential cannabinoid-like effects on sleep was raised. But what might be the neurobiological role on sleep of the endocannabinoid system? The very first approach to answer this question was carried out by Santucci and co-workers in 1996 [217]. They injected to rats the CB_1 cannabinoid receptor antagonist, SR141716A and a significant increase in W as well as a diminution in SWS was found. The results suggested that the wake-inducing properties of SR141716A might be due to the blocking of the CB_1 cannabinoid receptor.

Under other conditions, icv injections in rats of ANA induced an opposite effect that the one observed by Santucci and colleagues. Our group found a significant decrease in W and an enhancement in SWS and REM sleep after ANA administration [218] and these effects were more significant after being injected into the PPTg. Since ANA promoted sleep, it was hypothesized that administration of SR141716A before the injection of ANA might block the effects on sleep. Indeed, blocking the CB_1 cannabinoid receptor efficiently prevented the sleep-inducing effects of ANA [219].

The CB_1 cannabinoid receptor activates a phospholipase C (PLC) suggesting different elements that could be involved in the sleep-inducing properties of ANA. We found that the injection of the PLC inhibitor (U73122) administered before ANA application, diminished the sleep-inducing effects of this endocannabinoid. The results suggested that the sleep-inducing properties of ANA require, besides the CB_1 cannabinoid receptor, the PLC enzyme [220].

Finally, we hypothesized that ANA would be promoting sleep via acting on a sleep-inducing factor such as AD. Thus, using microdyalisis means it was found that systemic administration of ANA induced a significant enhancement in the levels of AD as well as sleep [220].

Despite the evidence provided above, there is indeed a lack of data to make a reliable conclusion about the neurobiological role of ANA on sleep. However, we have hypothesized the following mechanism Fig. (**3**): The CB_1 cannabinoid receptor has been localized in the pons and the basal forebrain, as demonstrated by others [221, 222]. Once ANA binds to the CB_1 cannabinoid receptor would activate the cholinergic neurons placed in these regions [38]. It is known that activation of the CB_1 cannabinoid receptor as well as the administration of cannabinoid agonists enhances the release of ACh [223, 224]. As mentioned previously, the release of ACh from the brainstem and/or the basal forebrain has been described to occur during sleep [225, 226]. In parallel, it might be also possible that activation of the CB_1 cannabinoid receptor in cholinergic neurons of the basal forebrain and/or the brainstem could activate the thalamus inducing cortical desynchronization [227]. There is solid evidence showing that the projections from the brainstem and the basal forebrain to the thalamus are important elements for sleep modulation [38, 228, 229]. This hypothetical mechanism of ANA modulating sleep is supported from different evidence. For instance, a diurnal variation of this endocannabinoid in CSF, pons, hippocampus, and hypothalamus in the rat has been described. In CSF, ANA displayed an increase in its concentration during the lights-on period and remarkable decreases in its values are present during the lights-off period (the active phase of the rodents). ANA showed the maximum values during the dark phase in the pons suggesting that this endocannabinoid is likely to be accumulated in parenchyma during the lights-off period (when the animal is awake) and then, released into the CSF in order to reach target regions that turn to modulate sleep [229].

Since the endocannabinoid system compromises endogenous ligands, receptors and enzymes, then it was imperative to study the neurophysiological role on the sleep modulation of the enzyme that hydrolyzes ANA: The fatty acid amide hydrolase (FAAH), which additionally catalyzes the degradation of the satiety factor oleoylethanolamide (OEA) and the analgesic-inducing lipid palmitoylethanolamide (PEA). Despite it has been previously demonstrated previously that the inhibition of the FAAH by the drug URB597 increases levels of ANA, OEA and PEA in the brain of rats [230], no direct evidence was available about the pharmacological effects of these compounds on sleep modulation. In experiments designed to resolve these doubts, it was found that after icv administrations of URB597, OEA or PEA (10, 20μg/5μL) during the lights-on period of rats, it was found an increase in W and a decrease in SWS in a dose-dependent fashion. Additionally, compared to controls, *c*-Fos immunoreactivity in hypothalamus and

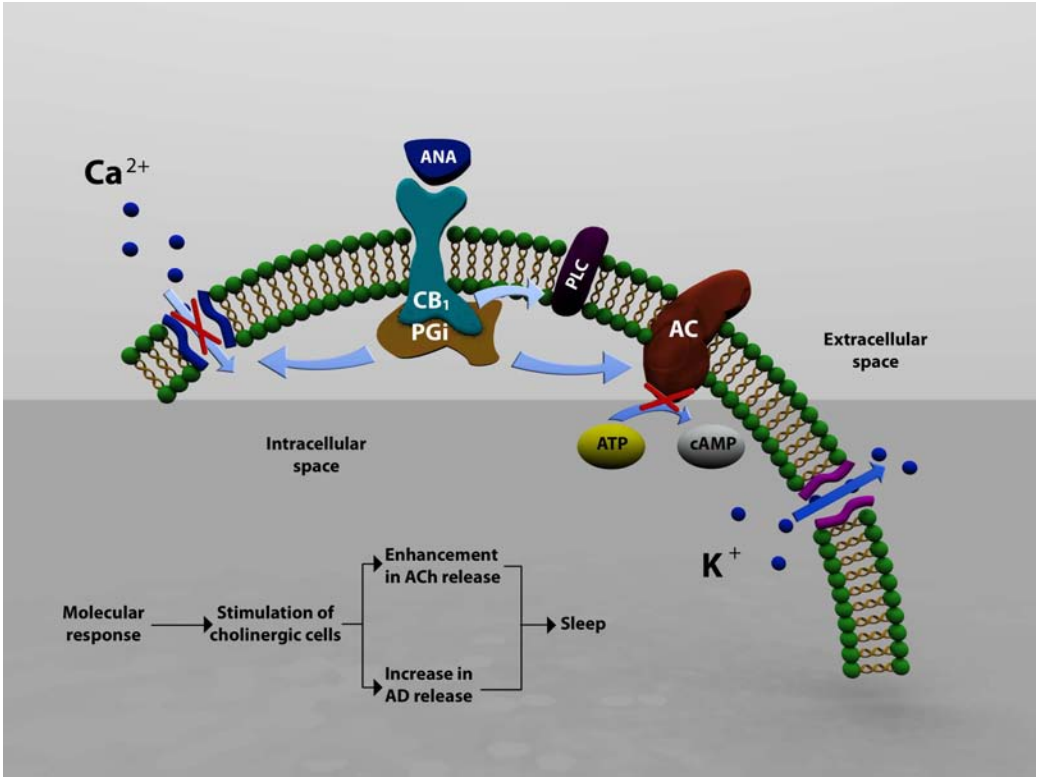

Fig. (3). The sleep-inducing properties of anandamide (ANA) involve diverse cellular elements such as the CB_1 cannabinoid receptor, phospholipase C (PLC) as well as the adenylate cyclase (AC). Activation of the CB_1 cannabinoid receptor activates the PLC, which in turns facilitate the K^+ conductance and blocks the Ca^{2+} channel. Additionally, the activation of the CB_1 cannabinoid receptor blocks the synthesis of cAMP via AC. The proposed mechanism of sleep-inducing properties of ANA involves the activation of the CB_1 cannabinoid receptor placed on cholinergic neurons in the basal forebrain and/or PPT/LDT nuclei which would increase the release of acetylcholine (ACh) and/or adenosine (AD) and then, promote sleep. *Abbreviations*: AC, adenylate cyclase; ACh, acetylcholine; AD, adenosine; ANA, anandamide; Ca^{2+}, calcium; CB_1 cannabinoid receptor; K^+, potassium; PLC, phospholipase C.

dorsal raphe nucleus was increased in rats that received URB597, OEA or PEA. Furthermore, using microdialysis probes placed in the nucleus accumbens, the extracellular contents of DA were collected and analyzed using HPLC means and it was found that the tested compounds enhanced the levels of DA. These findings indicate that that inhibition of the FAAH, via URB597, displays neurobiological properties modulating the sleep-wake cycle [230].

The endocannabinoid system involves also the putative ANA membrane transporter (AMT), which has been target of study since it has been proposed as part of the mechanism by which ANA induces neurobiological effects. Previous studies have shown that the injection of the AMT (VDM 11) enhances endogenous levels of ANA and potentiate its pharmacological actions [231]. However, no direct evidence was available about the role of the sleep modulation by increasing the endogenous levels of ANA. Then, it was described that injections of VDM-11 reduced W and increased REM sleep during the lights-off period (active phase of the rats). In addition, SR141716A partially reversed these sleep effects. Finally, VDM-11 injected in rats enhanced *c*-Fos expression in sleep-related brain areas, such as the anterior hypothalamic area, paraventricular thalamic nucleus, and PPT [232]. The plethora of positive pharmacological effects observed with the endocannabinoid system make the ligands, receptors and enzymes highly attractive for developing novel therapeutic approaches to treat sleep disorders.

6.5. Urotensin II

Urotensin II (UII) is a cyclic dodecapeptide with strong vasoconstrictive activity in the periphery [233, 234]. Autoradiographic binding experiments in rat brain have shown that 125I labeled-UII binds to the PPTg nucleus, the lateral dorsal tegmental area, and the lateral septal, medial habenular, and interpeduncular nuclei. Also, *in situ* hybridization reveals that UII receptor (UII-R) mRNA colocalizes with choline acetyltransferase [235]. The distribution of UII-R in cholinergic nucleus of the mesopontine tegmental area suggested that UII may be involved in functions regulated by ACh, such as the sleep-wake cycle. In agreement with this hypothesis is the finding which demonstrated that adult rats treated with an icv microinjection of 0.6 nmol of UII, resulting in a significant increase of 16.49% in the amount of REM sleep compared to animals treated with saline. Likewise, bilateral administration of 0.6 pmol of UII into PPTg nucleus showed an increase of 13.30% of REM sleep compared to controls [236]. In both experiments, the increase in REM sleep was due to a significant increase in the number of REM sleep episodes. Another key finding was that UII excited bNOS-immunopositive PPTg neurons by activating a slow inward

current without affecting recorded bNOS-immunonegative neurons, suggesting that local application of UII specifically targeted the cholinergic subpopulation of the PPTg [236].

Together with the fact that UII-Rs are expressed in PPTg nuclei, these results suggest that UII peptide is involved in the regulation of the cholinergic mechanisms that control REM sleep Fig. (**4**). However, additional studies are needed to determine whether UII acts at central cholinergic terminals and to valorate its possible effects on blood flow.

7. GENE EXPRESSION AND SLEEP

Sleep and waking differ significantly in terms of behavior, metabolism, and neuronal activity, and also with respect to the expression of certain genes. The best known of such genes studied so far are immediate-early genes (IEGs), including c-fos which shows an enhancement in the mRNA levels after a few minutes of stimulation. The protein of c-fos, Fos, is synthesized shortly thereafter and can be detected for several hours. The expression of c-fos can thus serve as a marker of neuronal activity. Using mRNA differential display and cDNA microarray technology to systematically establish the differences in gene expression that occur between sleep and waking, it has been demonstrated that 10,000 transcripts of the genes expressed in the cerebral cortex are up or down-regulated between sleep and natural or after prolonged waking. Most of the transcripts upregulated during spontaneous W and/or sleep deprivation correspond to known genes and can be grouped in few functional categories. Additionally, the transcription factor CREB is differentially phosphorylated depending on the behavioral state of the animals [237-239].

The role of the gene expression during sleep has been studied from different perspectives. For instance, the basal expression of the proto-oncogene c-fos was analyzed by Northern blot analysis in different regions of the rat brain during 24h. Grassi-Zucconi *et al.* [240] found a spontaneous oscillation of c-fos mRNA expression in animals that were kept in a 12h light/12h dark cycle. Under these experimental conditions, c-fos mRNA was detectable during the resting period of the rat, and was higher during the active period. Supporting these findings, the mRNA differential display and cDNA microarrays to screen approximately 10000 transcripts expressed in the cerebral cortex of rats after 8h of sleep, spontaneous waking, or sleep deprivation was analyzed. Forty four genes showed higher mRNA levels after W and/or sleep deprivation compared to the sleep period, whereas 10 genes were upregulated after sleep. This data provided a classification of genes in the following categories: IEG /transcription factors (including Arc, c fos, CHOP, IER5, NGFI-A, NGFI-B, N-Ras, Stat3), growth factors/ adhesion molecules (BDNF, TrkB, F3 adhesion molecule, just to mention a few), genes related to energy metabolism (such as Glut1 and, Vgf), vesicle- and synapse-related genes (chromogranin C and synaptotagmin IV), chaperones/heat shock proteins (including BiP, ERP72, GRP75, HSP60 and HSP70), neurotransmitter/hormone receptors (nicotinic acetylcholine receptor β_2, adrenergic receptor α_{1A} and β_2, $GABA_A$ receptor β_3, glutamate NMDA receptor 2_A, glutamate AMPA receptor GluR2 and GluR3), neurotransmitter transporters (glutamate/aspartate transporter GLAST, Na^+/Cl^-), enzymes (c-jun N-terminal kinase 1, serum/ glucocorticoid-induced serine/threonine kinase), and a miscellaneous group (calmodulin, cyclin D2, LMO-4) [237-239, 241].

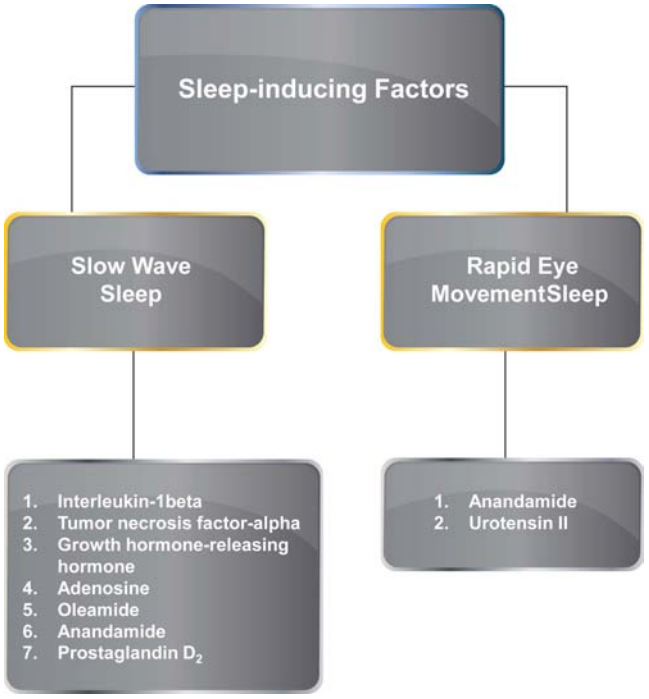

Fig. (4). Recently, hormones, peptides and lipids have been identified as endogenous compounds that could participate collectively in the generation and maintenance of the sleep-wake cycle. The varieties of substances which have been shown to alter sleep are known as sleep-inducing factors.

Glut1 is a gene related to energy metabolism that is active during W and is a major glucose transporter responsible for the transfer of glucose from blood to neurons and glia. It can be drawn the hypothesis that Glut1 induction could represent an alternative molecular mechanism by which the CNS responds to the enhancement in energy requirements during W. Furthermore, it has been demonstrated that the mRNA levels of heat shock proteins and molecular chaperones such as HSP60, HSP70 are also enhanced after 8h of alertness [242].

Taken together the evidence, it is recognized that there are significant changes in the expression of the IEG, c-fos and Fos protein in the brain between W and sleep. However, such expression differences implicate changes in transcriptional regulation across behavioral states and suggest that different transcription factors would be affected as well. Fos and Jun proteins are encoded by proto-oncogenes acting as IEG in that they are rapidly induced by different kinds of stimuli in the CNS. These two proteins bind to DNA regulating gene transcription, and thus determining the specificity of the neuronal response to the applied stimulation. Regarding this, the expression of the IEGs, c-fos and junB in the rat brain has been mapped in

response to sleep deprivation. Thus, animals confined to slowly rotating wheels for 3 or 6h to induce sleep deprivation displayed an increase c-fos expression in regions of the CNS such as medial preoptic area, cortex, and anterior and posterior paraventricular thalamic nuclei. Additionally, JunB was increased in response to the sleep deprivation in regions such as medial preoptic area, cortex, caudate-putamen and amygdala [240, 243]. In addition, Terao *et al.* [244] examined in mouse brain the expression of seven fos/jun family member mRNAs (including c-fos, fosB, fos related antigen (fra)1, fra-2, junB, c-jun, and junD) and other IEG mRNAs (such as egr-1, egr-3, and nur77) after 6h of sleep deprivation period and 4h of recovery sleep right after the period of prolonged waking. They found that the levels of c-fos and fosB mRNA were elevated during prolonged waking in cerebral cortex, basal forebrain, thalamus and cerebellum. Moreover, nur77 and erg-1 mRNA expression across conditions was similar to c-fos and fosB, whereas egr-3 mRNA was elevated in the cortex during both prolonged waking and the respective sleep recovery period. The importance of the identification of the genes that regulate the sleep-wake cycle has a potential to elucidate the genetics of sleep disorders in humans.

8. CONCLUSIONS

Sleep-wake cycle is maintained by different systems [162, 204, 245, 246]. Waking is generated and maintained by the activity of glutamate-, NA-, DA-, 5-HT-, HCRT-, ACh-, and histaminergic systems. These centres diffuse projections to the cerebral cortex, subcortical relays and brainstem [38]. According to diverse single-unit-recording studies, the firing rates of these nuclei have been described as higher during W, to diminish their activity during SWS and becoming silent across REM sleep. It has been hypothesized that these neurons are silenced by the activity from other cells which are active during sleep [41, 36, 38]. Opposite to that view, during the resting period, sleep induction is related with the activity of brain areas such as lateral hypothalamus, VLPO. Additionally, the participation of the release of molecules such as ACh, GABA, and sleep-inducing factors are also required.

The study of endogenous chemicals that produce sleep has also contributed to the understanding of the complex mechamisms that regulate sleep. The concept of endogenous factors was originally proposed by Ishimori [247] and Pieron [248]. They proposed that as a result from the prolonged periods of waking, there was an accumulation of a hypothetical endogenous substance that will induce sleep. At present, molecules from different origin such as brain, blood, cerebrospinal fluid, urine or even skeletal residues of bacteria [183, 249-253] have been isolated and identified as sleep-inducing factors such as PGD_2, AD, cytokines and ANA [148, 187, 205, 226].

Finally, the molecular changes occurring in the brain during the sleep-waking cycle involve the expression of ~10,000 transcripts that are expressed in the cerebral cortex and several brain structures. A few hours of W, either spontaneous or forced by sleep deprivation, increase the expression of a group of genes, including the IEG /transcription factors, genes related to energy metabolism, growth factors/adhesion molecules, chaperones/heat shock proteins, vesicle- and synapse-related genes, neurotrans-mitter/hormone receptors, neurotransmitter transporters, and enzymes, among others. Sleep, on the other hand, induces the expression of a few unknown transcripts [239].

Given the expansion of the knowledge in this neurobiological area, it is ambitious to describe all the multitude of the neuroanatomical, neurochemical and genetic systems involved in sleep modulation, including the pharmacological approaches. However, in this article we reviewed the current understanding of the brain circuits, molecules and genes that regulate the sleep-wake cycle. Future research should be directed at findind the missing elements that could explain how all the pieces that compose the sleep-wake machinery interact to originate such a complex function.

CONFLICT OF INTEREST

Declared none.

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ABBREVIATIONS

ACh	=	Acetylcholine
AD	=	Adenosine
AMT	=	ANA membrane transporter
ANA	=	Anandamide
CNS	=	Central nervous system
CSF	=	Cerebrospinal fluid
DA	=	Dopamine
EEG	=	Electroencephalogram
EMG	=	Electromyogram
FAAH	=	Fatty acid amide hydrolase
GBZ	=	Gabazine
GABA	=	Gamma-aminobutyric acid
GFP	=	Green fluorescent protein
GFs	=	Growth factors
GHRH	=	Growth hormone-releasing hormone
HCRT	=	Hypocretin
IEGs	=	Immediate-early genes
IgG	=	Immunoglobulin G
IL-1β	=	Interleukin-1beta
LPO	=	Lateral preoptic nucleus
LDTg	=	Laterodorsal tegmental nucleus
LC	=	Locus coeruleus
MnPN	=	Median preoptic nucleus
NPS	=	Neuropeptide S

NA = Noradrenaline

OEA = Oleoylethanolamide

PEA = Palmitoylethanolamide

PPTg = Pedunculopontine tegmental nucleus

PLC = Phospholipase C

POAH = Preoptic area/anterior hypothalamus

PG = Prostaglandin

PGD_2 = Prostaglandin D_2

REM = Rapid eye movement

RF = Reticular formation

5-HT = Serotonin

SWS = Slow wave sleep

SCN = Suprachiasmatic nucleus

TMN = Tuberomammillary nucleus

TNF = Tumor necrosis factor

TNFα = Tumor necrosis factor-alpha

UII = Urotensi II

VLPO = Ventrolateral preoptic area

W = Wakefulness

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