Roles of Neuropeptides in Sleep–Wake Regulation

Subjects: Neurosciences

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Sleep and wakefulness are basic behavioral states that require coordination between several brain regions, and they involve multiple neurochemical systems, including neuropeptides. Neuropeptides are a group of peptides produced by neurons and neuroendocrine cells of the central nervous system. Like traditional neurotransmitters, neuropeptides can bind to specific surface receptors and subsequently regulate neuronal activities. For example, orexin is a crucial component for the maintenance of wakefulness and the suppression of rapid eye movement (REM) sleep. In addition to orexin, melanin-concentrating hormone, and galanin may promote REM sleep. These results suggest that neuropeptides play an important role in sleep–wake regulation. These neuropeptides can be divided into three categories according to their effects on sleep–wake behaviors in rodents and humans. (i) Galanin, melanin-concentrating hormone, and vasoactive intestinal polypeptide are sleep-promoting peptides. It is also noticeable that vasoactive intestinal polypeptide particularly increases REM sleep. (ii) Orexin and neuropeptide S have been shown to induce wakefulness. (iii) Neuropeptide Y and substance P may have a bidirectional function as they can produce both arousal and sleep-inducing effects.

neuropeptides NREM REM sleep wake

1. Introduction

Sleep is one of the most important physiological functions in mammals. It is often described as the normal loss of consciousness. The main function of sleep is to eliminate fatigue. Sleep is also involved in the process of learning and memory consolidation. As a result, sleep disorders have a negative effect on physical and mental health. In terms of characteristics of the electroencephalogram (EEG), sleep in mammals can be divided into two distinct stages: rapid eye movement (REM) sleep and non-REM (NREM) sleep. Judging by the EEG, NREM sleep in humans can be further divided into four stages: stage 1, stage 2, stage 3 and stage 4. REM sleep, which is also called paradoxical sleep, is defined by REM, the entire absence of muscle tone, and the ability to dream vividly [1].

The sleep–wake cycle is primarily modulated by circadian rhythms and homeostatic regulation. Several specific brain regions are involved in the regulation of the sleep–wake cycle, including the forebrain, hypothalamus, and brain stem. Previous studies have revealed that the nuclei involved in the regulation of arousal response include the thalamus, basal forebrain (BF) [2], lateral hypothalamus (LH) [3], tuberomammillary nucleus (TMN) [4], ventral tegmental area [5][6], the pedunculopontine (PPT)/laterodorsal tegmental nucleus (LDT) [7], dorsal raphe nucleus (DRN) [8], parabrachial nucleus [9], and locus coeruleus (LC) [10] (**Figure 1**). The nuclei associated with NREM sleep regulation include those of the olfactory tubercles [11], ventrolateral periaqueductal gray (vlPAG) [12], preoptic

area (POA) [13], rostromedial tegmental nucleus [14], thalamic reticular nucleus [15], and other regions of the brain (**Figure 2**). The olfactory bulb [16], POA [17], vlPAG [12], PPT/LDT [7], DRN [18], and LC [19] have been reported to be involved in the regulation of REM sleep (**Figure 3**) [20][21].

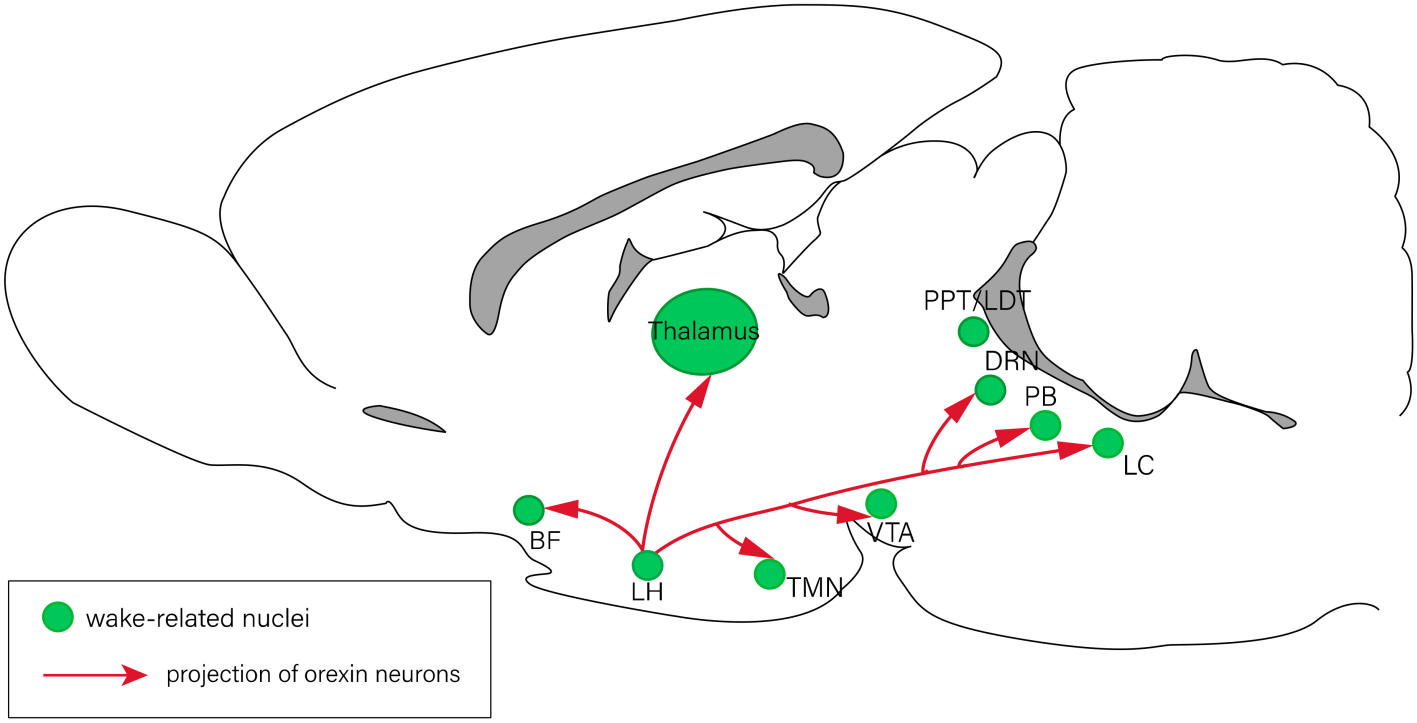

Figure 1. Neural circuits of arousal regulation. The nuclei related to arousal response include the BF, LH, TMN, VTA, PPT/LDT, DRN, PB, and LC. Red lines represent the projections of orexin neurons in the LH. BF: basal forebrain; DRN: dorsal raphe nucleus; LC: locus coeruleus; LDT: laterodorsal tegmental nucleus; LH: lateral hypothalamus; PB: parabrachial nucleus; PPT: pedunculopontine tegmental nucleus; TMN: tuberomammillary nucleus; VTA: ventral tegmental area.

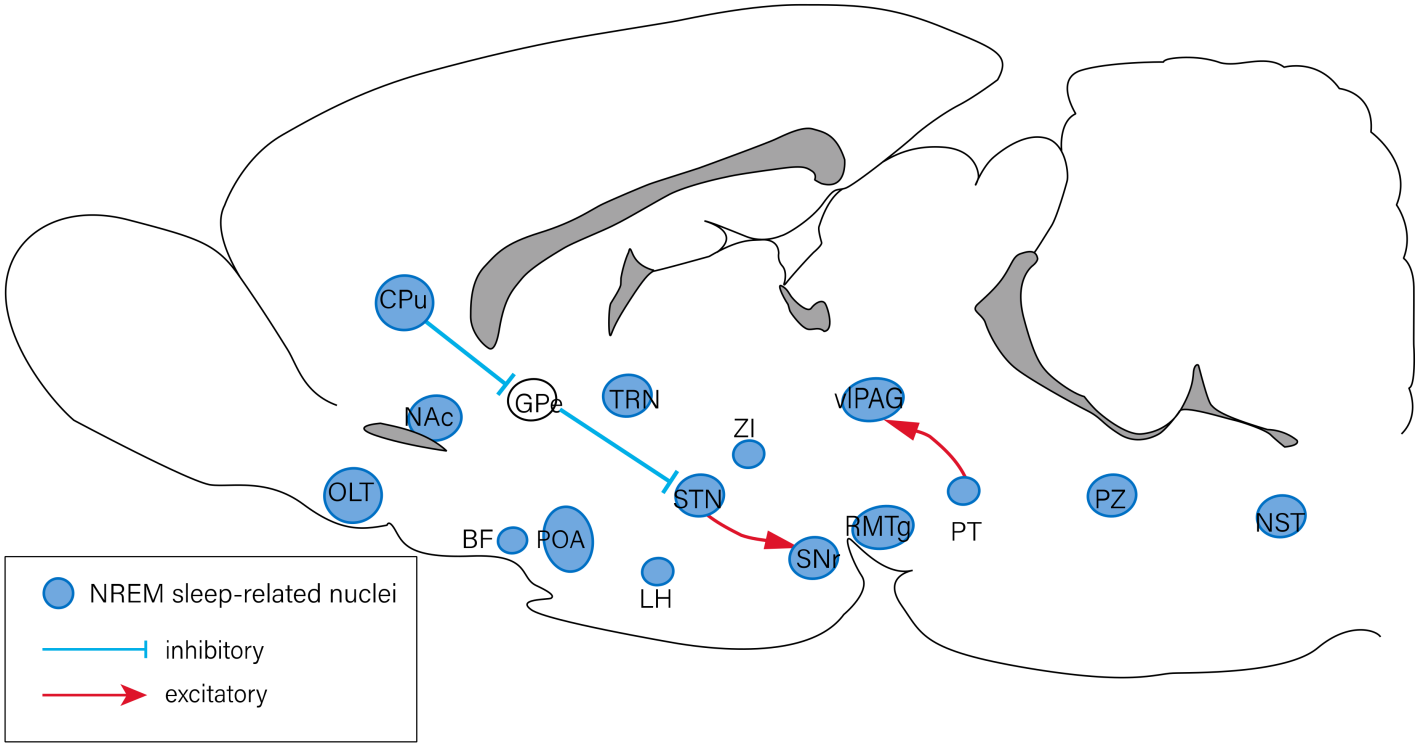

Figure 2. Neural circuits of NREM sleep regulation. The nuclei involved in the regulation of NREM sleep include the OLT, CPu, NAc, GPe, BF, POA, TRN, LH, STN, ZI, SNr, RMTg, vlPAG, PT, PZ, and NST. The PT has an excitatory projection to the vlPAG, and the CPu inhibits the STN neurons by suppressing the GPe. The STN has an excitatory projection to the SNr. BF: basal forebrain; CPu: caudate putamen; GPe: external globus pallidus; LH: lateral hypothalamus; NAc: nucleus accumbens; NST: nucleus of solitary tract; OLT: olfactory tubercles; POA: preoptic area; PT: pontine tegmentum; PZ: parafacial zone; RMTg: rostromedial tegmental nucleus; SNr: subtantia nigra pars reticulata; STN: subthalamic nucleus; TRN: thalamic reticular nucleus; vlPAG: ventrolateral periaqueductal gray; ZI: zona incerta.

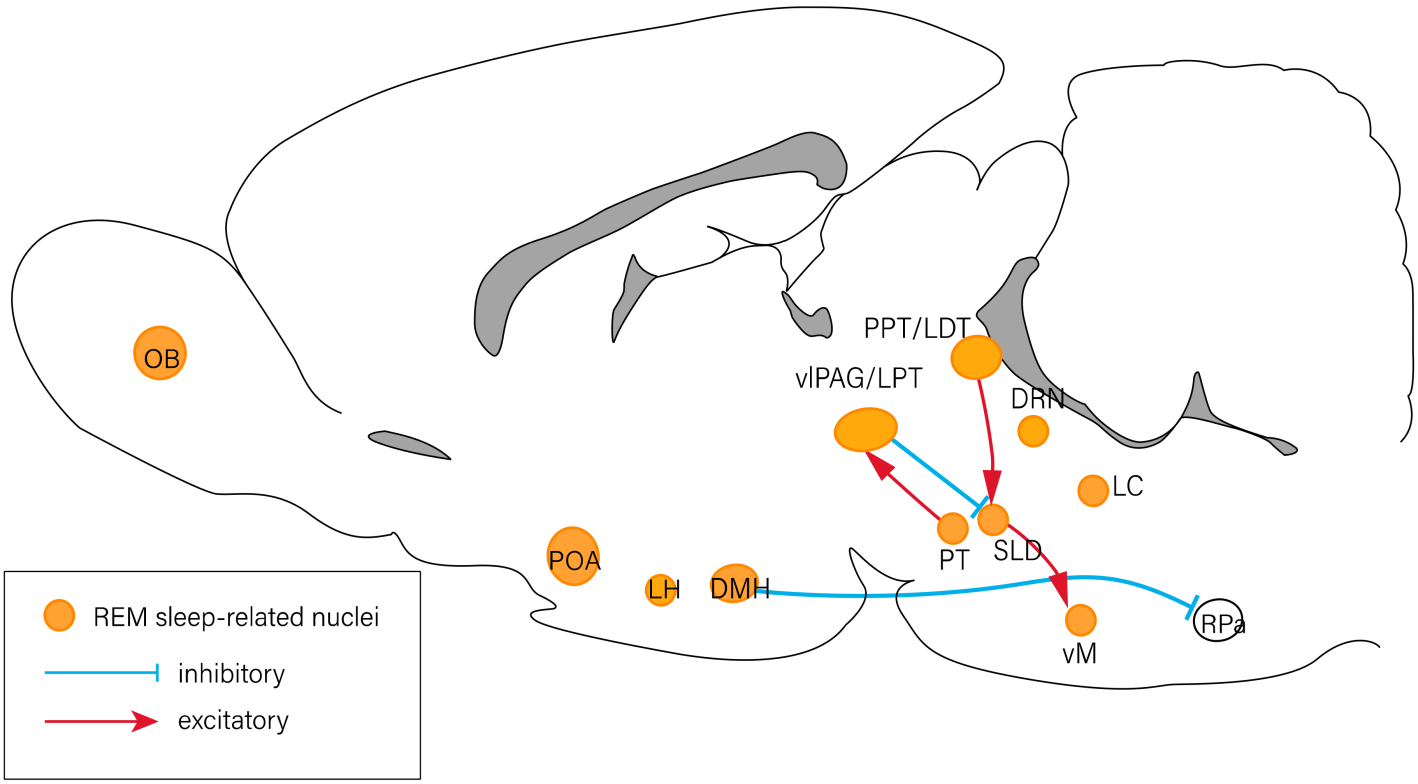

Figure 3. Neural circuits of REM sleep regulation. The OB, POA, LH, DMH, PT, vlPAG/LPT, PPT/LDT, DRN, LC, and vM are associated with the modulation of REM sleep. There exist inhibitory projections (blue lines) and excitatory projections (red lines) between nuclei. DMH: dorsomedial hypothalamus; DRN: dorsal raphe nucleus; LC: locus coeruleus; LDT: laterodorsal tegmental nucleus; LH: lateral hypothalamus; LPT: lateral pontine tegmentum; OB: olfactory bulb; POA: preoptic area; PPT: pedunculopontine tegmental nucleus; PT: pontine tegmentum; RPa: raphe pallidus area; vlPAG: ventrolateral periaqueductal gray; vM: ventral medulla.

In mammals, neuropeptides, which are engaged in many physiological functions, are the most diverse class of signaling molecules in the brain. In the mammalian genome, there are almost 70 genes encoding the bioactive neuropeptides and neuropeptide precursors [22]. Neuropeptides are small protein molecules composed of 3–100 amino acid residues [23]. Neuropeptides are synthesized from neuropeptide precursors that require proteolytic processing primarily within secretory vesicles. Mature neuropeptides are stored in these vesicles and secreted to modulate the activity of target cells [24]. Neuropeptides can be released from all parts of a neuron, including the axon, the soma, and especially the dendrite, which can be located in the central nervous system (CNS) or peripheral nervous system (PNS). After the secretion of neuropeptides, most of them bind to G protein-coupled receptors (GPCRs) and then elevate the intracellular Ca^{2+} concentrations to alter membrane excitability, transcription, and synaptogenesis, thus regulating a wide range of behaviors, including sleep–wake behaviors [25]. In addition, proteinases play a critical role in the regulation of the biological activity of neuropeptides in the CNS through proteolytic conversion and degradation. These enzymes, in turn, are regulated by inhibitors, which are involved in the regulation of many metabolic pathways [26].

2. The Neuropeptides Involved in Sleep–Wake Regulation

2.1. Galanin Promotes Sleep

Galanin was discovered by Mutt's team at the Karolinska Institute in Stockholm in the 1980s. It is composed of 29 amino acids (30 in humans) and is considered as a "classical neuropeptide" that regulates neurotransmission in the CNS and PNS. Galanin has been reported to play a significant role in the regulation of numerous physiological and pathophysiological processes through the interaction with three GPCRs [27][28][29], including feeding [30], energy homeostasis [31], osmotic regulation [32], water intake [33], and pain [34]. In addition, the mRNA expression of galanin is found in γ-aminobutyric acid (GABA)-positive neurons in the ventrolateral preoptic nucleus (VLPO) [35], which is a critical nucleus of the sleep–wake regulation. It indicates that galanin is involved in the regulation of VLPO activity. Moreover, several studies have demonstrated that the VLPO sends inhibitory projections to many sleep-related nuclei, such as the TMN and other arousal systems in the brain stem, including the DRN and the LC [36]. As a result, galanin affects sleep–wake behaviors.

2.2. Orexin Consolidates Wakefulness and Inhibits REM Sleep

Orexin exists in two molecular forms, orexin-A and orexin-B, which both perform physiological functions through the interaction with the GPCRs [37]. Rats have around 3000–4000 orexin-producing neurons in the brain [38], and they are located mainly in the peripherical area of the LH [39][40]. These neurons project widely to the CNS, regulating feeding and other behaviors. Many nuclei that regulate sleep–wake behaviors receive projections from the orexin neurons as well, including the LC [41], DRN [42], TMN [43], PPT/LDT [44], and BF [45]. Therefore, orexin is involved in sleep–wake regulation.

2.3. Melanin-Concentrating Hormone Has Positive Influence on Sleep

Melanin-concentrating hormone (MCH) is a cyclic neuropeptide consisting of 19 amino acids [46], which performs physiological functions through the interaction with two GPCRs known as MCH receptor-1 and MCH receptor-2. It serves as an important neuromodulator of homeostasis and performs a large range of integrative functions, which are mainly associated with homeostatic regulation and motivated behaviors [47][48]. In mammals, MCH neurons are mainly located in the LH and the zona incerta [49][50]. They project to many nuclei that promote REM sleep and arousal, including the LC, DRN, LDT/PPT, and the sub-LDT [51]. Although the location and projection of MCH neurons are remarkably similar to those of orexin neurons [51], they have opposite effects on the modulation of sleep–wake states. MCH neurons have a positive influence on sleep, especially REM sleep [46].

2.4. Neuropeptide S Is Associated with Arousal Induction

Neuropeptide S (NPS) is a peptide composed of 20 amino acids and an endogenous ligand for the NPS receptor. The NPS receptor is a typical GPCR, containing seven membrane-spanning domains. The N-terminal residue of NPS in all species is always serine, hence the name NPS [52]. NPS is expressed in the brainstem, amygdala, hippocampus, and in other regions of the limbic system. Rainer et al. have demonstrated that mRNA expression of the NPS receptor is widespread throughout the CNS, and it is especially abundant in the cortex, thalamus, hypothalamus, and amygdala [53]. In addition, low mRNA levels of the NPS receptor have been observed in the

brainstem. In contrast, mRNA expression of the NPS precursor is mainly observed in brainstem nuclei such as the LC and the lateral parabrachial nucleus, while a small number of scattered NPS-positive neurons are found in other brain areas, such as the amygdala and hypothalamus [52][54]. NPS induces the mobilization of intracellular Ca^{2+} [55], increases the intracellular cAMP levels, and stimulates the phosphorylation of mitogen-activated protein kinase [56]. NPS modulates a variety of physiological functions such as food intake [57][58][59], the regulation of the endocrine system, spatial memory, alcohol seeking, nociception, and anxiety.

2.5. Neuropeptide Y Has a Dual Impact on Sleep–Wake Behaviors

Neuropeptide Y (NPY) is a highly conserved endogenous peptide consisting of 36 amino acids, which is widely distributed in the CNS and PNS of all mammals and acts as a neurohormone and neuromodulator. NPY exerts its biological functions via the interaction with five subtypes of GPCRs [60]. NPY and its receptors are involved in a variety of behaviors, such as food intake, circadian rhythms, chronic pain, the stress response, and anxiety [61][62][63][64][65][66]. NPY is expressed in many nuclei associated with sleep–wake regulation, such as the amygdala, hypothalamus, hippocampus, periaqueductal gray, LC, and the cerebral cortex [67][68][69]. Therefore, NPY is thought to affect sleep–wake behaviors [70].

2.6. Substance P Induces Either Sleep or Arousal

Substance P (SP) is a neuropeptide consisting of 11 amino acids [71]. It exerts its functions by binding to neurokinin receptors, particularly neurokinin type 1 receptors (NK-1Rs) and NK-2Rs [72]. NK-1Rs in the CNS are critical for the regulation of affective behaviors, neurochemical responses to stress, and pain transmission [73][74]. NK-1Rs are distributed throughout the CNS, including many brain regions that are highly involved in sleep–wake regulation, such as the hypothalamus, brainstem, and cortex [75][76]. Therefore, SP affects sleep–wake states.

SP is reported to induce sleep. For example, bilateral microinjection of SP into the VLPO increases NREM sleep in rats [77]. Microinjection of SP into the cerebral cortex enhances the slow-wave activity in mice as well [78]. Furthermore, a previous study has shown that the intracerebroventricular administration of SP conjugated with cholera toxin A subunit can enhance NREM sleep but induce sleep fragmentation [79]. However, on the contrary, the systemic administration of non-nociceptive doses of SP has been reported to increase the duration of wakefulness episodes in mice [80], and to increase the latency of REM sleep and wakefulness in healthy young men [81]. Sergeeva et al. have also found that SP induces arousal by activating histaminergic neurons in the TMN [82].

2.7. Vasoactive Intestinal Peptide Promotes REM Sleep

Vasoactive intestinal peptide (VIP), a peptide consisting of 28 amino acids, is produced in many regions of the human body, including the gut, pancreas, and suprachiasmatic nucleus (SCN) [83]. The SCN is the center of the circadian rhythm, and the circadian rhythm determines sleep–wake states in mammals. Disruption of the circadian rhythm usually causes sleep disorders [84]. VIP, a neurotransmitter expressed by a subset of the SCN neurons, appears to play a critical role in the regulation of the circadian rhythm and sleep–wake behaviors [85][86][87].

VIPergic neurons project densely throughout the SCN. A previous study revealed that VIP kickout mice showed an 8-h advance of the predicted activity phase with less precision when exposed to constant darkness [88]. This shows that VIP and its receptors are critical for maintaining normal circadian rhythms, which is a significant function of the SCN.

2.8. Other Neuropeptides Associated with Sleep and Wake Regulation

Previous studies have shown that neuropeptides have diverse effects on sleep–wake regulation in rodents and humans. Adrenocorticotropic hormone, cocaine- and amphetamine-regulated transcript, ghrelin, neurotensin, pituitary adenylyl cyclase-activating polypeptide, and somatostatin induce arousal [89][90][91][92][93][94]. Some of them (neurotensin, pituitary adenylyl cyclase-activating polypeptide, and somatostatin) tend to suppress NREM sleep, but they have a positive impact on REM sleep [91][92][93]. Other neuropeptides, including brain-derived neurotrophic factor, growth hormone, growth hormone-releasing hormone, interleukin 1 beta, leptin, melanocyte-stimulating hormone, neuropeptide B, opioid peptides, and tumor necrosis factor, can promote NREM sleep [95][96][97][98][99][100][101]. Cholecystokinin has been shown to play a complex role in the regulation of sleep–wake behaviors, because it induces both NREM sleep and wakefulness [97]. Recent studies have also suggested that both cholecystokinin and transforming growth factor alpha can potentially inhibit the transition from sleep to wakefulness [102].

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