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The neurotransmitters of sleep and arousal

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Abstract. The sleep and arousal, or the vigilance state, is controlled by a highly dynamic brain system that involves numerous interconnected brain circuits. However, while many reviews presented the anatomical bases of how different components of the brain area contribute to the vigilance states, less attention is paid from the perspective of different neurotransmitters. As multiple different neuronal populations could exist and express in the same brain area, attributing the effect of different brain areas on sleep and arousal would not be precise without consideration of the act of neurotransmitters. This review summarizes the recent progress on how different neurotransmitters affect vigilance states. By doing so, this review aims to provide an alternative angle in understanding how different vigilance state is regulated by the brain.

Keywords: Neurotransmitters, sleep, arousal.

1. Introduction

Sleep is a fundamental and essential biological process that is crucial for maintaining overall health and well-being. Through centuries of studies, numerous benefits of sleep have been discovered. Also, various factors have been discovered that contribute to the complex mechanisms of sleep/awake regulation [1]. However, people suffering from sleep issues often are unable to drive themselves to sleep and they could be attributed to various physiological factors that involve abnormality of neurotransmitters. Therefore, understanding the physiological mechanism of different sleep issues, especially the neurotransmitter aspect, is essential for improved diagnosis and personalized medicine in sleep issues.

Many previous reviews address the mechanism of sleep/wake regulation from the aspect of different neuronal circuits and anatomy. However, how the neurotransmitter system regulates the sleep-wake cycle was less addressed. Many sleep/wake-related areas consist of multiple neuronal populations that play diverse roles. For example, the GABAergic population in VLPO could potently promote sleep [2], while non-LTS cells in VLPO can potently promote arousal [3, 4]. There are currently 5 known distinct neuronal populations in VLPO [5]. The basal forebrain contains distinct neuronal populations that function in different states [6]. Besides the functional difference of neuronal populations within one area, the same neuronal populations are not necessarily separated by anatomical location [7] and require a neurotransmitter aspect to explain their function. Hence, it is also crucial to assess how different neurotransmitters affect sleep and awake to understand the how vigilance state is regulated.

The function of different neurotransmitters on sleep has been reviewed previously twenty years before [8]. However, the advances in experimental methods in the last two decades have promoted our

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understanding of how different neurotransmitters function in sleep-wake regulation, and it is time to summarize and reupdate the relationship between these neurotransmitters and sleep.

2. Neurological system that promotes sleep

The mechanism of sleep/wake regulation has always been an intriguing field in earlier ages. Among numerous models, the two-process and Flip-Flop models are currently the most popular. The Two-process model proposed two fundamental processes: the homeostatic process (Process S) and the circadian process (Process C), direct to or not to sleep [9]. Process S is the sleep debt that increases during wakefulness and decreases during sleep. Process C represents the internal body clock in a 24-hour cycle regulated by the suprachiasmatic nucleus (SCN) and light exposure. A more complex influence of process S and process C has been discovered decades after this model was proposed. For example, Process S also shows regional influences in which highly activated brain regions during the day show increased slow-wave activity during sleep. Also, several models suggest that high sleep pressure can reduce circadian amplitude, while the circadian phase influences sleep pressure reflected by slow wave activity. The interaction between the circadian clock and sleep pressure in the three-process model expands the two-process model with another process, M, representing external factors such as social activities. However, while SCN in the past century was commonly acknowledged as the only master circadian control center, many more recent findings opposed this 'dogma'. Activities that follow a circadian rhythm have been observed in numerous areas such as, and many of them own their independence.

The Flip-Flop model focuses more on the neuronal mechanism of Sleep-awake transition. Sleep and awake are generally regulated by two distinct neuronal groups, and excitation on one group would inhibit the other. The significant wake-promoting population consists Lateral hypothalamus (LH), Parabrachial Nucleus(PBN), precuneus area(PC), nucleus accumbens(NAc), paraventricular hypothalamic nucleus(PVN), Locus Coeruleus(LC), Tuberomammillary Nucleus(TMN), ventral tegmental area(VTA), Basal Forebrain(BF), Dorsal Raphe Nucleus(DR), median raphe nucleus, pedunculopontine, laterodorsal tegmental nuclei, medial septum [10]. The major sleep-promoting populations include ventral lateral preoptic Area (VLPO), median preoptic nuclei (MPO), and lateral preoptic area(LPO).

Sleep promotion under the Flip-Flop model can be understood as the brain-wide inhibition of the wake-promoting neurons, many of which send inhibitory signals to many sleep-promoting areas. For example, disinhibiting the VLPO population due to decreased Orexin release in LH promotes inhibitory signal projections to TMN, DR, LC, and LH, therefore driving sleep. Noteworthily, the idea of "whole-brain on-off shifting" between sleep and awake state has been challenged by many recent studies from many perspectives. For example, sleep and wake can co-occur in different brain regions [11]. This suggests the need to revise the classical view of the flip-flop model(see review [12]). Overall, the revolutionization of the current understanding of sleep from the dichotomic flip-flop model to a multidimensional framework could be the future for understanding sleep.

2.1. Acetylcholine(Ach)

Acetylcholine is an excitatory neurotransmitter mainly derived from PPT/LDT and BF could either ultimately promote wakefulness or sleep depending on the projection region and receptor types [13, 14]. Cholinergic neuronal activity is higher during awake and REM sleep but not NREM sleep, suggesting their role in driving cortical activation [15].

Cholinergic neurons in PPT and LDT play a variant but important role in Wake-sleep switches, and NREM-REM switches [16]. It projects mainly towards SLD which is likely to promote REM sleep [17] and BF to enhance cortical activity [15]. Moreover, although the innervation effect on sleep is not determined, cholinergic neurons in PPT also project to various sleep-regulating areas such as the reticular nucleus of the thalamus(RTN), VTA, and SN, suggesting more potential sleep-regulating role that Ach from PPT could play [16, 18]. While less studied, the cholinergic neuron from TRN has been shown to promote sleep, by innervating the neighboring GABAergic neurons [14]. As PPT and LDT

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cholinergic neurons also project to TRN, a sleep-promoting circuit between Acetylcholine from PPT, LDT, and TRN is possible [1].

The cholinergic neurons in BF are innervated by orexin neurons in the LH, and they in turn innervate the cortex, promoting cortical activity and cognitive function [14]. Cholinergic neurons in the BF are also innervated by the glutamatergic neurons, and exhibit strong projection to neighboring wake-promoting PV+ GABAergic neurons, forming a strict hierarchical local wake-promoting circuit, while being inhibited by SOM+ GABAergic neuron [14]. Noteworthily, cortical arousal requires both cholinergic and non-cholinergic neurons from BF neurons, a study has suggested that cholinergic neurons from BF promote wakefulness by activating neighboring PV+ GABA neurons, and PV+GABA neurons in turn activate the cortex [14]. While the BFAch projection toward the cortex promotes wakefulness, acetylcholine could also provide short-term cortical vigilance inhibition during awake mainly by activation of muscarinic receptors in layer 4 [19]

2.2. Hypocretins(Hcrt)/Orexin(Ore)

Hypocretins, also named orexins, are an important neuropeptide expressed in the lateral hypothalamus that promotes wakefulness [20]. Hypocretins contain two excitatory subtypes, Hcrt-1, and Hcrt-2, and they bind to orexin receptor-1 and -2, respectively [21]. Orexin neurons are active during wakefulness and quiet during sleep. According to the Flip-flop model, the sleep-promoting circuit during sleep projects inhibitory inputs to orexin neurons, suppressing the excitatory projection to wake-promoting areas and inhibitory inputs to sleep-promoting areas, to maintain the sleep state [22]. Orexin has a widespread projection throughout the brain, mostly wake-promoting areas like LC, TMN, PVT, NAc, VTA, BF, PAG, PPT, LDT and, which are all considered wake-promoting areas and directly innervating other wake-inducing glutamatergic, cholinergic, histaminergic, serotonergic, dopaminergic and noradrenergic neuron populations [7, 23-25]. This widespread excitatory projection also signifies its connection with other wake-promoting neuronal circuits. For instance, the Hcrt-1 from LH is projected to the BF, innervating the BFAch projection to various cortical regions, promoting cortical wakefulness. Besides, orexin can also have an inhibitory effect on sleep-promoting VLPOGABA/Gal neurons and excitatory effects on VLPOGABA neurons, which directly inhibit VLPOGABA/Gal [26]. While Orexin is projected to multiple regions, the orexin neuron from the LH also integrates input from various sleep-wake regulating neurotransmitters and hormonal signals from areas such as POA, BF, DR, VTA, SCN, NAc, VTA, and amygdala. Not only so, but the orexin neuron activity in LH I is also maintained by self-projected, positive feedback [27].

Orexin is considered one of the most important neuropeptides that promote wakefulness, Depletion of Hcrt neurons is a major cause of Narcolepsy, a neurological disorder characterized by sudden, involuntary sleep during the day and excessive daytime sleepiness. Furthermore, orexin neurons are known to respond to adenosine, a representation of the sleep debt in the Two-Process model, It has been discovered that adenosine, a representation of the sleep debt in the Two-Process model accumulation during awake, can bind to A1 receptor expressed in orexin neurons and inhibit its activity, which is suggested to induce sleep [28, 29]. Caffeine is renowned for its wake-promoting effect by inhibiting adenosine activity via adenosine receptor antagonism [30]. However, a recent study also reported that Caffeine could excite orexin activity [31]. Depletion of Hcrt neurons is also a major cause of Narcolepsy, a neurological disorder characterized by sudden, involuntary sleep during the day and excessive daytime sleepiness. Orexin can also mediate hunger-induced wakefulness. Besides, orexin is also crucial for regulating appetite, motor activity, stress response, and mood [32-35]. Therefore, orexin mediates many factors that prevent sleep, such as hunger, stress, and fear.

2.3. Monoamines

Serotonin, histamine, dopamine, and norepinephrine are the four common sleep-regulating monoamine neurotransmitters that are active during waking and inactive during both REM and NREM sleep. Another monoamine is dopamine, which is more active during wakefulness and REM sleep. All

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monoamines have widespread projection to other sleep-wake regulation areas in the brain which suggests their important role in sleep-wake regulation.

2.4. Serotonin(5-HT)

Serotonin is a neurotransmitter produced in dorsal raphe(DR), primarily known for its mood-regulating function which lack of serotonin is associated with depression [36]. Meanwhile, numerous evidence indicates the serotonergic system is involved in sleep/wake regulation, but the accurate function has raised controversies in past decades. Studies that applied 5-HT antagonist on the excitatory 5HT2 receptor induce sleep in mice and humans but wakefulness in cats [37, 38]. Similarly, agonists of 5HT1A induce wakefulness in rats [39] but REM sleep in cats [40]. Also, mice that do not express 5HT1A or 5HT1B showed increased REM sleep [41, 42]. To make the issue more complex, the sleep-promoting role of 5HT has also been reported [43]

A brief explanation corresponding to the inconsistent finding across species is that the sleep/wake regulation mediated by serotonin is complex, one example is that 5HT excites Type-2 VLPO sleep-promoting neurons but inhibits Type-1 VLPO sleep-promoting neurons [44]. Type-2 VLPO sleep-promoting neurons are highly responsive to adenosine are more excitable, and are responsible for the initiation of sleep. Meanwhile, Type-2 VLPO sleep-promoting neurons reduce the inhibitory input received by the type-1 VLPO neurons, and type-1 VLPO neurons proceed to consolidate the sleep [45]. Therefore, serotonin seems to promote sleep during awake by exciting the type-2 VLPO neurons and promote arousal during sleep by inhibiting type-1 VLPO neurons. This idea is supported by a previous study that reported that raphe lesions during the awake state promote sleep whereas raphe lesions during the sleeping state promote wakefulness [46].

Serotonin also interacts with multiple sleep-promoting areas to regulate the vigilance state. Serotonin is primarily found in the Dorsal raphe(DR) and pedunculopontine tegmental(PPT) nucleus. It also has a widespread projection to many brain areas. The 5HT from DR projects to the cortex, thalamus, hypothalamus, amygdala, basal forebrain, and pontine reticular formation innervating histaminergic orexinergic, noradrenergic, dopaminergic, cholinergic, and GABAergic neurons [47]. Overall, serotonin could exhibit both wake-promoting and sleep-promoting effects, based on its projection and subtypes.

2.5. Histamine (HA)

Histamine originates majorly from the tuberomammillary nucleus(TMN) and projects widely throughout the brain, including the cortex, striatum, SNc, posterior pituitary, and thalamic areas. Histamine acts via four different histamine receptors: H1, H2, H3, and H4, and only the first three are present in the brain [48]. So far, it has been reported that the H1 receptor promotes waking while the H3 receptor antagonizes it. Optogenetic inhibition of TMNHA induces NREM sleep and H1 receptor blockage also increases NREM sleep. However, the removal of HA neurons did not significantly reduce the amount of time being awake, besides exhibiting more drowsy behaviors. This overall suggests that while HA has a wake-promoting role, ablation of HA can be partially compensated by other arousal systems [49]. TMMHA also projects to sleep-promoting areas like VLPO, indirectly inducing wakefulness by increasing the local GABAergic tone [50]. Another interesting phenomenon is that histamine can co-transmit together with GABA. While the exact mechanism of how GABA and histamine can be packaged together is still a contentious topic [51, 52], GABA and histamine are co-released into the striatum, neocortex, and prefrontal cortex to coordinate tonic inhibition and induce wakefulness [53]. However, the major role of Histamine on wake generation has been challenged recently by a study that suggests histamine contributes little to baseline arousal [54]

Interestingly, besides TMN, histamine can be also produced by mast cells [55, 56], and could provide an alternative, brain-wide histaminergic arousal effect. Activation of brain mast cells promotes wakefulness [57]. Furthermore, an increase in histamine production from mast cells during stressful conditions also contributes to sleeplessness [58]. However, as mice that express fewer mast cells did not show different amounts of time in sleep and wakefulness compared to normal mice [57], how histamine produced by mast cells influences sleep/wake remains to be addressed.

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The Histamine might also reflect circadian rhythms, as the preoptic histamine levels are highest during wakefulness, less active during NREM, and almost silent during REM sleep, while no histamine level change was observed under sleep-deprived conditions [59].

2.6. Domaine(DA)

Dopamine is mainly produced in the SN and VTA and a large body of dopamine is projected to NAc. There are in total five Dopamine receptors found, and they exhibit different functions in different brain areas and some of their function are still controversial.

For NAc, the Microinjection of D1R, D2R, and D3R agonists in NAc has been shown to enhance wakefulness [60]. However, when administrated at a low dose, D2R receptor agonists decrease wakefulness while the effect is reversed after increasing the dose [61].

While the involvement of VTA dopamine neurons in sleep/wake control was highly controversial based on lesion studies [62], the effect of VTA dopamine neurons has been clarified more recently. Chemogenetic inhibition of VTADA induces sleep-related nesting behaviors and prevents arousal in response to salient stimuli such as mating, food, and predation. Conversely, optogenetic activation of VTADA initiates and maintains wakefulness and prevents sleep-related behavior [63]. Another study suggests that NAc contains mainly D1R and D2R-expressing neurons, and are considered to play different roles in sleep regulation. It suggests that D2R(also D3R) generates wakefulness but no effect was found with D1R [64]. Conversely, another study reported that D1R-expressing neurons induce wakefulness possibly by disinhibiting the LH orexin neurons and VTA dopamine neurons [65].

The function of SNcDA is less obscure compared to the function of dopamine from another area. In earlier optogenetic and chemogenetic studies, no relationship between SNcDA and sleep was found [64]. However, a later study dissects the dopamine neurons found in SNc based on its projecting destination, as dorsal striatum projecting DA enhances sleep while ventral striatum projecting DA decreases sleep [66].

Besides, dopamine neurons are also found in ventral periaqueductal grey(vPAG) which has a causal role in sleep/wake regulation as stimulation of vPAGDA induces wakefulness yet inhibition induces sleep [67]. However, lesion studies suggested that loss of vPAGDA neurons increases the amount of sleep. Interestingly, vPAGDA also regulates sleep/wake regulation according to the outside stimuli from the environment [67], like VTADA and the relationship between vPAGDA and VTADA could be elucidated.

A very interesting phenomenon is that the dopamine activity in the VTA and NAc follows the circadian rhythms [68], and has been proposed as an alternative circadian rhythm master control clock. This question remains controversial. There is no evidence to suggest SCN directly projected to VTA or NAc, even though some indirect pathways such as via mPOA or PVT have been reported. Furthermore, ablation of VTA has disabled the correct circadian rhythms. [69].

2.7. Norepinephrine(NE)

As a key neurotransmitter enhancing the sympathetic tone, Norepinephrine is well-known for its wake-promoting function. Activation of NE signaling drives wakefulness whereas inhibition leads to sleep [70] and NE activity is enhanced before arousal [71]. Norepinephrine is often sourced from locus coeruleus(LC). NE level accounts for many causes of sleep disruption. During stressful situations, the activity of NE neurons in LC is enhanced, and it interacts with POA to induce microarousal [72] similarly, bursting release of NE is also elicited to enhance vigilance state when exposed to salient stimulus [73].

The role of NE from LC is more complex than a simple wake-promoting substrate. A more recent study reported that the regulation of sleep by LC-NE is mediated by their level of intensity: a slow activity induces unresponsiveness during sleep and a higher-level activity induces wakefulness [74].

2.8. GABA

GABA is the most prevalent inhibitory neurotransmitter that is involved in sleep. The generation of GABA is widely spread and projected to almost all brain regions [75]. GABA is generally regarded as

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a sleep-promoting neurotransmitter while the wake-promoting function of GABA in some circuits has also been reported. For example, as mentioned above, VTADA promotes wakefulness and induces sleep preparations. The GABA from VTA could locally inhibit VTADA action and their hyperarousal and sequentially, the VTAGABA is inhibited by the VPGABA. Therefore, VPGABA could promote wakefulness via VTADA disinhibition and VTADA induces sleep [76]. Table 1 lists recent reports about the origination, projection, and function of GABA that is related to sleep generation or inhibition.

Still, GABA is crucial in sleep generation and maintenance. GABA from VLPO, the sleep center, projects to the lateral hypothalamus and powerfully inhibits its wake-promoting neurotransmitter such as orexin and glutamate. GABA from vlPAG, SNr, SCN, and numerous places also send inhibitory signals to many commonly known wake-promoting areas and induce sleep. The local projection is also common in GABA, evident in BFGABA and VTAGABA. Also, as mentioned above, GABA is often co-transmitted with another neurotransmitter to achieve complex sleep/wake-related regulation.

Table 1. The origination, projection, and function of GABA contribute to sleep regulation as reported in some recent studies. While most GABA promotes sleep, some contribute to wake generation.

Neurotransmitter	Origination	Function	Projection
GABA	DMH	Promote sleep	VLPO [77]
GABA	TRN	Promote sleep	Unclear [78]
GABA	VTA	Induce NREM sleep, prevent hyperarousal	VTA, LH [79, 80]
GABA	MnPO	Induce NREM sleep, decrease REM sleep during active phase, increase sleep under sleep deprivation	VLPO, LH TMN, vlPAG, PBN, LC(but the function of these projections is unclear)
GABA	LH	Promote wakefulness	DR [81], TRN [82], VLPO [83]
GABA	VP	Promote wakefulness	
GABA	DR	Promote wakefulness	LH [81]
GABA	BF	Promote and inhibit wakefulness based on subpopulation	BF [84], VTA [85]
GABA	RMTg	Promote sleep	VTA, SNc [86]
GABA	POA	Promote sleep	TMN [87]
GABA	SCN	Promote sleep	PVN [88]
GABA	CPU	Promote sleep	GPe [89]
GABA	PZ	Promote sleep	PB [90]
GABA	NAc	promote sleep	VP [91]
GABA	OT	Promote sleep	VP, LH [92]
GABA	SNr	Promote sleep	VTA, LC, DR [93]
GABAergic	vlPAG	Promote sleep	LC, DR, VTA

2.9. Glutamate (Glut)

Glutamate is the most prevalent neurotransmitter in the brain and a major wake-promoting neurotransmitter. Most neurons from the brain reticular projection that promote wakefulness are glutamate neurons originating from VTA and LH, Glu projected to LHGlu to excite LHORE to generate wakefulness(however, LHGlu can also induce sleep-preparation behavior [94]), while glutamate from

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Medial septum further project to LHGlu to enhance the wake induction. Glutamate is also projected to BF, and NAc area from PVT, VTA, and parabrachial nucleus and promotes wakefulness. Also, glutamate from sleep-promoting areas such as MnPO can induce wakefulness, under stressful conditions, which might be mediated by the cortical releasing hormone. Even though most glutamate powerfully promotes and maintains wakefulness, exceptions do exist. The Glutamate from the posterior thalamus could promote sleep via projection to CeA. Glutamate also plays a pivotal role in thalamocortical projection, and is thought that not only the Glutamate enhance wakefulness in the cortex, but its activity also acts on the regulation of wakefulness and sleep.

Table 2. The origination, projection, and function of Glutamate that contribute to sleep regulation are reported in recent studies. The majority of Glutamate neurotransmitters promote wakefulness and reduce sleep, yet a study has also reported a subpopulation of glutamate can promote sleep.

Neurotransmitter	Origination	Function	Projection
Glutamate	Lateral hypothalamus	wake generation and maintenance	LH [10]
Glutamate	Medial septum	Wake generation by activating LH glutamatergic neurons	LH [10]
Glutamate	Parabrachial nucleus	Promote wakefulness	BF [84]
Glutamate	VTA	Maintain wakefulness	NAc, LH [79]
Glutamate	MnPO	Reduce sleep under stress	VLPO, LH TMN, vlPAG, PBN, LC
Glutamate	BF	Promote wakefulness	VTA [95]
Glutamate	PVT	Promote wakefulness	NAc [23]
Glutamate	PB	Promote wakefulness	BF, LH [96]
Glutamate	Brainstem reticular formation	Promote wakefulness	Various places in thalamus [97]

3. Other neurotransmitters

Besides the major commonly known neurotransmitters there are still numerous neurotransmitters that also mediate sleep/wake regulation. Here, some mostly studied neurotransmitters are listed.

3.1. Galanin

Galanin is usually an inhibitory neurotransmitter that mainly induces and consolidates sleep. It is commonly found in LPO and VLPO, and projects to many wake-promoting areas including LH, TMN, PPT, PB, LC, and vIPAG [77, 98]. Besides the sleep-promoting function, Galanin has a special role in sleep regulation: it generates sleep homeostasis in the preoptic area [99]. Galanin is selectively active during rebound sleep [100]. The lesion of the Galanin neuron and Galanin-mutant in the PO showed reduced sleep rebound after sleep deprivation compared to the control group in terms of delta power and sleep time [99, 100].

3.2. Corticotrophin

Corticotrophin-releasing factor(CRF) is known as a stress mediator, but it is also involved in sleep regulation [101]. Exogenous CRF increases wakefulness and reduces NREM sleep [102]. Similarly, CRF agonists also promote wakefulness and inhibit NREM sleep and REM sleep [103]. Also, under stressful conditions, CRF antagonists could diminish the stress response mediated by CRF, which ultimately prevents sleep loss [101]. CRF mediates sleep/wake regulation via stress-level signaling by projecting excitatory signals to LCNA and LHORE, which enhance wakefulness [104, 105].CRF could also project to sleep-promoting areas such as VLPO, MPO, and POA, and suppress GABAergic, sleep-promoting activity [106].

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3.3. Melanin-concentrating hormone(MCH)

Melanin-concentrating hormones are located in the lateral hypothalamus, in proximity to Orexin neurons, and are mainly inhibitory and sleep-promoting. MCH neurons are only active during sleep. Optogenetic activation on MCH neurons induces sleep and it becomes more expressed during recovery sleep [107, 108]. Due to the spatial overlapping, Melanin neuron often receives similar input as orexin neurons. However, they do mediate opposite effects by possibly expressing different types of receptors. For example, both MCH and Orexin neuron receives NE and Ach input, but they exhibit different responses via different receptors [109]. Besides inhibitory projection to wake-promoting areas such as TMN and MS, MCH also contributes to VLPO and promotes NREM sleep. However, the exact mechanism of MCH on VLPO remains unclear [108].

3.4. Cholecystokinin(CCK)

Cholecystokinin, CCK, is also a neurotransmitter that promotes NREM sleep [110]. CCK receptor-expressing neurons spread across the brain [111], but the exact mechanism of how CCK induces sleep is not fully understood. One current speculated circuit in which CCK mediates sleep-inducing function is via reciprocal activation between CALCA and CCK neuro, and they both in turn project to the hypothalamic preoptic area and excite the sleep-promoting neurons [112]. However, the sleep regulatory role of CCK might be more complex than the current knowledge. CCK can also activate orexin neurons, implication a potential wake-promoting role [113]. Furthermore, the action of CCK is known to be cell-type specific, suggesting that the widespread projection of CCK would exert heterogeneous actions [111].

3.5. Neurotensin(NT)

Neurotensin, NT, is commonly known for its importance in the peripheral nervous system that controls for instance gut mobility and blood pressure. Neurotensin can induce both wakefulness and sleep. A study reported that inhibitory NT from the amygdala projects to many wake-promoting areas to induce sleep, and retrograde tracing further revealed that these inhibitory NT are activated by the excitatory NT from the posterior thalamic region [114]. Excitatory neurotensin from vlPAG can also promote sleep by innervating GABAergic neurons from the medulla and these GABAergic neuron further inhibit monoamine groups from LC, VTA, and DR [93]. On the other hand, activation of NT from LH can generate wakefulness [115].

3.6. Somatostatin(SST)

Somatostatin, SST, expressed mainly in SOM+, is a GABAnergic neurotransmitter closely related to sleep. Activation of SOM+ neurons generates slow-wave activity during NREM sleep [116]. SST could also be a neurotransmitter reflection of the internal state of tiredness, Activation of SST from the prefrontal cortex initiates sleep and stimulates the SST projecting end in the lateral hypothalamus and lateral preoptic hypothalamus individually induced recovery sleep-like phenomenon and sleep-preparation behavior [117].VTA somatostatin neurons can also induce NREM and REM sleep after sensing social defeat stress by projection of LH and inhibiting the release of CRF [118].

3.7. Substance P(SP)

Substance P or SP mediates response to stress and pain and is widely distributed throughout the brain. Based on injection studies, SP could induce both sleep-promoting and sleep-inhibiting action based on different injection locations. Injection of SP into VLPO promotes sleep [119] and injection into the cortex enhances slow-wave activity [120]. However, SP is also reported to activate the histaminergic neurons in the TMN and thus promote wakefulness [121], and drug studies on people also shown that SP promote arousal [122]. Interestingly, SP level is found to be lower among people suffering with obstructive sleep apnea [123], but the exact mechanism is unclear.

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4. Conclusion

The regulation of sleep and wakefulness remains a perplexing question that requires large effort. There are numerous neurotransmitter which are involved and cooperatively constitute the intricate network of sleep and wakefulness, and understanding sleep from the perspective of neurotransmitters is essential not only for understanding sleep but also for the pharmaceutical and treatment of sleep abnormalities. There are still many questions regarding how different neurotransmitters remain unsolved, such as the opposing effects of 5HT and dopamine. Future studies on neurotransmitters related to sleep should investigate how spatial location and projection, receptor-subtypes, and projection-ending cell type of a neurotransmitter could exert various effect.

References

[1] Sulaman, B.A., et al., Neuro-orchestration of sleep and wakefulness. Nature Neuroscience, 2023. 26(2): p. 196-212.
[2] Venner, A., et al., A novel population of wake-promoting GABAergic neurons in the ventral lateral hypothalamus. Current Biology, 2016. 26(16): p. 2137-2143.
[3] Gallopin, T., et al., Identification of sleep-promoting neurons in vitro. Nature, 2000. 404(6781): p. 992-995.
[4] Rothhaas, R. and S. Chung, Role of the Preoptic Area in Sleep and Thermoregulation. Front Neurosci, 2021. 15: p. 664781.
[5] Dubourget, R., et al., Multiparametric characterization of neuronal subpopulations in the ventrolateral preoptic nucleus. Brain Struct Funct, 2017. 222(3): p. 1153-1167.
[6] Lee, M.G., et al., Sleep-wake related discharge properties of basal forebrain neurons recorded with micropipettes in head-fixed rats. J Neurophysiol, 2004. 92(2): p. 1182-98.
[7] Iyer, M., et al., Identification of discrete, intermingled hypocretin neuronal populations. J Comp Neurol, 2018. 526(18): p. 2937-2954.
[8] Siegel, J.M., The neurotransmitters of sleep. J Clin Psychiatry, 2004. 65 Suppl 16(Suppl 16): p. 4-7.
[9] Borbély, A.A., et al., The two-process model of sleep regulation: a reappraisal. J Sleep Res, 2016. 25(2): p. 131-43.
[10] An, S., et al., Medial septum glutamatergic neurons control wakefulness through a septo-hypothalamic circuit. Current Biology, 2021. 31(7): p. 1379-1392.e4.
[11] Siclari, F. and G. Tononi, Local aspects of sleep and wakefulness. Curr Opin Neurobiol, 2017. 44: p. 222-227.
[12] Nir, Y. and L. de Lecea, Sleep and vigilance states: Embracing spatiotemporal dynamics. Neuron, 2023. 111(13): p. 1998-2011.
[13] Han, Y., et al., Selective activation of cholinergic basal forebrain neurons induces immediate sleep-wake transitions. Current Biology, 2014. 24(6): p. 693-698.
[14] Ni, K.-M., et al., Selectively driving cholinergic fibers optically in the thalamic reticular nucleus promotes sleep. eLife, 2016. 5: p. e10382.
[15] Scammell, T.E., E. Arrigoni, and J.O. Lipton, Neural Circuitry of Wakefulness and Sleep. Neuron, 2017. 93(4): p. 747-765.
[16] Kroeger, D., et al., Cholinergic, Glutamatergic, and GABAergic Neurons of the Pedunculopontine Tegmental Nucleus Have Distinct Effects on Sleep/Wake Behavior in Mice. J Neurosci, 2017. 37(5): p. 1352-1366.
[17] Weng, F.J., et al., Carbachol excites sublaterodorsal nucleus neurons projecting to the spinal cord. The Journal of Physiology, 2014. 592(7): p. 1601-1617.
[18] Holmstrand, E.C. and S.R. Sesack, Projections from the rat pedunculopontine and laterodorsal tegmental nuclei to the anterior thalamus and ventral tegmental area arise from largely separate populations of neurons. Brain Structure and Function, 2011. 216(4): p. 331-345.

DOI: 10.54254/2753-8818/37/20240186

[19] Dasgupta, R., F. Seibt, and M. Beierlein, Synaptic Release of Acetylcholine Rapidly Suppresses Cortical Activity by Recruiting Muscarinic Receptors in Layer 4. J Neurosci, 2018. 38(23): p. 5338-5350.
[20] De Lecea, L., et al., The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. Proceedings of the National Academy of Sciences, 1998. 95(1): p. 322-327.
[21] Sakurai, T., et al., Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell, 1998. 92(4): p. 573-585.
[22] Saper, C.B., et al., Sleep state switching. Neuron, 2010. 68(6): p. 1023-42.
[23] Ren, S., et al., The paraventricular thalamus is a critical thalamic area for wakefulness. Science, 2018. 362(6413): p. 429-434.
[24] Eban-Rothschild, A., L. Appelbaum, and L. de Lecea, Neuronal Mechanisms for Sleep/Wake Regulation and Modulatory Drive. Neuropsychopharmacology, 2018. 43(5): p. 937-952.
[25] Ho, Y.C., et al., Activation of orexin 1 receptors in the periaqueductal gray of male rats leads to antinociception via retrograde endocannabinoid (2-arachidonoylglycerol)-induced disinhibition. J Neurosci, 2011. 31(41): p. 14600-10.
[26] De Luca, R., et al., Orexin neurons inhibit sleep to promote arousal. Nature Communications, 2022. 13(1): p. 4163.
[27] Yamanaka, A., et al., Orexin directly excites orexin neurons through the orexin 2 receptor. Journal of Neuroscience, 2010. 30(38): p. 12642-12652.
[28] Futatsuki, T., et al., Involvement of orexin neurons in fasting- and central adenosine-induced hypothermia. Scientific Reports, 2018. 8(1): p. 2717.
[29] Liu, Z.W., and X.B. Gao, Adenosine inhibits activity of hypocretin/orexin neurons by the A1 receptor in the lateral hypothalamus: a possible sleep-promoting effect. J Neurophysiol, 2007. 97(1): p. 837-48.
[30] Huang, Z.L., et al., Adenosine A2A, but not A1, receptors mediate the arousal effect of caffeine. Nat Neurosci, 2005. 8(7): p. 858-9.
[31] Li, Y., et al., The orexinergic system mediates the excitatory effects of caffeine on arousal and sympathetic activity. Heliyon, 2023. 9(3): p. e14170.
[32] Mahler, S.V., et al., Motivational activation: a unifying hypothesis of orexin/hypocretin function. Nature Neuroscience, 2014. 17(10): p. 1298-1303.
[33] Dube, M.G., S.P. Kalra, and P.S. Kalra, Food intake elicited by central administration of orexins/hypocretins: identification of hypothalamic sites of action. Brain research, 1999. 842(2): p. 473-477.
[34] Johnson, P.L., et al., A key role for orexin in panic anxiety. Nature Medicine, 2010. 16(1): p. 111-115.
[35] Brundin, L., et al., Reduced orexin levels in the cerebrospinal fluid of suicidal patients with major depressive disorder. European Neuropsychopharmacology, 2007. 17(9): p. 573-579.
[36] Sun, N., et al., Design of fast-onset antidepressant by dissociating SERT from nNOS in the DRN. Science, 2022. 378(6618): p. 390-398.
[37] Idzikowski, C., F.J. Mills, and R. Glennard, 5-Hydroxytryptamine-2 antagonist increases human slow wave sleep. Brain Research, 1986. 378(1): p. 164-168.
[38] Dugovic, C. and A. Wauquier, 5-HT2 receptors could be primarily involved in the regulation of slow-wave sleep in the rat. European Journal of Pharmacology, 1987. 137(1): p. 145-146.
[39] Monti, J.M. and H. Jantos, Dose-dependent effects of the 5-HT1A receptor agonist 8-OH-DPAT on sleep and wakefulness in the rat. J Sleep Res, 1992. 1(3): p. 169-175.
[40] Portas, C.M., et al., Microdialysis perfusion of 8-hydroxy-2-(di-n-propyl amino)tetralin (8-OH-DPAT) in the dorsal raphe nucleus decreases serotonin release and increases rapid eye movement sleep in the freely moving cat. J Neurosci, 1996. 16(8): p. 2820-8.
[41] Boutrel, B., et al., Involvement of 5-HT_{1A} Receptors in Homeostatic and Stress-Induced Adaptive Regulations of Paradoxical Sleep: Studies in 5-HT_{1A} Knock-Out Mice. The Journal of Neuroscience, 2002. 22(11): p. 4686-4692.

DOI: 10.54254/2753-8818/37/20240186

[42] Boutrel, B., et al., Key Role of 5-HT_{1B} Receptors in the Regulation of Paradoxical Sleep as Evidenced in 5-HT_{1B} Knock-Out Mice. The Journal of Neuroscience, 1999. 19(8): p. 3204-3212.
[43] Oikonomou, G., et al., The Serotonergic Raphe Promote Sleep in Zebrafish and Mice. Neuron, 2019. 103(4): p. 686-701.e8.
[44] Gallopin, T., et al., The endogenous somnogen adenosine excites a subset of sleep-promoting neurons via A2A receptors in the ventrolateral preoptic nucleus. Neuroscience, 2005. 134(4): p. 1377-90.
[45] Rancillac, A., Serotonin and sleep-promoting neurons. Oncotarget, 2016. 7(48): p. 78222-78223.
[46] Bouhuys, A.L. and R.H. Van Den Hoofdakker, Effects of midbrain raphe destruction on sleep and locomotor activity in rats. Physiol Behav, 1977. 19(4): p. 535-41.
[47] Vaseghi, S., et al., Modulating role of serotonergic signaling in sleep and memory. Pharmacological Reports, 2022. 74(1): p. 1-26.
[48] Haas, H.L., O.A. Sergeeva, and O. Selbach, Histamine in the nervous system. Physiol Rev, 2008. 88(3): p. 1183-241.
[49] Scammell, T.E., et al., Histamine: neural circuits and new medications. Sleep, 2018. 42(1).
[50] Williams, R.H., et al., Optogenetic-mediated release of histamine reveals distal and autoregulatory mechanisms for controlling arousal. J Neurosci, 2014. 34(17): p. 6023-9.
[51] Tritsch, N.X., J.B. Ding, and B.L. Sabatini, Dopaminergic neurons inhibit striatal output through non-canonical release of GABA. Nature, 2012. 490(7419): p. 262-6.
[52] Tritsch, N.X., A.J. Granger, and B.L. Sabatini, Mechanisms and functions of GABA co-release. Nature Reviews Neuroscience, 2016. 17(3): p. 139-145.
[53] Yu, X., et al., Wakefulness Is Governed by GABA and Histamine Cotransmission. Neuron, 2015. 87(1): p. 164-78.
[54] Venner, A., et al., Reassessing the Role of Histaminergic Tuberomammillary Neurons in Arousal Control. The Journal of Neuroscience, 2019. 39(45): p. 8929-8939.
[55] Katoh, Y., et al., Histamine production by cultured microglial cells of the mouse. Neurosci Lett, 2001. 305(3): p. 181-4.
[56] Martres, M.P., M. Baudry, and J.C. Schwartz, Histamine synthesis in the developing rat brain: evidence for a multiple compartmentation. Brain Res, 1975. 83(2): p. 261-75.
[57] Chikahisa, S., et al., Histamine from brain resident MAST cells promotes wakefulness and modulates behavioral states. PLoS One, 2013. 8(10): p. e78434.
[58] Chikahisa, S., et al., Mast cell involvement in glucose tolerance impairment caused by chronic mild stress with sleep disturbance. Sci Rep, 2017. 7(1): p. 13640.
[59] Haas, H.L., O.A. Sergeeva, and O. Selbach, Histamine in the Nervous System. Physiological Reviews, 2008. 88(3): p. 1183-1241.
[60] Wisor, J.P., et al., Dopaminergic role in stimulant-induced wakefulness. J Neurosci, 2001. 21(5): p. 1787-94.
[61] Monti, J.M., et al., Biphasic effects of dopamine D-2 receptor agonists on sleep and wakefulness in the rat. Psychopharmacology (Berl), 1988. 95(3): p. 395-400.
[62] España, R.A. and T.E. Scammell, Sleep neurobiology from a clinical perspective. Sleep, 2011. 34(7): p. 845-58.
[63] Eban-Rothschild, A., et al., VTA dopaminergic neurons regulate ethologically relevant sleep–wake behaviors. Nature Neuroscience, 2016. 19(10): p. 1356-1366.
[64] Oishi, Y., et al., Slow-wave sleep is controlled by a subset of nucleus accumbens core neurons in mice. Nature Communications, 2017. 8.
[65] Luo, Y.-J., et al., Nucleus accumbens controls wakefulness by a subpopulation of neurons expressing dopamine D1 receptors. Nature Communications, 2018. 9(1): p. 1576.
[66] Qiu, M.-H., et al., Nigrostriatal and mesolimbic control of sleep–wake behavior in rat. Brain Structure and Function, 2019. 224(7): p. 2525-2535.

DOI: 10.54254/2753-8818/37/20240186

[67] Cho, J.R., et al., Dorsal Raphe Dopamine Neurons Modulate Arousal and Promote Wakefulness by Salient Stimuli. Neuron, 2017. 94(6): p. 1205-1219.e8.
[68] Korshunov, K.S., L.J. Blakemore, and P.Q. Trombley, Dopamine: A Modulator of Circadian Rhythms in the Central Nervous System. Front Cell Neurosci, 2017. 11: p. 91.
[69] Becker-Krail, D.D., W.H. Walker, 2nd, and R.J. Nelson, The Ventral Tegmental Area and Nucleus Accumbens as Circadian Oscillators: Implications for Drug Abuse and Substance Use Disorders. Front Physiol, 2022. 13: p. 886704.
[70] Singh, C., G. Oikonomou, and D.A. Prober, Norepinephrine is required to promote wakefulness and for hypocretin-induced arousal in zebrafish. eLife, 2015. 4: p. e07000.
[71] Aston-Jones, G. and F. Bloom, Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. The Journal of Neuroscience, 1981. 1(8): p. 876-886.
[72] Antila, H., et al., A noradrenergic-hypothalamic neural substrate for stress-induced sleep disturbances. Proc Natl Acad Sci U S A, 2022. 119(45): p. e2123528119.
[73] Holland, N., T.W. Robbins, and J.B. Rowe, The role of noradrenaline in cognition and cognitive disorders. Brain, 2021. 144(8): p. 2243-2256.
[74] Osorio-Forero, A., et al., Noradrenergic circuit control of non-REM sleep substates. Curr Biol, 2021. 31(22): p. 5009-5023.e7.
[75] Gottesmann, C., GABA mechanisms and sleep. Neuroscience, 2002. 111(2): p. 231-9.
[76] Li, Y.-D., et al., Ventral pallidal GABAergic neurons control wakefulness associated with motivation through the ventral tegmental pathway. Molecular Psychiatry, 2021. 26(7): p. 2912-2928.
[77] Chen, K.S., et al., A Hypothalamic Switch for REM and Non-REM Sleep. Neuron, 2018. 97(5): p. 1168-1176.e4.
[78] Ni, K.M., et al., Selectively driving cholinergic fibers optically in the thalamic reticular nucleus promotes sleep. Elife, 2016. 5.
[79] Yu, X., et al., GABA and glutamate neurons in the VTA regulate sleep and wakefulness. Nat Neurosci, 2019. 22(1): p. 106-119.
[80] Yu, X., et al., Dysfunction of ventral tegmental area GABA neurons causes mania-like behavior. Mol Psychiatry, 2021. 26(9): p. 5213-5228.
[81] Gazea, M., et al., Reciprocal Lateral Hypothalamic and Raphe GABAergic Projections Promote Wakefulness. J Neurosci, 2021. 41(22): p. 4840-4849.
[82] Herrera, C.G., et al., Hypothalamic feedforward inhibition of thalamocortical network controls arousal and consciousness. Nat Neurosci, 2016. 19(2): p. 290-8.
[83] Venner, A., et al., An Inhibitory Lateral Hypothalamic-Preoptic Circuit Mediates Rapid Arousals from Sleep. Current Biology, 2019. 29(24): p. 4155-4168.e5.
[84] Xu, M., et al., Basal forebrain circuit for sleep-wake control. Nature Neuroscience, 2015. 18(11): p. 1641-1647.
[85] Li, Y.D., et al., Ventral pallidal GABAergic neurons control wakefulness associated with motivation through the ventral tegmental pathway. Mol Psychiatry, 2021. 26(7): p. 2912-2928.
[86] Yang, S.R., et al., The rostromedial tegmental nucleus is essential for non-rapid eye movement sleep. PLoS Biol, 2018. 16(4): p. e2002909.
[87] Chung, S., et al., Identification of preoptic sleep neurons using retrograde labelling and gene profiling. Nature, 2017. 545(7655): p. 477-481.
[88] Ono, D., et al., The mammalian circadian pacemaker regulates wakefulness via CRF neurons in the paraventricular nucleus of the hypothalamus. Sci Adv, 2020. 6(45).
[89] Yuan, X.-S., et al., Striatal adenosine A2A receptor neurons control active-period sleep via parvalbumin neurons in external globus pallidus. eLife, 2017. 6: p. e29055.
[90] Anaclet, C., et al., The GABAergic parafacial zone is a medullary slow wave sleep–promoting center. Nature Neuroscience, 2014. 17(9): p. 1217-1224.

DOI: 10.54254/2753-8818/37/20240186

[91] Oishi, Y., et al., Slow-wave sleep is controlled by a subset of nucleus accumbens core neurons in mice. Nature Communications, 2017. 8(1): p. 734.
[92] Li, R., et al., Activation of adenosine A2A receptors in the olfactory tubercle promotes sleep in rodents. Neuropharmacology, 2020. 168: p. 107923.
[93] Zhong, P., et al., Control of Non-REM Sleep by Midbrain Neurotensinergic Neurons. Neuron, 2019. 104(4): p. 795-809.e6.
[94] Sotelo, M.I., et al., Lateral hypothalamic neuronal ensembles regulate pre-sleep nest-building behavior. Curr Biol, 2022. 32(4): p. 806-822.e7.
[95] Cai, P., et al., A glutamatergic basal forebrain to midbrain circuit mediates wakefulness and defensive behavior. Neuropharmacology, 2022. 208: p. 108979.
[96] Xu, Q., et al., Medial Parabrachial Nucleus Is Essential in Controlling Wakefulness in Rats. Front Neurosci, 2021. 15: p. 645877.
[97] Steriade, M., et al., Projections of cholinergic and non-cholinergic neurons of the brainstem core to relay and associational thalamic nuclei in the cat and macaque monkey. Neuroscience, 1988. 25(1): p. 47-67.
[98] Kroeger, D., et al., Galanin neurons in the ventrolateral preoptic area promote sleep and heat loss in mice. Nature Communications, 2018. 9.
[99] Ma, Y., et al., Galanin Neurons Unite Sleep Homeostasis and α2-Adrenergic Sedation. Curr Biol, 2019. 29(19): p. 3315-3322.e3.
[100] Reichert, S., O. Pavón Arocas, and J. Rihel, The Neuropeptide Galanin Is Required for Homeostatic Rebound Sleep following Increased Neuronal Activity. Neuron, 2019. 104(2): p. 370-384.e5.
[101] Chang, F.-C. and M.R. Opp, Role of corticotropin-releasing hormone in stressor-induced alterations of sleep in rat. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 2002. 283(2): p. R400-R407.
[102] BORN, J., et al., Influences of Corticotropin-Releasing Hormone, Adrenocorticotropin, and Cortisol on Sleep in Normal Man*. The Journal of Clinical Endocrinology & Metabolism, 1989. 68(5): p. 904-911.
[103] Chang, F.-C. and M.R. Opp, Corticotropin-releasing hormone (CRH) as a regulator of waking. Neuroscience & Biobehavioral Reviews, 2001. 25(5): p. 445-453.
[104] Winsky-Sommerer, R., et al., Interaction between the Corticotropin-Releasing Factor System and Hypocretins (Orexins): A Novel Circuit Mediating Stress Response. The Journal of Neuroscience, 2004. 24(50): p. 11439-11448.
[105] Lu, A., et al., Conditional CRH overexpressing mice: an animal model for stress-elicited pathologies and treatments that target the central CRH system. Molecular Psychiatry, 2008. 13(11): p. 989-989.
[106] Gvilia, I., et al., Suppression of preoptic sleep-regulatory neuronal activity during corticotropin-releasing factor-induced sleep disturbance. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 2015. 309(9): p. R1092-R1100.
[107] Verret, L., et al., A role of melanin-concentrating hormone producing neurons in the central regulation of paradoxical sleep. BMC Neuroscience, 2003. 4(1): p. 19.
[108] Jego, S. and A. Adamantidis, MCH Neurons: Vigilant Workers in the Night. Sleep, 2013. 36(12): p. 1783-1786.
[109] Bayer, L., et al., Opposite effects of noradrenaline and acetylcholine upon hypocretin/orexin versus melanin concentrating hormone neurons in rat hypothalamic slices. Neuroscience, 2005. 130(4): p. 807-11.
[110] Kapás, L., et al., Cholecystokinin promotes sleep and reduces food intake in diabetic rats. Physiol Behav, 1991. 50(2): p. 417-20.
[111] Lee, S.Y. and I. Soltesz, Cholecystokinin: a multi-functional molecular switch of neuronal circuits. Dev Neurobiol, 2011. 71(1): p. 83-91.

DOI: 10.54254/2753-8818/37/20240186

[112] Zhang, Z., et al., An Excitatory Circuit in the Perioculomotor Midbrain for Non-REM Sleep Control. Cell, 2019. 177(5): p. 1293-1307.e16.
[113] Tsujino, N., et al., Cholecystokinin activates orexin/hypocretin neurons through the cholecystokinin A receptor. J Neurosci, 2005. 25(32): p. 7459-69.
[114] Ma, C., et al., Sleep Regulation by Neurotensinergic Neurons in a Thalamo-Amygdala Circuit. Neuron, 2019. 103(2): p. 323-334.e7.
[115] Naganuma, F., et al., Lateral hypothalamic neurotensin neurons promote arousal and Funk, C.M., et al., Role of Somatostatin-Positive Cortical Interneurons in the Generation of Sleep Slow Waves. J Neurosci, 2017. 37(38): p. 9132-9148.
[116] Tossell, K., et al., Somatostatin neurons in prefrontal cortex initiate sleep-preparatory behavior and sleep via the preoptic and lateral hypothalamus. Nat Neurosci, 2023. 26(10): p. 1805-1819.
[117] Yu, X., et al., A specific circuit in the midbrain detects stress and induces restorative sleep. Science, 2022. 377(6601): p. 63-72.
[118] Zielinski, M.R., et al., Substance P and the neurokinin-1 receptor regulate electroencephalogram non-rapid eye movement sleep slow-wave activity locally. Neuroscience, 2015. 284: p. 260-272.
[119] Zielinski, M.R. and D. Gerashchenko, Sleep-inducing effect of substance P-cholera toxin A subunit in mice. Neuroscience Letters, 2017. 659: p. 44-47.
[120] Sergeeva, O.A., et al., Tachykinins amplify the action of capsaicin on central histaminergic neurons. Peptides, 2022. 150: p. 170729.
[121] Lieb, K., et al., Effects of the Neuropeptide Substance P on Sleep, Mood, and Neuroendocrine Measures in Healthy Young Men. Neuropsychopharmacology, 2002. 27(6): p. 1041-1049.
[122] Ursavas, A., Upregulating substance P levels to treat obstructive sleep apnea. Expert Opinion on Therapeutic Targets, 2008. 12(5): p. 583-588.