Sleep and sleep disorders

A practical handbook

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Part I

Basic aspects of waking and sleeping

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Neurobiology of sleep and waking

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1.1 INTRODUCTION

The discovery of orexins (hypothalamic peptides), the causes of narcolepsy, and the fact that a substance like modafinil can strongly influence wakefulness, has led to quite a new number of insights at the beginning of this century about which brain structures and mechanisms are involved in sleep-wake regulation. There was already extensive knowledge about nuclei in the brainstem, their neurotransmitters and their projections, but the picture is now fuller because the role of these structures in the hypothalamus and the basal forebrain has been identified. Much of this knowledge can be attributed to the lab work of Cliff Saper (Saper et al., 2017). Thanks to recent technological developments such as optogenetic and chemogenetic technologies, photostimulation and inhibition, our knowledge about the neurobiology of sleep and waking has taken another important step forward (see Tyree & de Lecea, 2017 as an example of application of these technologies).

Given that the sleep-wake mechanism is under the control of homeostatic as well as circadian processes, in this chapter we will consecutively discuss the neuroanatomy and the neurochemistry of wakefulness and sleep, their mutual relationship and, lastly, the interaction with the circadian timing system (for circadian rhythms, see Chapter 2).

1.2 NEURONAL CONTROL OF WAKEFULNESS

In 1930, von Economo described the lesions in the midbrain and the posterior hypothalamus for patients with lethargic encephalitis (von Economo, 1930). In the final stage some patients slept up to 24 hours a day. In 1935, Bremer described the 'isolated encephalon' and the 'isolated brain'. Isolated encephalon referred to a preparation in which a full cross-section is made in a cat above the brainstem (at the level of the mesencephalon), causing the animal to enter a state that resembled sleep. In addition to the hypothalamus, the brainstem was a target for research into neuronal control of wakefulness. In 1949, Moruzzi and Magoun described this zone as the 'ascending reticular activating system' (ARAS) because electrical stimulation of the reticular brainstem resulted in prolonged wakefulness. Sleep was also seen as a 'passive' condition when there was no exciting transmission to the cortex. The various components of this ascending system were identified shortly afterwards. Centres were also discovered that were located outside the brainstem, which is why 'reticular' was removed from the term 'ARAS' and it is now referred to as an 'ascending activating system' (AAS). This is a network of nuclei that all contribute to wakefulness and give positive and negative feedback to each other. Wakefulness-promoting ascending pathways split at the level of the midbrain in a dorsal pathway to the thalamus (Gent et al. 2018) and a ventral pathway that goes to the hypothalamus, the basal forebrain and the cortex. The latter is important for the behavioural aspects of the waking state (Scammell et al., 2017) (figure 1.1).

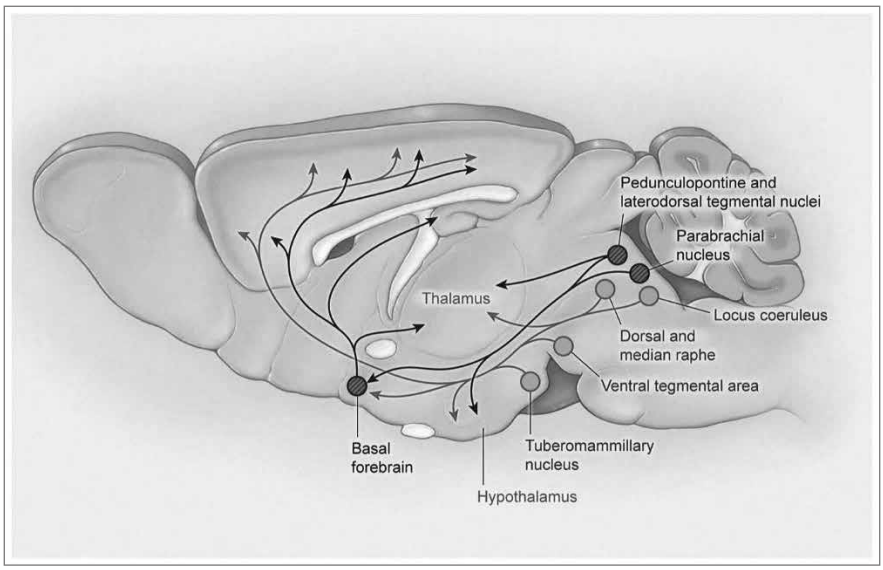

Figure 1.1. Centres and projections involved in the waking state (Scammell et al., 2017).

1.2.1 Cholinergic transmission

From the pons, especially the pedunculopontine (PPT) and laterodorsal tegmental nuclei (LDT), there is a cholinergic exciting transmission to the thalamus and the thalamocortical connections (Luppi et al., 2018). From the basal forebrain, the basal nucleus of Meynert, there is an excitative projection to the thalamus but primarily to the entire cortex. Electrical stimulation in these nuclei causes activation and cortical desynchronisation (Boucetta et al., 2014). It disappears during non-REM sleep.

Moreover, the excitation is enhanced by cortical disinhibition during wakefulness caused by a group of GABA-producing neurons in the aforementioned basal forebrain (Anaclet et al., 2015).

1.2.2 Monoaminergic transmission

The locus coeruleus, a group of dark-coloured neurons located rostrally at the bottom of the fourth ventricle, secretes noradrenaline. Adrenergic agonists cause wakefulness (Takahashi et al., 2010).

The medial and dorsal raphe nuclei, a group of nuclei along the midline of the pons and the medulla, secrete serotonin (Jacobs et al., 1999).

A group of neurons in the ventral region around the aqueduct of Sylvius (vPAG) and the ventral-tegmental area (VTA) has dopamine as neurotransmitter and is selectively active (with external stimuli) during the waking state (Cho et al., 2017).

Axons project from the tuberomammillary nucleus (lateroposterior hypothalamus), releasing histamine to the cortex and thereby becoming part of the AAS (Williams et al., 2014). Antihistamines lower wakefulness.

Monoaminergic activity is very limited during non-REM sleep and entirely absent during REM sleep (Luppi et al., 2018).

1.2.3 Orexins

Lastly, there is involvement of neurons in the lateral hypothalamus that produce orexin A and B (also called hypocretin 1 and 2) (Richter et al., 2014). The lateral hypothalamus additionally produces the sleep-involved melanin-concentrating hormone (MCH), and these two centres with their specific neurotransmitters also influence each other via negative and positive feedback systems (Ono et al., 2018).

Orexin-producing neurons are very active during wakefulness and increase the activity of neurons in the raphe nucleus, the tuberomammillary nuclei and the locus coeruleus (Luppi et al., 2018). There is also a co-release of glutamate (figure 1.2).

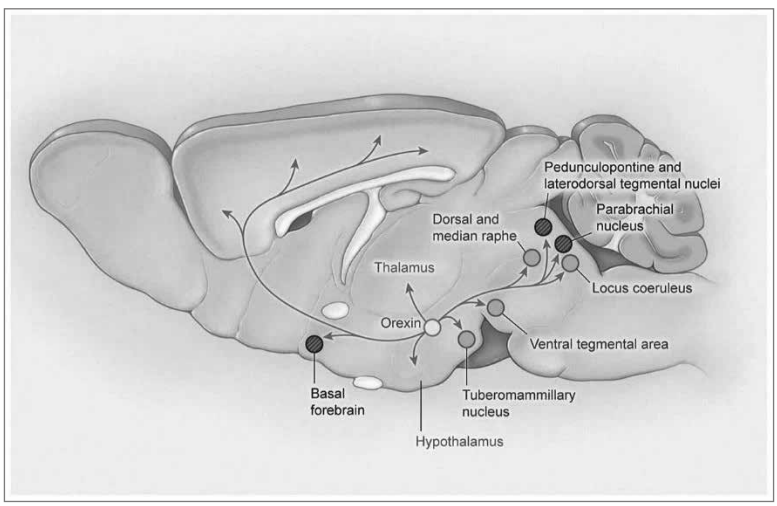

Figure 1.2. Orexin projections (Scammell et al., 2017).

Loss of hypocretin-producing neurons – or hypocretin receptors – causes a very unstable waking state (Branch et al., 2016). It results in narcolepsy, characterised by sleep attacks, among other things.

1.3 NEURONAL CONTROL OF THE SLEEP STATE

Neurons in the preoptic area have an inhibiting effect on the wakefulness-related nuclei discussed above. Two groups of neurons are involved in this process: one located in the ventrolateral (VLPO) and another in the medial (MnPO) area (figure 1.3) (Saper & Fuller, 2017). Increase of their activity promotes sleep, whereas when they are switched off it leads to sleeplessness. These axons secrete first the inhibiting neurotransmitter gamma aminobutiric acid (GABA) and then galanin (Kroeger et al., 2018). The neurons are active during and just before the start of non-REM sleep, not very active during REM sleep, and inactive during wakefulness.

The two discussed systems that steer wakefulness and sleep are obviously not active simultaneously, and under normal circumstances display mutual inhibition. In other words, when the sleep system is active, it inhibits the wakefulness system so that there is a stable sleep state. The opposite happens when the wakefulness system is active (Williams et al., 2014). That system is stabilised by hypocretin from the orexin-secreting neurons from the lateral hypothalamus. In this context the 'flip-flop' model has been posited, in which we thus can switch between stages without many intermediate states (Saper et al., 2010). The orexin-secreting neurons from the lateral hypothalamus would then be the guardians of the proposed flip-flop model (Saper & Fuller, 2017).

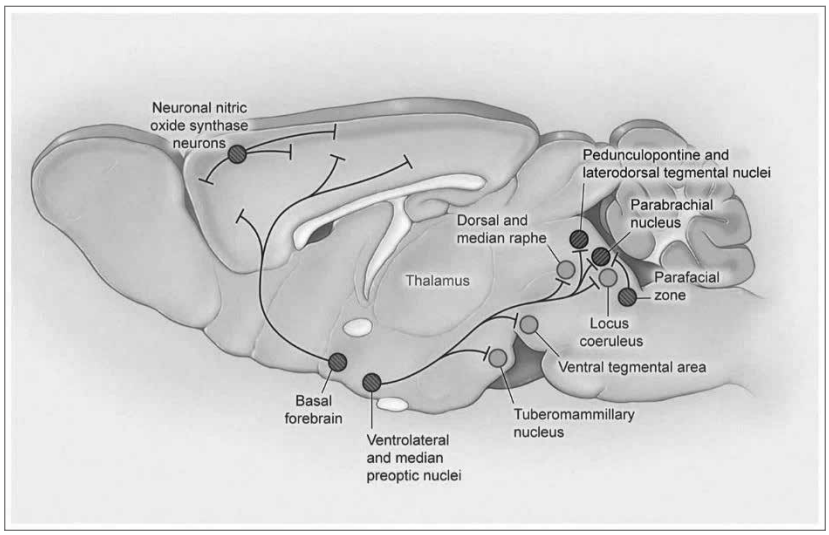

Figure 1.3. Centres and projections involved in non-REM sleep (Scammell et al., 2017).

1.4 NEURONAL CONTROL OF NREM/REM SLEEP

Alternation of NREM/REM sleep follows an ultradian cycle of 90 to 100 minutes, and the neurobiology of REM sleep at the time of writing remains a complex topic – but here, too, there is a 'flip-flop switch', as we keep switching quite abruptly from one state to another (Hericé et al., 2018). Reciprocal interactions between monoaminergic and GABAergic REM-OFF neurons, on the one hand, and cholinergic and glutaminergic REM-ON neurons in the pontine peduncle and laterodorsal tegmental nuclei, on the other, ensure a stable switching system (Fuller et al., 2007; McCarley, 2007; Van Dort et al., 2015).

The sublaterodorsal tegmental nucleus (SLD) of the pons is involved in the muscular atonia that characterises REM sleep. This nucleusis glutaminergic and is inhibited by GABA during NREM sleep. The absence of this GABAergic inhibition on REM-OFF cells (in the ventrolateral periaqueductal grey (vlPAG) and the lateral pontine tegmentum (LPT)) ends up causing REM sleep. There is a reciprocal interaction between GABAergic REM-ON and REM-OFF neurons. GABAergic transmission thus appears to play an important role and have multiple functions in sleep-wake regulation (Luppi et al., 2017) (figure 1.4).

Little is known about the oscillator that steers REM/NREM alternation (and ultradian rhythm) – for example, it could be an intrinsic property of the network of the involved nuclei (vlPAG+LPT and SLD) (Lu et al., 2006; Weber et al., 2015).

As mentioned above, melanin-concentrating hormone (MCH) also plays a role in REM sleep, given that the MCH-secreting neurons in the lateral hypothalamus are very active during REM sleep (through stimulation of the SLD) and less active during non-REM sleep (Tsunematsu et al., 2014).

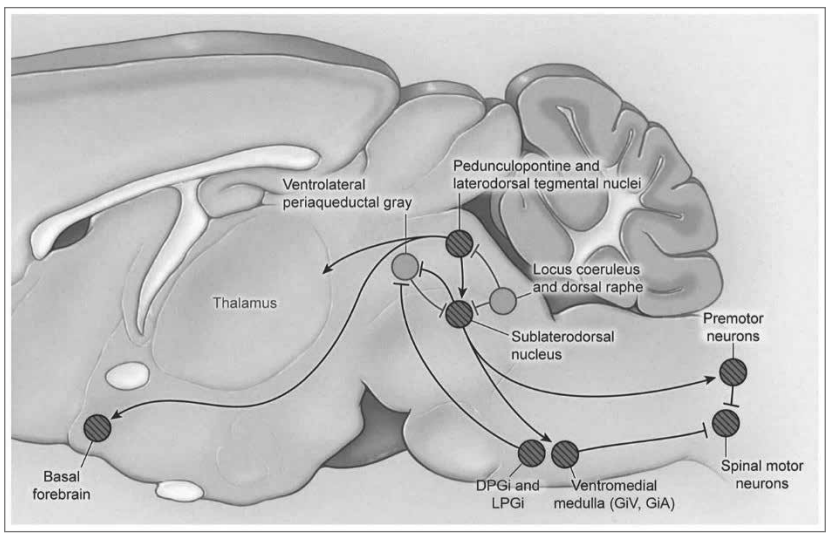

Figure 1.4. Centres and projections involved in REM sleep (Scammell et al., 2017).