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Sleep-wake control and the thalamus

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Sleep is an essential component of animal behavior, controlled by both circadian and homeostatic processes. Typical brain oscillations for sleep and wake states are distinctive and reflect recurrent activity amongst neural circuits spanning localized to global brain regions. Since the original discovery of hypothalamic centers controlling both sleep and wakefulness, current views now implicate networks of neuronal and non-neuronal cells distributed brain-wide. Yet the mechanisms of sleep-wake control remain unclear. In light of recent studies, here we review experimental evidence from lesional, correlational, pharmacological and genetics studies, which support a role for the thalamus in several aspects of sleep-wake states. How these thalamo-cortical network mechanisms contribute to other executive functions such as memory consolidation and cognition, remains an open question with direct implications for neuro-psychiatric diseases and stands as a future challenge for basic science and healthcare research.

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Introduction

Sleep is a primary and essential biological need for higher and lower vertebrates, yet the mechanisms and function of sleep remains a mystery. Sleep-wake states result from a complex interaction of wake-, non-rapid eye movement-(NREM) and rapid eye movement- (REM) sleep-promoting neuronal ensembles and are influenced by environmental and internal signals including, light, temperature, ecological niches, hormones, metabolic factors and neurotransmitters, respectively [1]. Neurons implicated in sleep-wake control are heterogenous in nature and broadly distributed across the brain with no obvious anatomical connectivity diagram in comparison to the laminar structures of the hippocampus or cerebellum. Nevertheless, several experimental-based models of the sleep-wake cycle exist. The hypothalamus-brainstem mutual inhibition hypothesizes that wake- and sleep-promoting circuits suppress each other's activity, to settle the behavioral state into either sleep or wakefulness [2•]. The reciprocal interaction model states that switching between NREM and REM sleep is controlled by interaction of cholinergic and aminergic cells in the brainstem [3]. The thalamo-cortical reverberation model posits that vigilance state is determined by the firing patterns of thalamocortical networks. Tonic firing promotes wakefulness and burst firing promotes sleep [4]. Together, these reflect both the chronological history and technological advances of investigation of the mechanisms of sleep.

Evidence now implicates sleep in memory consolidation, brain clearance, brain plasticity and energy conservation [5]. Accordingly, mild disturbances of global sleep architecture or local sleep oscillations have dramatic consequences on behavioral state/arousal instability (e.g. narcolepsy, insomnia), endocrine and metabolic homeostasis, as well as mood and cognitive performance [6,7]. At the same time, subtle changes of network oscillations during sleep are increasingly recognized as being associated with early stages of neurological (e.g. Alzheimer & Parkinson diseases) and neuropsychiatric (e.g. major depression, schizophrenia) disorders [8–10]. Thus, a better understanding of the neural substrates of the sleep-wake states, and altered states of consciousness, in the mammalian brain is currently one of the most important endeavours in neuroscience.

Current view: milestones and limitations

Numerous approaches have been employed to study sleep wake circuitry in the last 150 years. Early work started with clinical observations of patients with sleep-wake disorders, although patient populations were small and lesions often covered different anatomical areas. Trömner was amongst the first (in 1912 and 1928; [11]), to suggest that the thalamus plays a key-role in sleep-wake regulation, based on the direct projections of the thalamus to large areas rather than the indirect connections derived from the midbrain and lower centers of the brain. He also proposed a duality (inhibition–excitation) of thalamic influences. Exactly a century ago, original lesioning studies [11,12] revealed a single locus in the

lateral hypothalamus for sleep-wake control that was soon extended to a sleep-promoting role of the anterior hypothalamus and arousal centers in the lateral hypothalamus. Subsequent post-mortem studies of patients with traumatic brain injury identified lesions in the hypothalamus and brainstem closely correlated with disorders of sleep and arousal [13]. The first experimental demonstration of a central role for the thalamus in sleep came from Hess in the 1940s. In these studies, electrical stimulation of the thalamic region lateral to the massa intermedia induced sleep in cats. Subsequent studies suggested that the substrate for this effect was the midline thalamus [14], although the actual site of stimulation remains unclear.

These findings were refined by experimental lesions in animals using electric and chemical techniques. However, whilst anatomical accuracy was improved, such lesions could not discriminate between the contributions of different cell types. A further refinement came from injection of local pharmacological agents in the brain to target specific receptors, particularly GABA and NMDA receptors, however in many cases, non-quantifiable diffusion of drugs through brain tissue resulted in loss of anatomical accuracy. The advent of genetic knock-in and knock-out animal models were successful in identifying molecular determinants of sleep-wake control, in particular monoaminergic receptors and calcium channels. However, some of these mutations were fatal, preventing investigation and the others lacked anatomical accuracy as they were present in all cells. Additionally, the chronic and global nature of the mutations allowed for compensation mechanisms which masked potential contributions and often prevented anatomical localizations of the effects. More recently, such genetic techniques (e.g. optogenetics) allow anatomical localization and cell-type specificity to be combined with high temporal resolution and have been highly informative on the contribution of sleep-wake circuits in the healthy brain. However, the resulting behavioral changes are assumed to reflect the underling activity of the affected networks rather than those of downstream targets, demonstrating a need to investigate the extended network rather than a single locus [15].

Whilst this original finding of a single control hub for sleep-wake control would appear to be an attractive proposal, so far, no models fully replicate all the facets of sleep-wake control in mammals suggesting a complex and multi-centered control mechanism. At the onset of sleep monoaminergic wake activating neurons in both brainstem and hypothalamus [16•,17••,18–21] are inhibited *en masse* by anatomically-projecting sleep neurons, giving rise to the 'flip-flop' model [2•,3]. Interestingly, lesions of the main arousal centers did not increase sleep, but rather lead to a dramatic sleep fragmentation [2•,22–24], indicating that additional circuits, as well as precise temporal coordination of their activities, are required for stable sleep-wake patterns. This is further evidenced by the heterogenous regional changes in brain activity that occur at sleep onset [25,26,27••,28•,29], suggesting a wide distribution of sleep-wake networks throughout the brain.

On the other hand, sleep promoting cell groups have been identified, which include small ensembles of inhibitory (GABA- and galanin-ergic) neurons in the hypothalamus [2•,30,31••,32], brainstem [33–37] and nucleus accumbens [38]. Interestingly, these share common connectivity with modulatory circuits of the brain (dopamine, noradrenaline, histamine, etc.) and make synaptic contact with multiple downstream targets, some of which have been investigated while most of them are yet to be identified. Interestingly, these identified neurons are also tied to homeostatic control (e.g. temperature regulation), raising the possibility of the existence of either a subpopulation of purely sleep-promoting neurons or dual-function abilities for each cell group. Other recent works have characterized inhibitory cells of the parafacial zone of the brainstem as promoting NREM sleep [33] by inhibition of basal forebrain projecting parabrachial neurons. Accordingly, lesions of these neurons increases wakefulness at the expense of NREM [34]. Whilst this is an important finding, NREM was not abolished suggesting that there are other sleep promoting circuits which can compensate.

Whilst lesioning studies have been informative on regional neuronal ensembles with strong contributions to sleep-wake control, no study has demonstrated that a single sleep circuit is overwhelmingly necessary since compensatory mechanisms exist to assume control in their absence. Such compensation would support the evolutionary conserved vital function of sleep and involve heterogenic brain-wide circuitries, until a certain point where, for example, very large lesions of the ventrolateral preoptic nucleus result in fatal insomnia [12,39]. In this context, the role of the thalamus in sleep control has remained controversial.

A role for the thalamus in sleep-wake control

The thalamus (from the Greek: θάλαμος meaning nuptial suite see ref: [40]) resides in the midbrain and is composed of two symmetrical halves. The thalamus is the largest part of the diencephalon in mammals. It is composed of a collection of distinct nuclei that predominantly project to the cortex in a highly organized fashion, as well as other subcortical structures including the striatum, amygdala and hippocampus (Figure 1). In turn, thalamic structures receive important inputs from sub-cortical nuclei, including the lateral hypothalamus, brainstem, amygdala. As a general rule, thalamic nuclei project to one or more well-defined area(s) of the cortex — or send diffuse projections (non-specific), though this has been recently revisited (see below). Classical views of thalamic inputs to the cortex during sleep focused on primary