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THEORETICAL REVIEW

Top-down control of arousal and sleep: Fundamentals and clinical implications

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SUMMARY

Mammalian sleep emerges from attenuated activity in the ascending reticular arousal system (ARAS), the main arousal network of the brain. This system originates in the brainstem and activates the thalamus and cortex during wakefulness via a well-characterized 'bottom-up' pathway. Recent studies propose that a less investigated cortico-thalamic 'top-down' pathway also regulates sleep. The present work integrates the current evidence on sleep regulation with a focus on the 'top-down' pathway and explores the potential to translate this information into clinically relevant interventions. Specifically, we elaborate the concept that arousal and sleep continuity in humans can be modulated by non-invasive brain stimulation (NIBS) techniques that increase or decrease cortical excitability. Based on preclinical studies, the modulatory effects of the stimulation are thought to extend to subcortical arousal networks. Further exploration of the 'top-down' regulation of sleep and its modulation through non-invasive brain stimulation techniques may contribute to the development of novel treatments for clinical conditions of disrupted arousal and sleep, which are among the major health problems worldwide.

Introduction

Sleep is a ubiquitous phenomenon in animals and humans. Still, the exact mechanisms of sleep–wake regulation remain to be fully described. The aim of this work is to further elaborate the concept that arousal and sleep continuity can be modulated by cortical and concomitant subcortical arousal network activity changes induced by non-invasive brain stimulation techniques. We first integrate the current understanding of brain networks that regulate arousal and sleep, comprising a 'bottom-up' and a 'top-down' pathways. Subsequently, we discuss the clinical potential of different non-invasive brain stimulation techniques.

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Systems of sleep regulation

'Bottom-up' regulation of arousal and sleep

Early animal studies have shed light on the great importance of the reticular brainstem region for sustained wakefulness [1,2]. The majority of sleep-regulating stimuli are integrated in the ascending reticular activating system (ARAS), originating in the brainstem [3,4]. The main afferents to this system are wake-promoting and state-stabilizing orexinergic neurons from the lateral hypothalamus together with sleep-promoting gamma-aminobutyric acid (GABA)-containing neurons from the ventro-lateral preoptic nucleus [5–7]. These two projections integrate information about circadian and homeostatic sleep–wake signals and transfer it to the ARAS [4]. By this means, a homeostatic process S and a circadian process C, which are the two major processes that govern the sleep–wake cycle according to the pivotal two process model of

Abbreviations

ARAS	ascending reticular arousal system;
BDNF	brain-derived neurotrophic factor
dlAVC	dorso-lateral associative visual cortex
dlPFC	dorso-lateral prefrontal cortex
EEG	electroencephalogram
GABA	gamma-aminobutyric acid
IL	interleukin
LTP	long-term potentiation
NIBS	non-invasive brain stimulation
NMDA	N-methyl-d-aspartate
NREM	non-rapid eye movement
REM	rapid eye movement
RE	reticular thalamic
RF	radiofrequency
rTMS	repetitive transcranial magnetic stimulation
tACS	transcranial alternating current stimulation
TBS	theta-burst transcranial magnetic stimulation
TC	thalamo-cortical
TCS	transcranial current stimulation
tDCS	transcranial direct current stimulation
TMS	transcranial magnetic stimulation

Glossary of terms

'Bottom-up' regulation of arousal and sleep	The concept that the major sleep-regulating pathways are integrated in the ascending reticular activating system (ARAS), originating in the brainstem and relayed to cortical areas.
'Top-down' regulation of arousal and sleep	The concept that cortical activity levels orchestrate brain activity and physiological vigilance states via a cortico-thalamo-cortical feedback loop, emphasizing the crucial role of centro-frontal cortical areas for this process.
Non-invasive brain stimulation (NIBS)	A technique activating or deactivating parts of the brain through external stimulation.

sleep regulation [8], are bundled and translated into an 'on' or 'off' signal for the ARAS.

During active wakefulness, high activity of the ARAS forms a wake-promoting 'bottom-up' system. Ascending efferent connections from the ARAS contain cholinergic and aminergic neurotransmitters and activate higher order brain regions via two main pathways. One of them, the non-thalamic pathway, comprises activating aminergic projections from the locus coeruleus and the dorsal and median raphe nuclei to the basal forebrain and directly to the cortex. The second pathway originates in the cholinergic pedunculo-pontine and latero-dorsal tegmental nuclei and projects to the thalamus. It inhibits reticular thalamic (RE) neurons, activates thalamo-cortical (TC) neurons and enhances cortical activation and thalamo-cortical information transfer, which is essential for wakefulness [3,9]. Low activity in the ARAS is a prerequisite for non-rapid eye movement (NREM) sleep. During rapid eye movement (REM) sleep, the cholinergic pathway is selectively reactivated, while the monoaminergic neurons remain silent. This split function of the involved nuclei is relevant for the characteristics of REM sleep, including a high waking threshold to external stimuli along with an extensive activation of limbic/paralimbic structures and the occipital cortex ('paradoxical sleep'), thought to underlie emotional and vivid dreaming [10,11].

The clear neurochemistry of the ARAS provides a framework for the efficacy of current pharmaceutical interventions that manipulate the sleep–wake cycle at this level. Today, all common sleep medications, such as benzodiazepine receptor agonists, antihistaminergic drugs, and sedating antidepressants or antipsychotics, as well as the novel orexin receptor antagonist suvorexant, intervene with the ARAS [12,13]. Although benzodiazepine receptor agonists represent effective short-term treatments for sleep disruptions, these compounds do not induce a physiological or restorative sleep pattern in the long term. Side effects such as drowsiness, cognitive impairment, falls, and injuries are common [14]. Particularly, the frequent development of tolerance and dependency represents a major health problem. For other sleep medications, long-term data are missing and severe side effects have been described, e.g., cardiac damage or cognitive impairment [14]. Together, the manipulation of 'bottom-up' sleep regulation in the ARAS leads to global and non-physiological alterations of arousal and sleep, rendering current pharmacotherapies unsatisfactory.

'Top-down' regulation of arousal and sleep

Over the last few years, possible access points for a 'top-down' modulation of arousal and sleep have emerged (Fig. 1). Electrophysiological recordings in different mammalian species have revealed slow oscillations as a highly conserved pattern of electrical activity during NREM sleep, generated by an intricate interplay between the neocortex and thalamus [15–17]. First hints were described in unanesthetized cats where electrocortial synchronization and light sleep was induced by low-frequency stimulation of the subcallosal region and the orbital gyrus of the frontal lobe [18].

Neuronal populations in deep cortical layers IV–VI represent the primary oscillator of a cortico-thalamo-cortical feedback loop [15,17,19,20]. They generate synchronized rhythmic fluctuations of the membrane potential in form of hyperpolarized down-states and depolarized up-states. Particularly, large pyramidal cells in layer V with wide projection fields and strong synaptic input trigger the transition from silent down-states to active up-states [15,19–22]. During the up-states, the synchronous depolarization in the initiating region is rapidly transferred as a traveling wave to divergent cortical layers and areas and, importantly, also to the thalamus [23]. This cortico-thalamo-cortical feedback loop appears to be modulated by cortical sleep-active neurons, a specific subgroup of GABAergic interneurons, that might represent a neurobiological substrate of homeostatic sleep regulation [24,25].

Within the thalamus, the cortically generated up-states elicit a strong activation of GABAergic RE neurons due to their specific composition of glutamate receptors [26–28]. This leads to a bisynaptic inhibition and hyperpolarization of TC neurons, overwhelming their own weaker excitatory input from the cortex. By this means, RE neurons function as an important mediator between cortico-thalamic and TC neurons [28–30]. Finally, the hyperpolarization causes TC neurons to generate a low threshold calcium potential with sufficient duration and intensity to induce a powerful excitatory thalamo-cortical signal, thereby closing the loop of reciprocal cortico-thalamo-cortical excitation [15,31]. The