Pharmacology & Therapeutics 141 (2014) 300–334

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate editor: H. Bönisch

Neuroscience-driven discovery and development of sleep therapeutics

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ARTICLE INFO

Keywords:
Sleep
Neuroscience
Hypnotics
Insomnia
Depression

ABSTRACT

Until recently, neuroscience has given sleep research and discovery of better treatments of sleep disturbances little attention, despite the fact that disturbed sleep has overwhelming impact on human health. Sleep is a complex phenomenon in which specific psychological, electrophysiological, neurochemical, endocrinological, immunological and genetic factors are involved. The brain as both the generator and main object of sleep is obviously of particular interest, which makes a neuroscience-driven view the most promising approach to evaluate clinical implications and applications of sleep research. Polysomnography as the gold standard of sleep research, complemented by brain imaging, neuroendocrine testing, genomics and other laboratory measures can help to create composite biomarkers that allow maximizing the effects of individualized therapies while minimizing adverse effects. Here we review the current state of the neuroscience of sleep, sleep disorders and sleep therapeutics and will give some leads to promote the discovery and development of sleep medicines that are better than those we have today.

Contents

1. Introduction

1.1. Sleep and society

We spend a third of our lives asleep, however clinical and basic research cares comparably little about this phenomenon. This is surprising considering the fact that sleep-related health problems increasingly interfere with industrialized societies — and vice versa: The way into 24 h-societies in a globalized world increases the need for flexible sleep–wake patterns and shift work, and sleep debt seems to be ubiquitous. This is even more striking since information processing and health maintenance have been proposed as main functions of sleep — and an information society essentially depends on physically healthy and mentally capable members. In addition, the proportion of elderly individuals is growing in most societies — and aging is related to increasing sleep disturbances. Impaired sleep, in turn, shows co-morbidities with many diseases including psychiatric disorders — not only as a symptom, but in many cases as a risk factor. Hence, a deeper understanding of sleep and sleep-related disorders is not only an overdue goal of basic research, but also an important requisite for societal and economic development. The brain as both the generator and main object of sleep makes a neuroscience-driven view the most promising approach to evaluate clinical implications and applications of sleep research, leading to the discovery and development of novel sleep medicines.

Abbreviations: ACTH, corticotropin; CRH, corticotropin-releasing hormone; EEG, electroencephalogram; EMG, electromyogram; EOG, electrooculogram; fMRI, functional magnetic resonance tomography; GH, growth hormone; HLA, human leukocyte antigen; HPA, hypothalamic pituitary adrenocortical; LC, locus coeruleus; NREM, non rapid eye movement; PD, Parkinson's disease; PET, positron emission tomography; PTSD, post-traumatic stress disorder; RBD, REM behavior disorder; REM, rapid eye movement; RLS, restless legs syndrome; SARI, selective noradrenalin reuptake inhibitor; SNRI, selective serotonin and noradrenalin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; SWS, slow wave sleep; VLPO, ventrolateral preoptic nucleus.

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http://dx.doi.org/10.1016/j.pharmthera.2013.10.012

1.2. What is sleep?

In the ancient Greek culture the gods Hypnos for sleep and Thanatos for death were thought to be brothers. In contrast, neurobiological research since the 1960s showed that sleep is not a state of quiescent brain cells and circuits but rather an active process of and for the brain (Moruzzi, 1963; Hobson, 2005). However, there's no consensus among sleep researchers about the clear-cut defining criteria of sleep (Franken et al., 2009). The question whether sleep is the constellation of all parameters that change during the transition between coarse vigilance states or can be defined as a brain process that interacts with these parameters poses epistemological challenges to sleep research: the former option renders it impossible to isolate sleep as independent variable and limits conclusions about the causality of sleep, however the latter option is in need of further specification. Due to the success of polysomnography, sleep is today mainly characterized by polysomnographic criteria — and such criteria of course apply only to animals on which electroencephalogram (EEG) can be applied. However, if sleep is characterized by more unspecific or mundane criteria, e.g. reduced responsiveness, reversibility in response to strong waking stimuli, homeostatic pressure to rest after prolonged wakefulness, and cyclic occurrence of activity/rest behavior, also lower animals seem to show sleep-like behavior (Tobler, 1995). In recent years therefore several very simple model organisms have raised the attention of sleep researchers, e.g. zebra fishes, fruit flies or round worms (Hendricks et al., 2000a, 2000b; Shaw et al., 2000; Raizen et al., 2008). Obviously, these animals are well suited for providing genetic data in a fast way. Given the tremendous diversity of sleep even within mammals, however, it is unlikely that study results of organisms with comparably little neural complexity can be straightforwardly translated to insight in human sleep. This limitation applies also for the discovery of sleep therapeutics. On the background of polysomnography being the gold standard of sleep research in humans, only animals for which at least EEG recordings similar to humans are possible seem to be suited for research that aims for clinically relevant information.

1.3. Sleep research methods

Already during the 19th century, psychophysical experiments revealed the periodicity of sleep depth changes (Weber & Burgmair, 2009). The invention of the EEG in the 1920s allowed for a more detailed inquiry into the neural changes throughout the night (Loomis et al., 1935a, 1935b), and the discovery of oculomotor activity and muscle atonia related to REM sleep in the 1950s (Aserinksy & Kleitman, 1953; Jouvet et al., 1959) eventually established polysomnography as the gold standard in sleep research. Since then, also other powerful sleep research methods like blood sampling via a long catheter for later analysis of plasma concentrations (Steiger et al., 1987; Kerkhofs et al., 1989) or neuroimaging methods (Czisch & Wehrle, 2010) rely on parallel polysomnographic recordings.

1.3.1. Polysomnography

Sleep states in mammals (including humans) and birds can be classified into rapid eye movement (REM) and non-REM (NREM) periods according to the electrophysiological activity of the brain, alternating in a cyclic fashion. Such sleep stages are assessed by polysomnography, which analyzes electrical activity from electrodes fixed in various regions of the head to monitor brain (EEG), eye (electrooculogram, EOG) and muscle (electromyogram, EMG) activities. In experimental animals, polysomnography is applied similarly to the procedure in humans (Allison & Van Twyver, 1970), however most laboratories employ only EEG and EMG signals without EOG to distinguish REM sleep. According to the criteria by Rechtschaffen and Kales (1968), human NREM sleep consists of four stages, whereas a more recent classification (American Academy of Sleep Medicine et al., 2007) differentiates between three stages only. During sleep stage 1, a slowing of EEG activity characterizes the transition from drowsiness to light sleep. Sleep stage 2 is characterized by sleep spindles, bursts of 12–14 Hz waves occurring for at least 0.5 s, and K-complex slow wave forms. Synchronized slow waves are found in slow wave sleep (SWS), in human sleep denoted stages 3 and 4 (Rechtschaffen & Kales, 1968) or stage N3 (American Academy of Sleep Medicine et al., 2007), respectively. REM sleep is characterized by a faster EEG activity, horizontal rapid eye movements as measured by the EOG and hypotonus of skeletal muscles as measured by the EMG. Besides global state changes throughout the night, the electrophysiological microstructure of sleep is investigated in humans and animals by computerized EEG spectral analysis. Among the various EEG frequency bands, the delta band can be considered as of special interest: Slow wave activity of 0.5 to 4 Hz has been shown to be a reliable marker of sleep homeostatic processes (Achermann & Borbély, 2010; however see also Davis et al., 2011a, 2011b).

While EEG recordings have a high temporal resolution, their spatial resolution is very poor. Several methods to analyze EEG data have been developed to allow for approximate localization of neural activity. Low resolution electromagnetic tomography (LORETA) was developed to solve the EEG inverse problem of locating the neural source of the eletrophysiological surface signal (Pascual-Marqui et al., 1994). In sleep research, LORETA was used for analyzing neural correlates of sleep spindles (Ventouras et al., 2010), rapid eye movements (Abe et al., 2008), or sleep EEG arousal patterns (Ferri et al., 2005). EEG cordance is another low resolution measure of regional brain activity. It combines complementary information from absolute and relative EEG spectral power data, thereby providing a stronger correlation with regional cerebral perfusion than either component alone (Leuchter et al., 1999). Until now, cordance was applied mainly to waking subjects, however first pilot studies transferring this method to sleep seem very promising (Steiger & Kimura, 2010; Pawlowski et al., 2011).

1.3.2. Neuroimaging

Since surface EEG recordings do not allow for a detailed spatial mapping of brain activity particularly in deeper brain structures, the rise of neuroimaging methods like positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) provided sleep research new opportunities to study neural correlates of macro- and microprocesses. In the 1990s, PET studies demonstrated that the brain experiences widespread deactivations during SWS compared to wakefulness. In contrast, REM sleep was found to be associated with increased cerebral blood flow in the thalamus, visual areas and limbic regions as well as attenuated metabolism in the dorsolateral prefrontal cortex, parietal cortex and the precuneus (Maquet et al., 1996; Braun et al., 1997). In contrast to PET, fMRI repeatedly allows non-invasive measurements of neural activity changes with high spatial resolution, however fMRI faces several technical problems when applied to the study of sleep. While early fMRI sleep studies used behavioral measures to determine if the subject had fallen asleep (Hong et al., 2009), the development of MR-compatible EEG recording systems allowed polysomnography also in strong magnetic fields. Improvements in EEG postprocessing techniques have made it possible to substantiate that fMRI data were recorded during verified, unambiguous sleep (Czisch & Wehrle, 2010). Exploiting the temporal resolution of fMRI, it was shown that various brain regions successively reduce their activity levels in the transition to deep NREM sleep, which suggests a cascade of regional specific deactivation supporting initiation and stabilization of sleep (Kaufmann et al., 2006). Advanced approaches in fMRI data analysis demonstrate the functional interconnection between various brain regions, revealing sleep stage specific alterations in cerebral network organization (Spoormaker et al., 2010a; Larson-Prior et al., 2011). Fading consciousness during deep sleep has been attributed to a break-down of long-range functional connectivity (Spoormaker et al., 2010a; Sämann et al., 2011; Spoormaker et al., 2012), leading to a network configuration suboptimal for global information integration.