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THEORETICAL REVIEW

Synaptic plasticity model of therapeutic sleep deprivation in major depression

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SUMMARY

Therapeutic sleep deprivation (SD) is a rapid acting treatment for major depressive disorder (MDD). Within hours, SD leads to a dramatic decrease in depressive symptoms in 50–60% of patients with MDD. Scientifically, therapeutic SD presents a unique paradigm to study the neurobiology of MDD. Yet, up to now, the neurobiological basis of the antidepressant effect, which is most likely different from today's first-line treatments, is not sufficiently understood. This article puts the idea forward that sleep/wake-dependent shifts in *synaptic plasticity*, i.e., the neural basis of adaptive network function and behavior, represent a critical mechanism of therapeutic SD in MDD. Particularly, this article centers on two major hypotheses of MDD and sleep, the synaptic plasticity hypothesis of MDD and the synaptic homeostasis hypothesis of sleep-wake regulation, and on how they can be integrated into a novel synaptic plasticity model of therapeutic SD in MDD. As a major component, the model proposes that therapeutic SD, by homeostatically enhancing cortical synaptic strength, shifts the initially deficient inducibility of associative synaptic long-term potentiation (LTP) in patients with MDD in a more favorable window of associative plasticity. Research on the molecular effects of SD in animals and humans, including observations in the neurotrophic, adenosinergic, monoaminergic, and glutamatergic system, provides some support for the hypothesis of associative synaptic plasticity facilitation after therapeutic SD in MDD. The model proposes a novel framework for a mechanism of action of therapeutic SD that can be further tested in humans based on non-invasive indices and in animals based on direct studies of synaptic plasticity. Further determining the mechanisms of action of SD might contribute to the development of novel fast acting treatments for MDD, one of the major health problems worldwide.

Introduction

The World Health Organization (WHO) lists major depressive disorder (MDD) as the leading cause for illness-related reduction of quality of life worldwide (years of life lived with disability index; [1]). Current first-line treatments, i.e., antidepressants and psychotherapy, show a long latency to response. Still, only half of the patients achieve sustained remission with optimized treatment, indicating the need for further research [2].

Therapeutic sleep deprivation (SD) is a straight and rapid-acting treatment for MDD. Within hours, SD leads to a dramatic decrease in depressive symptoms in 50–60% of patients with MDD [3]. Yet, this effect is mostly transient. Approximately 80% of SD responders relapse into depression after the next night of sleep, and even brief daytime naps can reverse the therapeutic effect [4]. Strategies to preserve the clinical improvement, including concomitant pharmacotherapy, light therapy or sleep phase advance therapy, have shown some promise but are still not sufficient [5].

Scientifically, therapeutic SD presents a unique paradigm to study the neurobiology of MDD. Within a short period of time and without pharmacological or psychotherapeutical interference, one person can be investigated in a depressed, transitional and non-depressed state. Since the first scientific description [6],

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Abbreviations

AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BDNF	brain derived neurotrophic factor
EEG	electroencephalography
LTD	long-term depression
LTP	long-term potentiation
MDD	major depressive disorder
mGluR5	metabotropic glutamate receptor of subtype 5
MEP	motor evoked potential
NMDA	N-methyl-d-aspartate
NREM	non rapid eye movement
PAS	paired associative stimulation
REM	rapid eye movement
SD	sleep deprivation
SWA	slow wave activity
SWS	slow wave sleep
tDCS	transcranial direct current stimulation
TMS	transcranial magnetic stimulation
VEGF	vascular endothelial growth factor
WHO	World Health Organization

numerous studies have tried to unravel the therapeutic mechanisms of SD. Yet, up to now, the neurobiological basis of the antidepressant effect, which is most likely different from today's first-line treatments, is not sufficiently understood.

The current article centers on the idea that sleep/wake-dependent shifts of *synaptic plasticity*, i.e., the neural basis of adaptive network function and behavior, represent a critical neural mechanism of therapeutic SD in MDD. As such, we revisit the long-standing idea of investigating sleep in MDD as a window to the brain ('via regia') with new concepts. Particularly, this article is based on two hypotheses, the *synaptic plasticity hypothesis of MDD*, a recent conception on the pathomechanisms of MDD [7], and the *synaptic homeostasis hypothesis* of sleep-wake regulation [8]. These two lines of research have been relatively independent up to now and the main objective of this review is to integrate them into a novel *synaptic plasticity model of therapeutic SD in MDD*. After a general outline of this model, we will further discuss the potential neural mechanisms of SD on synaptic plasticity derived from animal and human studies. Finally, limitations and areas for future research will be identified. Further elucidating the mechanisms of therapeutic SD in MDD is expected to contribute to deciphering the pathomechanisms of the disorder and, potentially, to open new pathways to treatment.

The synaptic plasticity hypothesis of MDD

Impaired neural plasticity and related information processing within neural networks, rather than a chemical imbalance of neurotransmitters, have been proposed as a critical pathomechanism of MDD, and successful antidepressant treatments work through improvement of malfunctioning neural plasticity [9,10]. Neural plasticity occurs at several levels of the brain, from molecular processes at the connections between neurons (synaptic plasticity) over the modification of the macrostructure of neurons to the emergence of novel neurons (neurogenesis), and modulates both the function and structure of neural networks [9].

Among these levels of plasticity, synaptic plasticity is a prime candidate for a pathomechanism in MDD and the focus of this article. Higher-level plasticity, including the modification of the macrostructure of neurons and neurogenesis, are also critically important for the clinical neurosciences, e.g., for the therapy of different types of brain lesion or degeneration. However, these modifications cannot drive the therapeutic effect of SD in MDD. More specifically, neurogenesis has been demonstrated to be limited to specific brain regions like the dentate gyrus of the hippocampus in mammals, and changes in the macrostructure require several days to months to be functionally relevant. Fast-acting therapeutic SD may therefore influence short-term processes of synaptic plasticity rather than complex neurostructural changes, as supposed for traditional antidepressant medication [9].

Synaptic plasticity is defined as the activity-dependent change in the strength of information transmission between neurons [11]. Particularly, synaptic long-term potentiation (LTP) and long-term depression (LTD) of glutamatergic synaptic transmission represent the two basic mechanisms for experience-dependent modification of synaptic strength and have been described in virtually every brain region across species, including humans [12,13]. LTP leads to a long-lasting enhancement of synaptic strength, whereas LTD weakens synaptic connections. Distinct molecular mechanisms can be involved in producing LTP at different types of cortical synapses. Most studies demonstrate a primarily postsynaptic locus of LTP expression through increased insertion and phosphorylation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, thereby increasing the sensitivity to glutamatergic transmission [14]. LTP is an input-specific process, i.e., a single pathway can be potentiated without effect on inactive neighboring inputs to the same cell. A precise timing (coincidence) between pre- and postsynaptic activity is essential for the induction of associative forms of LTP, ensuring that a weak stimulus, which is not by itself capable of initiating LTP, can become potentiated through association with another synchronized stimulus. By contrast, asynchronous pairing of pre- and postsynaptic inputs decreases synaptic transmission by internalization of AMPA receptors and induces LTD [15,16]. LTP is a model for associative or classical Hebbian plasticity and provides the neural basis of memory and adaptive behavior [12].

Several studies in animals and humans provide support for the concept that synaptic plasticity is altered in MDD. For instance, animal studies demonstrate a facilitation of hippocampal LTD [17] and an impairment of hippocampal LTP [18] in rats exposed to chronic mild stress – one of the main precipitating factors of MDD in humans. Moreover, chronic stress decreases the number and function of AMPA receptors in the hippocampus, which relates to disrupted memory consolidation and anhedonic behavior in rats [19]. In turn, chronic application of the antidepressant fluvoxamine during stress protocols prevents the facilitation of LTD and increases the extent of LTP induction [17].

In humans, some studies have begun to provide evidence for an impairment of synaptic plasticity in MDD using non-invasive, indirect indices of LTP. Our group reported that the modification of early components of the visual evoked potential shares properties with Hebbian forms of synaptic plasticity and is altered in depressed relative to non-depressed individuals [20]. This has been interpreted as the first evidence for reduced LTP-like plasticity in the cortex of patients with MDD [21]. In a further study, learning and memory were examined as behavioral correlates of long-term synaptic plasticity in humans. Consistent with basic alterations in synaptic plasticity in MDD, the results showed indices of decreased synaptic plasticity in a dorsal executive network that comprises the hippocampus, as well as indices of elevated synaptic plasticity in a ventral emotional network that includes the amygdala in patients with MDD [22]. These results indicate a region-specific increase or decrease of LTP in functional networks. Player and colleagues