Rapid Eye Movement Sleep Deprivation

Subjects: Neurosciences
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In parallel with the growing incidence of endogenous depression, researchers in sleep science have discovered multiple links between rapid eye movement (REM) sleep patterns and endogenous depression. Prolonged periods of REM sleep are associated with different psychiatric disorders, including endogenous depression. In addition, a growing body of experimental work confidently describes REM sleep deprivation (REM-D) as the underlying mechanism of most pharmaceutical antidepressants, proving its utility as either an independent or adjuvant approach to alleviating the symptoms of endogenous depression.

endogenous depression | REM sleep deprivation | personalized medicine

1. Introduction

Sleep is a reversible physiological state characterized by a complex pattern of cerebral electrical activity. Once the wakefulness state is suppressed, the normal sleep cycle that follows is composed of two distinct, yet alternating, phases called non-rapid eye movement (NREM) and REM [1][2][3]. Normal REM sleep is mainly associated with dreaming, characterized by fast eye movements, mixed-frequency electroencephalographic rhythm, and muscle atonia. This common paralysis of the skeletal muscles has a protective role, as it obstructs the development of complex physical movements during REM sleep [4].

Several research studies have noticed a strong interplay between cholinergic and monoaminergic neurons in the brainstem, which form a complex intercellular relationship that appears to regulate the activation of REM sleep [5][6][7]. Among the most important neurotransmitters involved in the generation and maintenance of sleep are the biogenic amines (norepinephrine and serotonin). Although these essential neurotransmitters participate in the initiation of each sleep phase, both are at their lowest during REM sleep [8]. Disturbances of norepinephrine and serotonin systems may contribute to REM sleep abnormalities in different conditions, including endogenous depression [9] and anxiety [10].

Recently, a growing body of studies has emerged emphasizing the association between REM sleep behavior and different endogenous depression-associated symptoms, thus highlighting the diagnostic value of dysregulated REM sleep patterns [10][11][12][13]. Most depressed patients suffer from sleep abnormalities. Wang et al. reported that endogenous depression-induced sleep irregularities included a decrease in REM sleep latency, however, there was also an increase in REM sleep duration and density. Hence, in the sleep science community, REM sleep alterations started to be considered essential biomarkers for predicting the risk of endogenous depression. The

researchers have also found a consistent clinical association between altered norepinephrine–serotonin systems and REM sleep abnormalities in patients with endogenous depression [14]. Likewise, such findings were confirmed by other similar studies [15][16]. Hence, REM sleep pattern disruption is considered to be related to several psychiatric disorders, including endogenous depression and anxiety [17][18][19], which also confirms its potential as a diagnostic biomarker. REM-D can be defined as a repertoire of pharmaceutical and non-pharmaceutical approaches designed to reduce overall REM sleep duration. Although there is an association between total sleep deprivation and the impairment of several emotion- and cognition-based functions, including decision-making [20], perceived emotional intelligence, constructive thinking skills [19], moral judgement [18], and reactivity toward negative stimuli [20], there is currently no evidence linking these side effects with REM-D. In addition, almost all antidepressants influence sleep patterns, mainly by suppressing REM sleep. Hence, REM-D is considered the underlying mechanism of most pharmaceutical-based antidepressants and a valuable indicator of their efficacy [21][22][23][24].

The development of endogenous depression was recently described as a combination of two key factors: reduced levels of cerebral monoamines (particularly norepinephrine and serotonin) and prolonged periods of REM sleep. Thus, REM-D started to be explored as a non-drug treatment for endogenous depression [25][26].

2. REM Sleep Deprivation as a Non-Pharmaceutical Choice for Treating Endogenous Depression

Some of the first investigations conducted on the effects of REM-D in the treatment of endogenous depression date back to the early 1970s and start with the pioneering work of Vogel et al. They designed a research protocol to study the hypothesis that the symptoms of endogenous depression could be relieved by increased REM pressure, defined by the authors as an increase in REM sleep produced by REM-D via awakening. Their work proved that increasing REM pressure by the administration of an external agent (such as monoamine oxidase inhibitors or tricyclic antidepressants) decreases REM sleep and REM-D by awakening at the start of each REM period. The scientists reported that after experiencing increased REM pressure due to REM-D, five out of eight depressed patients improved markedly and one patient improved slightly, while the treatment had no effect on the remaining two subjects. Based on these results, Vogel et al. suggested that REM pressure may be the mechanism behind the effectiveness of most antidepressant drugs [27]. At the beginning of the next decade, Vogel et al. gathered additional evidence by comparing sleep variables in 14 drug-free endogenous depressive subjects and 14 age- and insomnia-matched, non-depressed controls before and after REM-D by awakening, thus strengthening his hypothesis that antidepressant drugs alleviate endogenous depression-associated symptoms by REM-D [28]. Three years later, Vogel formulated a set of criteria that validated REM-D as the primary mechanism of action underlying the effectiveness of antidepressant drugs [29].

Rosales-Lagarde and her group of sleep researchers conducted a study designed to assess the effects of REM-D on emotional reactivity to threatening visual stimuli in a cohort of 20 adult, male volunteers between 21 and 35 years of age. Subjects in the REM-D group were kept awake for 2 min every time the PSG showed slow-wave activity. Sleep spindles and K complexes were no longer present in the EEGs, which, instead, were characterized

by low-voltage fast activity accompanied by decreased EMG activity. This procedure reduced REM sleep to only 4% of total sleep time. Their findings showed an enhancement of emotional reactivity after REM-D in humans [30], which has been positively correlated with improved symptoms in patients with a depressive disorder [31].

In a separate study conducted by Cartwright et al., the contribution of controlled REM-D upon remission from untreated endogenous depression was investigated over five months in a cohort of 20 depressed subjects compared with 10 control volunteers. Surprisingly, at the end of the study, 60% of the individuals from the depressed group entered remission, admitting improved levels of self-reported symptoms. These findings support the utility of REM-D as an effective tool in the non-drug management of endogenous depression-related symptoms [32].

A recent study by Ju et al. investigated the mechanisms underlying the antidepressant effects of REM-D and fluoxetine, a selective serotonin reuptake inhibitor, in a depressive rat model. The researchers reported an enhanced repertoire of benefits, including increased body weight, prompted behavior, and some cellular protective effects, such as alleviating endogenous depression-induced damage, attenuating apoptosis, and maintaining A1 adenosine receptor activity. Hence, these findings indicate an adjuvant role for REM-D, when induced in combination with fluoxetine, for practical use against endogenous depression [33].

Besides its antidepressant efficacy, REM sleep fragmentation was closely associated with depressive status after a study conducted on 54 depressed patients with short-term insomnia disorder. Wu et al. developed a REM sleep fragmentation-based regression model that could predict the risk of endogenous depression with an 83.7% prediction accuracy, thus promoting REM as a viable index for estimating depression risk and a biomarker for treatment response [34].

A comprehensive summarization of these studies is further presented in **Table 1**.

Table 1. Studies supporting the efficacy of REM-D as a non-drug antidepressant (ED—endogenous depression; RD—reactive depression).

Study	Study Model	REM-D Method	Duration	Conclusions	Refs.
Vogel et al., 1972	12 EDs (seven experimental, five controls) 12 EDs (eight experimental, four controls)	Recurrent awakening during REM sleep	Up to 13.6 weeks	REM-D relieves the symptoms of ED REM pressure is the mechanism behind most antidepressant drugs	[27]
Vogel et al., 1980	14 drug-free EDs 14 matched controls	Recurrent awakening during REM sleep	Up to 13.6 weeks	REM-D improved depression to the extent that it stimulated the oscillator and corrected one manifestation of circadian rhythm disruption	[28]

Study	Study Model	REM-D Method	Duration	Conclusions	Refs.
Vogel, 1983	34 EDs (17 experimental, 17 controls) [35] 18 RDs (11 experimental, 7 controls) [35] Data from Imipramine-treated patients from the British Medical Research Council 1965 [36]	Recurrent awakening during REM sleep Imipramine-treated patients from the British Medical Research Council 1965 [36]	24 weeks	REM-D is the mechanism of action of antidepressant drugs	[29]
Rosales-Lagarde et al., 2012	20 right-handed adult male volunteers between 21–35 years of age (12 REM-D and 8 NREM-I)	Recurrent awakening during REM sleep	Four nights (one night for treatment)	Post-REM-D emotional reactivity, which has been positively correlated with improved ED symptoms	[30] [31]
Cartwright et al., 2003	20 depressed subjects compared with 10 control volunteers	Recurrent awakening during REM sleep	Five months	60% of the ED group entered remission. Hence, REM-D could be a non-drug antidepressant	[32]
Ju et al., 2021	Depressive male Sprague–Dawley rat model	Recurrent awakening during REM sleep, which reduced REM sleep to only 4% of total sleep time	28 days	These findings indicate an adjuvant role of REM-D when in combination with the administration of fluoxetine	[33]
Wu et al., 2021	54 depressed patients with short-term insomnia	REM sleep fragmentation	Three months	REM sleep is a characteristic marker for assessing the risk of ED	[34]
Maudhuit et al., 1996	Depressive male Sprague–Dawley rat model	Zimelidine dissolved in 1 mL saline was injected twice a day at a dose of 2.5 mg/kg IP for 14 days. On day 15, only the morning dose was administered. Control rats	Zimelidine twice a day for 14 days, once on the 15th day. Four successive REM-D sessions	Electrophysiological activity of 5-HT neurons in the nucleus raphe dorsalis revealed that chronic treatment with both zimelidine and REM-D induced hyporeactivity of 5-HT neurons to the inhibitory effect of depression-like citalopram administration	[37]

Study	Study Model	REM-D Method	Duration	Conclusions	Refs.
		received 1 mL saline REM-D by placing the rats on a platform fenced by water Control rats stood on a platform where they could lie down for REM sleep			[14][38]

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Then, using linear regression, they generated a regression model that could predict the risk of endogenous depression with 83.7% accuracy. These findings, together with other pioneering work, support the use of REM sleep behavior as a viable endogenous depression predictor marker, indicating that REM-D could also predict the therapeutic outcome [34][39].

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