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The Neurobiological Mechanisms and Treatments of REM Sleep Disturbances in Depression

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Abstract: Most depressed patients suffer from sleep abnormalities, which are one of the critical symptoms of depression. They are robust risk factors for the initiation and development of depression. Studies about sleep electroencephalograms have shown characteristic changes in depression such as reductions in non-rapid eye movement sleep production, disruptions of sleep continuity and disinhibition of rapid eye movement (REM) sleep. REM sleep alterations include a decrease in REM sleep latency, an increase in REM sleep duration and REM sleep density with respect to depressive episodes. Emotional brain processing dependent on the normal sleep-wake regulation seems to be failed in depression, which also promotes the development of clinical depression. Also, REM sleep alterations have been considered as biomarkers of depression. The disturbances of norepinephrine and serotonin systems may contribute to REM sleep abnormalities in depression. Lastly, this review also discusses the effects of different antidepressants on REM sleep disturbances in depression.

Keywords: Antidepressants, depression, mood disorders, norepinephrine, serotonin, sleep disorders.

1. INTRODUCTION

Currently, depression is a common disease and has become increasingly prevalent in the world [1]. Most depressed people show evidence of one or more changes in sleep neurophysiology; i.e., some complain of insomnia and the others suffer from hypersomnia [2, 3]; therefore, impaired sleep is a critical symptom of depressed patients. Gresham SC *et al*. [4] found there were more REM sleep alterations in the first third of the night in depressed patients, which was the first study on depression and sleep [5]. Later quantitative electroencephalogram (EEG) studies showed that there were characteristic changes in depression consisting of disturbed sleep continuity, inductions of rapid eye movement (REM) sleep; that is, reductions of REM sleep latency, increases in REM sleep time and REM sleep density, and decreases of non-REM (NREM) sleep [3, 6-8]. Of all the changes, REM sleep abnormalities are key involvements of EEG changes in depression, and they implicate the severity of disease and indicate the effect of individualized antidepressant therapy [8].

To truly understand depression, knowledge of REM sleep is required. Therefore, we reviewed the data on REM sleep disturbances in depression from different aspects. Furthermore, treatments of REM sleep disturbances in depression are also reviewed.

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2. OVERVIEW OF REM SLEEP ABNORMALITIES IN DEPRESSION

Although symptoms of depression vary from patient to patient and can overlap through different subtypes [9], sleep disturbances are always one of the most common complaints of depressed patients. Sleep EEG recordings in depression are often characterized by the following [3, 8, 10-13]: decreased sleep efficiency, for example, the time before falling asleep is prolonged and more awakening episodes after falling asleep [14-16]; reduced NREM sleep, disturbed distribution of delta activity, sleep cycle, and a reduced delta ratio (ratio between delta activity in the first and second NREM periods); longer time of REM sleep, such as reduced REM sleep latency and deeper REM sleep density, especially during the first REM sleep period [11, 16-25].

REM sleep disturbances have been considered to be more specific for depression since other sleep disturbances are common in many mental disorders. In 1966, Hartmann E and Green WJ *et al*. found that the latency of REM sleep was reduced at sleep onset and its percentage was increased [26, 27]. So the latency of REM sleep has been viewed as a marker of depression [28].

Animal models of depression also show changes in sleep. Interestingly, animal models show similar changes of REM sleep, but the other insomnia changes including prolonged wakefulness and shortened NREM sleep are not obvious [29, 30]. REM sleep increased significantly in the light period, especially in the afternoon, in olfactory bulbectomized rats, which is thought to be a classic depressive model [31]. Prenatally stressed rats showed an increased REM sleep, and

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the change of REM sleep was correlated positively with the increase of corticosterone levels in the plasma [32]. In the other depressive animal models, elevated REM sleep was a landmark [32, 33]. All these studies have suggested that increased REM sleep is supposed to be the characteristic change in depressive animal models.

Therefore, from these studies, we concluded that abnormalities in REM sleep are potential biomarker of depression.

3. THE NEUROBIOLOGICAL BASIS OF REM SLEEP ABNORMALITIES IN DEPRESSION

3.1. The Regulation of REM Sleep

There was the first description about REM sleep more than 60 years ago [34-36]. In both humans and other mammals, REM sleep is used to describe sleep accompanied by REM, fast and desynchronized rhythm in cortical EEG, an activation in autonomic activity and a loss of muscle tone [37]. REM sleep was shown to be regulated through the interplays of cholinergic and monoaminergic neurons in the brainstem, which activate or inactivate during REM sleep [38-43].

Noradrenergic (NE) neurons in the locus coeruleus (LC) have shown a negative regulation to REM sleep [44]. These neurons in the LC exhibit an increased activity during wakefulness, a decreased discharge rate during NREM sleep and a vanished firing during REM sleep [45]. However, others have suggested that cholinergic neurons in LCalpha, peri-LCalpha, laterodorsal (LDT) and pedunculopontine (PPT) tegmental nuclei may be responsible for REM sleep generation [46, 47]. Nucleus points oralis (NPO) has been emphasized to be involved in the coordination of the generation of REM sleep. It had been shown earlier that lesion of the ventral part of the NPO (vNPO) causes a decrease in REM sleep. Injection of carbachol into it could induce REM sleep with a shorter latency [48-51]. The vNPO receives cholinergic afferent fibers from the rostral peri-LCalpha, LDT, PPT and parabrachial nuclei (PB) and γ-aminobutyric acid (GABA)-ergic fibers from the postero-lateral hypothalamus [52]. So the interactions between those two systems play an important role in the regulation of REM sleep [53, 54].

With the development of the techniques to record the activity of single neurons in freely moving animals, it has been possible to assess the effect of pontine nuclei at the neuronal level. The concept of REM-on and REM-off neurons has come into being, and the former means neurons that start firing or increase firing rate significantly during REM sleep, while the latter indicates those stopping firing or decreasing firing rate significantly at the same time [55, 56]. Almost all the REM-off neurons are monoaminergic in the LC as NE-ergic neurons [43, 57, 58], in the dorsal raphe as the serotoninergic (5-HT) neurons [59] and in the tuberomammillary nucleus (TMN) within the hypothalamic region as the histaminergic neurons [60]. However, some non-monoaminergic neurons in the medulla have been demonstrated to be REM-off neurons [61]. The REM-on neurons are chiefly cholinergic and are distributed in the LDT [62, 63] and PPT [64]. Nevertheless, some non-cholinergic REM-on neurons have also been found in the brain [61, 65]. Both the generation and regulation of REM sleep directly depend on the interaction between those two neurons. It is still not clear how REM-off neurons stop firing during REM sleep, which is necessary to generate REM sleep. GABA has been supposed to inhibit REM-off neurons [66]. Lu J *et al*. proposed a flip–flop switch in brainstem, which involved a mutual inhibition between REM-on and REM-off regions in the mesopontine tegmentum [67]. There were GABAergic neurons in each side that heavily innervated the others. The REM-on and REM-off neurons are summarized in Fig. **1**.

3.2. The Basis of REM Sleep Dysregulation in Depression

Clinical antidepressant drugs selectively increase the function of monoaminergic systems such as the norepinephrine and serotonin systems. Dysfunction of the monoaminergic system has been demonstrated to have a close relationship

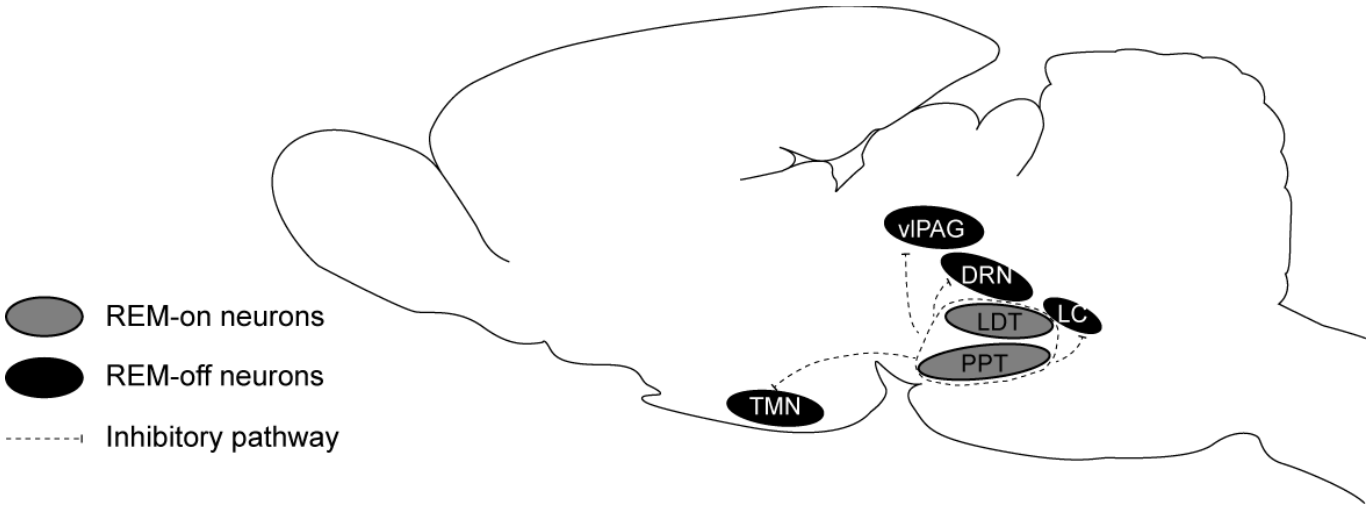

Fig. (1). The REM-on and REM-off neurons in REM sleep flip-flop circuit model. DRN: dorsal raphe nucleus; LC: locus coeruleus; LDT: laterodorsal tegmentum; PPT: pedunculopontine tegmentum; TMN: tuberomamillary nucleus; vlPAG: ventrolateral periaqueductal grey.

with the morbidity of depression [68]. It was found that the depletion of monoamine reserpine was associated with serious depression. Moreover, the inhibitors of monoamine oxidase, which inhibit the degradation of NE and 5-HT, could improve depressive emotions, suggesting that the NE and 5-HT systems play a critical role in the generation process of depression.

Increasing extracellular levels of NE and 5-HT *via* the use of monoamine reuptake inhibitors could inhibit REM sleep, which could also be helpful for treating depression [69]. However, selective lesions of either the cholinergic or monoaminergic nucleus in the brainstem did not have much influence on REM sleep [70-72]. Furthermore, also some evidence showed no causality between REM sleep abnormalities and depressive behaviors [31]. Therefore, there may be two parallel pathways for the regulation of REM sleep and depression, which have a close relationship with the monoaminergic system.

In addition to monoaminergic system, cholinergic system also plays a critical role in REM sleep abnormalities in depression. Cholinergic agonists such as arecoline and physostigmine shortened REM sleep latency and reduced REM sleep interval times preferentially in patients with depression [73]. Moreover, Prathiba J *et al*. found that REM sleep deprivation could reverse the sensitivity of central cholinergic receptors in rats given clomipramine neonatally, and the mechanism may be involved in mediating the antidepressant effects of REM sleep deprivation treatment in clomipramine model of depression [74].

Recently, it was found that depression may be related to the dysfunction of a network of structures that also regulate REM sleep, such as the limbic system including the hippocampus, amygdala and medial prefrontal cortex. Posttraumatic stress disorder and major depressive disorder (MDD) are two stress-related disorders that are associated with the disruption of REM sleep [75-79]. In MDD, REM sleep is characterized by activation of limbic and paralimbic brain regions compared to wakefulness. Posttraumatic stress disorder is associated with increased REM sleep limbic and paralimbic metabolism, whereas MDD is associated with wake and REM sleep hypermetabolism in these areas [80]. The hippocampus of the depressed patients was 12%–15% smaller than that of the non-depressed patients [81]. Hegde P *et al*. reported the effect of chronic immobilization stress on theta oscillations in the hippocampus and amygdala during REM sleep [82]. These studies demonstrated that chronic immobilization stress caused synchronized amygdalo-hippocampal theta activity and enhanced REM sleep duration. Mizuseki K *et al*. found that theta oscillations, which are the characteristics of REM sleep, decreased spike synchrony in the hippocampus and entorhinal cortex [83]. In addition, others found that stress affected theta activity in limbic networks including the hippocampus [84]. Apart from that, stress could also reduce long-term potentiation and facilitate long term depression, which has extensive effects on anxiety, depression and cognition [68, 85-87]. Therefore, the hippocampus is an important region in regulating REM sleep disturbances in the development of depression. Furthermore, the subregions of the medial prefrontal cortex (mPFC) showed great changes in neural activity in depressed patients. Lesions of the ventral mPFC enhanced REM sleep, reduced REM sleep latency and shortened the immobility time in a forced swimming test. Anatomic tracing studies showed that mPFC projected to the pontine REM-off neurons in the ventrolateral periaqueductal gray and adjacent lateral pontine tegmentum, which interacted with REM-on neurons in the dorsal pons. Therefore, the ventral mPFC may be a critical area for regulating both depression and sleep and it has been suggested to be a critical site for REM sleep abnormalities and other behaviors in depression [88].

The lateral habenula (LHb) is a nucleus that negatively regulates the monoaminergic system in the brain, since activation of LHb inhibits the firing activity of serotonergic neurons in the brainstem [89]. Aizawa H *et al*. found that the synchronous activity in the LHb was essential for the maintenance of REM sleep *via* regulation of serotonergic activity, which is also important for the development of depression [90]. The results suggested that the LHb regulates REM sleep abnormalities in depression *via* serotonergic neurons in the median raphe [91].

4. PHARMACOLOGICAL TREATMENTS FOR DEPRESSION AND REM SLEEP DISTURBANCES

4.1. Effects of Different Antidepressants on REM Sleep

Most antidepressants show suppressive effects on REM sleep, including prolonged REM sleep latency, decreased total duration of REM sleep, and reduced REM sleep density and the number of REM sleep episodes. These drugs include tricyclic antidepressants (TCAs) such as amitriptyline, imipramine and clomipramine [92-99]; tetracyclic antidepressants such as mianserin and maprotiline [98]; monoamine-oxidase inhibitors (MAOIs) such as phenelzine, tranylcypromine, clorgyline [100-103]; selective NE reuptake inhibitors (NARIs) such as desipramine and reboxetine [104, 105]; selective 5-HT reuptake inhibitors (SSRI) such as fluoxetine, paroxetine, zimelidine [106-108]; 5-HT/NE reuptake inhibitors (SNRIs) such as venlafaxine and duloxetine and 5-HT_2 receptor antagonists/reuptake inhibitor trazodone [98, 105, 109, 110].

The specific effects of different antidepressants on REM sleep are various. For example, duloxetine, amitriptyline, phenelzine and desipramine could significantly reduce REM sleep time and prolong the onset latency of REM sleep and phenelzine could completely suppress REM sleep after a few weeks of treatment [93, 98, 101, 102, 104, 110]. Clomipramine, imipramine and vilazodone showed profound REM sleep-suppressive effects, and venlafaxine may be the strongest REM sleep inhibitor among all SNRIs [96-98, 107]. Milnacipran, at a therapeutic dose, induced small effects on REM sleep compared with imipramine, paroxetine, and venlafaxine [95]. Moclobemide, a reversible MAOI, showed a less suppressive REM sleep effect than other traditional MAOIs [94]. Mianserin reduced REM sleep only in rats, but not in MDD patients [98]. The suppressive effect of trazodone was also relatively slight [109] and, therefore, this drug was included in the class of antidepressants that could not suppress REM sleep [111].

A REM sleep rebound is very common after a few weeks following withdrawl of most antidepressants, such as

Table 1. The comparisions of the effects of different antidepressants on REM sleep.

Antidepressants	Design	Subjects	n	Doses (per day)	Duration	Reference Treatment	Changes of Polysomnography
TCAs							
Amitriptyline [93, 131]	EEG recording before, during and after treatment	Depressed inpatients	6		370 nights		Suppressed REM sleep A REM sleep rebound after treatment
	Double-blind randomized trial	Patients with MDD	30	100-225 mg	6 weeks	Alprazolam 4-9 mg	Suppressed REM sleep
Clomipramine [96, 97]	EEG recording before and after treatment	Healthy man	1	Up to 100 mg	1 month	Placebo	Suppressed REM sleep A REM sleep rebound after withdrawal Increased wakefulness Decreased NREM sleep
	EEG recording after total sleep deprivation and treatment afterwards	Patients with MDD			19 days		Suppressed REM sleep
Imipramine [132]	Double-blind trial	Unipolar and bipolar patients hospitalized for MDD	79	100-250 mg	6 weeks	Amitriptyline 100-250 mg	Improvement in insomnia
Trimipramine [113, 133]	Double-blind trial	Depressed patients with insomnia and anxiety	30	75-200 mg	4 weeks	Imipramine 75-200 mg	Improvement in sleep disturbances Increased REM sleep in some cases
	Double-blind trial	Male patients with MDD	20	50-250 mg	4 weeks	Imipramine 50-200 mg	Increased REM sleep and NREM sleep
MAOIs							
Phenelzine [100, 118]	Open-label trial	Patients with MDD	11	30-90 mg	5 weeks		Suppressed REM sleep Increased stage 2 NREM sleep
	EEG recording before and after treatment	Depressed patients	3		18 months		Suppressed REM sleep initially A REM sleep rebound after 3 to 6 months of medication No change of NREM sleep
Tranylcypromine [101]	EEG recording before and after treatment	Patients with anergic bipolar depression	23	37 mg (average)			Suppressed REM sleep Decreased total sleep time
Moclobemide [134, 135]	Double-blind trial	Depressed patients			4 weeks	Placebo	Improvement in sleep continuity Increased stage 2 NREM sleep and REM sleep
		Patients with MDD	12	450 mg	6 weeks		REM sleep habituation A slight REM sleep rebound after withdrawal
SSRIs							
Paroxetine [92]	Double-blind randomized trial	Patients with MDD	40	30 mg	4 weeks for treatment	Amitriptyline 150 mg	Suppressed REM sleep
Fluoxetine [136]	Double-blind trial	Patients with MDD	34	60 mg	42 days for treatment	Amitriptyline 150 mg	Suppressed REM sleep Disrupted sleep continuity

Table 1. contd….

Antidepressants	Design	Subjects	n	Doses (per day)	Duration	Reference Treatment	Changes of Polysomnography
SSRIs							
Fluvoxamine [137]	Double-blind cross-over study	Normal volunteers	12	100 mg		Dothiepin 100 mg Placebo	Suppressed REM sleep
Clomipramine [138]	Double-blind, randomized, multicenter trial	Depressed patients	52	25-150 mg	6 weeks	Maprotiline 50-150 mg	Improvement in sleep disturbances
Zimelidine [107]	Double-blind trial	Depressed inpatients	27		28 days	Amitriptyline	No improvement, even worsening in sleep continuity Suppressed REM sleep
Nefazodone [108]	Multisite, randomized double-blind trial	Patients with MDD	125		8 weeks	Fluoxetine	Increased sleep efficiency Decreased awakenings Suppressed REM sleep
Citalopram [139]	EEG recording before and after treatment	Depressed patients	16		8 weeks	Placebo	Suppressed REM sleep A REM sleep rebound after withdrawal
SNRIs							
Venlafaxine [109]	Double-blind trial	Depressed patients	24	Up to 225 mg	29 days	Placebo	Decreased sleep continuity Suppressed REM sleep
Mirtazapin [140]	EEG recording before, during and after treatment	Patients with MDD	16	15-30 mg	2 weeks		Decreased sleep latency Increased total sleep time and efficiency No change of REM sleep
Milnacipran [141]	EEG recording before and after treatment	Depressed patients	8	100 mg	1 month		Increased total sleep time and sleep efficiency No change of REM sleep
Duloxetine [110]	EEG recording before and after treatment	Patients with MDD	10	60 mg	14 days		Increased stage 3 NREM sleep Suppressed REM sleep
NARIs							
Desipramine [104]	Double-blind trial	Depressed patients	17	150 mg	28 days	Placebo	Worsened sleep continuity Suppressed REM sleep
Trazodone [142]	EEG recording before, during and after treatment	Depressed patients		400-600 mg	1 month		Increased stage 2 NREM sleep Decreased sleep latency and intrasleep awakenings Suppressed REM sleep

amitriptyline, citalopram, clomipramine, phenelzine and tranylcypromine [93, 94, 96, 98]. Nortriptyline showed inhibition of REM sleep, such as increased REM sleep latency and decreased REM sleep time, but after withdrawl, REM sleep rebounded even higher than before [94]. Moreover, no rebound of REM sleep also occurred after the withdrawal of antidepressants milnacipran, imipramine and paroxetine [95].

Although most antidepressants showed a suppressive effect on REM sleep, some antidepressants did not have this effect, or even had the opposite effect. Many studies have demonstrated that trimipramine did not show a REM sleep suppressive effect at lower doses [103, 112], and even one study drew the conclusion that trimipramine could enhance REM sleep [113], which was a typical exception among TCAs. In addition, iprindole, viloxazine, nefazodone and tianeptine also did not have significant suppressive effect on REM sleep [98, 99]. In some studies, nefazodone even could increase the total time and percentage of REM sleep and decrease the latency of REM sleep [98, 108]. The same conclusion was reached for the SNRI bupropion, with which REM sleep latency was reduced, while the REM sleep percentage and time duration increased after treatment in depressed patients [99, 114]. Furthermore, the specific NE and 5-HT antidepressant mirtazapine showed many effects

on changing sleep structures in depressed patients, and some studies concluded that it could suppress REM sleep modestly [94]; however, more data showed there was no significant effect on REM sleep when patients were treated with mirtazapine [98, 99, 107, 110]. Escitalopram appeared to be an exception to other SSRIs. It was the only agent that did not show a suppressive effect on REM sleep among all the SSRIs [99]. The reversible MAOI moclobemide showed contradictory results. One study revealed it to be associated with enhanced REM sleep and shorter REM sleep latency, but another study showed an almost opposite result [98].

Interestingly, most antidepressants that showed suppressive effects on REM sleep were also associated with changing the sleep architecture and decreasing restorative sleep, while others that did not elicit this effect tended to improve sleep and return the sleep structure to a restorative function. However, it should be noted that there are also some exceptions. In general, the rebound effect varies for different categories and may be relative to the mechanisms underlying these drugs.

4.2. Effects of Different Antidepressants on other Sleep Architectures

TCAs such as clomipramine, desipramine, amitriptyline and protriptyline, almost all SSRIs (e.g., fluoxetine, paroxetine and sertraline) except for escitalopram, SNRIs such as venlafaxine, duloxetine and zimelidineand, and NARIs such as reboxetine, suppressed REM sleep but elongated sleep latency, increased awakenings, and decreased total sleep time and sleep continuity at the same time [94, 98, 99, 104, 105, 107, 108, 115]. Almost all MAOIs could inhibit REM sleep time, reduce sleep efficiency, increase sleep latency, and induce nocturnal disturbance and other negative influences on sleep efficiency [99, 102]. The SNRI bupropion and SARI nefazodone, which could increase REM sleep, have been revealed to improve overall sleep efficiency and decrease the number and duration of awakenings, similar to mirtazapine, which has not been associated with the changes in REM sleep [98, 99, 108, 116]. A novel antidepressant; i.e., agomelatine, was thought to have a unique mechanism of action. The melatonin MT_1 and MT_2 receptor agonists and 5-HT_{2C} receptor antagonist were also found to increase sleep efficiency, the duration of NREM and normalize sleep structure, but had no significant influence on REM sleep [95, 117].

Note that not all antidepressants abide by this principle. For example, both amitriptyline and doxepin could suppress REM sleep, but they also improved sleep structure with a shorter sleep latency and increased total sleep time, as well as a decreased awakening after sleep onset [99]. Another example was trazodone, which could slightly reduce REM sleep in depressed patients. Trazodone was shown to improve sleep quality and provide restorative sleep with enhanced NREM sleep and increased sleep time [98, 99]. Phenelzine was shown to suppress REM sleep strongly but did not change total sleep time and EEG slow-wave activity in NREM sleep [118]. It was also found with milnacipran and imipramine [95]. Various pathways responsible for different antidepressants taking effect may be the reason for the different relationship between REM sleep suppression and changes in sleep architecture.

4.3. The Relationship between the Effects of Antidepressants on REM Sleep and Depressive Behavior Abnormalities

In terms of REM sleep, suppressive effects appeared with most antidepressants several decades ago and many scientists believed that there must be some inherent association between the suppressive and therapeutic effects of antidepressants. Studies have shown that REM sleep deprivation can improve endogenous depression, measured on Hamiton and Global scales, and the extent of the improvement correlated positively and significantly with REM sleep pressure [110, 119]. Later, scientists proposed that REM sleep deprivation is the mechanism of antidepressant action or the mechanism of the drugs resided in their REM sleep suppressive effects [118, 120]. REM sleep latency can be a psychobiologic marker for depression [121]. These reports indicated that REM sleep suppression at the outset of antidepressant treatment could predict therapeutic effects for a time.

In recent years, more new antidepressants such as nefazodone, bupropion, mirtazapine and escitalopram, which do not suppress REM sleep, appear to be working well in treating depression, and more doubts are put on the hypotheses regarding REM sleep and depression [94, 99]. In one study on the effects of tranylcypromine on sleep in depressed patients, correlation analyses indicated that the antidepressant response was only weakly associated with changes in REM sleep [101]. A study on phenelzine and clomipramine also showed that their use did not rely on the cease of REM sleep or inhibition of NREM sleep [97, 100]. A common current viewpoint is that none of the hypotheses alone on NREM sleep, REM sleep or another sleep index is likely to predict therapeutic responses [122].

REM sleep suppression must be relative to the therapeutic effects of antidepressants more or less, and it should be considered combination with the mechanisms of these medications. Whether REM sleep suppression brought on by antidepressants is simply an epiphenomenon of drug actions or it participates positively in the therapeutic process of antidepressants is unclear and needs more investigation.

4.4. Mechanisms of the Suppressive Effects of Antidepressants on REM Sleep

The mechanisms of antidepressants differ in different classes of antidepressants and with specific medications. In general, the mechanism is associated with 5-HT and NE reuptake inhibition, the affinity or/and number of 5-HT_{1A} and 5-HT_2 receptors, α_1-, α_2-adrenoceptors, and histamine H_1 receptors. Most TCAs can inhibit the reuptake of both NE and 5-HT and block histamine H_1 receptors (except for lofepramine) and α_1-adrenoceptors (except for desipramine) [94]. MAIOs increase the availability of monoamines. NARIs, SSRIs and SNRIs are generally associated with 5-HT and/or NE reuptake inhibition, and some of them also have effects on receptor sites. The SARIs trazodone and nefazodone can block 5-HT reuptake weakly and are α_1-adrenoceptor, 5-HT_{1A} and 5-HT_2 receptor antagonists. The

NE and 5-HT antidepressant mirtazapine also acts as an antagonist of α_2-adrenoceptors, 5-HT_2 receptors and H_1 receptors [111, 123, 124].

The common point of different antidepressant action is to positively modulate the 5-HT and NE systems in the central nervous system. Both of these neurotransmitters, mostly derived from the dorsal raphe and LC, respectively, can inhibit cholinergic REM-on neurons in the LDT/PPT and lead to REM-off and arousal [125]. It may, to some extent, explain the REM sleep suppressive effect, sleep disturbances and fragmentation caused by most antidepressants. This part is also supported by the fact that most antidepressants, which cannot suppress REM sleep, having no potent or direct effects on NE or 5-HT neurotransmission. Others proposed that 5-HT_{1A} stimulation is linked to antidepressant suppression of REM sleep, while 5-HT_2 agonism is related to sleep disturbances. Blockade of α_1 and α_2-adrenoceptors is responsible for sleep promotion and fragmentation of sleep, respectively. Blockage of the histamine H_1 receptor is also regarded to have nonspecific sedative effects and may promote sleep [111]. Different subtypes of receptors that antidepressants act on may partially account for their various therapeutic effects.

5. DISCUSSION

As a result, impaired sleep could be common in patients with depression, while it also could be an independent cause to this psychiatric disorder. EEG studies proved that REM sleep disinhibition is the main and key performance of sleep disorder in patients suffering from different depressive disorders.

REM sleep could be modulated by complex neuro-biological process. Cholinergic and monoaminergic neurons in the brainstem are the earliest targets noticed by researchers. Cholinergic neurons in LCalpha, peri-LCalpha, LDT, PPT and NPO tend to induce and sustain REM sleep, while monoaminergic neurons in LC regulating REM sleep negatively. Antidepressants which increase the level of 5-HT and NE, or the affinity of their receptors in synapses are found to influence REM sleep strongly, while those that do not suppress REM sleep or decrease REM sleep moderately have no direct effects on monoaminegic system. GABAergic and histaminergic neurons are also important to regulate REM sleep. Besides, as one of the most important incentives of depression, stress could disturb the function of other REM sleep modulating regions including corticolimbic system such as hippocampus, amygdala and mPFC, and LHb.

This paper discusses the neurobiological basis of REM sleep regulation and REM sleep abnormalities in depressed patients, and explores the mechanisms of antidepressants in regulating REM sleep. It should be noted that most researches in the paper which explore the effect of antidepressants on REM sleep are studies on patients with MDD. In fact, there are still some studies on animals, healthy volunteers or patients with other types of depression that could draw a similar conclusion. An interesting fact is that most antidepressants which suppress REM sleep could weaken sleep efficiency (elongated sleep latency, increased awakenings, decreased total sleep and sleep continuity) while those which do not influence REM sleep or alter it moderately tend to improve overall sleep efficiency. It means there may be relative opposite neurobiological foundation to modulate REM sleep and sleep efficiency, and even antidepressants in same group act in some different ways.

Among other treatments of depression, brain stimulation such as electroconvulsive therapy (ECT) and repetitive magnetic stimulation (rTMS), combined with partial sleep deprivation, are reported to be effective among drug-resistant patients [126, 127]. It is suggested that EEG may be employed to monitor longitudinally the electrophysiological effects of ECT and rTMS [128]. Patients with MDD accepting dorsolateral prefrontal rTMS displayed decreases of the alpha activity during REM sleep and increases of slow-wave activity, which is proportion by clinical outcome, possibly reflecting locally enhanced synaptic plasticity [129, 130].

However, it is still not completely understood how REM sleep is induced and regulated. Some depressed patients, especially patients with atypical depression, do not suffer from REM sleep disturbances. And more and more researches proved that there is no direct and necessary causality between the effects of antidepressants on REM sleep and the prognosis of disease. It still needs more discussion about how important REM sleep abnormalities in depressed patients are and whether they could be an auxiliary index to diagnose disease or evaluate the effect of pharmacological treatments.

CONCLUSIONS

Although current studies have confirmed a strong relationship between the disturbances of REM sleep and depression, the role of REM sleep abnormalities should be better elucidated for understanding psychiatric consequences and treatments of depression.

SPECIFIC AUTHOR CONTRIBUTIONS

Y.Q.W., R.L., M.Q. Z. and Z.Z. wrote most of the sections; and Z.L.H. and W.M.Q. revised the entire manuscript.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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