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Neurotransmitter Dysregulation in Sleep and Circadian Rhythms: Implications for Postpartum Depression

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Abstract. Postpartum depression (PPD) is a major mental health disorder that affects mothers both emotionally and physically, hindering their ability to care for the child. Other neurotransmitter imbalances during the postpartum period include serotonin, dopamine, melatonin, GABA, and orexin, which result in disturbances in sleep. The reduction in serotonin concentration is related to mood and sleep, while altered dopamine levels are related to alertness and coordinating circadian rhythms. Further, women postpartum demonstrates higher melatonin levels and a subsequent neuronal excitation due to lesser functioning GABA-A receptors, which in addition combine to cause disturbances with sleep. This paper reviews the literature to analyze the effects of neurotransmitter disorders in sleep and circadian rhythm on postpartum depression. The review provides emerging treatment options for postpartum depression including selective serotonin reuptake inhibitors (SSRIs), melatonin agonists, and benzodiazepines, which have shown promising results in relieving symptoms by modulating neurotransmitter pathways. However, more research needs to be undertaken in the field of non-pharmacological interventions, the long-term outcome of neurotransmitter dysregulation, and preventive measures during pregnancy that would go a long way toward improving overall outcomes for mothers as well as their infants.

Keywords: Postpartum depression (PPD), Sleep and Circadian Rhythms, Neurotransmitter Dysregulation.

1. Introduction

Postpartum depression (PPD) is a serious clinical condition that causes important mood swings and physical symptoms that make it difficult for new mothers to take care of their newborns. PPD normally occurs within the first four weeks of the postpartum period, with women feeling extremely depressed, increased anxiety, and fatigue. All these symptoms compromise maternal and infant health. If untreated, PPD can become a chronic depressive disorder. Conversely, if there is low arousal and little emotional exchange between the mother and the child, it may result in developmental delays with bad emotional regulation, as reflected in retarded milestones and emotionally dysregulated behavior [1-3].

Sleep disturbances are prevalent in PPD, hence the need for much study and prevention. The human body clock, known as circadian rhythms, synchronizes with the 24-hour pattern of light and darkness, directing sleep-wake as normal. Light, other physical activities, hormonal changes can influence the quality of sleep. Some important neurotransmitters that play a significant role in normal wake-sleep

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cycles include serotonin, acetylcholine, and orexin. These neurotransmitters are often found to be imbalanced in people with PPD, which may indicate a neurochemical basis for sleep disturbances [4-10].

There is a small body of literature showing that the activity of neurotransmitters and some biological pathways relate to PPD. Hence, this review will try to look into the expanding body of literature on Google Scholar in the area using keywords such as 'depression', 'postpartum', 'hormonal therapy', and 'pharmacotherapy' to evaluate sleep and circadian rhythms, and how neurotransmitters may play a part in changes noted during PPD. Elucidating the relationships between the imbalances of neurotransmitters and changes in the regulation of sleep and circadian systems among PPD patients will not only shed light on the mechanisms but also help propose innovative treatment strategies. This may aid in the creation of much more effective interventions to reduce postpartum depression severity.

2. Neurotransmitters Involved in Sleep and Circadian Rhythms in PPD

2.1. Serotonin

Serotonin is a critical neurotransmitter in regulating sleep and circadian rhythms, as evidenced by numerous studies [11]. Research in animals prior to clinical trials has demonstrated that serotonin administration induces drowsiness and alters sleep patterns [12]. Serotonin interacts with the suprachiasmatic nucleus (SCN), the core circadian pacemaker located in the hypothalamus directly above the optic chiasm. This area is noted for its extensive serotonergic innervation, mediating these effects [12, 13]. The SCN receives a robust serotonin input from the brain's serotonergic neurons, which terminate predominantly in the central area of the SCN [14]. Current theories propose that serotonin modifies the timing of the circadian clock, advancing it during the subjective daytime and delaying it during the subjective nighttime, though these interactions are not yet fully understood [12]. During pregnancy and the postpartum period, serotonin levels typically decline, a condition linked to increased tryptophan degradation, a serotonin precursor during gestation [15]. Research correlates this reduction in serotonin with mood alterations, making it a significant factor in the depressive symptoms observed postpartum.

2.2. Dopamine

Dopamine, another vital neurotransmitter, affects wakefulness and modulates circadian rhythms, particularly in the retina. Specifically, the circadian release of vertebrate retinal dopamine facilitates proper light adaptation and transmission of light information to the SCN [16]. Additionally, dopamine receptors are known to influence clock gene expression in the dorsal striatum [17]. Instances of dopamine dysfunction, as seen in conditions like Parkinson’s disease, suggest potential impacts on circadian function [16]. In the context of PPD, there is evidence of striatal dopamine dysregulation, notably reduced dopamine D2 and D3 receptor binding. Researchers have also noted elevated levels of monoamine oxidase-A (MAO-A), resulting in dopamine deficiency [18].

2.3. Melatonin

The pineal gland secretes melatonin during the night as a hormonal signal to indicate the onset of environmental darkness [19]. Melatonin significantly influences the SCN, the body's master circadian clock, which possesses at least two high-affinity melatonin receptors, MT1 and MT2 [20]. Under synchronized conditions, the alignment between the endogenous circadian rhythm of melatonin and the sleep-wake cycle helps maintain stable neurobehavioral performance throughout a typical 16-hour waking day. This stability occurs because the circadian pacemaker counteracts the decline in neurobehavioral function associated with an increasing homeostatic sleep drive that accumulates with extended wakefulness [21]. Parry [22] and her team observed that during the postpartum period, depressed pregnant women exhibited higher nocturnal plasma melatonin concentrations compared to their healthy counterparts. This phenomenon might be due to reduced sensitivity to estradiol or progesterone effects on melatonin receptors in these patients. Consequently, the declining levels of

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estradiol and progesterone have less impact on women with major depression, resulting in elevated melatonin levels in women with postpartum depression compared to healthy postpartum mothers [22]. This observation establishes a link between postpartum depression and disruptions in melatonin regulation.

2.4. Gamma-Aminobutyric Acid (GABA)

GABA, an inhibitory neurotransmitter prevalent in the central nervous system (CNS) and peripheral tissues, is synthesized through the irreversible α-decarboxylation of L-glutamic acid or its salts, catalyzed by the enzyme glutamic acid decarboxylase in vertebrates. In the CNS, between 60% and 75% of synapses are GABAergic, highlighting GABA's essential role in neural functioning [23]. GABA's regulatory scope includes various behavioral aspects, such as modulation of the SCN to influence circadian rhythms, regulation of sleep through cortico-medullary pathways affecting both rapid eye movement (REM) and non-REM sleep, particularly slow-wave sleep (SWS), and mood regulation via its role in the amygdala, where it modulates stress and anxiety responses [23]. In the postpartum period, notable changes in GABAergic signaling include alterations in $GABA_A$ receptor functionality and disruptions in neurosteroid modulation. During pregnancy, increased levels of allopregnanolone amplify GABAergic inhibition, but a postpartum reduction in this effect diminishes the efficacy of $GABA_A$ receptors, thereby increasing neuronal excitability [25]. Such dysregulation is a significant factor in PPD.

2.5. Orexin (Hypocretin)

Neurons that produce orexin are located exclusively in the lateral posterior regions of the hypothalamus, including the perifornical zone, lateral hypothalamus, and posterior hypothalamus. The lateral hypothalamus plays a crucial role in regulating a variety of behavioral and homeostatic functions, particularly sleep-wake cycles, primarily due to the presence of orexin neurons [26]. Research has consistently shown that a deficiency of orexin-producing neurons in humans is associated with narcolepsy [27]. For example, Nishino's team found that orexin levels were undetectable in the cerebrospinal fluid (CSF) of narcolepsy patients, whereas they were readily detectable in individuals without this condition [28]. Additionally, the potential role of the orexin system in influencing depressive disorders has been examined in numerous studies. In 2001, Taheri and colleagues noted a significant reduction in orexin-immunoreactive neurons across several brain regions, including the hypothalamus, in an animal model designed to simulate human depression [29]. While the specific connection between the orexin system and PPD is not fully understood, imbalances in orexin are recognized to influence various depressive disorders. Further exploration of orexin's role in PPD could facilitate the development of targeted treatments for the sleep disturbances associated with this condition.

3. The balance between wakefulness and sleep is maintained

Through complex interactions among neurotransmitters and various feedback mechanisms. Disruptions in these systems commonly manifest as sleep disturbances, a prevalent symptom of PPD. The interaction between melatonin and dopaminergic pathways is critical for both nonphotic and photic synchronization of the biological clock within the striatum [30]. Furthermore, changes in neurotransmitter activity related to mood and sleep in PPD may be influenced by postpartum decreases in estrogen and progesterone [31]. Additionally, the stress and sleep deprivation from caring for a newborn can further exacerbate neurotransmitter imbalances. Even brief sleep deprivation, such as 12 hours, can alter GABAergic activities, while chronic sleep deprivation might profoundly affect synaptic plasticity, the balance between excitatory and inhibitory systems, and overall CNS function [32].

3.1. Hormonal Fluctuations

The postpartum period is characterized by significant hormonal fluctuations, especially in estrogen and progesterone, which play vital roles in neurotransmitter regulation. During pregnancy, the placenta

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produces these hormones, but their levels plummet sharply after childbirth, returning to pre-pregnancy levels by the fifth day post-delivery. This rapid decrease may disrupt the regulation of serotonin, a neurotransmitter critical for sleep management. Estradiol and estriol, active forms of estrogen produced by the placenta, accumulate throughout pregnancy, with estriol production primarily dependent on the metabolic activity of the fetal liver. Research indicates that estradiol may boost neurotransmitter efficacy by enhancing serotonin synthesis and reducing its degradation [31, 33]. Additionally, studies show mixed results regarding the potential impact of the sharp postpartum decline in progesterone on mood changes. One study tracking 27 women over six weeks postpartum found a modest correlation between changes in progesterone levels and postpartum depression [34]. The amygdala and hippocampus, crucial for sleep regulation, contain abundant progesterone receptors. These receptors interact with various other receptors, including voltage-gated ion channels and neurotransmitter receptors for GABA, serotonin, and dopamine [36].

3.2. Hypothalamic-Pituitary-Adrenal (HPA) Axis Dysregulation in Postpartum Depression

The postnatal period is characterized by the stress of new parental responsibilities, sleep deprivation, and physical recovery complications. This stress activates the HPA axis as a primary system in the activation of stress-related hormones such as Corticotropin-releasing hormone (CRH), Adrenocorticotropic hormone (ACTH), and cortisol. The anterior pituitary releases CRH, which stimulates the release of ACTH, and in turn activates the adrenal cortex to secrete cortisol. Many studies have shown that HPA axis upregulation predisposes an individual to PPD, with about 85% of all cases of depression being first primed by stress. Major Depressive Disorder (MDD) has long been considered having dysregulation of the HPA axis [38].

During pregnancy, significant changes occur within the maternal HPA axis. Starting by the seventh week, CRH is produced by syncytial cells in the human placenta, initiating the body's stress response. This hormone elicits a "fight or flight" reaction and permeates both the maternal and fetal environments. As pregnancy advances, placental CRH production escalates, leading to levels in the mother's bloodstream that resemble those seen in the hypothalamic-pituitary portal system under stress. Postpartum, the sudden halt in placental CRH production may disturb the HPA axis, potentially contributing to the pathophysiology of postpartum depression [37]. Additionally, CRH's interaction with neurotransmitter systems is noteworthy, especially its effect on central sympathetic and serotonergic systems. CRH modulates serotonergic system activity, notably enhancing activity at the 5-HT2A receptors and reducing it at the 5-HT1A receptors [39]. This change may lead to sleep disruptions, a common complaint among individuals with PPD.

4. Discussion

PPD poses a great number of risks for both the mother and the child.Neurotransmitter dysregulation in PPD may further reduce maternal behavior due to sleep disturbances. Neglect in children is likely to occur in mothers suffering from PPD; therefore, therapy aimed at sleep disturbances is important. Pharmacologic treatments have played an essential role in treating these sleep disorders, aiming at specific symptoms and overall improvement in sleep by several methods. They range from antidepressants acting on the serotonin and dopamine pathways to melatonin and its agonists in circadian regulation, among other drugs that augment the effect of GABAergic activity on sleep quality.

Selective Serotonin Reuptake Inhibitors (SSRIs) alleviate sleep disturbances that may be associated with mood changes. Agents like Nefazodone block the reuptake of serotonin and, in this way, are beneficial for improving the quality and quantity of sleep [40]. Research shows that SSRIs, by inhibiting the reuptake of serotonin back to the presynaptic neuron, increase the availability of serotonin in the synaptic cleft and elevate this important neurotransmitter level [41].

Melatonin receptors have been targeted for possible pharmacologic therapy in sleep-wake disorders. A new class of melatonin receptor agonists, such as ramelteon and tasimelteon, has been developed to modulate the effects of the melatonin system based on well-characterized pharmacological profiles and safety evaluations, and these drugs have obtained regulatory approval [42].

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GABA-A agonists, such as Benzodiazepines, are a favored treatment for insomnia due to their interaction with GABA neuroreceptors. Compared to earlier treatments, they pose a lower risk of overdose and dependence, making them a safer option for treating sleep disturbances. Their effectiveness stems from their unique mode of action, they do not activate GABA-A receptors directly but function as allosteric modulators, enhancing GABA inhibition. These agents are classified as benzodiazepine site agonists or positive allosteric modulators of the GABA-A receptor, distinct from inverse agonists, which diminish GABA efficacy by reducing chloride ion permeability [43]. Benzodiazepines enhance the effects of GABA at the GABA-A receptor, resulting in pronounced sedative and anxiolytic actions, valuable in treating conditions associated with sleep and anxiety disturbances.

5. Conclusion

The study describes PPD, an everyday mental disorder in women. The condition exhibits psychological symptoms such as sadness and physical symptoms, for instance, poor sleep. In the treatment of PPD, knowledge about the neurobiological basis is at the core, whereby it involves the dysregulation of neurotransmitters in relation to both poor sleep and disturbances in the circadian rhythm. The major neurotransmitters involved with the sleep wakefulness cycle are serotonin, dopamine, melatonin, GABA, and orexin. When these set of neurotransmitters are interfered with, they can be a great cause of impact on the general health of a person with PPD.

Therefore, it is important to consider the long-lasting impact of dysregulated neurotransmission in PPD. Prolonged effects of PPD may manipulate the levels of the neurotransmitters within the brain, thus resulting in lasting behavioral alterations, which may include sleep disorders. By studying women during and post-pregnancy, researchers can monitor changes in neurotransmitter levels influenced by hormonal shifts, stress, and environmental factors. Furthermore, research about neurotransmitter dysregulation in such women is important not only with respect to the pregnancy of women but also with respect to the status of pregnancy. If preventive treatments could be given during or after childbirth, PPD would greatly decrease.

However, there are several challenges in the pharmacologic treatment of PPD and its complications: metabolic changes occurring during the postpartum period; potential impacts of medications on breast milk and the infant; impacts of depression and treatment on the mother's caregiving capacity; and stigma toward the use of medications that may lead to a perception of inadequacy. Such factors impact patient and caregiver decisions about pharmacotherapy [44]. Researchers are also discussing non-medication therapies for the treatment of PPD. There is a need for further research work to establish the efficacy of psychotherapies, compare the effectiveness of antidepressant medications with psychotherapy, and see the outcome of combining psychotherapy with antidepressant medication treatment versus each one alone.

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