Neuroactive Molecules in the Etiology of Postpartum Depression
An overview

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Postpartum depression is a serious and frequent condition that affects a significant proportion of new mothers in developed countries. Despite its high prevalence and proven deleterious outcomes for both mother and child, there remains an increasing need to expand our knowledge regarding new methods that ensure the discovery of at-risk patients. Many theories have been developed over the years, mainly focusing on hormonal imbalances that occur after childbirth. This review has the purpose to analyze the existing literature and to summarize the latest findings on neuroactive molecules which may predict postpartum depression in new mothers.

Keywords: Postpartum depression, hormonal imbalances, neuroactive molecules

Nowadays, postpartum depression (PPD) is considered a serious medical disease that affects mothers during the first 4 weeks after birth. The diagnosis is made when new mothers associate at least five depressive symptoms out of nine, with a duration of 2 weeks minimum, with the nine symptoms being: depressed mood, loss of interest, loss of energy, insomnia/ hypersomnia, affected concentration/ hesitation, change in weight / appetite, psychomotor retardation/ restlessness, suicidal ideation/ attempt and repeated thoughts of death, feelings of worthlessness/ guilt [1, 2] . PPD has been shown to more likely affect women with a history of depression [3]. However, other aspects are implicated in the development of PPD, such as sociodemographic characteristics and personality traits, pregnancy complications, certain obstetric circumstances and biological factors [3, 4].

Pregnancy is characterized by hormonal fluctuations, with a gradual increase in estrogen and progesterone levels that is followed by a dramatic and rapid fall in these hormonal levels associated with delivery [5]. After having reached their peak, the massive reduction of estrogen and progesterone to baseline levels within 2–5 days after delivery has elicited the assumption that postpartum mood changes are generated by hormone withdrawal [6].

Neuroactive molecules in pregnancy

1. Pregnancy hormones

During the first 48 hours after birth, new mothers experience a dramatic fall in estrogen, progesterone, cortisol and neurosteroid levels. Although some studies argued against the involvement of hormonal fluctuations in the etiology of PPD [7, 8], more recent evidence supports the link between steroid withdrawal and the presence of PPD [8, 9].

Estrogen is one of the most important hormones in pregnancy, reaching a peak at the end of the third trimester which is followed by a sudden fall in the first 2-4 days after delivery [5, 6]. It plays a significant role in neuromodulation by reducing neuronal excitability in the basolateral amygdala complex and regulating GABAergic inhibition. Furthermore, the estrogen elevation seen during pregnancy, which is followed by a rapid drop postpartum, has a great influence on the GABAergic and glutamatergic synaptic plasticity in the basolateral amygdala complex [10]. Successful treatment of postnatal depression through estrogen replacement therapy demonstrates its crucial role in PPD [11, 12].

Progesterone and allopregnanolone are steroids that have been correlated with PPD since their lowest falls coincide with the peak of PPD symptoms [13, 14]. Several clinical trials showed that brexanolone, an intravenous formula of allopregnanolone, had a positive effect as a possible treatment for PPD [15]. Interestingly, however, administering progestagen to women in the puerperal period has been shown to boost the risk of developing PPD [16]. These steroids exert modulatory effects not only on the hypothalamic-pituitary-adrenal axis (HPA), but also on neuroplasticity, cellular energy, immune system activation and cortical activity, mechanisms to which depression is believed to be linked [17, 18]. Moreover, progesterone is recognized as a modulator of oxytocin mRNA expression in brain regions associated with lactation and maternal behavior [19-21].

Prolactin, the hormone responsible for the regulation of lactation, is mainly synthesized and secreted by the lactotroph cells in the anterior pituitary gland, which is also involved in maternal behavior. As a result of hormonal imbalances, unsuccessful lactation frequently co-occurs with and aggravates PPD [22].

Thyroid hormones are often culpable for mood disturbances. Although there are studies that could not

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illustrate a direct link between PPD and thyroid hormone imbalance [9, 23], it is believed that thyroid dysfunction contributes to the development of PPD. A prospective study that was performed on 303 euthyroid pregnant women showed that 38% of those that developed postpartum thyroid disorders associated PPD which resolved with treatment of the thyroid dysfunction [24].

Oxytocin, a neuropeptide released during psychosocial interactions, is assumed to facilitate social recognition and bonding [25]. Recent studies have found that low oxytocin levels during the third trimester are linked to numerous symptoms of depression both in pregnancy and in the postpartum period, leading to inadequate breastfeeding and PPD [26, 27].

Cortisol has been extensively researched as a possible predictor in psychiatric disorders. One predictive model measuring salivary cortisol along with markers of inflammation (IL 8 and 10) revealed that an initial postpartum cortisol elevation enhances the risk of PPD [28].

Corticotropin Releasing Hormone (CRH) is also investigated for its function within the HPA axis and during stress feedback. CRH is produced by the placenta and has a sharp fall after delivery, along with the reproductive hormones. Studies have shown that elevated CRH levels are correlated with an increased risk of PPD [29, 30], some authors going as far as proposing the implementation of PPD screening programs based on CRH measurements [28].

Beta-endorphin is an opioid neuropeptide which has an integrative function within the HPA axis. Yim et al. showed that measuring beta-endorphin levels in the 25th week of pregnancy could predict PPD at 9 weeks after childbirth [31].

2. Neurotransmitters correlated with PPD

Neurotransmitters are a distinct class of neuroactive molecules which modulate neural transmission within the nervous system. They are generally associated with depression and increasing evidence suggest they play a pivotal role in the development of PPD.

Serotonin plays a central role in the physiopathology of affective disorders, with current treatments targeting the serotonergic system. Serotonin levels are modulated not only by cortisol, but also by progesterone and estradiol, all of which undergo significant changes both during and after pregnancy [32]. PET studies have shown diminished postsynaptic 5-HT$_{1A}$-receptor binding in PPD patients [33], while the evaluation of peripheral serotonin activity among these patients has demonstrated decreased platelet serotonin levels [34] and reduced tryptophan levels [35]. When also taking into consideration the beneficial effect of the selective serotonin reuptake inhibitors (SSRI) on PPD patients, the evidence supporting the involvement of the serotonergic system becomes clearer.

Dopamine is actively involved in the mechanisms of depression, with deficits in its activity being a possible underlying cause of it [36]. Dopaminergic activity is regulated by various brain structures such as the basolateral complex and the ventral subiculum [37], but also by ovarian hormones, mainly estrogen, which has been shown to decrease dopamine uptake, especially in the nigrostriatal and mesolimbic systems [38].

Norepinephrine and epinephrine play important roles in affective regulation and have been associated with emotional disorders such as depression and anxiety. However, current research is unsure whether depression and anxiety necessarily require a deficiency in these catecholamines, with particular studies actually indicating an excess of these molecules [39, 40]. Hormonal fluctuations underwent during and after pregnancy greatly influence the synthesis and metabolism of these neurotransmitters, mostly through their impact on the central nervous system [41].

Glutamate has been reported to have a significant role in predicting major depression as a result of a glutamatergic dysregulation occurring in the medial prefrontal cortex [42]. Glutamate levels are mostly influenced by the fluctuation of female hormones during the menstrual cycle [43]. Several studies have pointed out the glutamatergic dysfunction witnessed in PPD patients [42, 44].

Gamma-aminobutyric acid (GABA) is the dominant neurotransmitter in the hypothalamus. Estrogen withdrawal in the postpartum period seems to impair the GABAergic and glutamatergic synaptic transmission, as well as the plasticity in the basolateral amygdala complex [1], while high concentrations of progesterone impede the amygdala activity in a manner comparable to that of benzodiazepines [45].

3. Monoamine Oxidase A (MAO-A)

MAO-A is an enzyme that mediates the deamination of amines like serotonin, dopamine and norepinephrine [46]. MAO-A appears to be excessively active in people suffering from depression, which would explain the reduced levels of these neurotransmitters among these patients. This theory was supported by PET studies highlighting the increased activity of MAO-A in depressed people's brains [47]. In PPD patients, Sacher et al showed a firm correlation between elevated MAO-A levels and depressive symptoms in postpartum women [48].

Conclusions

Postnatal emotional changes vary from baby blues to severe psychosis. Although etiology remains rather ambiguous, it is clear that external risk factors act in combination with hormonal variations and neurotransmitter dysregulation. This literature review is meant to highlight the necessity for further investigation into the neurobiology of postnatal psychiatric changes that will deepen the insight into postpartum depression, therefore contributing to the ultimate goal of developing new approaches for superior prevention and treatment measures.

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