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Mini Review

Making Room for Specific Molecules in the Treatment of Depression -

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INTRODUCTION

Depression as one of the most prevalent and life-threatening forms of mental illness affects about 1/5 of the world's population [1], and the number of patients suffering from it is still increasing [2]. The understanding of the pathophysiology and the treatment of this disorder remains greatly challenging to modern medicine. Though many different antidepressants were commercially available during the past years, not all patients were treated satisfactorily accompanied with some potential side effects of these drugs [3,4]. This highlights the imperative to the continuous search for new alternatives for the treatment of depression [5,6]. Some recent studies documented that some specific molecules such as chrysin [6], oxytocin [7], P11 [8], and OTX2 [9] are closely related to depression/depression-like behaviors, which suggests potentially important roles of these molecules in the treatment of depression. The current review will summarize some recent studies which focus on the potentially causal relationship between specific molecules and depression/depression-like behaviors with an aim to provide some insights into the therapeutic treatment of depression.

Some natural products from plants have been identified as supplemental interventions to treat or prevent central nervous system disorders, including depression [5,6,10-14]. In a mouse behavioral model of depression, green tea polyphenols could remarkably decrease immobility in both the Forced Swimming Test (FST) and Tail Suspension Test (TST), indicating the antidepressant-like effects of green tea polyphenols [5]. This natural compound could also reduce serum corticosterone and Adrenocorticotropic Hormone (ACTH) levels, suggesting that these antidepressant-like effects may involve the inhibition of the Hypothalamic-Pituitary-Adrenal (HPA) axis. Resveratrol is another kind of natural polyphenol abundant in *polygonum cuspidatum*. In a rat model of depression induced by the Chronic Unpredictable Mild Stress (CUMS), resveratrol could reverse the behavioral abnormalities and the elevated serum corticosterone levels observed in CUMS-treated rats, revealing the strong antidepressant-like effects of resveratrol [14]. Additionally, it was confirmed that such antidepressant-like effects were partly due to the mediation by normalizing serum corticosterone levels while up-regulating Phosphorylation Of Extracellular Signal-Regulated Kinase (pERK), cAMP response element-binding protein (pCREB) and Brain Derived Neurotrophic Factor (BDNF) levels in the hippocampus and amygdala. Interesting, chrysin as one important kind of natural polyphenols has also been studied more extensively due to its satisfactory effects on antidepressant therapy. Compared with fluoxetine, chrysin exhibited equivalent antidepressant effects on behavioral, neurotrophic and biochemistry aspects in a CUMS-induced mouse model of depression [12], which is possibly dependent on the up-regulation of BDNF and Nerve Growth Factor (NGF) levels. The potential role of chrysin for the treatment or supplementary treatment of depression was further reinforced by a recent study indicating that chrysin could ameliorate the depressive-like behaviors of a mouse model of agitated depression [6]. Beside polyphenols, another plant compound hesperidin could also produce antidepressant-like effects in mice through its interaction with the L-arginine-Nitric Oxide (NO)-Cyclic Guanosine Monophosphate (cGMP) pathway [13]. Collectively, natural products such as polyphenols and hesperidin from plants have great potentials in the antidepressant therapy, which may mediate by the regulation of cell signal pathways and neurotrophic/growth factors in specific brain areas. The role of these natural products in antidepressant-like effects also highlights the great possibility and perspective in exploring some other natural compounds potentially endowed with powerful effects in the treatment of depression.

Dysfunction or abnormal regulation of some proteins in specific brain areas are tightly closed with certain neurological disorders [15,16], including depression [7-9,17]. Great efforts have been made appealing to pay more attention to the crucial role of oxytocin in depression [7]. In the previously informative review, the authors detailed the interactions between the oxytocinergic system and HPA axis functioning as well as with monoaminergic activity. Moreover, oxytocin variations pertaining to variations of growth factors and inflammatory immune system changes that were implicated in depressive disorders were also examined. It was implicated that oxytocin was directly or indirectly involved in the development of depression, and reminded the necessary consideration of salient roles of oxytocin in future studies. In addition, the multifunctional protein p11 (also known as S100A10) has also been documented playing an important role in regulating depression-like behaviors [8,17]. A very recent study showed that knockdown of p11 expression in mouse Lateral Habenula (LHb) ameliorated the stressed-induced depression-like behaviors while the chronic stress induced up-regulation of p11 in LHb promoted the depression-like behaviors [8]. This work by Seo et al. highlighted p11 in LHb as a key molecular determinant regulating depression, and implicated LHb as an emerging brain region for investigating the pathophysiology of depression. Another new research dependent on RNA-sequencing recently reported that the developmental transcription factor Orthodenticle Homeobox 2 (OTX2) could mediate gene expression in Ventral Tegmental Area (VTA) during specific developmental periods in a stress-induced mouse model of depression, which, in the end, produced a life-long depressive like-primed state of mice [9]. This work indicated that OTX2 could regulate negative emotions even in the putative brain reward region, VTA. It also implied that certain proteins, though as single molecules, could produce significantly global depressive-like behavior changes under extraordinary circumstances, which could be supported by a previous study focusing on the relationship between β form of calcium/calmodulin-dependent protein kinase type II (βCaMKII) in LHb and depression [18]. It was documented that βCaMKII was remarkably up-regulated in the LHb of learned helpless rat model of depression, which could be rescued by antidepressants. Interestingly, increasing β- rather than α-CaMKII in the LHb was sufficient to induce profound core depressive symptoms such as behavioral despair and anhedonia. This work underscores βCaMKII as a key molecular determinant of depression depending on its powerful regulation of LHb neuron function. The crucial roles of p11 and βCaMKII in LHb as well as OTX2 in VTA in depression suggest that abnormal regulation of specific proteins involved in depression occurs in both brain regions (LHb) primarily encoding aversive signals [19] and areas (VTA) mediating reward signals [20].

Collectively, the severity and economic burden resulted from depression, the side effects of some antidepressants, as well as the great challenge of understanding the pathophysiology and the treatment of this disorder makes it imperative to a continuous search for new alternatives for the treatment of depression. Making room for specific molecules like aforementioned and continuously exploring new molecules pertaining to depression in specific target brain areas will definitely help to decipher the molecular and cellular basis of depression, and will shed some lights on the future clinical treatment of depression.

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