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Abnormal GABAergic Neurotransmission in Depression

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Commentary

Depression as a neuropsychiatric disorder is characterized by anhedonia and lack of motivation [1], which has led to great social and economic burdens. A plethora of recent studies have highlighted the underlying mechanisms of this mood disorder from different aspects [2-10]. Generally, the pathogenesis of depression is closely associated with dysfunctions in neural circuits which, to some extent, are largely resulted from the abnormal neurotransmitter release from presynaptic neurons to their corresponding postsynaptic targets. The γ-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in the central nervous system and functions *via* binding to A and B receptors. The presence of GABA neurotransmission in interneurons could modulate local neuronal circuitry, including serotonergic, dopaminergic, and noradrenergic neurons [11]. The potential association between the GABA and depression was firstly drew the attention of scientists by the fact that patients with depression exhibited a reduced GABA concentrations in the cerebrospinal fluid [12]. Thereafter several lines of evidence have documented that abnormal GABAergic neurotransmissions are responsible for the pathophysiology of depression [11,13-16].

GABA centrally origins from the plasma and GABA plasma levels are generally considered as an index of brain GABA activity [17,18]. It was indicated that plasma GABA levels was lower in about 40% of patients with depression [19]. Preclinical studies in animal models have highlighted the compensatory changes in the GABAergic system induced by chronic stress [20]. Several clinical studies demonstrated that reduced GABA concentrations in patients with depression were most observed consistently in the occipital cortex (OCC) [13]. GABA concentrations were also decreased in the anterior cingulate cortex [21] and in some prefrontal cortex areas [22] of depressive patients. The aforementioned evidence suggests that depression was probably associated with reduced GABA concentrations. The GABAergic neurotransmission depends on interactions between GABA and its corresponding GABA A and B receptors. There is evidence showing that GABA A receptors-deficient mice were used as animal models of depression [14]. Pharmacological and genetic studies suggested that loss-function of GABA B receptors induced antidepressant-like behavioral effects in a variety of rodent models of depression, and the activation of GABA B receptors could block the therapeutic effects of some known antidepressants and induced depression-like behaviors [23]. In addition, transcranial magnetic stimulation studies further confirmed that GABA B receptors neurophysiological deficits were closely associated with the pathogenesis of major depressive disorder [15]. More interestingly, this study also implied that major depressive disorder was related to GABA B receptors abnormalities, whereas treatment resistant major depressive disorder was associated with both GABA A receptors and GABA B receptors B dysfunctions, suggesting that more marked GABAergic neurotransmission dysfunctions were associated with more severe symptoms.

The very recent studies suggest that GABAergic deficits in the prefrontal cortex and nucleus accumbens are potentially responsible for the pathophysiology of depression [24,25]. Though great advances in deciphering the potential role of GABAergic neurotransmission in the pathogenesis of depression, yet much more are still needed to be addressed concerning GABAergic abnormalities being not peculiar to depression but being similarly documented in a plethora of other neuropsychiatric disorders, especially schizophrenia [26]. In addition, the possibility that whether and how taking GABAergic neurotransmission dysfunctions as a marker to differentiate between depression and other neuropsychiatric disorders remains much to be explored in the future studies.

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