Commentary

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Rapid-Onset Antidepressants and Radix Polygalae

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Major depression is a mood disorder that manifests various symptoms such as depressive mood, anhedonia, sleeping habit change and abnormal contents of thought. Depression and depressive disorders were the second cause of disability and the World Health Organization estimates that antidepressants will top the list of prescription drugs by 2020 [1].

Monoaminergic antidepressants have been developed since the coincidental discovery of the antidepressant effect of drugs that increase the concentration of serotonin and norepinephrine in the synapses. However, in many clinical trials, problems such as lack of efficacy, recurrence of depression, and side effects have been pointed out from monoaminergic antidepressants. Especially, the lag period, which is a delay in drug effect, is a problem in self-harming situations such as suicidal ideation. Therefore developments of rapid-onset antidepressants are required.

The "Glutamate hypothesis of depression", emerged from the discovery of antidepressant-like effects of glutamatergic synaptic modulators such as amantadine (NMDA antagonist), D-cycloserine (partial NMDA agonist), lamotrigine (glutamate release inhibitor), and riluzole (glutamate release inhibitor and AMPA potentiator). Especially ketamine, an dissociative anesthetic reagent acting on the NMDA receptor improved depressive symptoms of treatment resistant patients within 4 h [2]. Subsequent clinical trials revealed that the antidepressant effect of ketamine can be initiated within 2 and can last for a week after a single infusion [3]. Such rapid-onset antidepressant effect is associated with the GluR1 phosphorylation of AMPA receptor and mTORC1 dependent synaptic changes [4]. In addition, signaling of BDNF (brain derived neurotrophic factor), eEF2 (eukaryotic elongation factor 2) and GSK-3β (glycogen synthase kinase 3 beta) has been shown to be associated with ketamine's rapid onset properties. However, the development of alternative drugs with similar pharmacological reaction rather than ketamine, which is at high risk for drug abuse, has been viewed as a desirable direction.

Preclinical and clinical studies to develop drugs with rapid onset are underway in response to these needs [5]. Glutamatergic modulators such as Esketamine (non-competitive NMDA receptor antagonist) MK-0657 (CERC-301; GluN2B antagonist), GLYX-13 (rapastinel; glycine site partial agonist), AZD6765 (lanicemine; low affinity open channel NMDA antagonist), NRX-1074 (NMDA glycine site partial agonist, selective GluN2B antagonist), AV-101 (glycine receptor antagonist), dextromethorphan (non-competitive NMDA antagonist) and Basimglurant (RG-7090; mGluR5 negative allosteric modulator) are under clinical trials with positive results. Therapeutic targets beyond the glutamatergic system with rapid onset effect are also being tried clinically. Scopolamine (cholinergic muscarinic receptor antagonist) [6] and L-Acetylcarnitine (epigenetic regulation of mGluR2s by acetylation) [7] have shown positive results. Sleep deprivation [8] and deep brain stimulation into brain regions such as subgenual cingulate gyrus, nucleus accumbens, anterior limb of internal capsule and medial forebrain bundle [9] also exhibited rapid onset effects.

Root of Polygala tenuifolia (Radix polygalae) is a traditional herb used for its tranquillizing and anti-amnesic effects in East Asian countries. Recent research disclosed wide range of biological activities of Radix polygalae and it active compounds, such as dopaminergic D2 and serotonergic 5-HT2 receptor binding, NMDA toxicity protection, prevent depression symptoms in chronic mild stress model animals, and induction of brain-induced neurotrophic factor (BDNF) in the hippocampus. Behavioral tests such as female urine sniffing test, novelty suppressed feeding, learned helplessness paradigm and anhedonia in chronic mild stress exposed animals require repeated dose of monoaminergic antidepressant reagents to exert antidepressant-like effects. But single or two doses of Radix polygalae extract improved depression related behaviors in these tests. Like ketamine, pretreatment of an AMPA receptor antagonist abolished

the antidepressant-like effect of Radix polygalae. Also the phosphorylation of hippocampal AMPA receptor GluR1 subunit was changed.

Radix polygalae is a commonly prescribed reagent by practitioners of traditional medicine. According to these recent findings, Radix Polygalae extract may have rapid-onset antidepressant effect which can be a safer alternative to ketamine and lead to the development of life-saving medications by reducing the risk of suicide in emergency situations [10]. In addition, it may provide a pharmacological tool and valuable insights to understand the pathophysiology of depression.

References

1 Ferrari AJ, Charlson FJ, Norman RE (2013) Burden of depressive disorders by country, sex, age and year:Findings from the global burden of disease study. PLoS Med 10: e1001547.

2 Berman RM, Cappiello A, Anand A (2000) Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 47: 351-354.

3 Zarate CA, Singh JB, Carlson PJ (2006) A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 63: 856-864.

4 Li N, Lee B, Liu RJ (2010) mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science 329: 959-964.

5 Machado-Vieira R, Henter ID, Zarate CA (2017) New targets for rapid antidepressant action. Prog Neurobiol 152: 21-37.

6 Jaffe RJ, Novakovic V, Peselow ED (2013) Scopolamine as an antidepressant: A systematic review. Clin Neuropharmacol 36: 24-26.

7 Machado-Vieira R, Ibrahim L, Zarate CA (2011) Histone deacetylases and mood disorders: Epigenetic programming in gene-environment interactions. CNS Neurosci Ther 17: 699-704.

8 Bunney BG, Bunney WE (2013) Mechanisms of rapid antidepressant effects of sleep deprivation therapy: Clock genes and circadian rhythms. Biol Psychiatry 73: 1164-1171.

9 Bewernick BH, Hurlemann R, Matusch A (2010) Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. Biol Psychiatry 67: 110-116.

10 Shin IJ, Son SU, Park H (2014) Preclinical evidence of rapid-onset antidepressant-like effect in Radix Polygalae extract. PLoS ONE 9: e88617.