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•Commentary•

Fast-onset antidepressant targeting the nNOS-SERT interaction in the DRN

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Major depressive disorder is one of the most deleterious mental disorders with a high suicide rate, incidence and recurrence rate, which is manifested as continuous depression, retardation of thinking as well as loss of appetite and sleep disturbances [1, 2]. In addition, depression is a principal cause of disability and physical labor loss worldwide [3, 4]. Based on the hypothesis of predominant monoaminergic neurotransmitter deficiency towards depressive disorders, a series of antidepressants have been developed to inhibit the re-uptake of monoamine, especially serotonin (5-hydroxytryptamine) and noradrenaline. However, the drugs based on the monoamine deficiency hypothesis exert slow-onset effects, and patients with depression are usually reluctant to take currently available antidepressant drugs [5]. In China, traditional Chinese medicines have been long used to treat brain diseases [6-9]. Several traditional Chinese medicines have displayed good therapeutic effects on depression, such as Sini Powder, Lily Bulb and Rehmannia Decoction, and so on [2, 10, 11], but they also exert limited therapeutic effects on depression due to unpleasant side effects. Thus, there is an urgent need for new therapeutic strategies to develop fast-onset antidepressants against major depressive disorder.

In an article entitled "Design of fast-onset antidepressant by dissociating SERT from nNOS in the DRN" recently published in Science [12], Sun *et al.* discovered that the SERT-nNOS complex in the dorsal raphe nucleus (DRN) was selectively increased in chronic unpredictable mild stress (CUMS) mice, which subsequently augmented depressive behaviors. Most importantly, the authors screened a series of compounds targeting the nNOS-SERT interaction using cultured HEK293T cells co-transfected with nNOS- and SERT-encoding plasmids, and discovered ZLL-7 as a blocker of the nNOS-SERT interaction to specifically reduce the intercellular serotonin concentration in the DRN of the brain, which exerted an antidepressant effect 2 h after intragastric or intraperitoneal administration in 28 d-CMS-experienced mice. Particularly, ZZL-7 was detected in the mouse DRN 30 min after administration, indicating that ZZL-7 is able to easily pass through the blood-brain barrier. In addition, ZZL-7 as a fast-onset antidepressant, did not show undesirable side effects like other antidepressants such as ketamine. Ketamine may cause a series of hallucinatory symptoms, such as memory deficiency, hallucinations as well as panic state, vomiting and somnolence. This study found the antidepressant ZLL-7 has a fast onset of action, which overcomes the defects of the third-generation antidepressants characterized by slow-onset effects, and updates the understanding of monoaminergic neurotransmitter deficiency hypothesis which indicates a slow onset of action of antidepressant treatments.

This study has several limitations which need to be clarified in the future. First, it is not clear about the detailed pharmacokinetics of ZZL-7, such as its concentration ($ng \cdot mL^{-1}$) in plasma and the brain of 28d-CMS-experienced mice after intravenous injection of ZZL-7 (40 $mg \cdot kg^{-1}$), which requires further investigation to determine the effective concentration of ZZL-7 in the brain. Second, the authors verified that ZZL-7 possessed no unwanted side effects on general action or locomotor action, memory or cognitive ability and did not aggravate aggression, addictive behavior, or other abnormal brain-wave activity; however, it remains unclear about the potential side effects of ZZL-7 in other tissues except the brain, its potential long-term toxicity and drug dependency, its efficacy and safety even in nonhuman primates. Third, the

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therapeutic effects of ZZL-7 on other depression models have not been examined, such as chronic restraint stress model, olfactory bulb excision model, corticosterone-induced depression model. Forth, the effective dosage of ZZL-7 administrated at 40 mg·kg^{-1} in this study is pretty high, and the possible effective dosage of ZZL-7 in nonhuman primates needs to be explored for possible clinical trials. Finally, whether the SERT-nNOS coupling is associated with the depressive behaviors in clinical MDD patients, needs to be further investigated for clinical relevance.

Overall, this study provides a novel target and a lead compound for further development of first-in-class fast-onset antidepressants. Given that traditional Chinese medicines have been used for the treatment of depression [2, 11], effective natural products may also provide a valuable source for the discovery of novel blockers of the nNOS-SERT interaction, which would be further developed into a new class of fast-onset antidepressants.

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