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Letter to the editor:

ROLES OF SERINE IN NEURODEGENERATIVE DISEASES

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Neurodegenerative diseases are age-related diseases characterized by cognitive impairment, such as Alzheimer's disease (AD), Parkinson's disease, and schizophrenia (Wu et al., 2022). As a nonessential amino acid, serine plays fundamental roles in neurodegenerative diseases and has two optical isomers of L-serine and D-serine (Zhang and Bai, 2023).

Supplementary L-serine ameliorates cognitive dysfunction in both animals and humans (Handzlik and Metallo, 2023). In the brain, L-serine is predominantly synthesized *de novo* from glucose in astrocytes by 3-phosphoglycerate dehydrogenase due to the low permeability of the blood-brain barrier (BBB) for L-serine, and is indispensable to the biosynthesis of selenoproteins for the maintenance of cognitive functions (Zhang and Bai, 2023). Although the diffusion of D-serine through the BBB still remains slow and weak, its permeability across the BBB is higher than L-serine (Bai et al., 2023). Compared to L-serine, D-serine is a more potent neurotransmitter and a gliotransmitter for neurodegenerative diseases. D-serine is concentrated in the brain, especially the cerebral cortex and hippocampus. As an endogenous amino acid, D-serine is converted from L-serine by pyridoxal 5′-phosphate-dependent enzyme serine racemase (SR) in neurons and astrocytes (Bai et al., 2023), and degraded by D-amino acid oxidase (DAAO) in astrocytes (Ni and Mori, 2022). Overexpression and deficiency of SR are associated with some neurodegenerative diseases, such as AD (Madeira et al., 2015) and schizophrenia (Labrie et al., 2009) since D-serine content depends on SR.

D-serine is a potent co-agonist for N-methyl-D-aspartate glutamate receptor (NMDAR), which plays important pathophysiology roles in synaptic functions, such as synaptic plasticity, learning, and memory. D-serine-mediated NMDAR activation is crucial for the regulation of neurodegenerative diseases, however, the overactivation of NMDAR induces excitotoxicity, thus leading to cognitive impairment (Mota et al., 2014). D-serine is considered as a biomarker of neurodegenerative diseases because low D-serine levels were observed in AD animals and patients (Le Douce et al., 2020; Madeira et al., 2015). However, D-serine was not significantly different in cerebrospinal fluid between schizophrenic patients and healthy controls (Fuchs et al., 2008). Oral D-serine supplementation for 2 weeks restored the spatial memory deficits in transgenic AD mice (Le Douce et al., 2020), and oral 4-week D-serine at doses of 60 and 120

mg/kg/day effectively improved persistent symptoms and neurocognitive dysfunction in schizophrenic patients (Kantrowitz et al., 2010).

Taken together, serine shows promising potential in the prevention and treatment of neurodegenerative diseases, however its exact mechanism remains unclear. Further studies are needed to confirm the mechanism.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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REFERENCES

Bai YZ, Li JM, Zhang SQ. Potential novel mechanism of selenium on cognition. Metab Brain Dis. 2023 Sep 12. doi: 10.1007/s11011-023-01289-1. Epub ahead of print.

Fuchs SA, De Barse MM, Scheepers FE, Cahn W, Dorland L, de Sain-van der Velden MG, et al. Cerebrospinal fluid D-serine and glycine concentrations are unaltered and unaffected by olanzapine therapy in male schizophrenic patients. Eur Neuropsychopharmacol. 2008;18:333-8.

Handzlik MK, Metallo CM. Sources and sinks of serine in nutrition, health, and disease. Annu Rev Nutr. 2023;43:123-51.

Kantrowitz JT, Malhotra AK, Cornblatt B, Silipo G, Balla A, Suckow RF, et al. High dose D-serine in the treatment of schizophrenia. Schizophr Res. 2010;121:125-30.

Labrie V, Fukumura R, Rastogi A, Fick LJ, Wang W, Boutros PC, et al. Serine racemase is associated with schizophrenia susceptibility in humans and in a mouse model. Hum Mol Genet. 2009;18:3227-43.

Le Douce J, Maugard M, Veran J, Matos M, Jego P, Vigneron PA, et al. Impairment of glycolysis-derived L-serine production in astrocytes contributes to cognitive deficits in Alzheimer's disease. Cell Metab. 2020;31:503-17 e8.

Madeira C, Lourenco MV, Vargas-Lopes C, Suemoto CK, Brandao CO, Reis T, et al. D-serine levels in Alzheimer's disease: implications for novel biomarker development. Transl Psychiatry. 2015;5:e561.

Mota SI, Ferreira IL, Rego AC. Dysfunctional synapse in Alzheimer's disease - a focus on NMDA receptors. Neuropharmacology. 2014;76(Pt A):16-26.

Ni X, Mori H. Complex processes underlying the dynamic changes of D-serine levels in AD brains. Curr Alzheimer Res. 2022;19:485-93.

Wu S, Zhou J, Zhang H, Barger SW. Serine racemase expression differentiates aging from Alzheimer's brain. Curr Alzheimer Res. 2022;19:494-502.

Zhang SQ, Bai YZ. Strategies for enhancing beneficial effects of selenium on cognitive function. Metab Brain Dis. 2023;38:1857-8.