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A Role for D-aspartate Oxidase in Schizophrenia and in Schizophrenia-related Symptoms Induced by Phencyclidine in Mice.

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Introduction: D-aspartate (D-Asp) is an atypical amino acid that binds to and activates NMDARs. D-Asp occurs abundantly in the embryonic brain of mammals and rapidly decreases after birth, due to the activity of the enzyme D-Aspartate Oxidase (DDO). The agonistic activity of D-Asp on NMDARs and its neurodevelopmental occurrence make this D-amino acid a potential mediator for NMDAR-related alterations observed in schizophrenia. Consistently, substantial reduction of D-Asp was observed in *post-mortem* schizophrenia brains.

Aims: We evaluated the potential contribution of D-Asp as neurodevelopmental modulator of brain circuits and behaviors relevant to schizophrenia.

Objectives: We analyzed *DDO* mRNA expression in the *post-mortem* prefrontal cortex of schizophrenic patients. Moreover, we treated knockout mice for *Ddo* gene ($Ddo^{-/-}$) with the NMDAR antagonist phencyclidine to evaluate their schizophrenia-relevant behaviors and circuits. Finally, we assessed cortico-hippocampal connectivity of these mice.

Methods: *DDO* mRNA detection was performed by quantitative PCR. Phencyclidine-induced schizophrenia-like behaviours were assessed through motor activity and prepulse inhibition paradigms. Resting-state and pharmacological fMRI were used to evaluate functional circuits and connectivity.

Results: *DDO* mRNA expression is increased in frontal samples of schizophrenic patients. In mice, the absence of *Ddo* gene produces a significant reduction in phencyclidine-induced motor hyper-activity and prepulse inhibition deficit. Furthermore, increased levels of D-Asp in $Ddo^{-/-}$ animals significantly inhibit functional circuits activated by phencyclidine, and affect the development of cortico-hippocampal connectivity networks potentially involved in schizophrenia.
Conclusions: Our data suggest that D-Asp, through the regulation exerted by DDO, may have a role in the pathophysiology of schizophrenia.

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