D-aspartate: an endogenous NMDA receptor agonist enriched in the developing brain with potential involvement in schizophrenia

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Free D-aspartate and D-serine occur at substantial levels in the mammalian brain. D-serine is a physiological endogenous co-agonist for synaptic N-Methyl D-Aspartate (NMDA) receptors (NMDARs), and is involved in the pathophysiology of schizophrenia. Much less is known about the biological meaning of D-aspartate.D-aspartate is present at high levels in the embryo brain and strongly decreases at post-natal phases. Temporal reduction of D-aspartate levels depends on the post-natal onset of D-aspartate oxidase (DDO), an enzyme able to selectively catabolize this d-amino acid. Pharmacological evidence indicates that this D-aspartate binds to and activates NMDARs. Characterization of genetic and pharmacological mouse models with abnormally higher levels of D-aspartate has evidenced that its increase enhances hippocampal NMDAR-dependent synaptic plasticity and spatial memory. In line with its pharmacological features, we found that mice chronically treated with D-aspartate show enhanced NMDAR-mediated miniature excitatory postsynaptic currents and basal cerebral blood volume in fronto-hippocampal areas. In addition, we showed that both chronic administration of D-aspartate and deletion of the gene *Ddo* trigger plastic modifications of neuronal cytoarchitecture in the prefrontal cortex and CA1 subfield of the hippocampus and promote a cytochalasin D-sensitive form of synaptic plasticity in adult mouse brain. To translate these findings in humans, we performed a hierarchical stepwise translational genetic approach. Specifically, we investigated the association of variation in the *DDO* gene with complex human prefrontal phenotypes. We demonstrated that genetic variation predicting reduced expression of DDO in postmortem human prefrontal cortex is mapped on greater prefrontal gray matter and activity during working memory, as measured by fMRI. On the other side, evaluation of D-aspartate content in post-mortem patients with schizophrenia has shown a significant reduction of this D-amino acid in the prefrontal cortex and striatum.
In conclusion our results identify novel NMDAR-dependent effects for D-aspartate on plasticity and physiology in rodents, which also map to prefrontal phenotypes in humans.