D-amino acid metabolism is altered in the brain of autism spectrum disorder animal models.

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Glutamatergic synaptic dysfunction contributes to the pathophysiological alterations observed in neurodevelopmental psychiatric diseases, including schizophrenia and autism spectrum disorder (ASD). In support of this notion, altered metabolism of two NMDA receptor (NMDAR) modulators, D-serine (D-Ser) and D-aspartate (D-Asp), has been reported in schizophrenia brains.
Besides schizophrenia, recent studies also evidenced altered cerebral D-Asp levels in the idiopathic ASD mouse model, BTBR. Consistent with preclinical observations, a clinical investigation also identified a duplication of the D-aspartate oxidase gene, which encodes the enzyme responsible for endogenous D-Asp catabolism, in a young patient with ASD symptomatology and intellectual disability.
Based on these preliminary findings, we performed a comprehensive HPLC analysis of the endogenous ligands of NMDARs, including D-Ser, D-Asp, L-glutamate, L-aspartate, glycine and their precursors, in the serum of two different cohorts of ASD patients. Additionally, we measured the same neuroactive amino acids in the plasma and different brain regions of adolescent and adult ASD rat models, exposed during pregnancy to lipopolysaccharide (maternal infection) or valproate administration.
Despite unaltered amino acid blood levels in both ASD patients and rat models, compared to their respective controls, our results highlighted a remarkable deregulation of D-Asp and D-Ser levels in the striatum of ASD rats, accompanied by altered cerebral expression levels of serine racemase, an enzyme intimately involved in D-Ser and D-Asp biosynthesis.
Altogether, our clinical and preclinical findings suggest that neuroactive NMDAR-related amino acids may not be regarded as reliable peripheral markers of ASD despite their altered cerebral levels may be a key factor contributing to the glutamatergic dysfunctions observed in ASD.