The D-side of neurodevelopmental disorders

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Dysfunction of glutamatergic NMDA receptors (NMDARs) contributes to the motor and non-motor symptoms of Parkinson’s Disease (PD), and to L-DOPA-induced dyskinesia. Besides the main excitatory L-amino acids, also D-serine (D-Ser) activates NMDARs as a co-agonist at the glycine binding site of GluN1 subunit. We performed an extensive characterization of the levels of the endogenous ligands of NMDARs, including D-Ser, L-glutamate, D-aspartate, L-aspartate, glycine and their precursors, in PD patients and animal models of the disease. HPLC determinations highlighted abnormally higher D-Ser and L-Ser levels in the striatum of monkeys with severe MPTP-mediated denervation of nigrostriatal dopaminergic fibers (~75%), while no changes were found in the striatum of MPTP-treated mice, which showed mild dopaminergic degeneration (~30%). In line with results in MPTP-treated monkeys, we found greater D-Ser and L-Ser levels in the post-mortem caudate putamen of PD patients. We also put forward a significant elevation of both Ser enantiomers in the CSF of de novo PD patients but not in patients with other neurodegenerative disorders, including Alzheimer’s disease and amyotrophic lateral sclerosis. Beyond CSF and post-mortem brains, we reported that also the blood serum D-Ser levels were selectively upregulated in PD compared to controls. Overall, our biochemical analyses carried out in humans, monkeys and mice identify Ser metabolism variations as biochemical signatures of nigrostriatal dopaminergic degeneration in PD brain and let us hypothesize that such changes occur as a secondary response to support the metabolic and neurotransmission demands imposed by dopaminergic neuron degeneration.