

SYNAPTIC ZINC, A NOVEL PLAYER IN THE PATHOPHYSIOLOGY OF PARKINSON'S DISEASE

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Excessive glutamatergic transmission in the striatum is recognized as a key pathophysiological mechanism contributing to Parkinson's disease (PD). Subset of glutamatergic cortical-striatal projections uses ionic zinc (Zn^{2+}) as a co-transmitter, but its role in PD remains unexplored. Here we used pharmacological and genetic tools in combination with neurotoxic murine models of PD to investigate the pathophysiological role of synaptic zinc in PD. We first studied the behavioural effects of central injections of zinc in C57BL/6J mice. Bilateral infusions of zinc chloride ($ZnCl_2$) into dorsal striatum produced a dose-dependent locomotor hyperactivity. When injected unilaterally, $ZnCl_2$ restored motor impairments (forelimb asymmetry and reduced rearing activity) caused by the complete unilateral 6-OHDA lesion of the nigrostriatal dopaminergic pathway. The beneficial effect of $ZnCl_2$ was detected with a behaviourally silent dose in sham control mice, suggesting that reduced striatal synaptic zinc signalling contributes to the expression of the motor deficits. We next used synaptic zinc transporter-3 knockout (ZnT3-KO) mice and a partial unilateral 6-OHDA lesion that produces mild impairment of motor function to examine whether ablation of synaptic zinc could exacerbate the motor deficits. Lesioned wildtype mice displayed a locomotor impairment and a slight forelimb asymmetry. Unexpectedly, a significant improvement was detected in lesioned ZnT3-KO mice, pointing to a deleterious role of synaptic zinc during early stages of PD. Together, our findings show that synaptic zinc is an important player in PD. Ongoing studies seek to elucidate how synaptic zinc exerts its beneficial and deleterious actions during different stages of the disease.

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Effect of partial striatal DA lesion in ZnT3 KO mice

WT Sham WT Lesioned ZnT3KO Sham ZnT3KO Lesioned

