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The role of sphingosine kinase-1 and sphingosine-1-phosphate signaling in experimental model of Parkinson disease: The novel targets in therapy

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Our last data indicated disturbances in bioactive sphingolipids homeostasis in Parkinson Disease(PD) experimental models which could suggest their role in the pathomechanism of PD. We have demonstrated down-regulation and inhibition of the sphingosine kinases (SphKs) the enzymes which synthesized of sphingosine -1-phosphate (S1P) a potent intra- and intercellular messenger which can act through five G-protein coupled receptors, S1P1-5. Moreover, activation of S1P lyase in PD model was observed. It was also found that Sphks inhibition evoked alfa synuclein secretion, suppression of PI3K/Akt and activation of apoptotic cells death. Agonists of S1P 1 and S1P receptors modulator (FTY720) exerted the neuroprotective effect in an animal model of PD (MPTP) which was similar to this induced by the dopamine D2/D3 receptor agonist pramipexole (PPX). However only PPX but not FTY720 treatment significantly protected brain parts against inhibition of Sphk1 activity and expression. Both drugs abolished an observed loss of tyrosine hydroxylase and activate pro-survival enzyme Akt kinase, crucial in signal transduction of S1P receptors and enhanced the locomotor activity. In summary, our data indicated the new mechanism of PPX action connected with Sphk1 activation and demonstrated a neuroprotective role for FTY720 related to S1PR/Akt signaling as a new target in PD therapy.

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