MODULATION OF FGF-2 EXPRESSION IN ASTROCYTES VIA DOPAMINE RECEPTOR SIGNALING -- POTENTIAL IMPLICATIONS FOR THE TREATMENT OF PARKINSON'S DISEASE

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FGF-2 is predominantly synthesized and secreted by astrocytes in adult brain. Our previous study showed that activation of classical dopamine receptor D1 or D2 elicits FGF-2 biosynthesis and secretion in astrocytes. Here, we report that astrocytic FGF-2 expression is also regulated by phosphatidylinositol (PI)-linked D1-like receptor. SKF83959, a selective PI-linked D1-like receptor agonist, upregulates the levels of FGF-2 protein in striatal astrocyte cultures in classical dopamine D1 and D2 receptor-independent manner. The conditional medium derived from SKF83959-activated astrocytes promoted the number of TH+ neurons in vitro. Treatment of astrocytes with SKF83959 increased intracellular calcium in two phases. Inhibition of intracellular calcium oscillation by inositol 1,4,5-triphosphate (IP3) inhibitors blocked the SKF83959-induced increase in FGF-2 expression. Moreover, intraperitoneal administration of SKF83959 reversed MPTP-induced reduction in FGF-2 expression in both the striatum and ventral midbrain and resulted in marked protection of dopaminergic neurons from MPTP-induced neurotoxicity. These results indicate that IP3/Ca2+/calmodulin-dependent protein kinase (CaMK) is an uncharted intracellular signaling pathway that is crucial for the regulation of FGF-2 synthesis in astrocytes. PI-linked D1-like receptor plays an important role in the regulation of astrocytic FGF-2 expression and neuroprotection which may provide a potential target for the drug discovery in Parkinson’s disease.

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