Ret mediates the neuroprotective and neuroregenerative effects of GDNF in a MPTP model of Parkinson’s disease

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Glial cell line derived neurotrophic factor (GDNF) is a potent neurotrophic factor for dopaminergic neurons required for postnatal development and survival, regeneration and plasticity. GDNF holds great promise as a therapeutic molecule to treat diseases affecting the dopaminergic system, such as Parkinson’s disease. The signaling receptors mediating the beneficial effects of GDNF in dopaminergic neurons are however not yet defined. GDNF binds with high affinity to the GPI-linked GDNF family receptor α1. This receptor-ligand complex can activate the canonical GDNF receptor RET or alternative receptors such as the neuronal cell adhesion molecule or integrines. To address the question, if the receptor tyrosine kinase RET is essential for mediating the neuroprotective and regenerative effect of GDNF in dopaminergic neurons in vivo, we used a viral vector to overexpress GDNF in the striatum of mice deficient for RET in dopaminergic neurons and subsequently challenged these mice with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). In this MPTP induced Parkinson’s disease mouse model, exogenous GDNF could only in the presence of RET protect dopaminergic neurons in the substantia nigra pars compacta, the dopaminergic innervation of the striatum, and the levels of dopamine. In addition, exogenous GDNF required the RET receptor for mediated regeneration of dopaminergic fibers and terminals in mice investigated 90 days after MPTP treatment. We therefore conclude that so far all GDNF mediated beneficial effects on the dopaminergic system, such as adult maintenance, protection and regeneration, absolutely depend on the presence of the RET receptor.