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Small molecule GDNF receptor RET agonist supports the survival of dopamine neurons *in vitro* and protects their function in 6-OHDA lesioned rat midbrain

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Motor symptoms of Parkinson's disease (PD) are caused by degeneration and progressive loss of nigrostriatal dopamine neurons and affect up to 6–7 million people world-wide. Currently no cure for this disease is available. Existing therapeutic strategies based on dopamine replacement, alleviate PD symptoms, but do not prevent or slow down degeneration of dopamine neurons. Glial cell line-derived neurotrophic factor (GDNF) and its closely related protein neurturin (NRTN) can protect and repair dopamine neurons *in vitro* and in animal models of PD, but their clinical use is complicated because of their low bioavailability and poor diffusion in tissues. Previously, we discovered a small molecule called BT13 that selectively activates GDNF receptors and promotes neurite outgrowth from sensory neurons. Here, we report the ability of this molecule to support the survival of cultured dopamine neurons only when they express GDNF receptors. In addition, BT13 activates intracellular signaling cascades *in vivo*, stimulates release of dopamine and protect the function of dopaminergic neurons in a 6-hydroxydopamine (6-OHDA) rat model of PD. In contrast to GDNF, BT13 is able to penetrate through the blood-brain-barrier and it spreads well in brain tissue. Thus, although its solubility and stability require optimization, BT13 serves as an excellent tool compound for the development of novel disease-modifying treatments against PD.

Biography

Arun Mahato, PhD student at Institute of Biotechnology, University of Helsinki. He is interested in studying neurotrophic factors outside nervous system which could be neuroprotective and neurorestorative in Parkinson's disease. He holds master's degree in Physioology and Neuroscience from University of Helsinki. He has received Mari Curie Fellow fellowship as well as EFMC gant to get more insight in the field of computational and medicinal chemistry which helped me in optimization of GDNF mimetics

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