Non-invasive delivery of an amidated neuroactive peptide in models of Parkinson's disease

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Neurotrophic factors, such as glial cell line-derived neurotrophic factor (GDNF), have shown great promise in treating an array of neurodegenerative disorders including Parkinson's disease (PD). However, their clinical success has been limited due to challenges associated with invasive surgical delivery (and distribution) of large molecules to the brain. Previously, we have shown that DNSP-11, a small (eleven amino acid) amidated synthetic peptide derived from the GDNF prosequence, exhibits neurotrophic -like properties both in vitro and in vivo. We hypothesize, because of its small size and function, that DNSP-11 would enter brain parenchyma and provide neurotrophic-like effects following intranasal delivery. Distribution studies in normal Fischer (F344) rats administered a one-time 125I-labeled dose of DNSP-11(50 µCi/300 µg) indicated rapid uptake into the brain, cerebrospinal fluid and blood as measured by gamma counting and autoradiography. A dose response conducted in normal F344 rats treated with DNSP-11 intranasally, under light isoflurane anesthesia, showed a significant increase in dopamine turnover [(DOPAC+HVA)/DA] at 300 µg, in both the striatum and substantia nigra (*$p<0.05$, **$p<0.01$ respectively) compared to vehicle (0.9% saline). Furthermore, F344 rats treated 7 days a week (one week prior to 6-OHDA injection and 5 weeks post-surgery) with 300 µg DNSP-11 showed a significant decrease in amphetamine-induced rotation at both 2 and 4 weeks post-surgery (*$p<0.05$) compared to vehicle. Cumulatively, these studies indicate rapid uptake of DNSP-11, activation of DA systems in vivo and protection of the nigrostriatal system by intranasally delivered DNSP-11. We are currently investigating the optimization of an intranasal delivery system to accurately administer DNSP-11, in a dose-escalating manner in awake, chair-trained, MPTP hemiparkinsonian rhesus macaques to (1) examine the drug effect in non-human primates (NHP); and (2) determine efficacy of intranasal delivery in a NHP model of PD.