

## DOCTORAL THESIS

### Differential effects of neurokinins in models of Parkinson's disease

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**Differential Effects of Neurokinins in Models of  
Parkinson's Disease**

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**A thesis submitted in fulfillment of the requirements  
for the degree of**

**Doctor of Philosophy**

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# Abstract

Parkinson's disease (PD) is one of the serious motor disorders among the world. It is caused by the degeneration of dopaminergic neurons in substantia nigra (SN). Neurokinin (NK), also called tachykinin, is a group neuropeptide that is suggested to be involved in the pathogenesis of Parkinson's disease. NK functions are mediated by respective neurokinin subtype receptors that belong to the member of G-protein-coupled receptors (GPCR). NK receptors can be divided into 3 subtypes: NK1, NK2 and NK3 receptors. Different NK natural ligands were found to mediate cell survival or cell death in central nervous system (CNS).

In the present study, the localization of NK1 and NK3 receptor in striatal and nigral neurons were determined. The effects of NK1 and NK3 receptor agonist, septide and senktide, were investigated in 6-OHDA lesioned PD models. Present results revealed the localization of NK1 receptors and NK3 receptors with  $\gamma$ -amino-butyrate (GABA), cholinergic, dopaminergic neurons and N-methyl-D-aspartate (NMDA) receptor 1. After 6-OHDA lesion, the modulation of NK1 and NK3 receptor were investigated by Western blotting. These data reviewed the localization pattern of NK receptors, which provide some clues on how neurokinins involve in the basal ganglia circuit activities in striatum and substantia nigra.

Furthermore, NK1 receptor agonist septide and NK3 receptor agonist senktide were used to investigate their differential effects on dopaminergic system in PD models. The number of apomorphine-induced contralateral rotations of 6-OHDA lesioned rats was significantly increased and this behavior could be attenuated by the injection of septide. Septide was also demonstrated to protect TH-immunoreactive neurons and terminals in SN and striatum from 6-OHDA toxicity in rat CNS by immunofluorescence and Western blotting. Revealing of protein molecules in Akt/PKB pathway was demonstrated and increase of phosphorylation of Akt/PKB was found in SN and striatal neurons. For the downstream molecules, phosphorylation of Bad and cleavage of caspase 3 were reviewed. In septide treated SN neurons, phosphorylation of Bad was seen, but no significant reduction of cleaved caspase 3 expression was found. In *in vitro* model, septide was pretreated in SH-SY5Y cultures before challenging with 6-OHDA. And septide could reduce the cytotoxicity of 6-OHDA. Also, higher expression of phosphorylated Akt/PKB and Bad were found in 6-OHDA-treated SH-SY5Y culture after septide treatment, demonstrating the

neuroprotective effects of septide on human neuroblastoma cells.

On the other hand, activation of NK3 receptors by its agonist senktide exerted a deleterious effect on 6-OHDA lesioned rats. Although no significant reduction of dopaminergic degeneration was shown after 2 days senktide injection, exacerbation of rotation behavior in apomorphine rotation test and dopaminergic degeneration in striatum and SN were found after 7 days senktide post injection. To further confirm the working mechanisms of NK3 receptor and its agonist, phosphorylation of NR1 receptor was first examined in SN region in rats. And expressions of phosphorylated NR 1 were significant increased after 2 days senktide treatment in 6-OHDA lesioned rats. Finally, the expression of phosphorylated JNK/SAPK was examined in SN and striatal neurons. Significant up-regulation of expression of phosphorylated JNK/SAPK was discovered in SN and striatum region after 2 days senktide treatment in 6-OHDA lesioned rats. These evidences suggested that NK1 agonists and NK3 agonists have differential effects on PD models. NK1 agonists exerted neuroprotective effects in PD models while NK3 agonists provided detrimental effects in PD models. These findings may imply the role of neurokinin and its receptors on the pathology and treatment of Parkinson's disease.

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