

## DOCTORAL THESIS

### Endogenous neuroprotective mechanisms in early stages of rat parkinsonism

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**Endogenous Neuroprotective Mechanisms In Early Stages Of Rat  
Parkinsonism**

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**A thesis submitted in partial fulfilment of the requirements**

**for the degree of**

**Doctor of Philosophy**

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## Abstract

The present thesis reports a previously unknown self repair mechanism during extremely early stages of rat Parkinsonism. In the striatum of 6-hydroxydopamine-lesioned rat, nestin-positive reactive astrocytes appeared at post-lesion day 3 while very low levels of brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) dimers, which were believed to initiate the signal transduction cascades for anti-apoptotic actions, were found. Peak levels of BDNF and GDNF found at post-lesion day 7 while nestin-positive astrocytes had started to disappear. In the substantia nigra, the specific patterns of nestin and BDNF expressions were similar to those of the striatum except no GDNF could be detected during the whole period. At post-lesion day 14, expressions of nestin-positive reactive astrocytes, BDNF and GDNF were curtailed.

In addition, different molecular forms of the neurotrophic factors were studied. Under Western blotting, three forms of BDNF were visualized. They were Pro-BDNF (32 kDa), BDNF dimer (28 kDa) and BDNF monomer (14 kDa). For GDNF, only dimer form (32 kDa) could be detected. The functional dimer forms are important for the signal transduction. Two important cell survival signaling cascades, Phosphatidylinositol-3 kinases (PI3K)/Akt pathway and extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK pathway), could be activated by the functional forms of the neurotrophic factors. The phosphorylation of the kinases, Akt protein kinase and p44/42 MAPK protein kinase, as well as their downstream target, Bad, were explored in the study. The up-regulations of the phosphorylated p44/42 MAPK and the phosphorylated Bad at Ser 112 was detected at post-lesion day 3 and peaked at day 7. Although significant phosphorylation of Akt kinase could not be noted throughout the studied period, an up-regulation of the phosphorylated Bad at 136 was revealed from post-lesion day 3 and post-lesion day 14.

However, in ovariectomized lesioned rats, this endogenous neuroprotective mechanism was down-regulated. Less up-regulations of these molecules with a shorter time window was shown in the animals. GDNF was even hardly detected. The presence of estrogen might be important to the neuroprotective mechanism. Therefore, estrogen treatments with low dosage and high dosage were employed in the ovariectomized lesioned animals respectively. A partial restoration of the neuroprotective could be observed in the low-dose treatment while a more profound neuroprotection was found in the high-dose treatment. These data strongly suggest that there is an endogenous self repair effort by nestin-immunoreactive reactive astrocytes via releases of BDNF and GDNF in the striatum and release of BDNF in the substantia nigra. Estrogen may help enhance this neuroprotective process and

estrogen therapy could have significant implications in treatments of PD. Notably, the self repair effort is only functional within an extremely short time window immediately after onset.

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