7. SUMMARY

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Investigations on the development of a new mouse model of Parkinson's disease to assess neuroprotective drug effects.

Parkinson's disease (PD) is one of the most common neurodegenerative movement disorders characterized by a progressive degeneration of dopaminergic neurons of the substantia nigra. Etiological hypotheses include aging, genetic predisposition and environmental factors which lead to mitochondrial impairments in dopaminergic neurons. The pesticide rotenone and the neurotoxin 6-hydroxy dopamine (6-OHDA) inhibit the mitochondrial respiratory chain and induce degeneration of dopaminergic neurons. Since epidemiological studies suggest a pathogenetic impact of pesticides and chronic systemic applications of low doses of rotenone in rats provoke characteristics of PD, the rotenone rat model was proposed as a new animal model with progressive neurodegeneration to test neuroprotective drug effects. Striatal applications of 6-OHDA provoke a retrograde degeneration of nigral dopaminergic neurons. However, to date only acute injections are published.

Currently only genetic mice models (no rat models) are available to investigate a combination of genetic predispositions, exogenous factors and aging. This idea prompted us to investigate if chronic systemic administration of rotenone and subchronic intrastriatal microinjections of 6-OHDA in intact mice reproduce mouse models of PD, which could provide a basis to analyse a combination of genetic and other factors. During the treatment period the effects on vitality and motor behaviour were examined, followed by pathological investigations to assess central (especially degeneration of nigrostriatal dopaminergic neurons) and peripheral alterations.

C57Bl/6 mice at an age of 2.5, 5 or 12 months were chronically (30-45 d) injected with rotenone (2.5 or 4.0-5.0 mg/kg s.c.). Rotenone-treated mice exhibited parkinsonian symptoms like a reduced locomotion and even catalepsy; some animals developed a tremor. However, it was not associated with a significant neurodegeneration in the nigrostriatal dopaminergic system, but with signs of hepatotoxic alterations.

Furthermore it was investigated if repeated bilateral intrastriatal applications of 6-OHDA (8 µg) for 5 or 7 d in C57Bl/6 mice vs. acute microinjections provoke a retrograde progressive

degeneration of nigral neurons. In contrast to an acute application, an administration over 5 d caused a moderate loss of nigral neurons. However, a treatment over 7 d revealed no further aggravation.

The data indicate that chronic systemic applications of rotenone in intact mice do not provide a suitable model for PD, because rotenone is not able to cause the neuropathological characteristics. Subchronic intrastriatal injections of 6-OHDA in mice provoked a moderate degeneration of dopaminergic neurons as described for early stages of PD, nevertheless, because of the absence of a progressive neuronal loss it represents not a suitable animal model to test neuroprotective drug effects. Further studies have to clarify if genetic mouse models of PD might be more sensitive to the neurotoxic effects.