Introduction

Parkinson disease (PD) is a neurodegenerative disorder resulting from an excessive loss of dopaminergic neurons in the substantia nigra (SN). Animal models have been very helpful in gaining a better understanding of disease mechanisms and in the developing of new treatments for the disease. However, most animal models are based on an acute neuron loss and thus do not mirror the progressive neuron loss seen in patients. This may be an important reason why preclinical studies of neuroprotection have so far not been predictive of results in patients. In addition, high costs and ethical concerns are making it increasingly difficult to perform experiments on primates. To address these obstacles, we wanted to develop a functional non-primate large animal model of chronic PD based on continuous 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) intoxication in the Göttingen minipig.

Materials and methods

Eighteen Göttingen minipigs (Figure 1) were used for the study. Fourteen Göttingen minipigs were implanted subcutaneously with infusion pumps for continuous intramuscular MPTP delivery at daily doses of 2-24 mg's pr. day. Four animals served as normal controls. The animals were followed for 11 weeks, during which they were observed and scored behaviorally for mobility, coordination, rigidity, chewing, and vocalization.

All animals underwent digital movement analysis preoperatively, 4 and 11 weeks postoperatively using an infrared 3-D computerized Vicon system to measure the temporospatiale parameters of gait. Gait velocity, step length, gait cycle, raise of the leg from the floor, single stand and double support phase (hind legs) were measured (Figure 2).

Results

All MPTP-intoxicated animals developed symptoms of PD after 1-15 days. We observed decreased mobility (stiffness/slowness/skewness), coordination difficulties starting in the hind limbs, chewing difficulties and in some cases abnormal vocalization. However, the symptoms were mild and transient in the 2-12 mg groups. The 16 mg group developed moderate and stable symptoms, whereas the animals in the 24 mg group were severely parkinsonian after 11 days of intoxication and had their pumps turned off. Four weeks postoperatively the gait velocity in the 12 mg group was normal. At that time the 18 mg group had a significant decrease in their gait velocity. After 11 weeks of intoxication both groups showed a decreased gait velocity (Figure 3). Gait cycle showed the same pattern. After 11 weeks of intoxication, gait cycle was decreased in the 18 mg animals (Figure 4). After 11 weeks both groups walked with a decreased gait cycle. There was a small, but significant increase in step length after 11 weeks in the 18 mg group (Figure 5).

Conclusion

We conclude that it is possible to perform chronic MPTP-intoxication in Göttingen minipigs and thereby obtain a robust functional gait model of Parkinson disease.

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