Quantitative Behavioral Assessment Methods for the Analysis of Graft-Induced Motor and Cognitive Function in the MPTP-Treated Parkinsonian Monkey


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Although the MPTP-treated monkey is the best available model of Parkinson's disease in terms of neuropathophysiology, the usefulness of the model for the functional analysis of neural grafts requires methods that can determine the severity and persistence of the symptoms. Wide variation in response to MPTP and reports of "spontaneous" recovery may warrant a variety of assessment methods to determine the severity of parkinsonism and this requires large numbers of subjects and groups. It is critical that the severity of the MPTP deficit be known in order to compare MPTP-treated subjects with fetal substantia nigra (SN) implanted into the caudate nucleus (CN) with similarly affected subjects given sham surgery, "inappropriate" surgery (cerebellar tissue into the CN or SN tissue into the cortex), or no surgery. If subjects in these groups are not compared by severity it will not be possible to differentiate between graft-induced and spontaneously-induced improvements. We have aimed to establish a variety of behavioral assessment methods that can identify the severity of the MPTP-induced behavioral deficit. With these methods we can more accurately study the restorative effects of grafts in MPTP-treated monkeys with which the biochemical and morphological effects can be compared. We have used the following methodologies in our studies: 1) spontaneous behavioral ratings; 2) cognitive and subtle motor skill task performance, and 3) eye-blink rate measurements.

Over 70 African green monkeys given MPTP (cumulative dose 1.6 - 2.0 mg/kg) or vehicle have been used in these studies. Standardized, "blind" ratings of spontaneous behavior are made twice daily. Subjects were examined by observers who "scored" and "rated" individual behaviors. Observers are trained and are tested for inter-rater reliability. A "parkinsonian summary score" was derived and determined using a principal component factor analysis of the data. Each subject was assigned to a severity category 0-4, where 0=normal/untreated subjects, 1=subjects "asymptomatic" for a gross motor deficit (but previously found to have some subtle deficits on the object retrieval task), 2=mildly parkinsonian subjects, 3=moderately parkinsonian subjects, and 4=severely parkinsonian subjects. The initial severity was found to predict the extent of any recovery. In the category 1 subjects recovery occurred within a month, whereas in the category 4 severe subjects there was no recovery up to 5 months after MPTP. SN-CN grafts were found to reduce parkinsonism in moderate or severely parkinsonian subjects. Subjects with equivalent parkinsonism that did not receive SN-CN grafts (i.e. sham-surgery, inappropriate surgery, or no surgery) did not show improvements. Performance on an object retrieval/detour task that measures cognitive and subtle motor skills was also examined based on our analysis of severity. MPTP was found to significantly reduce successful reaching on the task. The degree of the impairment and its persistence was dependent upon the subject's initial severity. Although performance improved in category 1 and 2 subjects it was significantly worse than in category 0 subjects. Subjects in categories 3 and 4 often were too impaired even to perform. Successful reaches on the task were increased after SN-CN grafting whereas subjects not receiving this surgery remained impaired.
Severely Parkinsonian subjects in category 4 were also found to have a number of medical complications (ulcers and pneumonia). Although the deficit in category 4 subjects appeared to be permanent, making them optimal subjects for the assessment of neural graft effects, these subjects are difficult to maintain for extended periods of time. The percentage of subjects in category 4 that survived for more than three months after SN-CN surgery was found to be greater than for similarly affected subjects not receiving SN-CN grafts (80% vs 10%). Spontaneous eye blink rates, which are known to be reduced in Parkinson's disease, were also found to be affected by the severity of parkinsonism. In addition, there was a correlation between blink rate and the concentration of dopamine in the ventromedial CN, but not other regions, at sacrifice. These quantitative behavioral methods are necessary to characterize fully the MPTP model of Parkinson's disease in primates and for valid assessments of the restorative effects of fetal SN tissue grafts.

Supported by NS24032, Axion Research Foundation, St Kitts Biomedical Research Foundation, DER - RSA MH400643.