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REVIEW

Experimental Models and Behavioural Tests Used in the Study of Parkinson's Disease

J. MOKRÝ

Department of Histology and Embryology, Charles University Medical School, Hradec Králové, Czech Republic

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Summary

The present review brings the survey of the most frequently used behavioural tests in experimental models of Parkinson's disease (PD). Although there is no spontaneous occurrence of parkinsonism in animals, several experimental animal models of PD have been developed to achieve the same clinical features in animals. The techniques employing neurotoxins in lesioning the nigrostriatal dopaminergic (DA) system have a large selectivity and reproducibility. The most frequently used neurotoxins are 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA). MPTP-lesioned monkeys mimic best the symptomatology of PD in human patients while rats appear to be refractory to MPTP. For that reason, 6-OHDA is used to damage the substantia nigra in a rodent model. Behavioural tests of animals with nigrostriatal lesion represent valuable non-invasive methods for assessing the influence of damaged DA system on locomotor activity. The most frequently used experimental model of PD is the drug-evoked rotation in 6-OHDA unilaterally lesioned rats. This model produces well-defined and stable behavioural deficits. The rotation test is a useful parameter for evaluating imbalances of dopamine in both striata of the hemi-parkinsonian rat model. T-maze, treadmill running test or sensorimotor tests are used to evaluate spontaneous locomotor activity of lesioned animals. Skilled motor tasks measure the influence of dopamine-depleting lesions on complex motor acts. Transplantation of DA tissue into the striatum offers a new approach to the treatment of PD. Experimental models and behavioural tests are used to evaluate the extent of graft-induced recovery of MPTP- or 6-OHDA-lesioned animals. Different results obtained after the use of different tests reflect the level of graft integration into the host circuitry.

Key words

Parkinson's disease – MPTP – 6-OHDA – Neural grafting

Introduction

Parkinson's disease (PD) is one of the most common neurological disorders. Although this movement disorder had been defined a century and a half ago, its aetiology remains unknown. Parkinsonism is associated with the progressive degeneration of pigmented dopaminergic (DA) neurones in the compact zone of the substantia nigra that project to the neostriatum. The nigrostriatal DA system constitutes one of the major afferents of the putamen and the caudate. The human putamen and caudate are normally innervated by about 60 000 dopaminergic neurones each (Lindvall 1991). Striatal dopamine loss in PD affects the putamen more than the caudate. The putamen is thought to be more directly involved in motor function, whereas the caudate may have a more integrative function (Stoessl 1992). Thus lesions of the DA system have a profound influence on motor activity. Tremor at rest is the most typical symptom but the majority of patients are most functionally disabled by other motor signs of parkinsonism, i.e. by akinesia and rigidity.

Although there is no spontaneous occurrence of parkinsonism in animals, several experimental animal models of Parkinson's disease were developed to achieve the same clinical features in animals. These experimental models were used to study the influence

of damaged DA system on locomotor activity, mechanisms of selective degeneration of DA neurones in the substantia nigra and to assess the effectiveness of drugs used in the therapy of PD. Attempts to use manganese poisoning, which can lead to PD in man, resulted in neurologically impaired monkeys, but they only exhibited moderate reductions in striatal dopamine (Neff *et al.* 1969). Earlier animal models employed surgical destruction or stereotaxic electrocoagulation of the substantia nigra (e.g. Poirier and Sourkes 1965, Costal *et al.* 1976). However, the electrolesion of the substantia nigra additionally destroys non-aminergic pathways (Costal *et al.* 1976).

The current approach prefers neurotoxins that selectively destroy dopaminergic neurones. There are some differences in animal responses to electrolytic or neurotoxin lesions. Whereas electrolesions may cause hyposensitivity of the denervated striatal dopamine receptors, neurotoxin lesions result in hypersensitivity of the same receptor sites (Costal *et al.* 1976).

When the nigrostrial dopamine neuronal system is unilaterally lesioned or stimulated, animals develop serious motor disturbances. For example monkeys become hypokinetic in the limbs contralateral to the lesion. In rats, a unilateral lesion produces an asymmetric posture with the head and tail deviating towards the side of the lesion. This can be changed into vigorous rotation towards the lesioned side if dopamine is being released from the contralateral (unlesioned) striatum by systemic treatment with amphetamine or monoamine oxidase (MAO) inhibitors plus reserpine. As one striatum has a normal dopamine innervation while the other lacks such innervation (Ungerstedt and Arbuthnott 1970), the drug-induced turning response reflects an imbalance in dopamine release in the intact and the denervated striatum. The techniques employing neurotoxins in lesioning the nigrostriatal DA system have a larger selectivity and reproducibility that is superior to conventional lesioning techniques. The most frequently used neurotoxins are 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA).

1. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)

MPTP is a potent parkinsonian agent (Langston 1985). It caused chronic irreversible parkinsonism in young addicts who used a synthetic heroine analogue containing MPTP as a contaminant. MPTP is nontoxic systematically, it crosses the blood-brain barrier and is rapidly oxidized to an intermediate 1-methyl-4-phenyl-2,3-dihydropyridinium ($MPDP^+$) by MAO B in the glia (Beal *et al.* 1993). $MPDP^+$ is then converted to 1-methyl-4-phenylpyridinium ion (MPP^+). MPP^+ is taken up by the dopamine uptake system with the same affinity as dopamine (Drucker-Colín and García-Hernández 1992) and is accumulated within mitochondria of DA neurones in the substantia nigra (Beal *et al.* 1993, Langston 1985). MPP^+ selectively inhibits the mitochondrial complex I, thereby interfering with the electron transport chain. This results in decreased levels of ATP and generation of cytotoxic oxygen radicals in the neurones (Beal *et al.* 1993, Coyle and Puttfarcken 1993). These radicals are exceptionally neurotoxic and cause the death of the DA neurones in the compact zone of the substantia nigra.

Because of its unique properties, MPTP has been used to induce a parkinsonian-like state in primates. All primates are susceptible to MPTP toxicity (Bankiewicz 1991). When this drug is administered systematically it produces bilateral degeneration of nigral neurones. The MPTP-lesioned monkey model was introduced in the early 1980s. For bilateral lesions, MPTP may be administered intramuscularly, intraperitoneally, intravenously, perorally or subcutaneously (Bankiewicz 1991, Waters *et al.* 1987, Wolters *et al.* 1991). Severe nerve cell loss in the pars compacta of the substantia nigra was found under the light microscope 27 days after MPTP administration (Burns *et al.* 1983). MPTP induced lesions not only in the nigral neurones but also in the noradrenergic neurones of the locus coeruleus and DA neurones in the ventral tegmental area, paranigral nucleus, paraventricular area and parabrachial nucleus (Bankiewicz 1991). This model of PD in primates mirrors the neurological abnormalities manifested in human patients. Bilateral lesions of the substantia nigra in the monkey produced by peripheral administration of MPTP result in bradykinesia, rigidity of the trunk and limbs, flexed posture, poor movement initiation, masked face, eyelid-closure, impaired chewing movements, drooling, loss of vocalization and in some cases postural tremor (Bankiewicz 1991, Burns *et al.* 1983, Ridley and Baker 1991, Waters *et al.* 1987, Willis and Grossman 1977, Wolters *et al.* 1991). Some of these symptoms are very characteristic of Parkinson's disease but they are not so easy to quantify. Tremor observed in MPTP-lesioned monkeys displays more characteristics of an action tremor, in contrast to the resting tremor in PD (Wolters *et al.* 1991). But the resting tremor is produced by lesions in the ventral tegmentum, just above the substantia nigra, which interrupt nigral, cerebellar, and red nucleus projections (Willis and Grossman 1977). Parkinsonian symptomatology in the monkey can be reversed by the administration of levodopa (Burns *et al.* 1983). The neurotoxic effects of MPTP in the monkey may not be permanent since some partial, occasionally complete, behavioural recovery was observed after several months (Bankiewicz 1991, Waters *et al.* 1987).

Acute systemic administration of MPTP will develop akinesia, extreme rigidity with a catatonic and hunched posture, aphagia with drooling, adipsia, and bilateral sensory inattention. Such monkeys require extensive nursing care to prevent their death. A more elegant model will result using chronic systemic

administration of smaller doses of MPTP, by means of which more subtle clinical deficits may be achieved. If the decrease of the dopamine content is less than 80%, the animals show little or no locomotor abnormalities. To develop such a model is very time consuming. Another way to prevent problems encountered in acute systemic administration may be lesioning the animals unilaterally *via* the carotid artery (Wolters *et al.* 1991).

The major advantage of the unilateral MPTP model as compared to the bilateral model is that the serious complications of systemic MPTP administration can be avoided. In the primate model of Parkinson's disease, it is possible to produce either a bilateral or an unilateral lesion of the nigrostriatal tract. A unilateral lesion is usually carried out by direct injection of MPTP into the central part of the substantia nigra although it may be produced by unilateral infusion into the internal carotid artery as well (Bankiewicz 1991, Wolters *et al.* 1991). The unilateral method produces marked ipsilateral rotation of MPTP-treated animals (i.e. towards the lesioned side). Further, monkey MPTP hemiparkinsonism is characterized by unilateral arm bradykinesia, akinesia, tremor, spontaneous ipsilateral turning, drug-induced contralateral turning and hemineglect. Treatment with apomorphine alleviates all motor deficits and reverses the direction of turning. Such an apomorphine-induced turning response can also be quantified (Bankiewicz 1991). The clinical status of a patient with PD is highly correlated with the velocity of his movements. Measurement of arm movement velocities in the MPTP-treated monkey reveals the extent of the DA system damage. The unilateral model enables the study of motor velocities on the affected side and allows comparisons with the healthy side. Effects of hypokinesia may be evaluated by activity scores while tremor and rigidity can be measured by electromyography (Wolters *et al.* 1991). A neurological rating scale is used to standardize neurological rating in MPTP-treated primates. Monkey parkinsonism rating scale includes observation of parkinsonian features (tremor, posture, gait, bradykinesia, balance, gross motor skills, defence reaction), drug-related side effects, overall level of activity and clinical staging. The motor activity of the lesioned monkey is evident by direct observation or detected by the use of automated monitoring devices (Bankiewicz 1991).

The clinical analogy between PD and MPTP-induced parkinsonism in humans is nearly complete. MPTP is considered to be the best agent so far discovered for its ability to produce consistent and unalloyed parkinsonism (Drucker-Colín and García-Hernández 1992).

In contrast to the primates, the rat appears to be refractory to the neurotoxic effects of MPTP. The lack of MPTP neurotoxicity in rats may be related to species differences in monoaminoxidase B (MAO-B) activity and the inability to generate sufficient quantities of MPP^+ to cause neurotoxicity. A permanent loss of dopaminergic neurones in rats was observed after the long-term infusion of small doses of MPP^+ into the nigrostriatal tract (Sirinathsinghji 1991). As effects of MPTP in rodents are more unreliable than in primates, the MPTP model has proved to be really useful in primates for the purpose of creating a chronic animal model of PD. However, in a rat model of PD, investigators prefer the 6-OHDA neurotoxin.

2. 6-OHDA (6-hydroxydopamine)

6-OHDA is another toxic agent that can cause selective damage to nigral DA neurones (Hökfelt and Ungerstedt 1973) and induce irreversible parkinsonism. This catecholamine neurotoxin also reduces noradrenergic (NA) projections to about 46–74 %, while the serotoninergic (5-hydroxytryptamine) system is not altered (Costal *et al.* 1976). This compound has not been implicated as an aetiologic agent in Parkinson's disease because of its inability to cross the blood-brain barrier. For that reason 6-OHDA must be directly injected among DA cell bodies of the substantia nigra (Dunnett *et al.* 1981b). Injections of 6-OHDA in the lateral ventricles damages both DA and NA systems in the brain (Kalen *et al.* 1991). The selectivity of 6-OHDA is due to its accumulation by DA neurones through their high-affinity uptake system. Aqueous solutions of 6-OHDA as well as 6-aminodopamine undergo much more rapid autoxidation than does dopamine *in vivo* (Heikkila and Cohen 1971), forming superoxide, hydrogen peroxide and hence hydroxyl radicals in nigral neurones. Hydrogen peroxide damages the biogenic amine uptake system, cytotoxic radicals cause degeneration of nerve terminals and neurones (Heikkila and Cohen 1971). As a result, histological sections of lesioned brains reveal complete degeneration of the lesioned nigrostriatal DA system (Ungerstedt and Arbuthnott 1970).

A rat model employing the neurotoxin 6-hydroxydopamine is the most utilized animal system in the study of PD. DA neurones are destroyed unilaterally with stereotaxic injections of 6-OHDA within the ascending medial forebrain bundle (Kawaja *et al.* 1992). In this bundle, all nigrostrial fibres are packed closely together and it is therefore easier to remove DA innervation to the striatum at this point. Moreover, attempts to destroy DA innervation by direct injection of 6-OHDA into the substantia nigra often do not result in the complete destruction of all nigral neurones.

The dopaminergic system in the rat comprises a total of about 40 000 cells (Björklund 1991). Dopaminergic projection to the ipsilateral striatum degenerates within seven days after neurotoxin injection, inducing a subsequent increase in the

sensitivity, as well as in the number of post-synaptic dopamine receptors within the denervated striatum (Perlow *et al.* 1979). An imbalance in the levels of dopamine between the lesioned and unlesioned striatum initially causes the 6-OHDA-treated rats to display an asymmetric postural bias towards the lesion side and a spontaneous or tailpinch-induced lqcomotor activation characterized by a circular walking pattern, i.e. rotation (Ungerstedt and Arbuthnott 1970, Dunnett *et al.* 1981A). After a few days, the 6-OHDA-lesioned rats cease to display marked spontaneous asymmetries. In addition to asymmetric posture and motor behaviour, a unilateral complete 6-OHDA lesion produces sensory inattention and impaired initiation of movement in the direction contralateral to the lesion (Drucker-Colín and García-Hernández 1992).

2.1 Drug-induced rotational tests

There are several different behavioural tasks which are useful in the 6-OHDA-lesioned rats, each providing slightly different information. The drug-induced rotational test is the most widely used and the best characterized animal model system of PD because of its simplicity and sensitivity. The circular walking pattern in the 6-OHDA-treated rats can be easily evoked by subcutaneus or intraperitoneal administration of 5 mg/kg amphetamine or 0.1 mg/kg apomorphine (Björklund *et al.* 1980).

Such pharmacological treatment with amphetamine that stimulates the release of dopamine from intact neurones will increase the amount of dopamine reaching dopamine receptors of the innervated striatum and therefore will aggravate the imbalance between the innervated and denervated striatum inducing ipsilateral rotation, i.e. towards the lesioned side. This rotational behaviour is quantitatively related to the degree of dopamine receptor stimulation (Ungerstedt and Arbuthnott 1970). On the other hand, the extent of dopamine depletion can be reliably estimated from the rotational speed, i.e. from the average number of turns per minute (Costal *et al.* 1976). Rats with poor initial amphetamine-induced turning, i.e. 5 turns/min, have about 85 % dopamine depletion (Dunnett *et al.* 1987). Rats that display more than seven rotations per minute for a 60 min period after the subcutaneus injection of amphetamine have sustained a loss of dopamine within the denervated striatum of more than 95%. When the 6-OHDA-lesioned animal receives amphetamine, it begins to swift after about 5 min and then steady rotation towards the lesioned side develops. The evoked rotational behaviour can be automatically registered as number of complete 360° turns per minute versus time in a specially designed rotameter where the animal moves in a spherically shaped bowl while connected to the registering device by a thin steel wire (Ungerstedt and Arbuthnott 1970). The main increase in the rotational speed occurs during the first 30-60 min after the injection, and the speed then slowly declines to reach approximately zero about 210–270 min after the injection of amphetamine (Ungerstedt and Arbuthnott 1970).

Apomorphine is D_1/D_2 receptor agonist that stimulates upregulated dopamine receptors in the denervated striatum. The administration of low doses of this drug induces turning in the direction opposite to amphetamine, i.e. contralateral to the lesion (Ungerstedt and Arbuthnott 1970, Costal *et al.* 1976, Dunnett *et al.* 1987). The turning response reflects dopamine receptor supersensitivity in the denervated striatum and is again quantitatively related to the degree of dopamine depletion. Because the rats show a sensitization effect to both amphetamine and apomorphine (i.e. more turns with subsequent testing), it is necessary to test rats several times prior to measurement to achieve a stable baseline (Kawaja *et al.* 1992).

2.2 Spontaneous locomotor activity

2.2.1 T-maze

As a drug-evoked rotation is abnormal locomotor activity, there are several tests for assessment of spontaneous activity in 6-OHDA-lesioned animals. One test is choice behaviour in a T-maze. In this test, rats are placed at the beginning of a central arm of the T-maze and allowed to select one of two side arms. All animals are first tested in the absence of any manipulation. On the second test tailpinch is applied by affixing a paper-clip immediately prior to each trial. Tailpinch should further reduce the asymmetry in rotation. On the third test, 0.5 mg/kg amphetamine is injected 10 min before the first trial. Unlesioned rats will typically exhibit a random, non-biased side preference. In contrast, unilateral lesioned rats tend to select the arm ipsilateral to the side of the lesion, i.e. rats with a lesion in the right hemisphere will show a preference for the right arm of the T-maze (Dunnett *et al.* 1981a).

2.2.2 Treadmill running test

Rats are put on a conveyer belt of a treadmill apparatus and the treadmill speed is set at 1800 cm/min. If rats do not run, the conveyer belt brings them to the grid where rats receive weak electrostimulation (ES) to enforce running. The number of ES that the rats receive reflects the frequency with which the rats fail to meet the treadmill speed.

Control rats received 5–10 ES/10 min on the first day but only 0-1 ES after the second day. Rats with unilateral 6-OHDA lesions received over 100 ES on 6 successive days (Hattori *et al.* 1993). Using the treadmill apparatus enables to monitor and quantify motor functions of tested animals.

2.2.3 Sensorimotor tests

The destruction of ascending dopamine fibres results in a syndrome of profound sensorimotor disturbances (Marshall 1979). Postoperative recovery from somatosensory loss, when it occurs, assumes a characteristic sequence, but the extent of recovery after 6-OHDA injections varies greatly between animals (Marshall 1979). The sensorimotor test battery modified from that described by Marshall and Teitelbaum (1974) tests sensorimotor orientation and coordinated limb use on each side of the body. The degree of head orientation and biting of the stimulus probe is recorded first on one side of the body and then on the other side for each of the following stimuli: somaesthesis, whisker touch, snout probe or olfaction (Björklund *et al.* 1980). Sensorimotor tests use the fact that dopamine-depleted rats display a reduced attention to stimuli contralateral to the lesion. This contralateral "sensory neglect" is marked by a lack of responsiveness of the animal to direct probing of the whiskers or side of the body contralateral to the lesion (Björklund *et al.* 1980). Objective tests of sensory neglect record duration of EEG arousal after lateralized somatosensory stimulation (Siegfried and Bureš 1978).

2.3 Skilled motor tests

Dopamine-depleting lesions also influence complex motor acts. Disruption of central DA system results in severe impairment of skilled independent limb use in rats (Dunnett *et al.* 1987). Skilled motor tests (e.g. food retrieval or paw reaching test) represent a third level of behavioural testing for assessment of the performance and function of limb use in 6-OHDA-treated rats. In this test, food-deprived animals are trained to collect a food pellet from a narrow slot outside their cage. Unilateral 6-OHDA lesions severely reduce the frequency of use of the contralateral paw and rats will predominantly use the ipsilateral forepaw. If this "good" ipsilateral forepaw is disabled by the use of a cuff, bracelet or by injection of a local anaesthetic, the ability of the rats to use the affected limb can be assessed (Dunnett *et al.* 1987). There are several other coordinated limb use tests that have been used in testing 6-OHDA-lesioned rats, e.g. cortical placing reactions (forelimb placement, forelimb suspension, forelimb support), climbing grid, limb withdrawal, a lever-press operant task, mouth probe, ammonia swab or staircase test (Björklund *et al.* 1980, Dunnett *et al.* 1981a, Montoya *et al.* 1991).

2.4 Bilateral lesions

A serial bilateral destruction of both nigrostriatal DA pathways produces a well characterized syndrome of profound behavioural unresponsiveness involving the development of aphagia, adipsia, akinesia, bilateral sensory inattention and hunched posture in lesioned rats (Björklund *et al.* 1980, Dunnett *et al.* 1981b, Drucker-Colín and García-Hernández 1992). Daily measurements of the weight of the animal and of the water bottle, from which daily weight loss and water consumption were computed, is related to the degree of the lesion (Björklund *et al.* 1980). However, a large number of tested animals die as a result of prolonged aphagia and adipsia.

In primates, bilateral intrastriatal administration of 6-OHDA produces a behavioural syndrome reminiscent of parkinsonism (Drucker-Colín and García-Hernández 1992).

3. Neural grafting

All these behavioural tests are used first in lesioned animals to assess the extent of DA system damage and then effectiveness of various therapeutical approaches may be assessed on the same animal according to its improvement in behavioural tasks. Neural transplant experiments represent a typical example of the use of these experimental models of PD. Neural transplants of dopamine-rich and dopamine-releasing tissues could circumvent problems of pharmacological treatment of PD. Cell types used in neural grafting experiments include autologous adrenal medulla chromaffin cells, the carotid body, PC-12 pheochromocytoma cells, sympathetic ganglion cells and fetal dopaminergic neurones (Björklund and Stenevi 1979, Drucker-Colín and García-Hernández 1992, Mayer *et al.* 1993, Schueler *et al.* 1993). Rat transplantation studies have raised the possibility of developing a radically new therapy for the treatment of human parkinsonism.

Drug-induced rotational behaviour can assess dopamine graft survival and dopamine release in this animal model (Kawaja *et al.* 1992). Transplants of embryonic substantia nigra can reinnervate a substantial part of the denervated striatum of 6-OHDA-treated rats to an extent that apomorphine- (Dunnett *et al.* 1981a, Björklund *et al.* 1980, Perlow *et al.* 1979) or amphetamine-induced (Björklund and Stenevi 1979, Björklund *et al.* 1980) rotational behaviour was essentially abolished in proportion to the extent of reinnervation from the transplant (Dunnett *et al.* 1981a). After surgical removal of such a graft, the amphetamine-induced rotational response recorded prior to grafting was reinstated (Björklund *et al.* 1980). No improvement was seen in control animals (Perlow *et al.* 1979). Grafted rats, that showed no amphetamine-induced rotations at all, displayed running capacity (in the treadmill running test) that had not been completely restored (Hattori *et al.* 1993).

Transplanted rats showed a reduction of asymmetry in a battery of neurological tests of

sensorimotor function but a marked contralateral 'sensory neglect' remained in the treated animals (Björklund *et al.* 1980, Dunnett *et al.* 1987). DA-rich grafts, reinnervating the denervated caudate-putamen, provided no detectable benefit to the lesioned rats, in increasing their success in skilled motor tasks (Dunnett *et al.* 1987, Drucker-Colín and García-Hernández 1992). This differential sensitivity of behaviours to graft-induced recovery may reflect the level of integration of the graft into the host circuitry (Dunnett *et al.* 1987). While unilaterally lesioned animals showed functional improvement following grafting of the fetal dopamine-rich cell suspension into the ipsilateral basal ganglia, behavioural deficits following bilateral 6-OHDA lesions, such as the regulation of food and water intake, have proved to be resistant to graft-induced recovery (Dunnett *et al.* 1981b, Björklund *et al.* 1980). Intracerebral nigral grafts reinnervating parts of the dorsal caudate-putamen can reverse some, but not all, functional impairments associated with bilateral destruction of the nigrostriatal pathway (Dunnett *et al.* 1981b).

Conclusions

In primates, the most widely used model of PD is the destruction of nigral DA cells by MPTP as MPTP produces a clinical syndrome, indistinguishable from PD. For the time being, the MPTP-lesioned monkey offers a superb animal model for the study of etiological and therapeutic aspects of PD.

Behavioural tests of animals with a nigrostriatal lesion represent valuable, non-invasive methods for assessing the influence of damaged DA system on locomotor activity. The most frequently used experimental model of PD is the drug-evoked rotation in 6-OHDA unilaterally lesioned rats. This model produces well-defined and stable behavioural deficits. The test can be automated as each full turn of the animal is registered on a rotameter. The turning response reflects the extent of dopamine loss and the normalization of this behaviour reflects a recovery of dopamine-releasing capacity. This means that the rotation test is a useful parameter for evaluating imbalances of dopamine in both striata in the hemiparkinsonian rat model. To measure the recovery of motor function in grafted rats other tests have to be used. The spontaneous choice behaviour in the T-maze or treadmill running test may provide a sensitive measure of recovery from 6-OHDA lesions. Sensorimotor and complex motor tasks provide slightly different information concerning the functioning of the damaged DA system.

There are several other tests that can be employed in the study of PD. But some of them, e.g. intracranial self-stimulation of 6-OHDA-lesioned rats (Fray *et al.* 1983), are complicated. The present review brings the survey of the most frequently used behavioural tests in experimental models of PD.

In the future, model systems using the neurotoxin-lesioned substantia nigra could be enriched or replaced by mutants with defective enzymes involved in dopamine synthesis. Recently Clarke and Payne (1994) have described a new mutant rat strain with locomotor disorders and profound depletions of TH-positive neurones within the pars compacta of substantia nigra and corresponding areas of the neostriatum. Such mutants could represent new model systems for the study of Parkinson's disease and other movement disorders.

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Reprint Requests

MUDr. J. Mokrý, Department of Histology and Embryology, Charles University Medical School, 500 38 Hradec Králové, Šimkova 870, Czech Republic.