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REVIEW

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Classic toxin-induced animal models of Parkinson's disease: 6-OHDA and MPTP

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Abstract Neurological disorders in humans can be modeled in animals using standardized procedures that recreate specific pathogenic events and their behavioral outcomes. The development of animal models of Parkinson's disease (PD) is important to test new neuroprotective agents and strategies. Such animal models of PD have to mimic, at least partially, a Parkinson-like pathology and should reproduce specific features of the human disease. PD is characterized by massive degeneration of dopaminergic neurons in the substantia nigra, the loss of striatal dopaminergic fibers and a dramatic reduction of the striatal dopamine levels. The formation of cytoplasmic inclusion bodies (Lewy bodies) in surviving dopaminergic neurons represents the most important neuropathological feature of PD. Furthermore, the massive striatal dopamine deficiency causes easily detectable motor deficits in PD patients, including bradykinesia, rigidity, and resting tremor, which are the cardinal symptoms of PD. Over the years, a broad variety of experimental models of PD were developed and applied in diverse species. This review focuses on the two most common "classical" toxin-induced PD models, the 6-hydroxy-dopamine (6-OHDA model) and the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model. Both neurotoxins selectively and rapidly destroy catecholaminergic neurons, whereas in humans the PD pathogenesis follows a progressive course over decades. This discrepancy reflects one important and principal point of weakness related to most animal models. This review discusses the most important properties of 6-OHDA and MPTP, their modes of administration, and critically examines advantages and limitations of selected animal models. The new genetic and environmental toxin models of PD (e.g. rotenone, paraquat, maneb) are discussed elsewhere in this "special issue."

Keywords Parkinson's disease · Animal models · MPTP · 6-OHDA

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, primarily affecting people of ages over 55 years, although young adults and even children can also be affected. PD is characterized by the loss of 50–70% of dopaminergic neurons located in the substantia nigra. The neuropathological hallmark of PD is the formation of eosinophilic Lewy bodies in surviving dopaminergic neurons. Current evidence suggests an involvement of both environmental and genetic factors in the progression of PD. Research on the pathogenesis of PD has rapidly advanced due to the development of animal models. Through the use of these models, the striatal dopamine deficiency could be associated with the motor symptoms of PD, and levodopa (dihydroxyphenylalanine or L-dopa) was first applied to compensate striatal dopamine losses. L-Dopa treatment still remains the standard of PD therapies (Carlsson et al. 1957). Unfortunately, long-time use of L-dopa results in dyskinesia (involuntary movements). Moreover, the specific etiology of PD is still unknown. Thus, the development of animal models is essential for better understanding pathogenesis and progression of PD and testing therapeutic agents for the treatment of PD patients.

Early models were developed by using specific dopaminergic neurotoxins. Thus, agents that selectively disrupt or destroy catecholaminergic systems, such as 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) have been introduced (see Fig. 2, Dauer and Przedborski 2003). Recently, it was discovered that agricultural chemicals, such as rotenone, maneb and paraquat, when administered systemically, can

also induce specific features of PD (Betarbet et al. 2002). A common feature of all neurotoxin-induced models is that they all affect mitochondria, either by inhibiting mitochondrial complex I or complex III (see Fig. 1).

More recently, the finding of mutations in the alpha-synuclein gene (and some other genes) in a few PD patients has led to the development of gene based PD models, and transgenic or gene-deficient mice or flies are now available (for, e.g. synuclein, parkin, ubiquitin C-terminal hydrolase L1). This review describes the use and effects of the neurotoxins 6-OHDA and MPTP in a variety of species, discusses advantages and disadvantages (summarized in Table 1) of these animal models and considers their importance in revealing mechanisms and pathological properties involved in PD pathogenesis.

The 6-OHDA model

6-Hydroxydopamine (6-OHDA) is a hydroxylated analogue of the natural neurotransmitter dopamine (Blum et al. 2001). It was originally isolated by Senoh and Witkop (1959) and Senoh et al. (1959). Its biological effects were first demonstrated by Porter et al. (1963), who showed that 6-OHDA induces efficient and long lasting noradrenaline depletion in sympathetic nerves to the heart (Porter et al. 1963, 1965). Today, 6-OHDA represents one of the most common neurotoxins used in degeneration models of central catecholaminergic projections, including the nigrostriatal system, in vivo and in vitro (Ungerstedt 1968, 1976; Sachs and Jonsson 1975; Blum et al. 2001). 6-OHDA induced toxicity is relatively selective for cate-

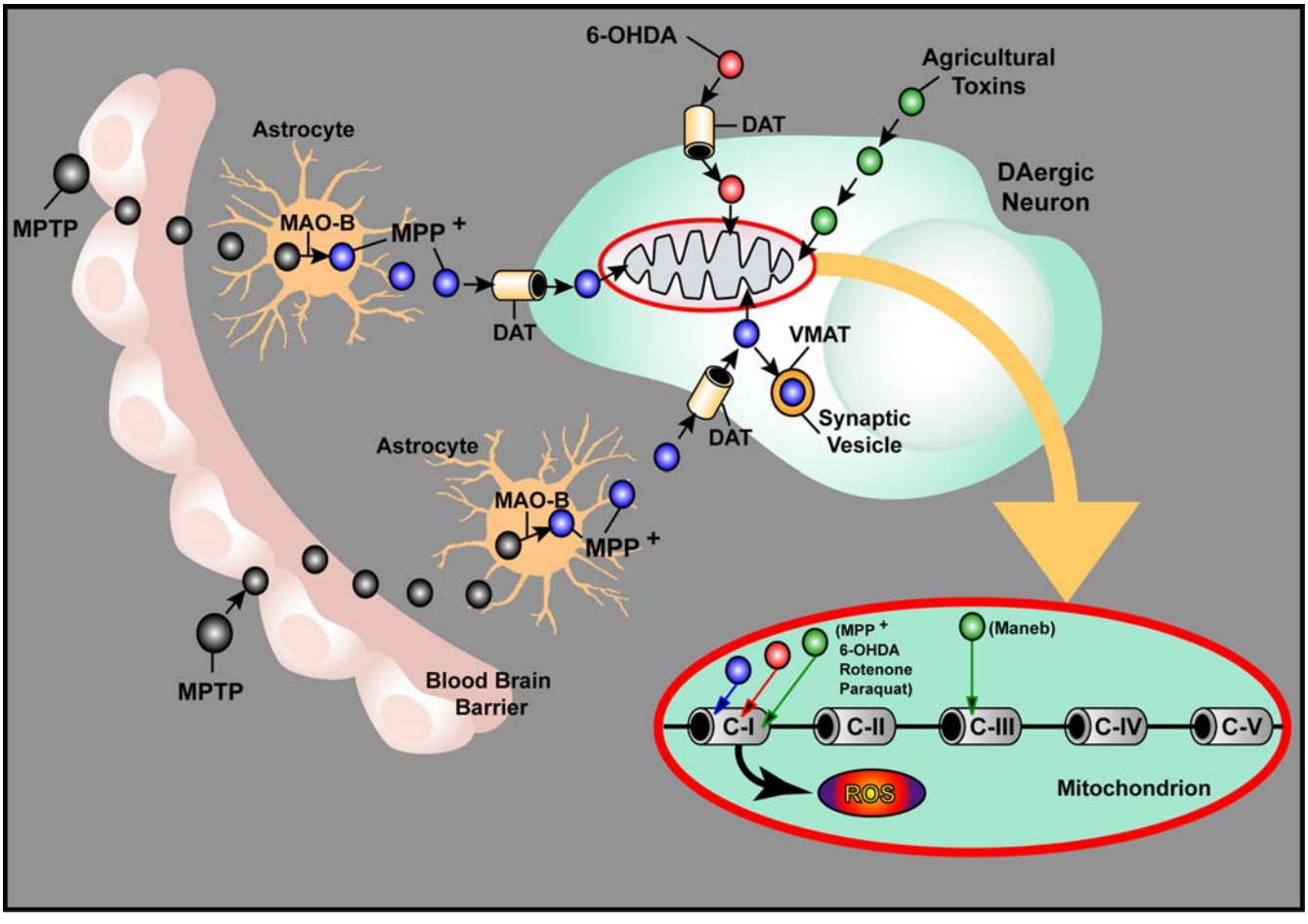

Fig. 1 Schematic overview of molecular and intracellular pathways of dopaminergic neurotoxins applied in animal models of Parkinson's disease. MPTP (*black vesicles*) enters the brain by crossing the blood–brain barrier after systemic injection. Thereafter, MPTP (*black vesicles*) is taken up by astrocytes and converted in its active form: MPP^+ (*blue vesicles*, catalyzed by the enzyme monoamine oxidase-B, *MAO-B*). Then, MPP^+ (*blue vesicles*) is released from astrocytes into the extracellular space and can be specifically transported into dopaminergic neurons via the dopamine transporter (*DAT*). Inside the dopaminergic neuron MPP^+ (*blue vesicle*) can be (i) concentrated in mitochondria or can (ii) be sequestrated into synaptic vesicles (*yellow-blue vesicle*) via the vesicular monoamine transporter (*VMAT*). 6-OHDA (*red vesicles*) has to be stereotactically targeted into the substantia nigra, the nigrostriatal tract or the striatum. 6-OHDA (*red vesicles*) is selectively taken up via DAT by dopaminergic neurons. As described for MPP^+, 6-OHDA (*red vesicle*) can also be accumulated by mitochondria. Agricultural toxins, e.g. rotenone, paraquat, maneb (*green vesicles*), penetrate into the dopaminergic neuron unspecifically and accumulate inside the mitochondria. *Inset* shows schematically the mitochondrial electron transfer chain (ETC) which consists of complex I–V (*C-I*, *C-II*, *C-III*, *C-IV*, *C-V*). MPP^+ (*blue vesicle*), rotenone (*red vesicle*) and paraquat (*green vesicle*) affect directly C-1, leading to C-1 inhibition and the generation of reactive oxygen species (ROS), whereas maneb (*green vesicle*) interrupts the ETC at C-III. In summary, all of these mitochondrial intoxications enhance the production of free radicals and decrease the synthesis of ATP

Table 1 Key properties of 6-OHDA and MPTP animal models of Parkinson's disease. *DA* dopamine, *DAergic* dopaminergic, *ir* immunoreactive, *TH* tyrosine hydroxylase

Model	Symptoms induced	Pathology	Favorite applications	Disadvantages
6-OHDA	Unilateral: rotation after, e.g. apomorphine treatment, bilateral: akinesia	Loss of Striatal DA-levels Striatal TH-ir fibers Nigral TH-ir neurons	Tests of preclinical therapies, tests of new pharmacological and genetic therapeutic strategies	Acute damage of the DAergic system, unilateral effects, intracerebral injection
MPTP	Akinesia, rigidity and tremor (not in rodents)	Loss of Striatal DA-levels Striatal TH-ir fibers Nigral TH-ir neurons (see Fig. 2) α-Synuclein aggregation (non fibrillar)	Tests for neuroprotective and neuro-restorative treatments	Acute damage of the DAergic system, non-progressive rare generation of inclusion bodies

cholaminergic neurons, resulting from a preferential uptake of 6-OHDA by dopamine and noradrenergic transporter molecules (Luthman et al. 1989). Inside neurons, 6-OHDA accumulates in the cytosol and induces cell death without apoptotic characteristics (Jeon et al. 1995). Electron-microscopic studies have provided evidence for the ability of 6-OHDA to destroy adrenergic nerve terminals after systemic injection (Thoenen and Tranzer 1968; Tranzer and Thoenen 1968). Furthermore, 6-OHDA was shown to cause ultrastructural changes in non-neuronal cells, e.g. in adrenocortical cells of lizards and rats (Unsicker et al. 1976a,b). However, the uptake of 6-OHDA into synaptic vesicles of adrenergic terminals is not necessary for its degenerating effect, because pretreatment with reserpine prevents both ultrastructural changes of adrenergic nerve endings and the reduction of tyrosine hydroxylase (TH) in sympathetically innervated organs (Thoenen 1972).

As far as mechanisms underlying toxicity of 6-OHDA are concerned, participation of oxidative stress, is firmly established (Sachs and Jonsson 1975). It has been reported that 6-OHDA-induced neuron degeneration involves the processing of hydrogen peroxidase and hydroxyl radicals in the presence of iron (Sachs and Jonsson 1975). The observation that intra-nigral injection of iron produces neurotoxic effects comparable to those induced by 6-OHDA may suggest an involvement of iron in 6-OHDA-induced neuronal degeneration (Ben-Shachar and Youdim 1991). Furthermore, it has been shown that 6-OHDA treatment reduces striatal glutathione (GSH) and superoxide dismutase (SOD) enzyme activity (Perumal et al. 1992), and increased levels of malondialdehyde (Kumar et al. 1995). 6-OHDA seems to be toxic to mitochondrial complex I (see Fig. 1; Cleeter et al. 1992; Betarbet et al. 2002) and leads to the formation of superoxide free radicals (Hasegawa et al. 1990). The prevention of neurotoxic effects of 6-OHDA and iron following pretreatment with iron chelating compounds, vitamin E, or sellegine, a monoamine oxidase B (MAO-B) inhibitor, may also be considered as indirect evidence for the production of free radicals and involvement of oxidative stress mechanisms (Knoll 1986; Cadet et al. 1989; Perumal et al. 1992). Interestingly, endogenous 6-OHDA has been found to be accumulated in patients suffering from PD (Andrew et al. 1993). Taken together, in neurodegenerative processes, 6-OHDA causes respiratory inhibition and oxidative stress, induced by free radical formation. Both toxic mechanisms are not necessarily linked, but appear to act synergistically during neuron degeneration. 6-OHDA is easily oxidizable and can also take part in free radical forming reactions, like the metabolic monoamine oxidation. Finally, 6-OHDA is not only a respiratory toxin, it acts also as clastogen and mutagen (Gee et al. 1992; Glinka et al. 1997).

Systemically administered 6-OHDA fails to cross the blood–brain barrier. Thus, 6-OHDA has to be injected stereotactically into the brain. Preferred injection sites are the substantia nigra, medial forebrain bundle, and striatum (Perese et al. 1989; Przedborski et al. 1995). Following 6-OHDA injections into the substantia nigra or the medial forebrain bundle, dopaminergic neurons begin to degenerate within 12 h and striatal dopamine levels are depleted 2–3 days later (Faull and Laverty 1969). Interestingly, intrastriatal injection of 6-OHDA causes a more progressive, retrogradely induced neuron death than its administration into the substantia nigra–ventral tegmental area complex (SN–VTA; Berger et al. 1991; Sauer and Oertel 1994; Przedborski et al. 1995). The magnitude of the lesion depends on the amount of 6-OHDA injected, the site of the injection, and the species used (Betarbet et al. 2002). At least in mice, rats, cats and primates, 6-OHDA is a highly effective toxin for dopaminergic (DAergic) neurons (Beal 2001). Bilateral 6-OHDA lesions induce, in part, parkinsonian motor symptoms, however, the bilateral lesion does not represent the most frequently used model, due to the fact that bilaterally affected animals require intensive nursing care (Cenci et al. 2002). Unilateral 6-OHDA-injection causes an asymmetric and quantifiable motor behavior induced by systemic administration of either dopaminergic receptor agonists (e.g. apomorphine), L-dopa, or dopamine releasing drugs (e.g. amphetamine; Hefti et al. 1980). In the unilateral 6-OHDA model, also known as "hemiparkinson model," the intact hemisphere serves as internal control structure (Perese et al. 1989). Amphetamines have been termed indirect dopamine agonists, since they affect dopaminergic

receptors indirectly by increasing the extracellular availability of endogenous striatal dopamine. This can occur by increasing dopamine release, and by decreasing its reuptake and enzymatic degradation (Schwarting and Huston 1996). The relationship of 6-OHDA lesion and rotation after amphetamine administration is not yet clarified in detail. Shortly after the lesion, amphetamine treatment can induce contralateral turning in response to the release of non-functional dopamine pools in the lesioned hemisphere. Afterwards, such pools are depleted and the direction of turning is contributed to the release of dopamine in the unlesioned hemisphere. However, no or only weak ipsilateral turnings were observed following an 70–80% loss of striatal dopamine, whereas in other studies, even after less severe lesions, an ipsilateral turning has been described (Schwarting and Huston 1996). These discrepancies may be caused by the administration of different doses of amphetamine.

Apomorphine (APO) is a dopamine receptor agonist which stimulates both classes of dopamine receptors (D_1, D_2). The expression of contralateral turnings after systemic injections of apomorphine is generally considered to be a typical feature of unilateral 6-OHDA-lesions. This contralateral response is attributed to the stimulation of supersensitive D_1-receptor and D_2-receptor activation, especially in the lesioned hemisphere. Surprisingly, in cases of moderate or compensated lesions (less than 80%), no turning or a weak ipsilateral turning has been monitored (Schwarting and Huston 1996). Further along this line, turning studies following 6-OHDA lesion and amphetamine or apomorphine administration have to be judged with caution. Unilateral lesions of the nigrostriatal projection may also have contralateral consequences, such as changes of striatal peptide and dopamine levels or changes in the electrical activity of neurons located in the subthalamic nucleus (Nieoullon et al. 1977; Salin et al. 1996; Périer et al. 2000). However, this approach allows easily the control of the extent of a dopaminergic lesion and evaluates the power of therapeutic treatments, a major advantage of the 6-OHDA model of PD (Beal 2001).

In summary, the 6-OHDA model does not mimic all pathological and clinical features of human parkinsonism. It induces dopaminergic neuron death with preservation of non-dopaminergic neurons, whereas the formation of cytoplasmatic inclusions (Lewy bodies) does not occur. 6-OHDA does not affect other brain areas involved in PD, such as in anterior olfactory structures, lower brain stem areas or the locus coeruleus (Betarbet et al. 2002; Del Tredici et al. 2002). Reports on parkinsonian-like tremor are rare in studies of 6-OHDA-lesioned rodents, however, occasional akinesia, rigidity and tremor have been described (Lindner et al. 1999; Cenci et al. 2002). Finally, the regimen of the 6-OHDA model with intrastriatal injections may be more useful for neuroprotective studies, whereas the regimen with 6-OHDA injections into the SN–VTA complex appears to be a more useful approach for testing new pharmacological or cell replacement therapies (Hirsch et al. 2003). In general, this model exclusively induces acute effects, which differs significantly from the slowly progressive pathology of human PD (Betarbet et al. 2002).

The MPTP model

In 1982, the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), an analogue of the narcotic meperidine (Demerol), was accidentally discovered (Langston et al. 1983). Young drug addicts developed an ideopathic parkinsonian syndrome after intravenous self-administration of a "synthetic heroin" (MPPP 1-methyl-4-phenyl-propion-oxypiperidine) (Davis et al. 1979; Langston and Ballard 1983; Langston et al. 1983). MPTP was the neurotoxic contaminant responsible for the effect. Most of the biochemical, neuropathological and clinical characteristics observed in these drug addicts corresponded exactly to the cardinal symptoms of human PD (Langston et al. 1983), with the exception of the formation of Lewy bodies (Langston et al. 1983). A more recent study of these patients, who had inadvertently contracted PD, provided evidence for a stable and irreversible PD induced by MPTP (Langston et al. 1999). Today, MPTP represents the most important and most frequently used parkinsonian toxin applied in animal models (Beal 2001; Przedborski et al. 2001) and has a competitive advantage over all other toxic PD models because: (i) it causes directly a specific intoxication of dopaminergic structures and (ii) it induces in humans symptoms virtually identical to PD (Przedborski and Vila 2003). MPTP is highly lipophilic, and after systemic administration rapidly crosses the blood–brain barrier. Subsequently, the protoxin MPTP is converted to 1-methyl-4-phenyl-2,3-dihydropyridium (MPDP) exclusively in non-dopaminergic cells (especially in astrocytes and serotonergic neurons) by monoamine oxidase B (MAO-B) and then spontaneously oxidizes to 1-methyl-4-phenylpyridinium (MPP^+) (Nicklas et al. 1985, 1987; Przedborski and Vila 2003). Thereafter, MPP^+ is released into the extracellular space by an unknown mechanism (Przedborski and Vila 2003). The polar molecule MPP^+ is not able to enter dopaminergic cells freely, thus, its uptake depends on active plasma membrane carrier systems (see Fig. 1). High affinities of MPP^+ to the dopamine transporter (DAT), as well as noradrenaline and serotonin transporter have been reported (Javitch and Snyder 1984; Javitch et al. 1985; Mayer et al. 1986). Consequently, mice lacking these transporters are protected from MPTP toxicity (Bezard et al. 1999). Inside dopaminergic neurons, MPP^+ can bind to the vesicular monoamine transporter (VMAT), which is associated with an incorporation of MPP^+ into synaptic vesicles containing dopamine (Del Zompo et al. 1993). In addition, MPP^+ can accumulate within mitochondria (see Fig. 1) or can remain inside the cytoplasm and interact with several cytosolic enzymes (Ramsay and Singer 1986; Adams et al. 1993; Klaidman et al. 1993). MPP^+ impairs mitochondrial respiration by inhibiting complex I (see Fig. 1) of the electron transport chain (Nicklas et al. 1985; Mizuno et al. 1987).

Interestingly, sequestration into vesicles decreases MPP^+ toxicity by preventing its interaction with mitochondria (Reinhard et al. 1987; Liu et al. 1992). Thus, mice with a 50% depletion of VMAT show increased vulnerability to MPTP (Takahashi et al. 1997).

MPTP is mainly used in non-human primates and in mice but also in several other species such as dogs, cats, sheep, rats and goldfishes (Gerlach and Riederer 1996; Przedborski et al. 2001). In contrast to primates, rodents are less sensitive to MPTP toxicity (Schmidt and Ferger 2001). Nevertheless, the C57black6 mice strain was found to be sensitive to a systemic injection of MPTP and was significantly more selective than other mice strains in terms of affecting mesencephalic dopaminergic neurons. At present, the MPTP mouse model provides the most useful animal model of PD to study neuropathological and neurochemical changes (Schmidt and Ferger 2001). On the other hand, for behavioral tests the MPTP monkey model appears much more suitable, because behavioral changes monitored in rodents tend to be reversed nearly completely. With regard to the species used, several distinct routes of MPTP administration have been established. In principle, MPTP can be given by a variety of regimens such as gavage or stereotactical injection, but the most common and reproducible form is still the systemic administration (e.g. subcutaneous, intravenous, intraperitoneal or intramuscular; Przedborski et al. 2001).

Regarding the comparison between human PD and MPTP-induced neuropathology, such data derive mostly from MPTP studies in monkeys (Forno et al. 1993), because only four humans with accidental MPTP injection have come to autopsy (Davis et al. 1979; Langston et al. 1999). The most commonly used administration mode in monkeys are multiple intraperitoneal or intramuscular injections as well as intracarotid infusions (Petzinger and Langston 1998). Monkeys often exhibit a generalized parkinsonian syndrome (bilateral), so that an accompanying application of levodopa is required to allow the MPTP treated animals to eat and drink adequately (Petzinger and Langston 1998). The unilateral intracarotid infusion is technically much more complicated, but causes mostly symptoms on one side (Bankiewicz et al. 1986), which enables the monkeys to maintain a normal nutrition without supporting therapeutics (Przedborski et al. 1991). In the past, primates were nearly exclusively treated with high doses of MPTP to induce a spontaneous and severe degeneration of dopaminergic neurons. Recently, views concerning regimens of MPTP administration have changed. At present, monkeys are treated more and more with low doses of the neurotoxin (e.g. 0.05 mg MPTP/kg, 2–3 times/week) for a prolonged period of time (over weeks or months) (Przedborski et al. 2001). This approach causes chronic degeneration effects, thus, this modification mirrors the human PD pathogenesis more appropriately (Schneider and Roeltgen 1993; Bezard et al. 1997a,b; Schneider et al. 1999). On the other hand, the monkey MPTP model does not include two important characteristic features of PD: (i) neurons are not consistently lost within other monoaminergic brain areas, such as the locus coeruleus (Forno et al. 1986, 1993; Dauer and Przedborski 2003), and (ii) although intraneural inclusions have been described (Forno et al. 1986), classical Lewy bodies, a typical feature of PD, have not been demonstrated convincingly in MPTP-intoxicated patients or monkeys (Forno et al. 1993). Taken together, both the chronic and the acute MPTP-application mode are used for testing new therapies in monkeys, whereas the chronic monkey model represents the most suitable model for testing new neuroprotective strategies (Przedborski et al. 2001). Nevertheless, because of the economical, logistic and ethical constraints that are related to experimental research in primates, primate models of PD are used in relatively few laboratories worldwide (Cenci et al. 2002).

There are numerous indications from the literature that trophic factors may rescue neuronal cells from experimental induced neuron degeneration and cell death. Glial cell line-derived neurotrophic factor (GDNF) is one of the most potent neurotrophic factors that have been identified for DAergic neurons (Unsicker 1996; Kirik et al. 2004). GDNF promote survival and function of DAergic neurons in vivo, both for the intact brain and after neurotoxin (e.g. by MPTP or 6-OHDA) induced nigrostriatal lesions (Hoffer et al. 1994; Hudson et al. 1995; Tomac et al. 1995, Gash et al. 1996). Recently, it has been shown that chronic infusions of glial cell line-derived neurotrophic factor (GDNF) into the lateral ventricle, the putamen or the substantia nigra, promotes restoration of the nigrostriatal dopaminergic system and significantly improves motor functions in MPTP-lesioned rhesus monkeys with neural deficits modeling the terminal stages of PD and in aged rhesus monkeys modeling the early stages of PD (Grondin et al. 2003). Based on these promising studies of the chronic effects of GDNF in non-human primate models of PD, a study was recently conducted in England on five advanced PD patients. Chronic GDNF infusion into the dorsal putamen, via programmable pumps, resulted in improved motor function in all patients and limited side effects were observed (Gill et al. 2003). However, while the data from this intraparenchymal clinical trial in humans look encouraging, extensive blinded efficacy trials will need to be conducted before it can be determined if chronic treatment with GDNF or other trophic molecules will prove useful in treating patients with PD (Grondin et al. 2003; Kirik et al. 2004).

The use of MPTP in rats is not being widely used, and the significance of data obtained from MPTP-treated rats are controversial (Kopin and Markey 1988). Rats injected with MPTP doses comparable to those used in mice do not show any significant dopaminergic neurodegeneration (Giovanni et al. 1994a,b). Only injections of much higher doses of MPTP (multiple applications of 30–60 mg/kg body weight) cause significant dopaminergic neurodegeneration in rats. Remarkably, these rats have to be therapeutically pretreated, e.g. with guanethidine, to prevent peripheral catecholamine release and extensive mortality (Giovanni et al. 1994a). These findings indicate that rats are relatively insensitive to MPTP. In conclusion,

rats are not recommended for MPTP studies, because rats fail to develop parkinsonian features, as shown, e.g. for monkeys and mice (Schmidt and Ferger 2001). The conspicuous insensitivity of rats to MPTP toxicity may be related to a species specific metabolism of MPTP and/or sequestration of MPP^+, which could be different in rats compared to mice and monkeys (Schmidt and Ferger 2001).

Mice have become the most commonly used species for MPTP treatment studies (see Fig. 2), basically a consequence of both technical and economical reasons (Przedborski et al. 2001; Schmidt and Ferger 2001). However, several problems need to be addressed. It has been shown that mice are significantly less sensitive to MPTP than monkeys. Consequently, higher doses are required to induce a significant loss of dopaminergic neurons. In contrast to the situation in monkeys, mice treated with MPTP do not develop persistent and progressive motor symptoms (Przedborski et al. 2001). Last but not least, the level of the dopaminergic impairment depends on the dose and schedule of MPTP administration (Sonsalla and Heikkila 1986; Schmidt and Ferger 2001). The schedule of MPTP intoxication does not only influence the time course of nigrostriatal damage but may also provide new insights into the underlying mechanisms of PD pathogenesis, e.g. induction and manifestation of neuronal death (necrotic/apoptotic), which appears to be correlated to different stages of the human PD (presymptomatic, immediate onset, progressive and final stage).

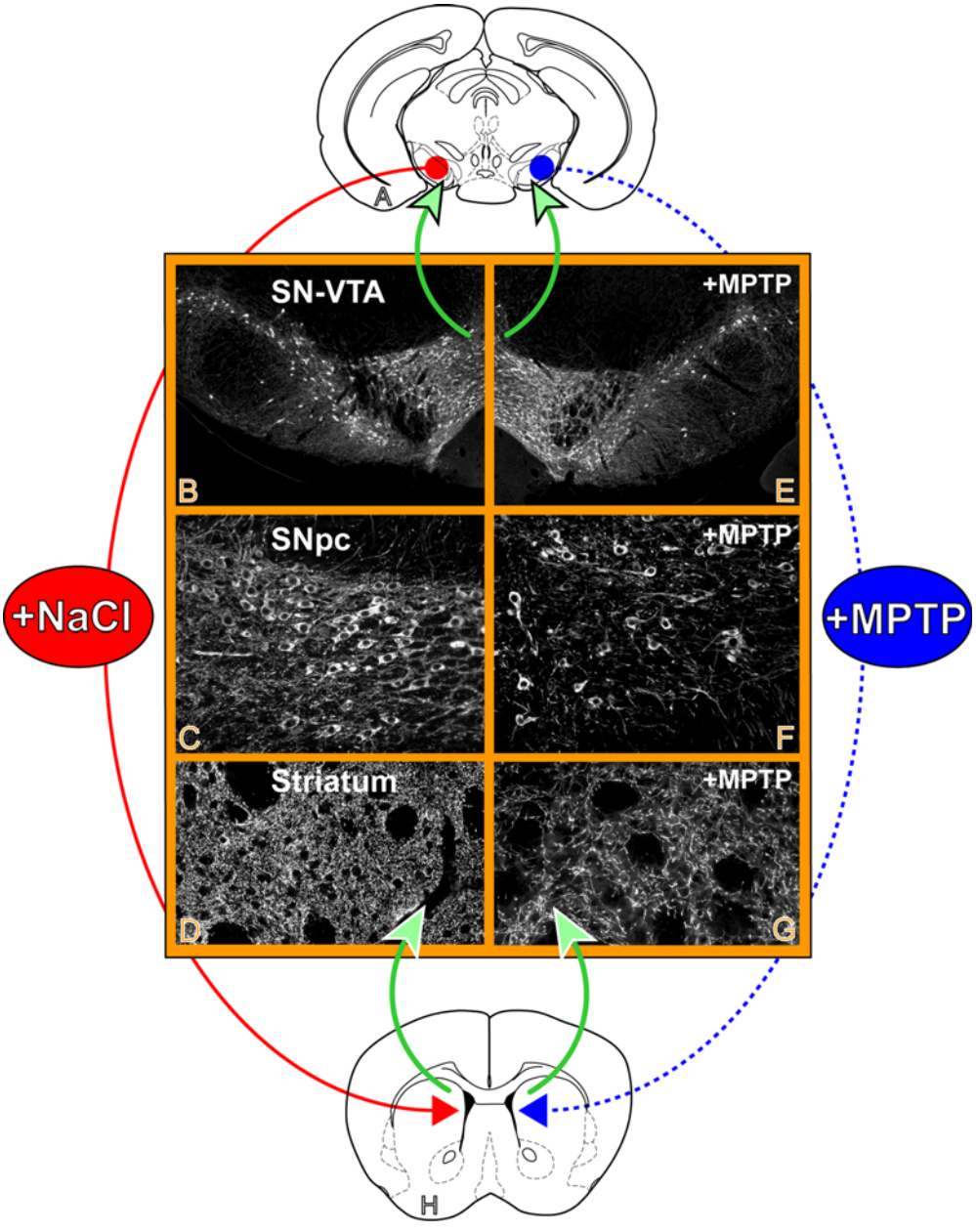

Fig. 2 Schematic illustration of the nigrostriatal projection of adult mice. Dopaminergic neurons located in the substantia nigra–ventral tegmental area (*SN–VTA*) complex project to the dorsal striatum **A**,**B**,**H**. These dopaminergic neurons can be visualized by tyrosine hydroxylase (TH) immunohistochemistry **B**–**G**. MPTP treatment induces a significant loss of TH-immunoreactive (ir) neurons, especially in the substantia nigra pars compacta (*SNpc*, **E**,**F**) as compared to NaCl-treated control mice **B**,**C**. Densities of TH-ir striatal fibers are clearly reduced at day 4 following last MPTP injection **G** as compared to the densities of striatal TH-ir fibers in NaCl-control mice **D**

According to Schmidt and Ferger (2001), at least four different MPTP models can be distinguished in mice:

(1) Model for presymptomatic PD. This regimen is particularly suitable for studies of compensatory mechanisms. MPTP has to be applied in an acute manner and at low doses, e.g. 1×10–20 mg/kg.
(2) Model for immediate onset of PD (Jackson-Lewis et al. 1995). This approach requires an acute treatment with a medial dose of MPTP, e.g. 4×20 mg/kg, at 2 h intervals. This application mode induces a rapid dopaminergic degeneration with predominantly necrotic cell death (Jackson-Lewis et al. 1995).
(3) Model for subchronic PD (Tatton and Kish 1997; Vila et al. 2000). MPTP has to be injected 1–2 times in a dose of 20–30 mg/kg over a time period of at least 5 days. In contrast to model (1) and (2), this treatment induces a so called "delayed degeneration" of the nigrostriatal dopaminergic system, including apoptotic cell death of dopaminergic neurons located in the substantia nigra, pars compacta (Tatton and Kish 1997).
(4) Model for progressive chronic PD (Bezard et al. 1997a,b). This chronic administration paradigm is based on one daily MPTP injection at low doses, e.g. 4 mg/kg over a time period of 20 days. The chronic MPTP-mouse protocol mirrors most closely the pattern of progression assumed to be that of PD and appears useful for studies on neuroprotection and compensatory mechanisms.

In summary, the comparison of these different models indicates clearly that different schedules of administration of MPTP mimic distinct stages of the disease and might induce different mechanisms of neuronal death. The general discussion whether mouse models of PD are suitable tools to replicate the progression of human Parkinson's disease will continue. In this context, the mouse model does not reproduce the end stage of PD, where non-dopaminergic neurodegeneration also becomes manifest. Moreover, the formation of Lewy bodies have never been described in rodents treated with MPTP, indicating a major difference in the pathogenesis of MPTP-induced parkinsonism and idiopathic PD (Hirsch et al. 2003). In addition, mice show only transient behavioral symptoms as an initial short term toxic effect of MPTP. They exhibit hypersalivation, convulsions, piloerection and hypokinesia, but recover within 24–48 h (Schmidt and Ferger 2001). Finally, we have to recall that all alterations induced by MPTP administration in mice appear in a range of days or weeks, whereas PD in humans develops over decades (Schmidt and Ferger 2001).

Conclusions and outlook

Currently available animal models of PD have contributed greatly to our understanding of both the pathogenesis of the human disease and potential neuroprotective therapeutics, but both, the 6-OHDA and MPTP animal models, fail to replicate either the progressive loss of dopaminergic neurons, the clinical symptoms of a movement disorder, or the generation of Lewy bodies. In general, animal models of PD, such as the toxin-induced models, fulfill most of the required features at least partially. At present and despite its limitations, application of MPTP neurotoxicity is the best available and the most popular animal model of PD (Beal 2001; Schmidt and Ferger 2001; Betarbet et al. 2002; Dauer and Przedborski 2003; Hirsch et al. 2003; Orth and Tabrizi 2003; Przedborski and Vila 2003). Injection of 6-OHDA into the striatum or substantia nigra, an early model of parkinsonism, kills dopaminergic neurons and induces quantifiable motor deficits (rotation)—the major advantage of this model. However, a novel improved model appears desirable. Such a model should have the following features: (i) a normal set of nigral dopaminergic neurons at birth followed by a selective gradual loss of these cells beginning in adulthood; (ii) easily detectable and quantifiable motor deficits (e.g. akinesia, regity, tremor); (iii) Lewy bodies should be generated; (iv) the model should have a relatively short time course to mimic the pathogenesis of PD (about 3–6 months), which would allow a rapid screening of therapeutic substances and strategies. Future models should comprise a combination of neurotoxin-induced and genetically-induced alterations considering the current valid concept that environmental and genetic factors are both involved in the pathogenesis of PD. Following this line, Song et al. (2004) presented an analysis of α-synuclein transgenic mice that were treated with MPTP. They found extensive mitochondrial alterations, increases in mitochondrial size, filamentous neuritic aggregations, axonal degeneration, and formation of electron dense perinuclear cytoplasmic inclusions in the SN–VTA complex. Interestingly, these effects occurred neither in the hippocampus or neocortex, nor in MPTP-treated non-transgenic mice. Thus, these data support the potential involvement of α-synuclein expression in the vulnerability of SN–VTA neurons to toxicity from mitochondrial complex I inhibitors (e.g. MPTP) and the subsequent development of neurodegenerative pathology (Song et al. 2004).

Final remark

The neurotoxin MPTP, as described above, displays the best experimental model of PD. Thus, it is extensively used, but even as a research tool it is an extremely hazardous agent (Przedborski et al. 2001). Young drug addicts developed a stable and irreversible ideopathic parkinsonism following accidental intravenous injection of MPTP. Consequently, the use of MPTP represents a

serious risk and concern, because MPTP can also enter the human body via ingestion, inhalation, and/or absorption. Thus, MPTP users should always be very careful and, furthermore, they have to follow strictly all safety rules during their contact with MPTP and MPTP-treated animals (for a summary, see Przedborski et al. 2001).

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