ACTA NEUROBIOLOGIAE EXPERIMENTALIS

Review Acta Neurobiol Exp 2011, 71: 269–280

Neuropharmacological approach against MPTP (1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine)-induced mouse model of Parkinson's disease

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Parkinson's disease (PD) is a common neurodegenerative disease that appears essentially as a sporadic condition. PD is well known to be a chronic and progressive neurodegenerative disease produced by a selective degeneration of dopaminergic neurons in the substantia nigra pars compacta. The main clinical features of PD include tremor, bradykinesia, rigidity and postural instability. Most insights into pathogenesis of PD come from investigations performed in experimental models of PD, especially those produced by neurotoxins. The biochemical and cellular alterations that occur after 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine (MPTP) treatment are remarkably similar to that observed in idiopathic PD. Furthermore, it is well known that acute treatment with MPTP can cause a severe loss of tyrosine hydroxylase and dopamine transporter protein levels and dopamine contents in the striatum of mice, as compared to continuous MPTP treatment. Thus these findings may support the validity of acute MPTP treatment model for unraveling in the neurodegenerative processes in PD. In this review, we discuss the neuroprotective effects of various compounds against neuronal cell loss in an MPTP model of PD. This review may lead to a much better understanding of PD as well as provide novel clues to new targets for therapeutic interventions in PD patients.

Key words: MPTP, neurodegeneration, Parkinson's disease, striatum, substantia nigra

INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disorder characterized mainly by tremor, bradykinesia, rigidity, slowness of movement, and postural instability. The main anatomical feature of PD is the reduction in number of dopaminergic neurons located in the substantia nigra pars compacta. These dopaminergic neurons project to the striatum as well as to a number of other subcortical regions. PD symptoms first manifest when approximately 60% of the dopaminergic neurons have already died (German et al. 1989, Agid 1991) and 70% of dopamine responsiveness disappears (Ma et al. 2002).

PD is treated by administration of the dopaminergic precursor, L-3,4- dihydroxyphenylalanine (L-DOPA), which is transformed in residual dopaminergic neurons of the substantia nigra (Rascol et al. 2003). Furthermore, L-DOPA is suspected to exert neurotoxic properties that accelerate the loss of dopaminergic neurons (Blum et al. 2001, Whone et al. 2003). There have been additional anti-parkinsonian agents, such as dopamine receptor agonists and selective inhibitor of monoamine oxydase-B (MAO-B), but the available therapies do not protect against dopaminergic neuronal cell death. PD patients begin not to respond well to treatment, and start to suffer disabilities which cannot be controlled with existing medical therapies. The prevalence of PD is likely to increase in the coming decades, as the number of elderly people increases. Therefore, it is of utmost importance to develop new drugs or targets that show or halt the rate of progression of PD patients in the world.

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Received 03 March 2010, accepted 01 October 2010

[1]Deceased during publishing process.

Table I

Experimental schedules with MPTP treatment

Experimental schedule number	MPTP treatment	*n*	Dose per day (mg/kg)	Total dose (mg/kg)
(1)	15 mg/kg once a day for 14 consecutive days	5-7	15	210
(2)	30 mg/kg twice a day for 5 consecutive days	5-6	60	300
(3)	10 mg/kg four times a day for 2 consecutive days	5-7	40	80
(4)	20 mg/kg once a day for 4 consecutive days	4	20	80
(5)	20 mg/kg twice a day for 2 consecutive days	5	40	80
(6)	20 mg/kg twice a day for 4 consecutive days	5	40	160
(7)	20 mg/kg four times a day within a day	4-6	80	80

THE MPTP-MOUSE MODEL OF PARKINSON'S DISEASE

A previous interesting study reported the occurrence of an akinetic rigid syndrome responsive to L-DOPA resembling the clinical features of PD in seven individuals after intravenous administration of an illicit synthetic heroin analog (meperidine) that contained high amounts of by-product MPTP (1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine, Langston et al. 1983). Subsequent studies demonstrated that systemic administration of MPTP into non-human primates (Langston et al. 1984) and mice (Ricaurte et al. 1987) caused an irreversible and selective loss of dopaminergic neurons in the substantia nigra. MPTP is a highly lipophilic molecule and crosses rapidly the blood-brain barrier in a matter of seconds of systematic injection (Markey et al. 1984). MPTP is also a neurotoxin that produces a parkinsonian syndrome in both humans and experimental animals (Langston et al. 1983, Dauer and Przedbroski 2003). Furthermore, MPTP is rapidly converted to the hydrophilic metabolite 1-methyl-4-phenylpyridinium (MPP^+) by MAO-B in astrocytes (Tipton and Singer 1993). MPP^+ is selectively accumulated by high affinity dopamine transporters (DAT) and taken up into the mitochondria of dopaminergic neurons, where it disrupts oxidative phosphorylation by inhibiting complex I (NADH-ubiquinone oxidoreductase) of the mitochondrial electron transport chain (Gluck et al. 1994, Good et al. 1998). This leads to impairment of ATP production, elevated intracellular calcium levels, and free radical generation, thereby exhibiting dopaminergic neurotoxicity (Hasegawa et al. 1990, Sriram et al. 1997). Furthermore, a previous interesting study with biochemical and genetic data also suggests that iron accumulation and subsequent oxidative stress may be a primary event in the neurodegenerative processes (Kauer and Andersen 2004). A number of iron chelators have been shown to attenuate MPTP toxicity in mice, suggesting that iron either mediates or accentuates subsequent neuropathological events associated with its administration (Lan and Jiang 1997, Grunblatt et al. 1999). Therefore, MPTP treatment is known to cause a marked depletion of dopamine and nigrostriatal neuronal cell death in a wide variety of animal species, including mice, dogs and non-human primates (Heikkila

et al. 1984a, b, Johannessen et al. 1991, Hantraye et al. 1996). Although MPTP-treated monkey model remains the best, most studies have been performed in MPTP-treated mice as a good model of PD (Heikkila et al. 1984a, b). Many studies into the mechanisms and possible neuroprotective amelioration against MPTP neurotoxicity have been carried out for many years. However, less is known about therapeutic effects of various compounds against MPTP neurotoxicity in mice under the same conditions.

CHANGE IN THE STRIATAL DOPAMINE CONTENTS AFTER ACUTE AND SUB-ACUTE MPTP TREATMENT

To examine the neurotoxic effect of MPTP, in our laboratory, the animals were divided into 7 groups, as shown in Table I: (1) The mice that received MPTP hydrochloride (15 mg/kg in saline, i.p.) once a day for 14 consecutive days; (2) The mice that received MPTP hydrochloride (30 mg/kg in saline, i.p.) twice a day for 5 consecutive days; (3) The mice that received MPTP hydrochloride (10 mg/kg in saline, i.p.) four times a day at 1-hr intervals for 2 consecutive days; (4) The mice that received MPTP hydrochloride (20 mg/kg in saline, i.p.) once a day for 4 consecutive days; (5) The mice that received MPTP hydrochloride (20 mg/kg in saline, i.p.) twice a day for 2 consecutive days; (6) The mice that received MPTP hydrochloride (20 mg/kg in saline, i.p.) twice a day for 4 consecutive days; (7) The mice that received MPTP hydrochloride (20 mg/kg in saline, i.p.) four times at 2-hr intervals within a day. Among the 7 experimental schedules, we demonstrated that the acute treatment with MPTP is a very useful model of PD, as compared to the models with the continuous treatment with MPTP, as shown in Fig. 1. From these findings, we suggest that the dopamine depletion caused by the acute treatment with MPTP in mice is accompanied by sustained nigral degeneration (Kuroiwa et al. 2010). Furthermore, our western blot analysis study also demonstrated that the decrease of the striatal TH (tyrosine hydroxylase) levels and the increase of the striatal GFAP (glial fibrillary acidic protein) levels following the acute treatment with MPTP in mice may play an important role in the development of neuronal damage after MPTP neurotoxicity, as shown in Fig. 2. Interestingly, a recent study indicates that age- and sex-differences in the striatal dopamine content and NOS (nitric oxide synthase) expression after intoxication may depend on the increased susceptibility of males as well as older mice to MPTP neurotoxicity (Joniec et al. 2009). Thus our findings provide valuable information on age-related disease progression and mechanisms of neurodegeneration.

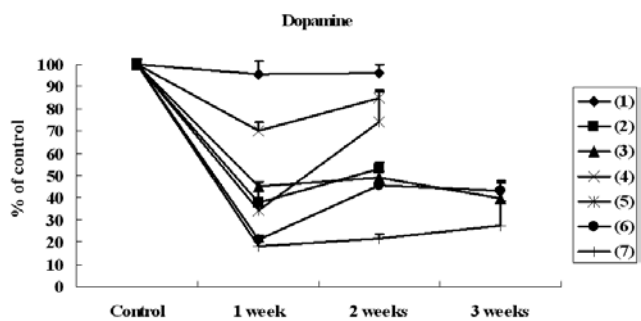

Fig. 1. Time-course effects of (1) MPTP (15 mg/kg i.p.) treatment once a day for 14 consecutive days, (2) MPTP (30 mg/kg i.p.) treatment twice a day for 5 consecutive days, (3) MPTP (10 mg/kg i.p.) treatment four times a day for 2 consecutive days, (4) MPTP (20 mg/kg i.p.) treatment once a day for 4 consecutive days, (5) MPTP (20 mg/kg i.p.) treatment twice a day for 2 consecutive days, (6) MPTP (20 mg/kg i.p.) treatment twice a day for 4 consecutive days and (7) MPTP (20 mg/kg i.p.) treatment four times a day on the striatal dopamine levels. Values were expressed as % of control. Mean ± SE. *n*=4-7.

PHARMACOLOGICAL APPROACH WITH FREE RADICAL SCAVENGER, INDUCIBLE NOS INHIBITOR, NEURONAL NOS INHIBITOR, ENDOTHELIAL NOS ACTIVATOR, COX INHIBITER AND COX-2 INHIBITOR AGAINST MPTP NEUROTOXICITY

To examine the role of oxidative stress and inflammation against MPTP neurotoxicity, we investigated the effects of edaravone as a free radical scavenger (Watanabe et al. 1994), minocycline as an inducible NOS (iNOS) inhibitor (Amin et al. 1996), 7-nitroindazole as a neuronal NOS (nNOS) inhibitor (Schulz et al. 1995), fluvastatin and pitavastatin as an endothelial NOS (eNOS) activator (Endres et al. 1998, Kreisler et al. 2007), indomethacin as a cyclooxygenase (COX) inhibiter (Aubin et al. 1998) and etodolac as a COX-2 inhibitor (Jones 1999) against MPTP neurotoxicity in mice under the same conditions. In our laboratory, we confirmed that 7-nitroindazole can protect dose-dependently against the striatal dopamine depletions in mice after MPTP treatment. In contrast, edaravone, minocycline, fluvastatin, pitavastatin and etodolac did

not show the neuroprotective effect on MPTP-induced striatal dopamine depletion. These results demonstrate that the overexpression of nNOS may play a major role in the neurotoxic processes of MPTP, as compared to the production of reactive oxygen species (ROS)/ reactive nitrogen species (RNS), the overexpression of iNOS, the modulation of eNOS and the involvement of inflammatory response. Thus our findings may provide strong evidence for properties of nNOS inhibitor in animal models of PD (Yokoyama et al. 2008).

There are several lines of evidence in human as well as in animal models favoring an implication of nitric oxide (NO) and NOS in the etiology of PD. In particular, the inhibition of nNOS using pharmacological compounds or gene-deficient mice prevents the damage of dopaminergic neurons in MPTP-treated models of PD (Schulz et al. 1995, Hantraye et al. 1996, Przedborski et al. 1996). A previous study demonstrates that high levels of 3-nitrotyrosine as a footprint of previous exposure to peroxynitrite, have been found in the central core of Lewy bodies, the pathological hallmark of PD (Good et al. 1998). Interestingly, a previous study also suggests that the overexpression of nNOS has been observed in brains of patients with PD (Eve et al. 1998). Furthermore, it is known that the overexpression of nNOS or the formation of peroxynitrite in cells from PD patients emphasizes a potential causal role of NO in the physiopathology of the disease (Gatto et al. 2000). On the other hand, increased amounts of iNOS have also been found in the substantia nigra from autopsied PD patients, as compared to the brains from healthy individuals. These increased expression of iNOS correlated with NO overproduction in the substantia nigra of PD patients (Huerta et al. 2007). The excess of NO could contribute to the formation of free radicals that could be involved in the damage of dopaminergic neurons, leading to the development of PD symptoms. It is known that null mice for the iNOS are more resistant to neurodegeneration caused by MPTP and iNOS inhibitors can protect against the damage of dopaminergic neurons in MPTP-treated mice (Liberatore et al. 1999, Dehmer et al. 2000). Furthermore, glial cells directly contribute to the toxicity seen following treatment with MPTP through several mechanisms, including the mediation of free radical formation and damage by the induction of iNOS (Hirsch et al. 1998, McElroy et al. 2005). iNOS expression in the microglia of the substantia nigra has also been suggested to play a role in the pathogenesis of PD (Hunot et al. 1996, Dehmer et al. 2000). A previous study reports that microglial activation in the substantia nigra, which is accompanies by the up-regulation of iNOS, may have a pivotal role in PD (Hunot et al. 1997). Minocycline has emerged as a potent inhibitor of microglial activation (Tikka and Koistinaho 2001). Minocycline also inhibits the inflammatory reactions caused by glial cells (Popovic et al. 2002). However, previous studies have shown that

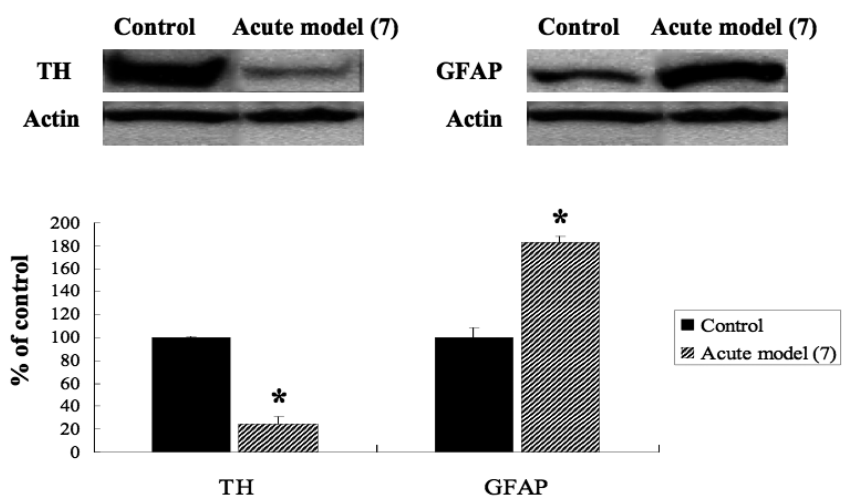

Fig. 2. Western blot analysis of TH and GFAP protein levels in the mouse striatum 3 weeks after MPTP treatment. Actin protein was detected as a house keeping protein. Left half: TH protein levels; Right half: GFAP protein levels. Control: Sham-operated mice; Acute model (7): The mice that received MPTP hydrochloride (20 mg/kg in saline, i.p.) four times at 2-hr intervals within a day. *p<0.01 compared with control (Student's t-test). Mean ± SE. n=3-5.

despite of microglial activation, minocycline treatment exacerbated MPTP-induced damage of dopaminergic neurons in mice (Yang et al. 2003, Diguet et al. 2004). A recent study also demonstrates dose-dependent albeit suppression of microglial markers by minocycline, without achieving neuroprotection against MPTP or methamphetamine (METH) neurotoxicity in the mouse striatum (Sriram et al. 2006). Thus the possible causes of such effects produced by minocycline remain presently unclear. Based on these observations, it is conceivable that the overexpression of nNOS may play a major role in the pathogenesis of PD, as compared with the overexpression of iNOS. In this review, however, we can not rule out that minocycline has many pharmacological actions such as radical scavenging effect, anti-inflammatory action, iNOS inhibition and so on. Therefore, further studies should be performed to investigate the precise mechanisms responsible for the role of ROS, inflammation and iNOS expression.

For the expression of eNOS, in addition, a previous study demonstrated that 3-hydroxy-3-methylglutaryl co-enzyme A (HMG-CoA) reductase inhibitors can reduce cerebral ischemia and infarct size by up-regulating of eNOS expression in mice (Endres et al. 1998). However, a recent interesting study suggests that HMG-CoA reductase inhibitors such as atorvastatin and simvastatin had a deleterious effect on the number of TH-positive cells in MPTP-treated mice (Kreisler et al. 2007). Therefore, the overexpression of eNOS may have no beneficial effect in treatment of PD.

Interestingly, recent experimental studies have shown that treatment with MPTP can induce the mRNA expression of nNOS and guanylyl cyclase beta-1 subunit (GCβ1), which leads to elevation in their protein levels and activities within the striatum and substantia nigra. The effects are accompanied by a marked enhancement of cGMP formation (Chalimoniuk et al. 2004, 2006). Administration of 7-nitroindazole is able to decrease the MPTP-induced evaluations in cGMP levels and prevent the death of dopaminergic neurons (Chalimoniuk et al. 2006). These observations suggest that the NO/GC/cGMP signaling may play a role in maintaining dopaminergic neurons function in pathogenesis of parkinsonism (Chalimoniuk et al. 2006, 2007). Based on these findings, it is conceivable that nNOS inhibitor 7-nitroindazole may prevent the death of dopaminergic neurons in MPTP-treated animals via the regulation of NO/GC/cGMP signaling pathway. However, Schulz and others (1995) have reported no effect of 7-nitroindazole for MAO-B activity. In contrast, Castagnoli and coworkers (1997) showed that 7-nitroindazole can protect a significant inhibition of MAO-B activity. Thus the role of 7-nitroindazole on MAO-B activity is still contradictory at present. Therefore, further studies are needed to investigate the precise mechanisms of the neuroprotective effects of nNOS inhibitors as well as iNOS inhibitors.

NEW PHARMACOLOGICAL APPROACH WITH POLY (ADP-RIBOSE) POLYMERASE INHIBITOR BENZAMIDE AND ANTI-CONVULSANT DRUG ZONISAMIDE AGAINST MPTP NEUROTOXICITY

Poly (ADP-ribose) polymerase (PARP) is an abundant nuclear enzyme that uses nicotinamide adenine dinucleotide (NAD^+) as a substrate. PARP is also known to be involved in DNA plasticity such as repair of DNA damage, gene expression, and carcinogenesis. However, extensive PARP activation can promote cell death through processes involving energy depletion. Several studies have reported that ROS-induced damage of DNA activates PARP, culminating in cell death or necrosis (Berger 1985, Szabo and Dawson 1998, Ha and Snyder 1999). On the other hand, PARP plays a key role in a caspase-independent apoptosis pathway mediated by apoptosis-inducing factor (AIF) and translocation of AIF from mitochondria to the nucleus is dependent on PARP activation in neurons after various DNA-damaging stimuli (Yu et al. 2002). The cellular suicide mechanisms of both apoptosis and necrosis by PARP activation have been implicated in the pathogenesis of neurodegenerative disorders such as PD.

Several studies demonstrate that the toxic effect of MPTP is mediated through an excessive production of PARP (Cosi et al. 1996, Wang et al. 2003, Iwashita et al. 2004). In mice, PARP inhibitors including benzamide are known to prevent MPTP-induced neurotoxicity (Cosi et al. 1996, 1998, Mukherjee et al. 1997, Iwashita et al. 2004). PARP inhibitors have also been demonstrated to attenuate the excitotoxic damage in vitro (Zhang et al. 1994) and the infarct size after middle cerebral artery occlusion in mice (Endres et al. 1997) and rats (Tokime et al. 1998). The involvement of PARP activation in neuronal cell death following MPTP neurotoxicity, excitotoxicity and focal cerebral ischemia is further substantiated by the resistance to these types of insults observed in PARP gene-depleted mice (Eliasson et al. 1997, Endres et al. 1997, Mandir

et al. 2000). These observations have attracted great interest for the contribution of PARP to MPTP neurotoxicity. In our laboratory, we confirmed that benzamide, a potent PARP inhibitor, can prevent a significant decrease of the dopaminergic neuronal cell loss following MPTP treatment, when this compound is administered 1 and 3 h after MPTP treatment (Yokoyama et al. 2010a). These findings seem to suggest important implication for the therapeutic time window and choice of PARP inhibitors in patient with PD. Thus we speculate that PARP inhibitor benzamide can exert the neuroprotective effect through its potent PARP inhibitory actions in PD model, indicating that PARP inhibitors could be an attractive candidate for several neurodegenerative disorders, including PD.

Zonisamide (1,2-benzisoxazole-3-methanesulfonamide) was developed as an anti-convulsant drug and is used widely in the world such as Japan, Korea, USA and Europe. For proposed mechanisms of its anti-epileptic activity, it is thought to involve the antagonism of sodium (Schauf 1987, Rock et al. 1989) and T-type calcium channels (Suzuki et al. 1992). Furthermore, zonisamide has been shown to attenuate neonatal hypoxic-ischemic damage in experimental animals by a mechanism independent of its anti-convulsant properties (Hayakawa et al. 1994). Interestingly, a recent clinical study reports that zonisamide has clinical efficacies in the treatment of PD by a randomized, double blind study (Murata et al. 2007). It is known that anti-convulsant drug, zonisamide, has a wide clinical spectrum of use in both psychiatric and neurological disorders such as epilepsy, mood disorders and PD (Ito et al. 1982, McElroy et al. 2005, Murata et al. 2007). In patients with PD, in particular, several studies demonstrate that long-term treatment of levodopa causes various adverse side effects such as wearing-off phenomenon, dyskinesia, and psychiatric symptom (Ahlskog and Munenter 2001, Ogawa et al. 2005). Furthermore, a recent double-blind controlled study in Japan reported that an adjunctive treatment with zonisamide to levodopa can improve all the cardinal symptoms of PD (Murata 2004, Murata et al. 2007). From these observations, it is suggested that zonisamide has a therapeutic effect in the treatment of PD, particularly in regard to avoiding the adverse side effects of levodopa. Therefore, it would be interesting to know the effects of zonisamide in models of PD, but a more marked benefit against parkinsonism and dyskinesia can be anticipated.

In our laboratory, we confirmed that anti-convulsant drug, zonisamide, has the therapeutic effect in the MPTP model of PD in mice (Yano et al. 2009). Our study also demonstrated that the neuroprotective effect of zonisamide against dopaminergic cell damage may be mediated through the elevation of TH activity and/or the inhibition of microglial activation on dopaminergic system after MPTP treatment in mice (Yokoyama et al. 2010b). Furthermore, our findings suggest that therapeutic strategies targeted to the activation of TH activity and/or the inhibition of microglial activation with zonisamide may offer a great potential for restoring the functional capacity of the surviving dopaminergic neurons in individuals affected with PD. These results demonstrate further evidence that anti-convulsant drug, zonisamide, may offer a new approach for the treatment of PD.

ROLE OF NEUROTROPHIC FACTORS IN PARKINSON'S DISEASE

It is well known that astrocytes have been shown to produce a number of neurotrophic factors (Nakajima et al. 2001, Chen et al. 2004). Several neurotrophins have been shown to protect dopaminergic neurons from neuronal death after MPTP or MPP^+ intoxication (Nagatsu et al. 2000). These neurotrophic factors include brain-derived neurotrophic factor (BDNF; Spina et al. 1992, Frim et al. 1994, Tsukahara et al. 1995), glial derived neurotrophic factor (GDNF; Cheng et al. 1998, Date et al. 1998), fibroblast growth factor (FGF; Otto and Unsicker 1994), epidermal growth factor (EGF; Hadjiconstantinou et al. 1991) and ciliary neurotrophic factor (CNTF; Garcia de Yebenes et al. 2000). Neurotrophins act to prevent neuronal cell loss though a number of mechanisms such as modulation of oxidative stress and inflammation (Spina et al. 1992, Kirschner et al. 1996, Skaper et al. 1996) as well as interference with the intrinsic cell death programs (Schäbitz et al. 2000, Heaton et al. 2003). Among neurotrophins, GDNF is a potent neurotrophic factor that has restorative effects in a wide variety of rodent and primate models of PD (Bjorklund et al. 2000). In early clinical studies, no beneficial effects were observed, but side-effects were reported. When GDNF was delivered directly into the putamen of several individuals with PD in a Phase I safety trial, the direct intraputamenal GDNF delivery in PD patients can be tolerated for at least 1 year, leads to a significant increase in dopamine storage in the putamen, and improves the

patient's clinical conditions (Gill et al. 2003). In the randomized trial of 34 patients receiving infusion of either placebo or GDNF, however, there were no significant improvements in primary or secondary clinical end points after 6 months (Lang et al. 2006). The reason for the different outcomes between the open-label and randomized controlled clinical trials is presently unclear. Based on these observations, we suggest that neurotrophins may have partially a potential therapeutic effect for the treatment of PD patients. However, little is known about the exact relationship among nNOS inhibitor, PARP inhibitor, anti-convulsant drug and neurotrophins after MPTP neurotoxicity in mice. Further studies are needed to investigate the precise mechanisms of the therapeutic effects of nNOS inhibitors, PARP inhibitors and anti-convulsant drugs. In addition, Fig. 3 illustrates the molecular mechanism underlying the neurorescue effect of PARP inhibitor benzamide and anti-convulsant drug zonisamide against MPTP neurotoxicity in mice. Although increased oxidative stress (Beal 2003), mitochondrial dysfunction (Lin and Beal 2006), apoptosis (Anglade et al. 1997), neuroinflammation (MacGeer et al. 1988), and proteasomal dysfunction (McNaught et al. 2003) are suggested to be initiators or mediators of neuronal cell death in PD, the exact mechanisms of cell death underlying PD have not been fully elucidated yet at present. Therefore, further studies are needed in order to understand the molecular mechanisms of n NOS inhibitors, PARP inhibitors and anti-convulsant drugs against MPTP neurotoxicity.

CONCLUSIONS

Multiple signaling pathways may play a crucial role in the degenerative processes in MPTP-treated mice. So far, many studies into mechanisms and possible neuroprotection against MPTP neurotoxicity have

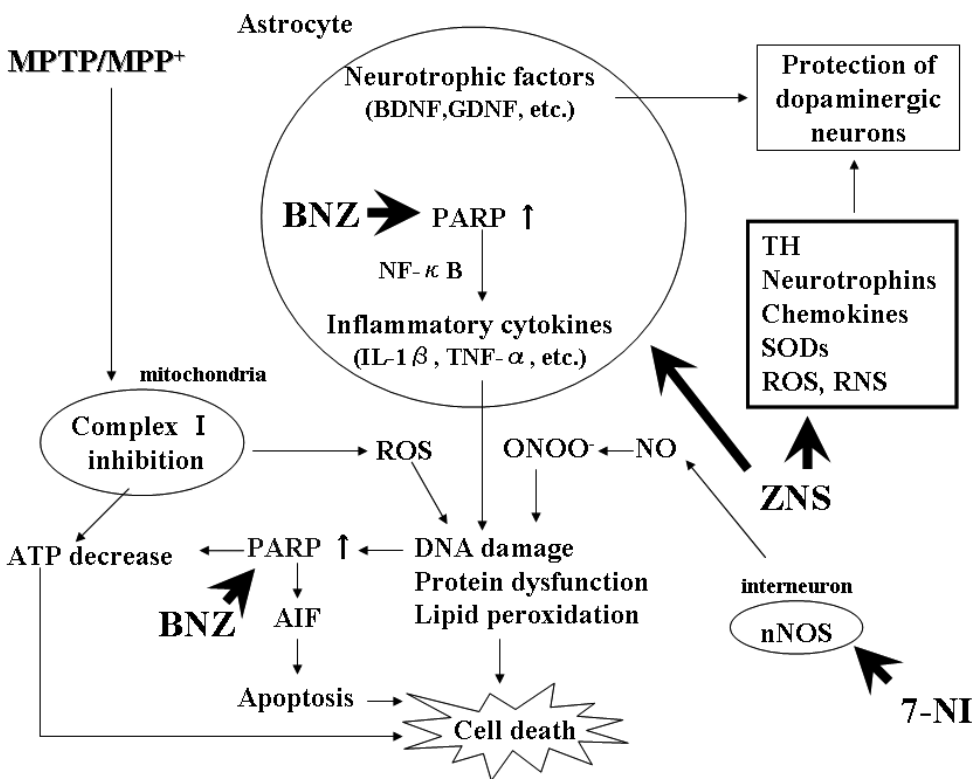

Fig. 3. Schematic representation of the mechanisms of MPTP action in the nigrostriatal system. MPTP crosses easily the blood brain-barrier (BBB) and is converted to its metabolites MPP^+ by glial monoamine oxidase-B (MAO-B). MPP^+ is selectively taken in dopaminergic neurons through dopamine transporters (DAT) and accumulated in the mitochondria, where it inhibits complex I of the mitochondrial electron transport chain. The mitochondrial inhibition leads to reductions of oxygen consumption and ATP production. Oxidative stress and inflammation generated by MPP^+ and ATP decrease lead to neuronal cell damage. Several neurotrophins protect dopaminergic neurons from neuronal death after MPTP or MPP^+ intoxication. Big arrows indicate the novel targets of 7-nitoroindazole (7-NI), benzamide (BNZ) or zonisamide (ZNS).

been carried out for many years. However, little is known about neuroprotective effects of various compounds against MPTP neurotoxicity under the same conditions. In this review, we show that acute treatment with MPTP can cause a severe loss of TH protein levels and dopamine contents in the striatum of mice, as compared to continuous MPTP treatment. Furthermore, we discuss that the neuroprotective effect of nNOS inhibitor, PARP inhibitor and anticonvulsant drug against dopaminergic neuronal loss in the model of acute MPTP treatment model. However, the precise mechanisms responsible for dopaminergic cell loss are presently unclear. Therefore, although further studies are needed to examine the precise mechanisms of the neuroprotective effects of various compounds, the mechanisms of the neuroprotective effects of nNOS inhibitors, PARP inhibitor and anticonvulsant drug may lead to a much better understanding of PD as well as provide clues to novel targets for therapeutic interventions in PD patients. This review summarizes recent studies for possible treatment of PD, using conventional MPTP model.

ACKNOWLEDGEMENTS

This work was supported in part by a Grant-in-Aid for Scientific Research (21790376 and 22590935) from the Ministry of Science and Education in Japan.

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