

Cyclosporin-Mediated Amelioration of Degeneration of Dopaminergic Neurons in Experimental Models of Parkinsonism

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INTRODUCTION

Parkinson's disease (PD) is a slowly progressive neurodegenerative disease, the principal pathological feature of which is the progressive degeneration of dopaminergic neurons in the nigrostriatal system. This degeneration of the nigrostriatal system results in a deficiency in dopamine (DA) content both in the striatum and substantia nigra, which causes the characteristic symptoms of PD, that is, resting tremor, rigidity, and bradykinesia or akinesia. There are several strategies for the treatment of PD, such as supplying DA by providing the precursor levodopa, activating the DA receptor with DA agonists, or grafting with DA-producing tissues. Levodopa treatment, which was developed based on the observation of a decrease in striatal DA levels, has been the most successful of these strategies. Levodopa is the gold standard for the treatment of PD and is widely used because of its outstanding clinical efficacy. However, long-term levodopa treatment causes severe clinical complications, including the wearing-off phenomenon, on-off phenomenon, dyskinesia, and psychiatric symptoms (1–3). Moreover, since degeneration of dopaminergic neurons continues even during levodopa treatment, recent efforts in the treatment of PD have focused on the development of agents and strategies that suppress or delay disease progression. These include free-radical scavengers (4), antioxidants (5), the iron-chelator desferrioxamine (6), excitatory amino acid receptor antagonists (4,7), and neurotrophic factors such as glial cell-derived neurotrophic factor (GDNF) (8,9) and brain-derived neurotrophic factor (BDNF) (10–13).

It has also been suggested that immunological reactions play an important role in PD, Alzheimer's disease, and cerebrovascular disease (14–17).

Cyclosporin A (CsA) is a potent immunosuppressant widely used to inhibit rejection after transplantation and to treat autoimmune diseases, and protective effects of CsA against ischemia–reperfusion injury in rat and gerbil models of transient ischemia (15,16,18), and against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced striatal DA depletion in mice (19) have been reported. In this chapter, we summarize the effects of CsA on the depletion and degeneration of dopaminergic neurons in experimental animal models of parkinsonism.

EFFECTS OF CYCLOSPORIN A ON THE DEGENERATION OF DOPAMINERGIC NEURONS IN EXPERIMENTAL ANIMAL MODELS OF PARKINSONISM

Several animal models of parkinsonism have been established that employ intracerebroventricular, intranigral, or intraforebrain bundle injections of 6-hydroxydopamine (6-OHDA), or systemic injections of MPTP to induce rapid and selective lesioning of nigrostriatal dopaminergic neurons. However, these models have faster time courses than PD, the slow progression of which is due to a sustained loss of nigrostriatal dopaminergic neurons. Furthermore, the MPTP model can show spontaneous improvement in indices of dopaminergic function (20–22). We have previously used two experimental animal models of parkinsonism: acute degeneration of dopaminergic neurons induced by intracerebroventricular injection of 6-OHDA in mice, and slowly progressive degeneration of dopaminergic neurons induced by intrastriatal injection of 6-OHDA in rats.

6-Hydroxydopamine-Induced Parkinsonism in Mice

In the first study, we investigated the protective effects of the immunosuppressant CsA against 6-OHDA-induced injury of nigrostriatal dopaminergic neurons in male ICR mice (23). Intracerebroventricular (icv) injections of 6-OHDA (80 μ g) or physiological saline containing ascorbic acid (SA) as a control were performed under light ether anesthesia 30 min after injection of desipramine (25 mg/kg ip), which prevents the uptake of 6-OHDA by noradrenergic neurons. CsA or the same volume of vehicle (V; 0.2% castor oil) was injected subcutaneously 24 h and 30 min before, 5 h after, and once daily from d 1 to d 6 after 6-OHDA injection. At 7 d after the injection of 6-OHDA, the concentrations of DA and its metabolites dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) in the striatum and the substantia nigra were determined (Fig. 1).

Although CsA had no effect on DA or its metabolites in the substantia nigra of SA-treated control mice, it induced a slight increase in striatal HVA in such mice. At 7 d after the induction of 6-OHDA lesions, DA, DOPAC,

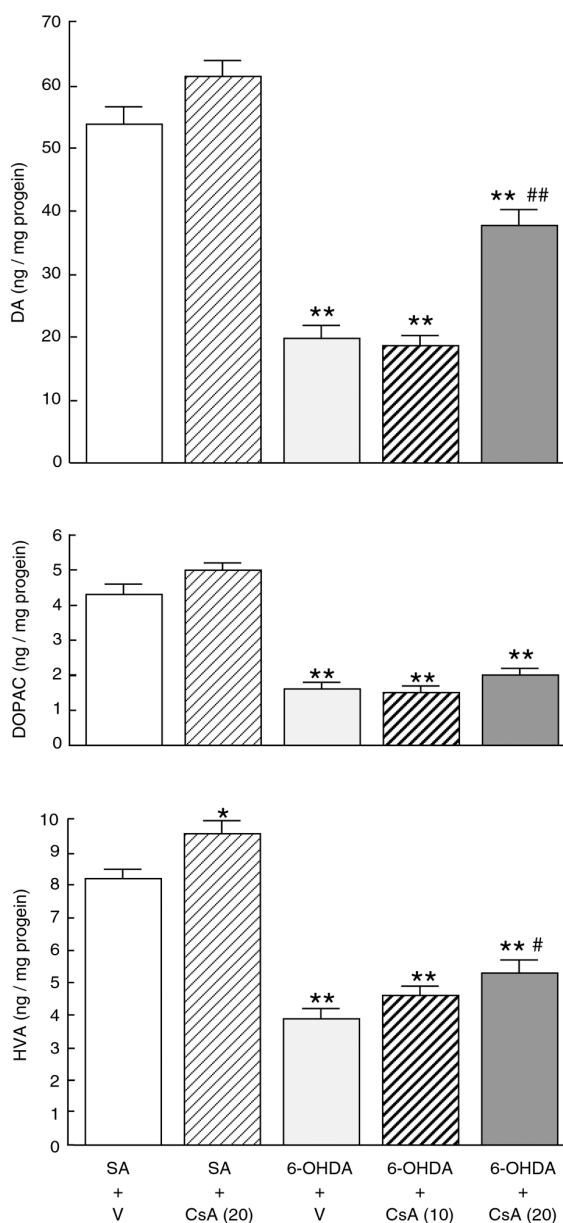


Fig. 1. Effects of CsA on the striatal DA, DOPAC, and HVA concentrations in mice at 7 d after intracerebroventricular injection of 6-OHDA. Numbers in parentheses are the daily dose of CsA in milligrams per kilogram. Each value is the mean \pm SEM for 30–35 mice. * $p < .05$, ** $p < .01$ vs SA (i.c.v.) + V (vehicle)-injected group; # $p < .05$, ## $p < .01$ vs 6-OHDA (i.c.v.) + V-injected group.

and HVA in the striatum were depleted by 63%, 63%, and 52%, respectively (Fig. 1). However, striatal DA and HVA in the 6-OHDA+CsA (20 mg/kg)-treated group were significantly higher than in the 6-OHDA+V-treated group, indicating that CsA (20 mg/kg) elevated both striatal DA and striatal HVA in the 6-OHDA-lesioned mice. Although HVA and DOPAC in the substantia nigra were depleted by 40% in 6-OHDA-lesioned mice, CsA significantly increased both HVA and DOPAC (data not shown in Fig. 1). Thus, CsA is beneficial in reducing 6-OHDA-induced injury of nigrostriatal DA neurons in mice, indicating its therapeutic potential in the treatment of PD. Similar protective effects were obtained by another immunosuppressant, FK506, and the nonimmunosuppressive analogue GPI1046 (data not shown in Fig. 1).

Slowly Progressive Dopaminergic Neurodegeneration Model in Rats

In the second study, we investigated the effects of CsA on the degeneration of dopaminergic neurons in a rat model of slowly progressive dopaminergic neurodegeneration after intrastriatal injections of 6-OHDA (24). In this animal model, intrastriatal injection of 6-OHDA induces slowly progressive degeneration of dopaminergic neurons, and neurotrophins or other factors can be tested for their effects on the residual dopaminergic neurons (5,11). Under sodium pentobarbital anesthesia (35 mg/kg, ip), rats were intrastriatally injected with 6-OHDA (5 µg at four sites) or SA as a control. CsA or the same volume of vehicle (V; 0.2% castor oil) was injected subcutaneously (s.c.) 24 h and 30 min before, 5 h after, and once daily on d 1 to d 6 after 6-OHDA (or SA) injection. Rats were sacrificed 1 or 4 wk after 6-OHDA injection and were divided into two groups: one for neurochemical analysis and the other for histological analysis.

At 1 and 4 wk after 6-OHDA injection, DA, DOPAC, and HVA in the striatum and the substantia nigra were measured (Fig. 2). At 1 wk after 6-OHDA injection, there was no difference in DA levels in the striatum or substantia nigra between SA+V- and SA+CsA-treated groups, although DA levels of 6-OHDA+V- and 6-OHDA+CsA-treated groups were significantly lower than those of control (SA+V-treated) rats in the striatum (Fig. 2). At 4 wk after 6-OHDA injection, however, the striatal DA level in the CsA-treated group was significantly higher than in the V-treated group, indicating that CsA significantly attenuated the toxic effects of 6-OHDA on dopaminergic neurons (Fig. 2). Nigral DA level in the 6-OHDA+V-treated group was significantly lower than that in the SA+V treated group, but there was no significant difference in DA levels between SA+V-treated rats and 6-OHDA+CsA-treated rats at 4 wk after 6-OHDA injection, indicating that the CsA also had an effect on nigral DA depletion (Fig. 2).

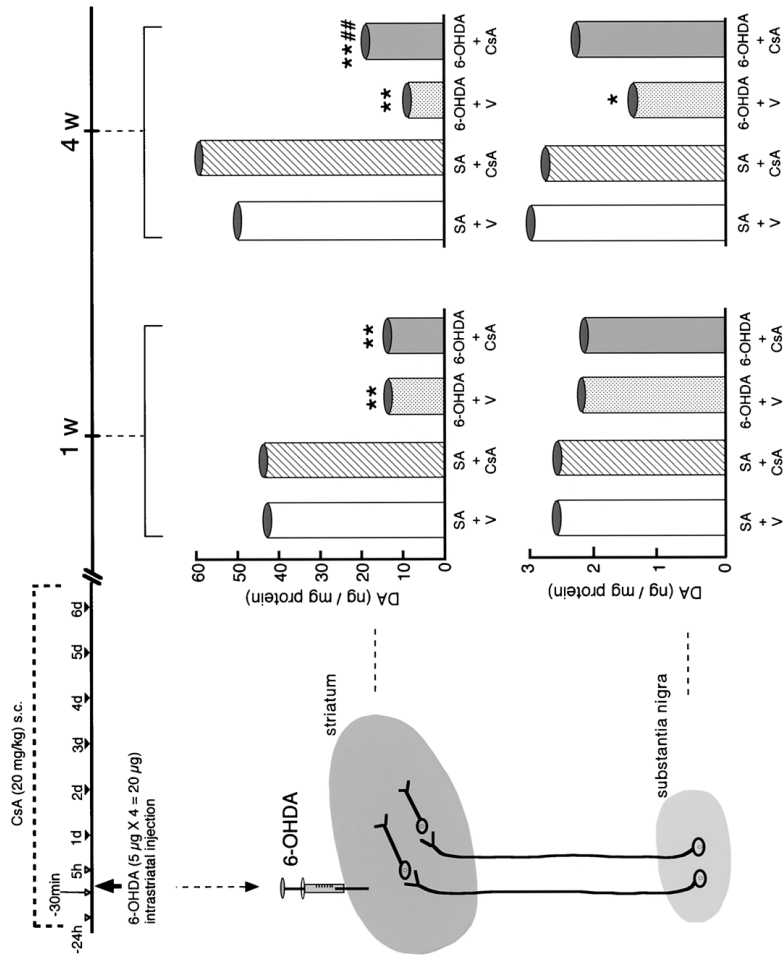


Fig. 2. Effects of CsA on DA concentrations in the striatum and substantia nigra of rats at 1 wk and 4 wk after intrastriatal injections of 6-OHDA. Data are expressed as the mean of 6 animals. * $p < .05$, ** $p < .01$ vs SA (intrastriatal) + V (vehicle)-injected group; *** $p < .01$ vs 6-OHDA (intrastriatal) + V-injected group.

Previous studies have given contradictory results on neurochemical changes in the striatum of intrastriatal 6-OHDA-lesioned rats. Although Altar and colleagues (25) found that the levels of DA and its metabolites partially recovered between 1 and 4 wk after striatal injection of 6-OHDA, Venero and colleagues (26) observed no recovery in the levels of striatal DA and its metabolites between 2 d and 4 wk after striatal injection of 6-OHDA. In the present study, we also observed no spontaneous recovery of nigrostriatal DA content (Fig. 2). There was no significant difference in striatal DA levels between 1 and 4 wk after 6-OHDA injection in the SA-treated group. Further, although the nigral DA level in this group was not significantly different from the level in controls at 1 wk after injection, it was significantly decreased at 4 wk (Fig. 2), indicating that progressive degeneration of dopaminergic neurons occurred in this rat model.

In a previous histological study, tyrosine hydroxylase (TH) immunoreactivity (TH-IR) of nigral cell bodies and dendrites in the substantia nigra ipsilateral to injection was lower than that on the contralateral side at 4 wk after 6-OHDA injection (24). The number of TH-positive neurons in the substantia nigra pars compacta on the 6-OHDA-injected side was decreased by 36% in the V-treated group and by 13% in the CsA-treated group. The loss of TH-IR was therefore significantly less in the CsA-treated group, indicating that CsA attenuated damage to the dopaminergic neurons. Without 6-OHDA injection, there was no decrease in the number of TH-immunoreactive neurons in the V-treated group or CsA-treated group, indicating that neither SA nor CsA by itself had any effect on the number of TH-immunoreactive neurons in the substantia nigra.

TH-IR is a good and sufficient marker for evaluating the depletion of tissue DA levels in the nigrostriatal system (27), and changes in nigral TH-IR can be detected from 2 wk after 6-OHDA injection (27). Thus, CsA treatment for 7 d significantly attenuated the decrease in TH-IR in the substantia nigra at 4 wk postinjection. These data again indicate that there is progressive degeneration of dopaminergic neurons in the present rat model, as in PD, and that CsA treatment significantly attenuated this degeneration.

MECHANISM OF ACTION OF CYCLOSPORIN A

The major findings of the above-mentioned two studies are that CsA elevated striatal DA levels in 6-OHDA-lesioned mice and rats. In the mouse model study, DA in the striatum was depleted by 63% at 7 d after intracerebroventricular injection of 6-OHDA, and repeated high-dose CsA (20 mg/kg) treatment significantly protected against this DA depletion (23). Intrastriatal injection of 6-OHDA in the rat can cause a slowly progressive degeneration of

dopaminergic neurons (5,10,25,27–29). High-dose CsA daily for 7 d significantly attenuated the decrease in DA on the lesioned side of the striatum, and the number of TH-immunoreactive neurons in the substantia nigra at 4 wk after 6-OHDA lesions. Because tissue DA levels are known to be a good index of the degree of striatal dopaminergic denervation after the administration of 6-OHDA (30), the present findings indicate that CsA may inhibit degeneration and/or promote regeneration of dopaminergic neurons. This is in agreement with earlier studies in which CsA was found to protect against MPTP-induced DA depletion in the striatum of mice (19).

There have been a number of reports on the neuroprotective effects of various substances on damaged dopaminergic neurons *in vivo* (4). We have provided the first evidence that CsA has a neuroprotective effect on dopaminergic neurons in experimental animal models of parkinsonism (23,24).

One might not expect CsA to cross the blood–brain barrier. However, when brain lesions appear, the barrier is impaired, and CsA is able to cross it (15,17,23); for this reason, long-term administration of CsA produces various central nervous system (CNS) side effects (31), indicating that peripherally administered CsA can affect the CNS.

Immunosuppressive Effects via Calcineurin

It is known that glial cells accumulate at sites surrounding lesioned regions in PD, Alzheimer's disease, cerebrovascular disease, and in animal models of these diseases (14–16,32). Several studies have reported that CsA particularly suppresses the ischemia-induced accumulation of reactive glial cells in the brain (15,16,18). Thus, it is possible that CsA protects dopaminergic neurons by suppressing microglial cytotoxicity, which can occur via mechanisms such as the production of reactive oxygen intermediates, proteinases, and cytokines (32,33).

CsA achieves immunosuppression mainly by inhibiting production of interleukin (IL)-2, which activates T cells. Foreign antigens displayed on the surface of antigen-presenting cells activate the T-cell receptor to initiate signal pathways that lead to increases in intracellular Ca^{2+} . Ca^{2+} binds to calmodulin and calcineurin B, which activate the phosphatase activity of the catalytic subunit (calcineurin A) of calcineurin. The phosphatase dephosphorylates the nuclear factor of activated T-cell (NFAT), allowing it to enter the nucleus and activate the transcription of IL-2 and IL-2 receptor (34). CsA forms a complex with cyclophilin, an immunophilin. The CsA–cyclophilin complex binds to and inhibits calcineurin, preventing NFAT dephosphorylation and its subsequent transcription to the nucleus, leading to inhibition of T-cell activation (35,36). Since calcineurin has been reported

to dephosphorylate DARPP-32 (a dopamine-regulated neuronal phosphoprotein) and to be richly distributed in the caudate putamen, substantia nigra, and striatonigral pathway, calcineurin may play a role in the function of dopaminergic neurons (37–40). Thus, it might be assumed that CsA protects striatal DA and elevates nigral TH-IR–striatal DA levels by inhibiting calcineurin activity.

Neuroprotective and Neurorestorative Effects Independent of Immunosuppressive Properties

The intrastriatal 6-OHDA injection model is advantageous for studies of the microglial and astrocytic response because there is no mechanical damage to the substantia nigra. In the rat model (24), a strong microglial reaction was observed in the substantia nigra after injection of either SA or 6-OHDA, although the 6-OHDA injection induced a more lasting reaction than did the SA. This reaction occurred during the initial neuronal degeneration stage but declined after about 4 wk, even though neuronal degeneration was still progressing in the 6-OHDA injection group (27,41). It might be expected that CsA protects dopaminergic neurons by suppressing microglial cytotoxicity, which occurs via mechanisms such as the production of reactive oxygen intermediates, proteinases, and cytokines (32,33). In our study, however, microglial activation in the substantia nigra was not affected by CsA treatment, and no significant change in GFAP staining was observed in the substantia nigra (24). This suggests that CsA acts directly on neurons of the damaged dopaminergic system, rather than indirectly through immunosuppression. This is further supported by the finding that short-term CsA treatment during only the initial stages of neuronal damage either prevented degeneration or accelerated regeneration of the nigrostriatal dopaminergic neurons (24). We have also shown that, in the mouse intracerebroventricular 6-OHDA injection model, both the initial CsA treatment (42) and continuous daily administration of CsA (23) promote the recovery of striatal DA levels.

Activated microglia generate free radicals. It is believed that this activity can be inhibited by the administration of immunosuppressants, which involves binding of the CsA–cyclophilin complex with calcineurin to inhibit the dephosphorylating effect of calcineurin. However, cyclophilin has been identified with peptidylprolyl-*cis-trans*-isomerase (rotamase), an enzyme related to folding of proteins (43,44), and CsA specifically suppresses the rotamase activity of cyclophilin. Furthermore, long-term continuous administration of CsA is not always necessary for neuroprotective action. In experiments using animal models of transient cerebral ischemia (45) and PD (23,24), we have found that administration only in the initial

stage after injury was sufficient. This raises the possibility that the neuroprotective and neurorestorative mechanisms of CsA differ from the immunosuppressive mechanisms.

Recently, it has been reported that agents that bind to immunophilins but have no immunosuppressive effect show neurotrophiclike activity (46,47). These agents (nonimmunosuppressive immunophilin ligands) are attracting attention as new candidates for neuroprotection and neurorestoration because they are not expected to have the adverse effects of immunosuppressants. Thus, the neuroprotective effects of CsA and other immunophilin ligands do not parallel their calcineurin-inhibitory effects, but are in parallel with the inhibitory effect on rotamase activity (47); furthermore, the neuroprotective effects are not related to the inhibition of calcineurin, as was assumed in the past (47).

POSSIBLE RESTORATIVE EFFECTS OF CYCLOSPORIN A ON DOPAMINERGIC NEURONS

In addition to its protective effects, CsA may also promote dopaminergic neurons. In the iminodipropionitrile (IDPN)-induced rat model of dyskinesia, the addition of CsA treatment exacerbated IDPN-induced dyskinesia (48). The injection of both CsA and IDPN increased the concentration of DA and the binding activities of transcription factors to the TPA (12-*O*-tetradecanoylphorbol-13-acetate)-responsive element (TRE) and to the cAMP response element (CRE) in the striatum, compared with those in rats treated with IDPN alone (Fig. 3). Since the 5' upstream region of the rat tyrosine hydroxylase (TH) gene contains both TRE and CRE (49), increased DA levels in the basal ganglia of the CsA + IDPN group may be partly due to transcriptional activation of the TH gene by increases in the DNA-binding activity of both TRE and CREB. In the present study, the levels of D1-receptor mRNA, but not D2-receptor mRNA, in the striatum were significantly decreased in the IDPN-treated rats but were at the control level in the rats given CsA + IDPN (Fig. 3). Since the rat D1-receptor gene possesses both TRE and CRE in the promoter region (50), while the rat D2-receptor gene has only TRE (51), increases in the activity of these transcription factors in the striatum of CsA + IDPN-treated rats may lead to the increases in the striatal D1-receptor mRNA. These findings suggest that the behavioral aggravation of the IDPN-induced dyskinesia caused by CsA administration may be due to the acceleration of the pre- and postsynaptic dopaminergic systems via activation of transcription factors that bind upstream to TH- and D1-receptor genes. Thus, CsA both restores and protects dopaminergic neurons, and, further, the restorative-neurotrophic effects of immunophilin ligands are restricted to damaged neurons (46–48).

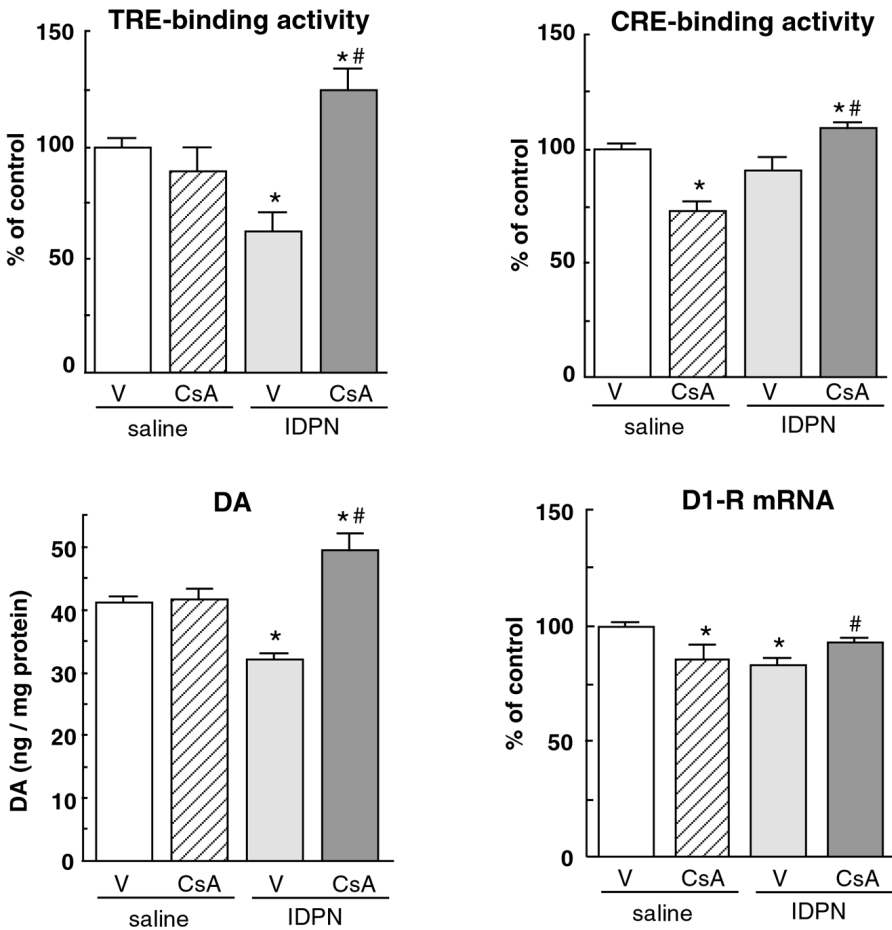


Fig. 3. Effects of CsA and IDPN, alone or together, on TRE-binding activity, CRE-binding activity, DA concentrations, and D1-R mRNA levels in the rat striatum. Data are the mean \pm SEM ($n = 4-6$). * $p < .05$ vs V (vehicle) + saline-injected group; # $p < .05$ vs V + IDPN-injected group.

These findings indicate that CsA should be advantageous for therapeutic use for PD.

CONCLUDING REMARKS

The pathogenesis of various important neurodegenerative diseases appears to be related to structural abnormalities, inactivation, or deposition of proteins such as β -amyloid, α -synuclein, polyglutamine, or prions (52). CsA has a neuroprotective effect against degeneration of dopaminergic neu-

rons and shows neurotrophiclike activity. Through its interaction with cyclophilins, which are a highly conserved family of protein chaperones showing prolyl isomerase (rotamase) activity, CsA is deeply involved in the modulation of protein conformation. Therefore, it is possible that the neuroprotective action of immunophilin ligands can be applied to the treatment of conformational diseases. Cyclophilin is one of the immunophilins and is a highly efficient catalyst for the delayed refolding of damaged proteins (53), but it shows almost no catalytic effect on delayed refolding of intact proteins (54). Because immunophilin ligands act mainly on damaged proteins (46–48), they are unlikely to have much effect on normal tissues, and should cause few adverse reactions. Thus, immunophilin ligands that were initially considered to be immunosuppressants are now expected to be useful in the treatment of neurodegenerative diseases via modulation of protein structures.

In conclusion, CsA showed protective and restorative effects against dopaminergic neuronal damage in experimental animal models, and these results suggest that CsA might offer a new approach to the treatment of PD and other neurodegenerative diseases.

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Immunosuppressant Analogs in Neuroprotection

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