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ORIGINAL ARTICLE

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# Noradrenoceptor antagonism with idazoxan improves L-dopa-induced dyskinesias in MPTP monkeys

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**Abstract** Treatment of Parkinson's disease with L-dopa is plagued in a majority of patients by dyskinesias. Noradrenaline/dopamine interactions are proposed on behavioral, biochemical, physiological and anatomical grounds. The aim of the study was to test the potential antidyskinetic effect of the $\alpha_2$-adrenoceptor antagonist, idazoxan, in a primate model of Parkinson's disease. Six female cynomolgus monkeys previously rendered parkinsonian by the toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and presenting an unchanged syndrome for several months were used. All responded readily to L-dopa but had developed dyskinesias which were manifested with each dose. In the first part of the study, seven doses of idazoxan (ranging from 0.25 mg/kg to 10 mg/kg, p.o.) were administered together with the vehicle or in combination with a fixed dose of L-dopa/benserazide (100/25 mg, p.o.). In the second part of the study, a fixed dose of idazoxan (7.5 mg/kg) was administered daily for 10 days and L-dopa was added to idazoxan on days 1, 4, 7 and 10. Vehicle (empty capsule) was used as control. Idazoxan, by itself (ranging from 5 mg/kg to 10 mg/kg), increased locomotor activity and improved the disability score with virtually no dyskinesias in three animals. In combination with L-dopa, idazoxan did not impair the antiparkinsonian response but significantly reduced dyskinesias in all six animals up to 65% at doses of 7.5 mg/kg and 10 mg/kg and delayed their onset, so that the "ON" state without dyskinesias was prolonged. The antidyskinetic effect of idazoxan was maintained when repeatedly administered for 10 days. On day 10, the locomotor response to L-dopa was significantly potentiated by chronic administration of idazoxan. Our results indicate that idazoxan has some antiparkinsonian effect of its own and may constitute a useful adjunct to L-dopa as it can reduce dyskinesias without impairing the relief of symptoms, this effect being maintained over time in this model.

**Key words** Idazoxan · L-dopa · MPTP · Parkinson · Dyskinesias · $\alpha_2$-adrenoceptor

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## Introduction

The most common treatment for Parkinson's disease (PD) aims at pharmacologically augmenting striatal dopamine (DA) levels using the DA precursor L-3,4-dihydroxyphenylalanine (L-dopa). Although L-dopa is a valuable agent in the treatment of PD, motor complications such as dyskinesias can arise with prolonged use and often become as debilitating as the parkinsonian symptoms themselves. As alternative for L-dopa treatment, synthetic DA receptor agonists were developed. However, both DA $D_1$- and $D_2$-like receptor agonists can also induce dyskinesias in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned monkeys otherwise untreated (i.e. drug-naive). For instance, pulsatile administration of molecules with reported selectivity for the DA $D_2$ receptor (+)-PHNO ((+)-4-propyl-9-hydroxynaphthoxazine hydrochloride), quinpirole and U-91356A ((*R*)-5,6-dihydro-5-(propylamino)-4H-imidazo[4,5,1-ij] quinolin-2-(1H)-one, monohydrochloride) rapidly induced dyskinesias in all drug-naive animals tested while demonstrating a significant antiparkinsonian efficacy (Blanchet et al. 1995; Gomez-Mancilla and Bédard 1992; Luquin et al. 1992). Of the DA $D_1$ receptor agonists tested in drug-naive animals, CY-208243 ((-)-4,6,6a,7,8,12b-hexahydro-7-methyl-indolo-(4,3-ab)phenanthoridine) displayed strong antiparkinsonian activity, but induced dyskinesias after a few weeks in three out of five animals (Bédard et al. 1997) while SKF-82958 (6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide) also rapidly induced prominent dyskinesias in two out of three animals (Blanchet et al. 1996).

In recent years, considerable effort has been devoted to the search for nondopaminergic therapies that are as efficacious as DA replacement therapy but might not elicit dyskinesias. Other than its neurotoxicity to the nigrostriatal DA system, MPTP is also toxic to the noradrenergic neurons originating in the locus coeruleus (LC), leading to a reduction of cerebral noradrenaline (NA) levels in nonhuman primates (Elsworth et al. 1990; Mitchell et al. 1985; Pifl et al. 1991). Similarly, LC lesions and reduced concentrations in NA can be observed in several motor areas of the cortex of parkinsonian patients, which may contribute to the symptomology of PD (Gaspard et al. 1991; Hornykiewicz and Kish 1986; Scatton et al. 1983). In fact, disruption of the noradrenergic system reduces the basal release and turnover of DA in the rat striatum (Geyer and Lee 1984; Lategan et al. 1990). Thus, the increase in NA cerebral content may be of therapeutic value in the treatment of PD. Previous studies in rats showed that idazoxan, a potent and selective $\alpha_2$-adrenoceptor antagonist, enhances the turnover and release of cerebral NA (L'Heureux et al. 1986), modulates DA release in some brain regions, and potentiates the amphetamine-induced ipsilateral circling (Marvidis et al. 1991) as well as the apomorphine-induced contralateral circling (Dickinson et al. 1988; Marvidis et al. 1990) in the unilateral nigral-lesioned rat. Idazoxan increases noradrenergic transmission by blocking inhibitory presynaptic $\alpha_2$-adrenoceptors (Dennis et al. 1987). Moreover, our group has shown that yohimbine, another $\alpha_2$-adrenoceptor antagonist, reduces L-dopa-induced dyskinesias in MPTP-treated monkeys without affecting significantly the antiparkinsonian response (Gomez-Mancilla and Bédard 1993). However, other than its noradrenergic properties, yohimbine acts at other receptors including DA receptors (Scatton et al. 1980) so that the role of $\alpha_2$-adrenoceptors in mediating the antidyskinetic effects of yohimbine is unclear. Conversely, idazoxan ($K_i$ = 3 nM) is over ten times more potent than yohimbine ($K_i$ = 40 nM) at inhibiting [$^3$H]clonidine binding at the $\alpha_2$ sites in brain tissue (P. Ladure, personal communication; Walter et al. 1984). The affinity of idazoxan for the $\alpha_2$ binding site is approximately 50 times higher than its affinity for the $\alpha_1$ sites ($K_i$ = 142 nM), with negligible affinity for DA receptors ($K_i$>100 μM; P. Ladure, personal communication; Walter et al. 1984). Thus, in order to extend our previous findings on the potential antidyskinetic effect of $\alpha_2$-adrenoceptor antagonists, we tested if idazoxan would have a similar profile of action in reducing dyskinesias to yohimbine, and if so, whether this antidyskinetic effect would be maintained over time with repeated administrations in MPTP-treated cynomolgus monkeys presenting L-dopa-induced dyskinesias.

## Materials and methods

*Animals and pretreatments.* This study was performed in six female cynomolgus (*Macaca fascicularis*) monkeys weighing 3.25–4.50 kg and rendered parkinsonian by weekly subcutaneous (s.c.) injections of MPTP (1–3 mg per injection). The animals received a total of 11 mg MPTP on average. All animals had disability scores of 5 or more (maximum 10) that had been unchanged for several months before the present study. All animals also had dyskinetic movements which had been induced over several weeks by repeated, once daily, oral administration of a single capsule containing L-dopa (100 mg) and benserazide (25 mg; Prolopa; Hoffmann-La Roche, Mississauga, Ontario, Canada). Once established, the dyskinetic response was thereafter reproducible to each subsequent dose of L-dopa or DA receptor agonists. The animals received no other treatment than L-dopa in the month preceding the present study.

*Experimental treatments.* In the first part of the study (dose-response), we administered seven oral doses of idazoxan together with the vehicle (empty capsule) or in combination with L-dopa/benserazide (100/25 mg) given orally. Idazoxan (2-[2-(1,4-benzodioxanyl)]-2-imidazoline hydrochloride; Pierre Fabre Research Institute, Plantaurel, Labège Innopole Cedex, France) was administered as a single capsule at 0.25, 0.50, 1.0, 2.0, 5.0, 7.5 and 10 mg/kg. The dose of idazoxan was increased each week. For each dose, capsules containing idazoxan administered with the vehicle and in combination with L-dopa were separated by a drug-free period of 24 h. Weekly administration of empty capsules (vehicle) given orally served as control. L-dopa/benserazide (100/25 mg), together with the vehicle, was also administered each week.

In the second part of the study (chronic), a fixed dose of idazoxan was administered daily for 10 days. After a rest of 2 weeks, the same animals received an oral dose of idazoxan (7.5 mg/kg) selected as the most advantageous (see Results). L-dopa/benserazide (100/25 mg) was administered with the vehicle the day preceding the onset of the protocol (day 0) and added to idazoxan on days 1, 4, 7 and 10. The animals were also administered with empty capsules (vehicle) as control treatment (day –1).

*Evaluation of the response.* During the study, the animals were housed individually in the same room in six observation cages equipped with glass doors and submitted to a 12-h light/12-h dark cycle. On experimental days, the animals were assessed through a one-way screen and scored every 30 min up to 4 h after treatment. The *antiparkinsonian response* was evaluated in a non-blinded fashion, according to a disability scale which we have used in several published studies. It includes assessment of: (a) posture: normal = 0, flexed = 1, crouched = 2; (b) mobility: normal = 0, reduced = 1, passive = 2; (c) climbing: present = 0, absent = 1; (d) gait: normal = 0, abnormal = 1; (e) tremor: present = 1, absent = 0; (f) social interactions: present = 0, absent = 1; (g) vocalization: present = 0, absent = 1; and (h) grooming: present = 0, absent = 1. A score of 10 represents maximal disability. The *dyskinetic response* was also rated for the face, neck, trunk, arms and legs in the following way: none = 0, mild (occasional) = 1; moderate (intermittent) = 2; severe (continuous) = 3. The dyskinetic score obtained was the sum of the scores for all body segments for a maximal score of 21 points. The score reflects the intensity and frequency of dyskinesias in the preceding 30 min. The timing of administration of the various treatments as well as the appearance and end of the antiparkinsonian and dyskinetic responses were carefully noted to appreciate the duration of dyskinesias in relation to the duration of the antiparkinsonian activity. Particular attention was paid to the occurrence of sleepiness. *Locomotor activity* was quantified every 5 min with an electronic motility monitoring system (Dataquest IV; Data Sciences, St. Paul, Minn., USA). Using radiowaves frequency, a probe implanted s.c. in the back of each animal transmits the signal to a receiver attached to the cage which is connected to a computer. Counts of locomotor activity per 5 min for each animal were accumulated over a period of 4 h after treatment. This period covers the duration of the effects observed during this study.

*Statistical analysis.* The total mobility counts recorded over 4 h for each animal were compared using an analysis of variance (ANOVA) for repeated measures, followed by a Fisher's probability of least significance difference (PLSD) a posteriori test. The disability scores obtained every 30 min up to 4 h (maximum of eight scores) for each animal were cumulated and averaged, giving us an average individ-

ual disability score per treatment. The mean disability scores were compared using the nonparametric Friedman's test. Following vehicle treatments, we considered a time interval corresponding to the duration of the effect of L-dopa. We used a similar procedure for the dyskinetic scores.

## Results

### Dose-response study

If one considers the whole group ($n = 6$), oral administration of *idazoxan* together with the vehicle had no significant effect vs. vehicle. However, a significant increase of locomotion was observed in three animals with severe parkinsonism (8< parkinsonian score <10) at doses ranging from 5 mg/kg to 10 mg/kg of idazoxan (not shown, ANOVA + Fisher PLSD; $P<0.05$ vs. vehicle). This increase in locomotor activity (two- to threefold on average vs. vehicle) was less intense than that produced by L-dopa (sixfold on average vs. vehicle in these three animals) and somewhat irregular with alternating periods of high and low mobility. The disability score was also significantly improved by idazoxan in these three monkeys only (not shown; Friedman; $P<0.05$ vs. vehicle). There were mild dyskinesias in one animal. The three other animals with moderate parkinsonism (5< parkinsonian score <8) showed signs of somnolence including eye closure and yawning. No other side-effect was observed.

Oral administration of L-dopa/benserazide alone (100/25 mg) caused a significant 4.5-fold increase of locomotion in all six animals vs. vehicle (Fig. 1A, black bar). The disability score was also improved by L-dopa in all six animals by 3.5 points on average (~50% vs. vehicle; Fig. 1B, top panel). However, this improvement in disability was accompanied by dyskinesias in all six animals (Fig. 1B, bottom panel). Idazoxan combined to L-dopa did not significantly modify the locomotor response (Fig. 1A, gray bars) or the improvement in disability caused by L-dopa in all animals, except at the highest dose of idazoxan tested (10 mg/kg) which slightly increased the disability score (Fig. 1B, top panel). However, we observed in all six animals a clear reduction in L-dopa-induced dyskinesias up to 65% at doses of 7.5 mg/kg and 10 mg/kg idazoxan (Fig. 1B, bottom panel). The dose of 7.5 mg/kg appeared optimal since at the higher dose, a certain reduction of the antiparkinsonian effect of L-dopa was observed. The improvement of the dyskinetic score obtained during the "ON" state is the result of a reduction in intensity and a delay in the appearance of dyskinesias with respect to the antiparkinsonian effect. For instance, a significant increase (paired *t*-test; $P<0.003$) of about 30 min of the "ON" state without dyskinesia was observed mostly at the beginning of the "ON" state (not shown).

### Chronic study

Repeated administration of idazoxan (7.5 mg/kg) combined with L-dopa did not decrease the locomotor response to L-dopa which was maintained at days 1, 4 and 7, and was even significantly potentiated at day 10 (Fig. 2A, hatched bars). Idazoxan did not modify the improvement in disability caused by L-dopa (Fig. 2B, top panel). However, we observed again a clear reduction in L-dopa-induced dyskinesias which was maintained for the 10-day period (Fig. 2B, bottom panel). As for the dose-response study, the improvement of the dyskinetic score obtained during the "ON" state results from a significant decrease in intensity and a significant 30-min delay in the appearance of dyskinesias compared to the antiparkinsonian effect, so that the "ON" state without dyskinesias was prolonged.

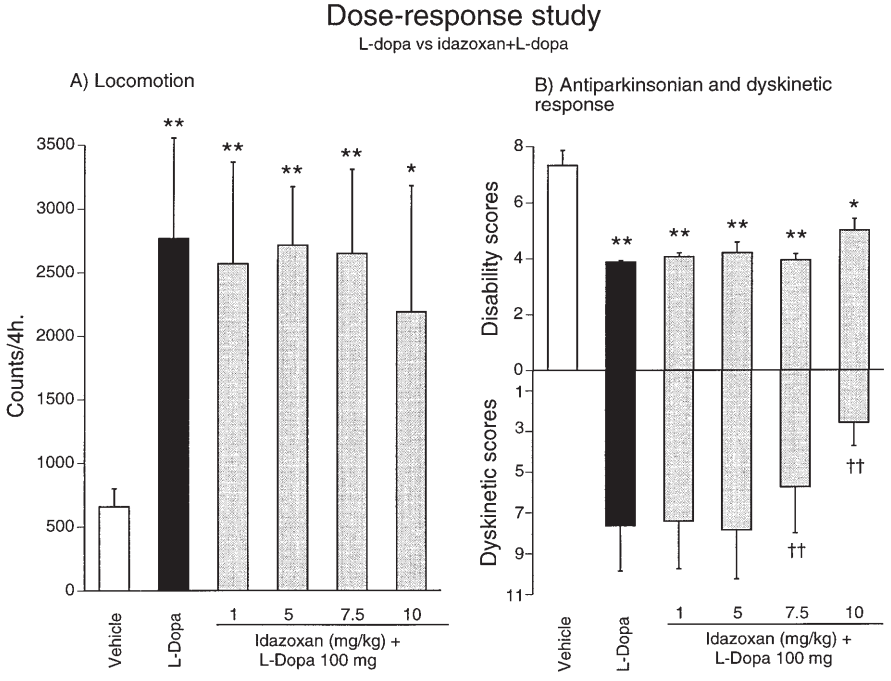


**Fig. 1A, B** Dose-response study. **A** Effects of vehicle, L-dopa and idazoxan + L-dopa on locomotor activity. The mobility counts cumulated over 4 h for each animal were compared using an analysis of variance (ANOVA) for repeated measures followed by a Fisher's probability of least significance difference (PLSD) test. Counts ± SEM (**P*<0.05 and ***P*<0.01 vs. vehicle). **B** Antiparkinsonian (*top panel*) and dyskinetic (*bottom panel*) effects of vehicle, L-dopa and idazoxan + L-dopa. The disability scores obtained every 30 min (up to 4 h) for each animal were cumulated and averaged, giving us an average individual disability score per treatment. The values were compared using the nonparametric Friedman's test. The same procedure was used for the dyskinetic scores. Scores ± SEM (**P*<0.05 and ***P*<0.01 vs. vehicle; ††*P*<0.01 vs. L-dopa)

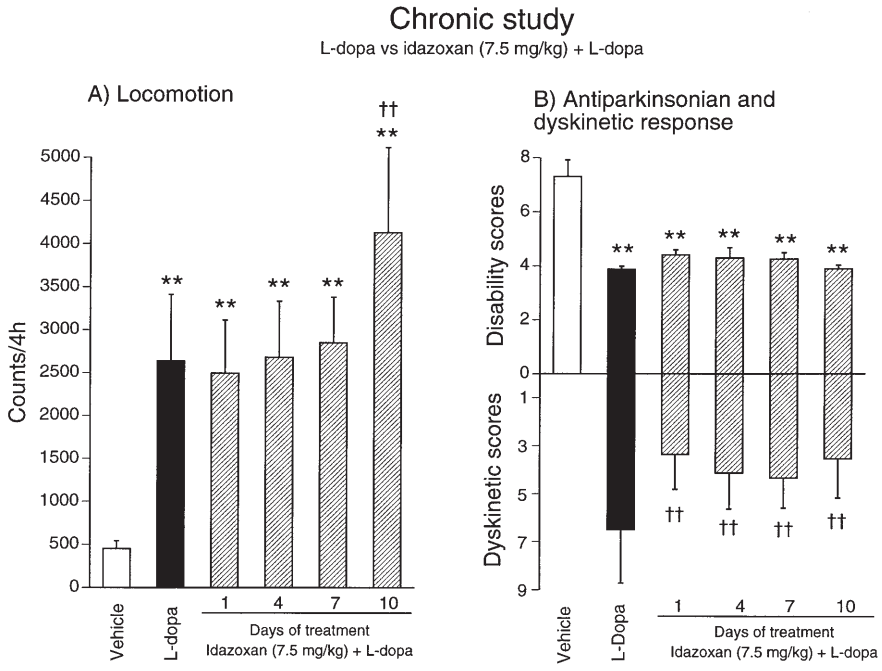


**Fig. 2A, B** Chronic administrations. **A** Effects of vehicle, L-dopa and chronic administrations of idazoxan (7.5 mg/kg) + L-dopa on locomotor activity. Counts ± SEM (***P*<0.01 vs. vehicle; ††*P*<0.01 vs. L-dopa). **B** Antiparkinsonian (*top panel*) and dyskinetic (*bottom panel*) effects of vehicle, L-dopa and chronic administrations of idazoxan (7.5 mg/kg) + L-dopa. Scores ± SEM (***P*<0.01 vs. vehicle; ††*P*<0.01 vs. L-dopa). See Fig. 1 for additional details

## Discussion

The present study suggests that pharmacological manipulations of the noradrenergic neurotransmission may benefit parkinsonian patients. For one, $\alpha_2$-adrenoceptors may influence the mechanisms underlying PD signs in our model as idazoxan administered with the vehicle was capable of reversing the parkinsonian features in half of the animals. This finding supports other studies in MPTP monkeys which have similarly reported a beneficial symptomatic effect in a limited number of animals ($n$ = 1–2) using idazoxan (Bezard et al. 1997) and the $\alpha_2$-adrenoceptor antagonist R47243 (Clopaert et al. 1991). The present results also indicate that idazoxan has a facilitatory influence on DA-mediated locomotor activity in MPTP-exposed cynomolgus monkeys as it can potentiate L-dopa-induced increase in locomotor activity after repeated administrations. Accordingly, the antagonism of $\alpha_2$-adrenoceptors with efaroxan significantly improved motor performance of PD patients under L-dopa (Ruzicka et al. 1997). The present results are also coherent with evidence in other animal models that idazoxan can potentiate nigrostriatal dopaminergic neurotransmission in vivo, e.g. its ability to potentiate DA-dependent circling in the unilateral nigral-lesioned rat (Dickinson et al. 1988; Marvidis et al. 1990, 1991).

The reduction of dyskinesias obtained in the present study is consistent with our previous report in nonhuman primates using yohimbine (Gomez-Mancilla and Bédard 1993) as well as with the report by Rascol et al. (1997) on the ability of idazoxan to reduce L-dopa-induced dyskinesias without any deterioration of the antiparkinsonian response in human patients. The $\alpha_2$-adrenoceptor antagonists yohimbine and rauwolscine were also reported to reduce peak-dose L-dopa-induced dyskinesias in the MPTP-treated common marmoset with no effect on the peak antiparkinsonian action of L-dopa (Henry et al. 1999). In the present study, the improvement of the dyskinetic score obtained during the "ON" state is the result of a decrease in intensity and a delay in the appearance of dyskinesias with respect to the antiparkinsonian effect, so that the "ON" state without dyskinesia is prolonged.

The precise mechanisms by which the noradrenergic system can influence the dopaminergic system and/or other systems to reduce L-dopa-induced dyskinesias remain unclear. Neurons in the LC project widely to the cerebral hemispheres and are the major sources of NA released in the brain (Raisman-Vozari 1994). Although disputed (Mason and Fibiger 1979) there is no clear anatomical evidence for a direct monosynaptic link between the LC and the nigrostriatal pathway (Jones and Moore 1977; Room et al. 1981). However, axonal projections from the LC to the dorsal raphe, thalamus and cortex are well described (Baraban and Aghajanian 1981; Jones and Moore 1977; Room et al. 1981; Westlund et al. 1990). In one of these circuits, NA fibers projecting from the LC to the neocortex may influence DA function indirectly by modulating the corticostriatal pathway. In a second circuit, NA fibers may affect the activity of the nigrostriatal DA system by modulating the influence of the serotonin-containing system projecting from the dorsal raphe to the substantia nigra (Antelman and Caggiula 1977). Thus, there are a number of circuits through which NA can indirectly (directly?) influence DA activity. Moreover, $\alpha_2$-adrenoceptors are present in the basal ganglia. In fact, in situ hybridization studies in rats show high levels of $\alpha_2$-adrenoceptor mRNAs in the cortex, the thalamus and the basal ganglia, namely, the nucleus accumbens and the caudate-putamen (Nicholas et al. 1993; Scheinin et al. 1994). Similarly, binding studies in human postmortem brains show high to intermediate levels of $\alpha_2$-adrenoceptors in the cortex, thalamus, caudate-putamen, nucleus accumbens, globus pallidus and substan-

tia nigra (De Vos et al. 1991, 1992). The presence of $\alpha_2$-adrenoceptors in these regions involved in motor functions represent potential sites at which idazoxan or similar drugs might interfere with DA or other neurotransmitters involved in the genesis of L-dopa-induced dyskinesias. Indeed, an abnormal decrease in GABAergic transmission along the striato-external globus pallidus (GPe) pathway was proposed as a mechanism underlying L-dopa-induced dyskinesias (Crossman 1990). $\alpha_2$-adrenoceptors seem to be located presynaptically on GABAergic inputs to the GPe (Henry et al. 1998). Thus, it was proposed that blockade of presynaptic $\alpha_2$-adrenoceptors in the GPe may increase GABA transmission and underlie the antidyskinetic effects of $\alpha_2$-adrenoceptor antagonists such as idazoxan (Henry et al. 1998). In addition to acting as an $\alpha_2$-adrenoceptor antagonist, idazoxan has high affinity for nonadrenergic imidazoline (I), binding $I_1$ and $I_2$ sites (Regunathan and Reis 1996). However, given the similarity of behavioral effects of idazoxan with other $\alpha_2$-adrenoceptor antagonists such as yohimbine (Gomez-Mancilla and Bédard 1993) lacking affinity for $I_1$ or $I_2$ sites (Regunathan and Reis 1996), it is likely that the effects of idazoxan reported here result from its antagonist action at $\alpha_2$-adrenoceptors.

In summary, our results indicate that idazoxan has some antiparkinsonian effect of its own and that it can reduce dyskinesias caused by L-dopa without impairing its antiparkinsonian activity. This benefit of idazoxan is maintained during repeated administrations. Thus, idazoxan appears to be a useful drug to be used as an adjunct to L-dopa in parkinsonian patients in whom the current therapy is complicated by dyskinesias. It may be worth considering further development and testing of selective $\alpha_2$-adrenoceptor antagonists in the search for additional antiparkinsonian agents with potential low risk of inducing unwanted and often troublesome side-effects.

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## References

Antelman SM, Caggiula AR (1977) Norepinephrine-dopamine interactions and behavior. Science 195:646–653

Baraban JM, Aghajanian GK (1981) Noradrenergic innervation of serotonergic neurons in the dorsal raphe: demonstration by electron microscopic autoradiography. Brain Res 204:1–11

Bédard PJ, Gomez-Mancilla B, Blanchet PJ, Calon F, Grondin R, Gagnon C, Falardeau P, Goulet M, Morissette M, Rouillard C, Di Paolo T (1997) Dopamine agonists as first line therapy of parkinsonism in MPTP monkeys. In: Olanow CW, Obeso JA (eds) Beyond the decade of the brain: dopamine agonists in early Parkinson's disease, vol 2. Wells Medical, Royal Tunbridge Wells, pp 101–113

Bezard E, Brefel C, Tison F, Peyro Saint Paul H, Ladure P, Rascol O, Gross C (1997) Effects of the $\alpha_2$ antagonist idazoxan in experimental parkinsonism: a pilot study. Mov Disord 12:114 (abstr)

Blanchet PJ, Calon F, Martel JC, Bédard PJ, Di Paolo T, Walters RR, Piercey MF (1995) Continuous administration decreases and pulsatile administration increases behavioral sensitivity to a novel dopamine $D_2$ agonist (U-91356A) in MPTP-exposed monkeys. J Pharmacol Exp Ther 272:854–859

Blanchet PJ, Grondin R, Bédard PJ (1996) Dyskinesia and wearing-off following dopamine $D_1$ agonist treatment in drug-naive 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned primates. Mov Disord 11:91–94

Clopaert FC, Degryse AD, Van Craenendonck H (1991) Effects of an alpha$_2$ antagonist in a 20-year-old Java monkey with MPTP-induced parkinsonian signs. Brain Res Bull 26:627–631

Crossman AR (1990) A hypothesis on the pathophysiological mechanisms that underlie levodopa- or dopamine agonist-induced dyskinesia in Parkinson's disease: implications for future strategies in treatment. Mov Disord 5:100–108

Dennis T, L'Heureux R, Carter C, Scatton B (1987) Presynaptic alpha-2 adrenoceptors play a major role in the effects of idazoxan on cortical noradrenaline release (as measured by in vivo dialysis) in the rat. J Pharmacol Exp Ther 241:642–649

De Vos H, Convents A, De Keyser J, De Backer JP, Van Megen IJ, Ebinger G, Vauquelin G (1991) Autoradiographic distribution of $\alpha_2$-adrenoceptors, NAIBS, and 5-$HT_{1A}$ receptors in human brain using [$^3$H]idazoxan and [$^3$H]rauwolscine. Brain Res 566:13–20

De Vos H, Vauquelin G, De Keyser J, De Backer J-P, Van Liefde I (1992) Regional distribution of $\alpha_{2A}$- and $\alpha_{2B}$-adrenoceptor subtypes in postmortem human brain. J Neurochem 58:1555–1560

Dickinson SL, Gadie B, Tulloch IF (1988) $\alpha_1$- and $\alpha_2$-adrenoreceptor antagonists differentially influence locomotor and stereotyped behaviour induced by d-amphetamine and apomorphine in the rat. Psychopharmacology 96:521–527

Elsworth JD, Deutch AY, Redmond DE Jr, Sladek JR Jr, Roth RH (1990) MPTP reduces dopamine and norepinephrine concentrations in the supplementary motor area and cingulate cortex of the primate. Neurosci Lett 114:316–322

Gaspard P, Duyckaerts C, Alvarez C, Javoy-Agid F, Berger B (1991) Alterations of dopaminergic and noradrenergic innervations in motor cortex in Parkinson's disease. Ann Neurol 30:365–374

Geyer MA, Lee EHY (1984) Effects of clonidine, piperoxane and locus coeruleus lesion on the serotoninergic and dopaminergic systems in raphe and caudate nucleus. Biochem Pharmacol 33: 3399–3404

Gomez-Mancilla B, Bédard PJ (1992) Effect of chronic treatment with (+)-PHNO, a $D_2$ agonist in MPTP-treated monkeys. Exp Neurol 117:185–188

Gomez-Mancilla B, Bédard PJ (1993) Effects of nondopaminergic drugs on L-dopa-induced dyskinesias in MPTP-treated monkeys. Clin Neuropharmacol 16:418–427

Henry B, Owens SH, Fox D, Peggs D, Hill MP, Crossman AR, Brotchie JM (1998) The role of $\alpha_2$-adrenergic receptors in L-dopa-induced dyskinesia in Parkinson's disease. Soc Neurosci 24:410 (abstr)

Henry B, Fox SH, Peggs D, Crossman AR, Brotchie JM (1999) The alpha2-adrenergic receptor antagonist idazoxan reduces dyskinesia and enhances anti-parkinsonian actions of L-dopa in the MPTP-lesioned primate model of Parkinson's disease. Mov Disord 14:744–753

Hornykiewicz O, Kish SJ (1986) Biochemical pathophysiology in Parkinson's disease. Adv Neurol 45:19–34

Jones BE, Moore RY (1977) Ascending projections of the locus coeruleus in the rat. II. Autoradiographic study. Brain Res 127: 23–53

Lategan AJ, Marien MR, Colpaert FC (1990) Effects of locus coeruleus lesions on the release of endogenous dopamine in the rat nucleus accumbens and caudate nucleus as determined by intracerebral microdialysis. Brain Res 523:134–138

L'Heureux R, Dennis T, Curet O, Scatton B (1986) Measurement of endogenous noradrenaline release in the rat cerebral cortex in vivo by transcortical dialysis: effects of drugs affecting noradrenergic transmission. J Neurochem 46:1794–1801

Luquin MR, Laguna J, Obeso JA (1992) Selective $D_2$ receptor stimulation induces dyskinesia in parkinsonian monkeys. Ann Neurol 31:551–554

Marvidis M, Millan MJ, Colpaert FC (1990) Alpha-1 and alpha-2 antagonists differentially modulate d-amphetamine and apomorphine-induced rotation in substantia nigra-lesioned rats. Eur J Pharmacol 183:448 (abstr)

Marvidis M, Colpaert FC, Millan MJ (1991) Differential modulation of (+)amphetamine-induced rotation in unilateral substantia nigra-lesioned rats by $\alpha_1$ as to compared to $\alpha_2$ agonists and antagonists. Brain Res 562:216–224

Mason ST, Fibiger HC (1979) Regional topography within noradrenergic locus coeruleus as revealed by retrograde transport of horseradish peroxidase. J Comp Neurol 187:703–724

Mitchell IJ, Cross AJ, Sambrook MA, Crossman AR (1985) Sites of the neurotoxic action of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in the macaque monkey include the ventral tegmental area and the locus coeruleus. Neurosci Lett 61:195–200

Nicholas AP, Pieribone V, Hokfelt T (1993) Distribution of mRNAs for alpha-2 adrenergic receptor subtypes in rat brain: an in situ hybridization study. J Comp Neurol 328:575–594

Pifl C, Schingnitz G, Hornykiewicz (1991) Effect of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine on the regional distribution of brain monoamines in the rhesus monkey. Neuroscience 44: 591–605

Raisman-Vozari R (1994) The locus coeruleus in Parkinson's disease. In: Briley M, Marien M (eds) Noradrenergic mechanisms in Parkinson's disease. CRC Press, Boca Raton, pp 89–103

Rascol O, Arnulf I, Brefel C, Vidailhet M, Thalamas C, Bonnet AM, Descombes S, Bejjani B, Montastruc JL, Pyero-Saint Paul H, Agid Y (1997) L-dopa-induced dyskinesia improvement by an $\alpha_2$ antagonist, idazoxan, in patients with Parkinson's disease. Mov Disord 12:111 (abstr)

Regunathan S, Reis DJ (1996) Imidazoline receptors and their endogenous ligands. Ann Rev Pharmacol 36:511–544

Room P, Postema F, Korf J (1981) Divergent axon collaterals of rat locus coeruleus neurons: demonstration by a fluorescent double labeling technique. Brain Res 221:219–303

Ruzicka E, Ladure P, Roth J, Jech R, Mecir P, Peyro-Saint-Paul H (1997) Efficacy and safety of efaroxan, an alpha-2 adrenoceptor antagonist, in Parkinson' disease: an oral short-term study. Mov Disord 12:123 (abstr)

Scatton B, Zivkovic B, Dedek J (1980) Antidopaminergic properties of yohimbine. J Pharmacol Exp Ther 215:494–499

Scatton B, Javoy-Agid F, Rouquier L, Dubois B, Agid Y (1983) Reduction of cortical dopamine, noradrenaline, serotonin and their metabolites in Parkinson's disease. Brain Res 275:321–328

Scheinin M, Lomasney JW, Hayden-Hixson DM, Schambra UB, Caron MG, Lefkowitz RJ, Fremeau RT Jr (1994) Distribution of $\alpha_2$-adrenergic receptor subtype gene expression in rat brain. Mol Brain Res 21:133–149

Walter DS, Flockhart IR, Haynes MJ, Howlett DR, Lane AC, Burton R, Johnson J, Dettmar PW (1984) Effects of idazoxan on catecholamine systems in rat brain. Biochem Pharmacol 33: 2553–2557

Westlund KN, Sorkin LS, Ferrington DG, Carlton SM, Willcockson HH, Willis WD (1990) Serotoninergic and noradrenergic projections to the ventral posterolateral nucleus of the monkey thalamus. J Comp Neurol 295:197–207