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Failure of SKF 38393-A to relieve parkinsonian symptoms induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in the marmoset

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Chronic administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced parkinsonian symptoms, predominantly bradykinesia and tremor, in marmosets. These symptoms were reduced by L-DOPA plus benserazide but the putative D_1-receptor agonist SKF 38393-A did not affect tremor and increased the bradykinesia. Neither treatment affected behaviour in normal marmosets. It is suggested that D_1-receptor agonists are unlikely to be effective in the treatment of Parkinson's disease.

Introduction Severe parkinsonism has been described in both man and Rhesus monkey following intravenous administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Langston *et al.*, 1983; Burns *et al.*, 1983). This syndrome was characterized by severe loss of nigral dopaminergic neurones and was reversed by L-DOPA (Burns *et al.*, 1983; Langston *et al.*, 1983). MPTP also induces a similar syndrome in marmosets and this can be reversed by L-DOPA or bromocriptine (Close *et al.*, 1985).

Although dopamine D_2-receptor agonists are effective in the treatment of Parkinson's disease (Calne, 1982), the role of dopamine D_1-receptor agonists is uncertain. The putative D_1-receptor agonist SKF 38393-A (2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine HCl) interacts with dopamine-sensitive adenylate cyclase and induces contralateral rotation in rats with unilateral nigrostriatal lesions but does not cause stereotypy, emesis or inhibition of prolactin release (Setler *et al.*, 1978). In view of its novel pharmacological profile, it was of interest to determine whether SKF 38393-A might be expected to relieve the symptoms of Parkinson's disease. We have therefore compared the actions of SKF 38393-A with those of L-DOPA (plus benserazide) on MPTP-induced bradykinesia and tremor in the marmoset.

Methods Male marmosets (*Callithrix jacchus*), body weight 270–350g, were used. Parkinsonism was induced by repeated intraperitoneal injections of MPTP in eight marmosets. The initial dose was 4 mg kg^{-1} followed by further daily doses of 2 mg kg^{-1} until the animals exhibited marked parkinsonian symptoms. On average, three doses of 2 mg kg^{-1} were required. Thereafter, two to three doses of 2 mg kg^{-1} day^{-1} were required weekly to maintain the symptoms. Four control animals received vehicle.

One to three days after completing each MPTP or vehicle treatment, SKF 38393-A (3,6 or 12 mg kg^{-1}), vehicle (5% gum acacia solution) or L-DOPA (20 mg kg^{-1} in combination with the peripheral dopa decarboxylase inhibitor benserazide, 5 mg kg^{-1}) was administered intraperitoneally to both test and control animals. Each animal received each treatment in random sequence over the course of 5 weekly sessions. The severity of bradykinesia and limb tremor, as indices of parkinsonism, was assessed 'blind' on a 7-point scale before and at intervals after each treatment. Differences between pre- and post-drug scores were assessed at peak effect for statistical significance using the Wilcoxon matched-pairs signed-ranks test or, where group sizes were less than 6 animals, the signs test.

MPTP (Aldrich) was dissolved in distilled water acidified with 2M HCl and neutralised with 1M NaOH. SKF 38393-A (Smith, Kline and French), L-DOPA (Aldrich) and benserazide (Roche) were suspended in 5% gum acacia solution. All drugs were injected in a volume of 1 ml kg^{-1} body weight.

Results

Effects of MPTP MPTP caused acute and more slowly developing chronic changes in behaviour. The main acute effects, seen after each injection, were mydriasis, bradykinesia and a rigid posture. Effects occasionally seen, in decreasing order of incidence, included piloerection, repetitive head weaving, chewing and salivation. These symptoms had a quick onset (2 min) and lasted for approximately 30 min.

Repeated administration of MPTP induced a syndrome resembling Parkinson's disease in all 8 marmosets. Within 1–2 days of starting MPTP treatment

the predominant symptom was bradykinesia. This increased in severity with continued dosing and was manifested as a reduction in the speed and incidence of locomotor movements. Initiation of movement became difficult and 'freezing' episodes developed in which ongoing movements were suddenly arrested. Within approximately 7 days of starting treatment, a coarse tremor of the forelimbs, most noticeable during movement initiation, developed in 6 of the MPTP-treated marmosets. Additional symptoms included fixed gaze, flexed forelimb posture, decreased vocalisation and, in more severely affected cases, a drooped head posture. Within 2–4 weeks of discontinuing MPTP treatment all symptoms gradually diminished.

Drug effects The effects of SKF 38393-A and L-DOPA plus benserazide on bradykinesia and tremor in MPTP-treated marmosets are shown in Figure 1. Animals without tremor were excluded from mean tremor scores. SKF 38393-A (6 and 12 mg kg^{-1} i.p.) caused a significant increase in bradykinesia but failed to affect tremor. In contrast, L-DOPA (20 mg kg^{-1}, i.p.) plus benserazide (5 mg kg^{-1} i.p.) caused a dramatic reduction in both bradykinesia and tremor.

Neither L-DOPA (20 mg kg^{-1}, i.p.) plus benserazide (5 mg kg^{-1}, i.p.) nor SKF 38393-A (3 or 6 mg kg^{-1}, i.p.) caused any visible behavioural changes in control marmosets. SKF 38393-A (12 mg kg^{-1}, i.p.) caused emesis in 4 marmosets (3 control and 1 MPTP-treated) and slight mydriasis in 3 MPTP-treated marmosets.

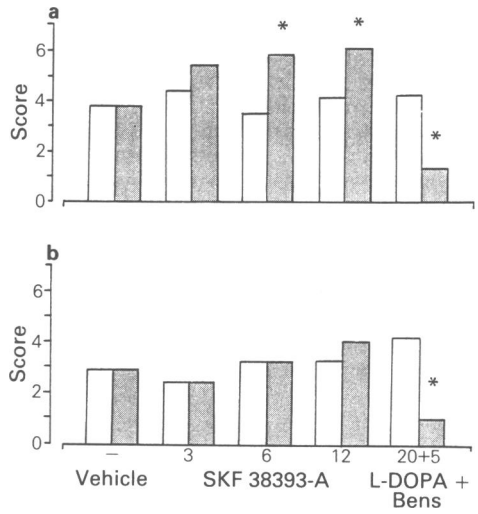

Figure 1 Effects of SKF 38393-A, L-DOPA plus benserazide (Bens) and vehicle on (a) bradykinesia ($n = 8$) and (b) tremor ($n = 4–6$) in MPTP-treated marmosets. Values plotted are means. Open columns are pre-dose scores; stippled columns are post-dose scores. *Significant differences between pre- and post-dose scores: $P < 0.05$.

Discussion The long-lasting behavioural syndrome induced by MPTP in marmosets in many respects resembles that induced by this agent in both the Rhesus monkey and man (Burns *et al.*, 1983; Langston *et al.*, 1983). However, in the marmoset some differences were found. In particular, postural rigidity only occurred as an acute symptom in these animals and the bradykinesia, although severe in some marmosets initially, was clearly not permanent. Nevertheless, in other respects the overall prolonged behavioural syndrome induced by MPTP in the marmoset bears a striking resemblance to human Parkinson's disease and therefore appears to provide a useful preclinical model for the evaluation of anti-parkinsonian drugs. Bradykinesia and forelimb tremor provided the most consistent indices for quantifying drug effects. As previously reported (Close *et al.*, 1984) L-DOPA plus benserazide caused a dramatic reversal of the MPTP-induced syndrome in the marmoset at doses causing no overt changes in control animals.

The finding that SKF 38393-A did not reverse the MPTP-induced syndrome was of particular interest. The possibility that this lack of effect was due to rapid metabolism following intraperitoneal administration is unlikely since the drug caused a significant increase in bradykinesia and at similar intraperitoneal doses induces marked contralateral rotation in rats with unilateral nigro-striatal lesions (Gower & Marriott, 1982).

The mechanism by which SKF 38393-A increased MPTP-induced bradykinesia is not known but was evidently due to an interaction with the effects of MPTP since SKF 38393-A did not induce bradykinesia in non-MPTP-treated control animals.

The present results suggest that selective dopamine D_1-receptor agonists are unlikely to be effective in the treatment of Parkinson's disease.

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