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Motor activity following the administration of selective D-1 and D-2 dopaminergic drugs to MPTP-treated common marmosets

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Abstract. The ability of selective D-1 agonist and antagonist drugs to alter motor deficits and locomotor activity was studied in MPTP-treated common marmosets. Both the D-2 agonist quinpirole and the mixed D-1/D-2 agonist apomorphine reversed the motor impairments and induced locomotor activity. The D-1 antagonist SCH 23390 and the D-2 antagonist raclopride given alone further reduced motor function in MPTP-treated animals. The actions of quinpirole were potently and completely inhibited by raclopride but only partially and inconsistently by SCH 23390. In contrast, the effects of apomorphine were markedly but incompletely inhibited by both raclopride and SCH 23390. The D-1 agonist SKF 38393 alone caused a dose related reduction in motor activity. SKF 38393 weakly and partially inhibited the improvements in motor function produced by quinpirole but had a more pronounced effect on apomorphine induced motor activity. The induction of motor activity in MPTP treated common marmosets may separately involve both D-1 and D-2 receptors. Comparison with our previous data on the effect of the same drugs in normal common marmosets provides some evidence for a breakdown of linkage between D-1 and D-2 systems following MPTP treatment. The actions of SKF 38393 in MPTP-treated common marmosets contrasts with its ability to induce behavioural activation and a facilitation of D-2 mediated behaviour in rodents. SKF 38393 may not be the compound with which to delineate the role of D-1 receptors in primates.

Key words: Raclopride – Quinpirole – SCH 23390 – Apomorphine – Marmosets – Dopamine receptors

Brain dopamine receptors are families divided into D-1-like adenylate cyclase (AC) linked and D-2-like sites (Kebabian and Calne 1979). The latter are either negatively linked or not coupled to AC (Stoof and Kebabian 1981). In intact rodents distinct behaviours have been related to stimulation of D-1 and D-2 receptors. In addition, a complex functional interaction exists between D-1 and D-2 receptors. For example, D-1 receptor occupation by SKF 38393 enhances stereotyped behaviour induced by the D-2 agonist RU 24213 (Pugh et al. 1985; Mashurano and Waddington 1986). Conversely, D-2 antagonist drugs can inhibit grooming induced by SKF 38393 (Murray and Waddington 1989). In addition, blockade of either D-1 or D-2 receptors can allow the expression of novel behaviour through activation of the other class of dopamine receptors (Chandler et al. 1990). For example, treatment of rats with the D-2 antagonist sulpiride allows the expression of vacuous chewing in rats by SKF 38393.

In primates, similar interactions between D-1 and D-2 systems may not occur. In a preceding paper (Löschmann et al. 1991) we reported on the effects of apomorphine and quinpirole alone and in combination with SKF 38393, SCH 23390 and the D-2 antagonist raclopride on locomotor activity and behaviour in normal common marmosets. The results indicated that although there were some similarities between the functional interaction between D-1 and D-2 receptors in primates, there were significant differences indicative of a species difference. For example, SKF 38393 did not stimulate locomotor activity and inhibited that produced by quinpirole.

Following the depletion of dopamine or the destruction of dopamine neurones in rodents the linkage between D-1 and D-2 receptor systems may be altered such that both D-1 and D-2 agonists now induce identical locomotor response but these are mediated independently through D-1 and D-2 receptor systems (Gershanik et al. 1983; Arnt 1985; Arnt and Perregaard 1987; Sonsalla et al. 1988). In addition, in mice depleted of endogeneous dopamine by treatment with reserpine and alpha-methyl-p-tyrosine (AMPT), D-2 agonists such as bromocriptine (Jackson and Hashizume 1986) or quinpirole (Starr and Starr 1989) no longer induce locomotor activity unless there is concurrent administration of the D-1 agonist SKF 38393.

These results might suggest that D-1 agonist drugs would themselves be useful in treating illnesses such as Parkinson's disease or as adjuncts to therapy with D-2 agonist compounds. However, in the MPTP-treated

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primate, administration of SKF 38393 had no effect on motor activity (Close et al. 1985; 1990; Nomoto et al. 1985) and antagonized locomotor stimulation induced by the D-2 agonist quinpirole (Nomoto et al. 1988). In other species of monkeys treated with MPTP, SKF 38393 alone has been reported to have no effect and to inhibit D-2 mediated motor behaviours (Barone et al. 1987; Boyce et al. 1990).

It appears, therefore, that the relationship between D-1 and D-2 systems in primates may be different in animals with nigrostriatal lesions compared to events occurring in rodents. For this reason, we have studied the effects of D-1 and D-2 agonist and antagonist drugs in the MPTP treated common marmoset using the manipulations previously employed in normal animals (Löschmann et al. 1991).

Materials and methods

Animals. Common marmosets (*Callithrix jacchus*) of either sex weighing 280–420 g, aged 2–10 years at the beginning of the study were used ($n = 24$). The animals were housed either in pairs or alone under standard conditions at a temperature of 27° (± 1°C) and 50% relative humidity using a 12 h light-dark cycle (light on from 6.00 to 18.00 hours). The animals had free access to food pellets (Mazuri primate diet) and tap water, and in addition received a daily ration of fresh fruit and Mazuri marmoset jelly. During MPTP treatment and throughout the following weeks the animals were hand-fed with Mazuri marmoset jelly and fresh fruit puree until they were able to maintain themselves. Electrolyte, nutrient and fluid balance was maintained by SC infusion of an electrolyte, amino acid and vitamin solution (Duphalyte, Duphar, UK) when necessary.

Rating of disability. When treated with MPTP and throughout the pharmacological experiments, the disability of the animals was scored using the following items: alertness (normal 0, reduced 1, sleepy 2); reaction to stimuli (normal 0, reduced 1, slow 2, absent 3), checking movements (present 0, reduced 1, absent 2); attention and eye movements (normal 0, abnormal 1); posture (normal 0, abnormal trunk 1, abnormal limbs + 1, abnormal tail + 1 or grossly abnormal 4); balance/coordination (normal 0, impaired 1, unstable 2, spontaneous falls 3), vocalisation (normal 0, reduced 1, absent 2), tremor (absent 0, present 1). The maximum disability score possible was 18 whereas normal marmosets score 0.

Measurement of locomotor activity. Locomotor activity was measured simultaneously in four aluminium cages (50 × 60 × 70 cm) with stainless steel grid doors (50 × 70 cm) identical to the animals home cage but equipped with eight horizontally orientated sets of infrared photocells. Across the cage three beams were located at floor level and one along each of the two perches. Other beams were directed from front-to-back of the cage at floor level and above each perch. The number of light beam interruptions due to the animal's movements were accumulated in 10 min intervals and recorded for 120 min using a Commodore CBM 4032 computer. The animals were allowed to acclimatize to the test cage for a minimum of 30 min prior to drug treatment.

Behavioural observations. In parallel to the automated recording of locomotor activity the animals were observed through a one-way mirror. Immediately before drug treatments and throughout the experiment each animal was rated in 10 min intervals by an experienced observer using the disability scoring system. In addition, motor behaviour was rated qualitatively to determine the presence or absence of stereotypy, the degree of stimulation or inhibition, incidence of head twitches, wet dog shakes or grooming, oral movements and other obvious motor signs again in 10 min intervals for 120 min after drug administration. In addition a video recording of one animal in each treatment group was taken to allow post-hoc assessment of alterations in behaviour.

Drug solutions. The following compounds were employed: MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride; Research Biochemicals Inc., USA), SKF 38393 (2,3,4,5-tetrahydro-7, 8-dihydroxy-1-phenyl)-1H-3-benzazepine hydrochloride, Research Biochemicals Inc., USA), SCH 23390 (1-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepine-7-ol hemimaleate; Schering Corp., USA), apomorphine hydrochloride (Macfarlan Smith Ltd., UK), quinpirole (LY 171555; trans-(-)-4aR-4, 4a, 5,6,7,8, 8a,9-octahydro-5-propyl-1H (or-2H)-pyrazolo(3,4g)quinoline monohydrochloride; Eli Lilly, USA), raclopride (S-(-)-3, 5-dichloro-N-[1-ethyl-2-pyrrolidinyl)methyl]-2-hydroxy-6-methoxy-benzamide; Astra, Sweden) and domperidone (Jansssen, Belgium). The solutions were prepared under sterile conditions. All compounds, except domperidone, were dissolved in sterile physiological saline and administered in a final volume of 1 ml/kg body weight. Domperidone was suspended in some drops of ethanol (70%) and diluted to volume (2 ml/kg body weight) with 10% sucrose/water solution and administered by oral gavage.

MPTP treatment. The animals were treated with MPTP in doses of 2 mg/kg SC daily for up to 6 days since the response of individual animals differed markedly, variable dose regimes were applied to obtain stable motor deficits. The cumulative doses administered ranged between 8 and 12 mg/kg. Following MPTP treatment the animals recovered from acute effects over a period of some weeks. In the following months a further gradual recovery from the MPTP effects was observed. Before behavioural testing, 6 weeks to 8 months after exposure to MPTP, the animals showed a marked reduction of basal locomotor activity, exhibiting slower and less coordinated movements, reduced checking movements of the head and eye blinks as well abnormal postures of some parts of the body.

Drug treatments. Marmosets were randomly divided into groups of four and were subsequently treated with vehicle and the three doses of one test compound over the following weeks allowing a 1 week recovery period between doses. Individual animals were maximally employed in three such treatment groups with at least a 4 week period between experiments. A latin square design was used for the allocation of treatments within the groups.

Dose response studies. Animals were pretreated with domperidone (2 mg/kg PO) 30 min prior to the subcutaneous (SC) administration of apomorphine (0.37, 0.75, 1.5 mg/kg or vehicle) or intraperitoneal (IP) administration of quinpirole (0.15, 0.3. 0.6 mg/kg or vehicle). Locomotor activity was recorded over the following 2 h period. The effects of SKF 38393 (1.25, 2.5, 5.0 mg/kg IP or vehicle), SCH 23390 (1.25, 2.5, 5.0 mg/kg IP or vehicle) or raclopride (0.31, 1.25, 5.0 mg/kg IP or vehicle) were examined in an identical manner except that pretreatment with domperidone was not necessary. In contrast to others (Close et al. 1990) and in agreement with our findings in normal common marmosets (Löschmann et al. 1991) SKF 38393 did not induce nausea or vomitting in doses up to 5 mg/kg IP.

Interaction studies. Animals were pretreated with domperidone (2 mg/kg PO) 15 min prior to the administration of SKF 38393, SCH 23390 (both 1.25, 2.5, 5.0 mg/kg or vehicle IP). A further 15 min later apomorphine (0.5 mg/kg SC) or quinpirole (0.5 mg/kg IP) were administered. Raclopride (0.31, 1.25, 5.0 mg/kg IP, or vehicle) was administered 15 min prior to apomorphine administration (0.5 mg/kg SC) or quinpirole (0.3 mg/kg IP). Monitoring of locomotor activity was started immediately following the last injection.

Data analysis. The mean ± SEM were calculated for time courses and accumulated locomotor counts of the different treatment groups. Statistical differences were calculated for accumulated locomotor counts by the non-parametric Page test for ordered alternatives using exact distributions.

Statistical differences in disability scores were calculated comparing scores prior to treatments to those at peak effects of treatments by the non-parametric Mann-Whitney U test.

Results

Effects of apomorphine and quinpirole on motor behaviour

Administration of apomorphine (0.37–1.5 mg/kg SC) or quinpirole (0.15–0.6 mg/kg IP) caused a reversal of motor deficits and a dose dependent increase of locomotor activity in MPTP-treated common marmosets (Figs 1 and 2). The effect of apomorphine was maximal within 10 min of administration and lasted for 80 min. At higher doses (0.75 and 1.5 mg/kg SC) stereotyped movements of the limbs or the whole body were observed with an increase in poorly coordinated movements. Based on this observation a dose of 0.5 mg/kg SC was chosen for the subsequent drug interaction experiments.

Administration of quinpirole (0.15–0.60 mg/kg IP) also produced a reversal of motor deficits and a sustained increase in motor activity which lasted throughout the observation period. In animals treated with quinpirole (0.6 mg/kg IP) pronounced stereotyped movements in the form of repetitive grasping or body waving occurred which reduced overall activity counts. A dose of 0.3 mg/kg quinpirole was chosen for subsequent interaction experiments.

The effect of both apomorphine and quinpirole was to produce an increase in motor behaviour which took the form of very fast movements. Animals did not exhibit dyskinesia or dystonia. Increased grooming and oral movements were observed with quinpirole. Nausea and vomiting did not occur as animals were pretreated with domperidone.

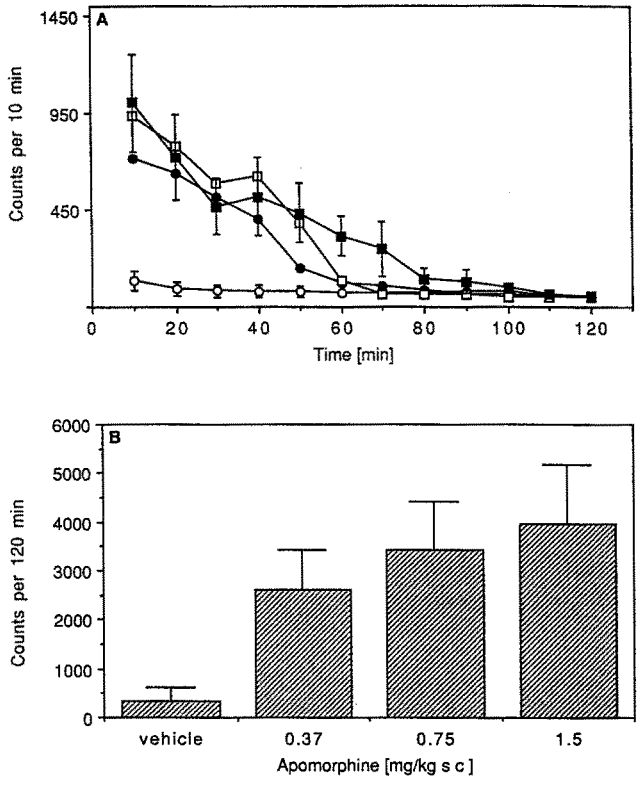


Fig. 1A, B. The effect of apomorphine on motor activity in MPTP-treated common marmosets. **A** Mean cumulative movement counts accumulated in 10 min intervals over 2 h (± SEM, $n = 4$) of MPTP-treated common marmosets pretreated with domperidone (2 mg/kg PO) 30 min prior to the subcutaneous administration of vehicle (–○–) or 0.37 (–●–), 0.75 (–□–) or 1.5 (–■–) mg/kg apomorphine. *Error bars* for the lower doses of apomorphine are omitted for clarity but were in the same range as those shown for the vehicle and apomorphine 1.5 mg/kg SC treatment. **B** Mean cumulative movement counts accumulated over 2 h (± SEM, $n = 4$) for the data shown in **A**. Locomotor activity was increased by apomorphine ($P < 0.05$, Page test, ordered alternative: vehicle < 0.37 < 0.75 < 1.5 mg/kg apomorphine)

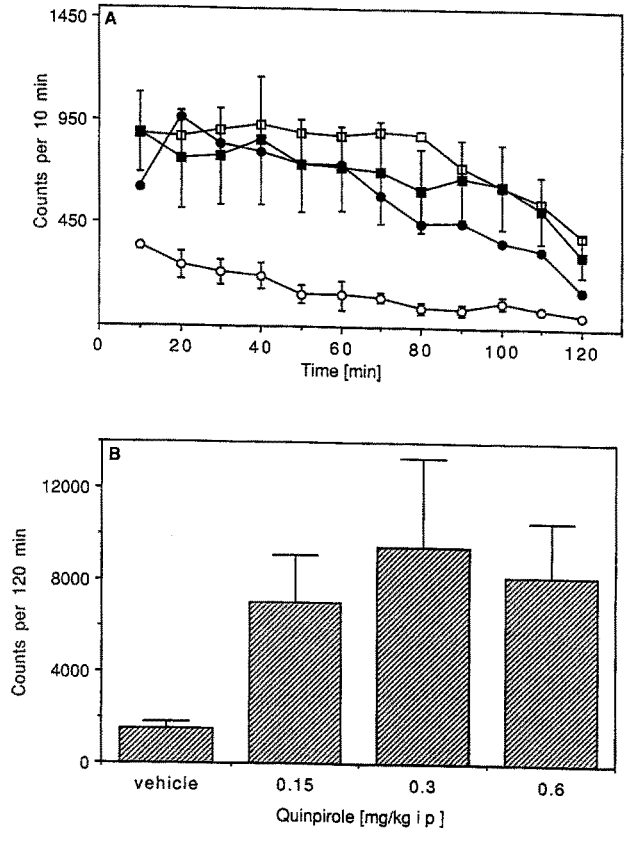
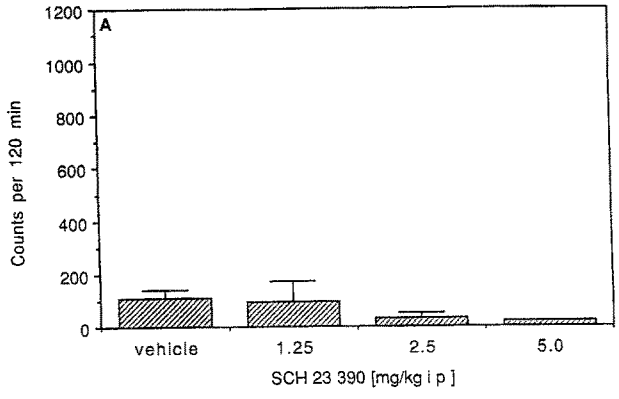


Fig. 2A, B. The effect of quinpirole on motor activity in MPTP-treated common marmosets. **A** Mean cumulative movement counts accumulated in 10 min intervals over 2 h (± SEM, $n = 4$) of MPTP-treated common marmosets pretreated with domperidone (2 mg/kg PO) 30 min prior to the intraperitoneal administration of vehicle (–○–) or 0.15 (–●–), 0.3 (–□–) or 0.6 (–■–) mg/kg quinpirole. *Error bars* for the lower doses of quinpirole are omitted for clarity but were in the same range as those shown for the vehicle and quinpirole 0.6 mg/kg IP treatment. **B** Mean cumulative movement counts accumulated over 2 h (± SEM, $n = 4$) for the data shown in **A**. Locomotor activity was increased by quinpirole ($P < 0.01$, Page test, ordered alternative: vehicle < 0.15 < 0.3 < 0.6 mg/kg quinpirole)

Effects of SCH 23390 and raclopride on motor behaviour

Administration of SCH 23390 (1.25–5.0 mg/kg IP) caused a dose related decrease in locomotor activity in MPTP-treated common marmosets (Fig. 3A) and a significant increase in motor disability (Table 1). The effect of SCH 23390 took the form of an inhibition of locomotor activity, reduced vigilance, catalepsy and complete akinesia in the highest dose tested (5 mg/kg IP). These effects were apparent within 10 min and lasted throughout the observation period.

Similarly, raclopride (0.31–5.0 mg/kg IP) decreased locomotor activity (Fig. 3B) and enhanced motor disability. The animals were cataleptic and akinetic for more than 120 min. Qualitatively there was no difference in the effects of SCH 23390 or raclopride although raclopride was more potent in augumenting disability (Table 1).



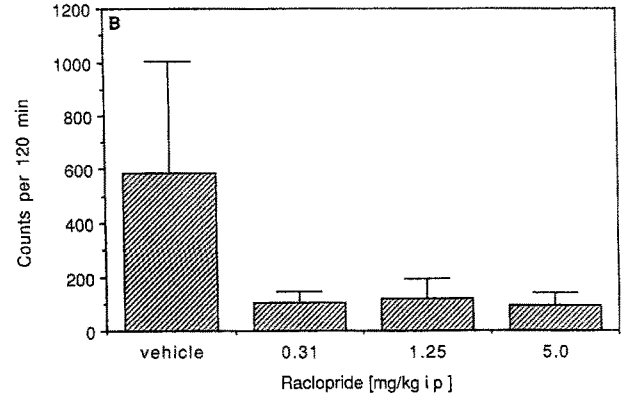


Fig. 3A, B. The effect of SCH 23390 or raclopride on motor activity in MPTP-treated common marmosets. **A** Mean cumulative movement counts accumulated over 2 h (± SEM, $n = 4$) of MPTP-treated common marmosets following IP administration of vehicle, 1.25, 2.5 or 5.0 mg/kg SCH 23390. Locomotor activity was decreased ($P < 0.05$, Page test, ordered alternative: vehicle > 1.25 > 2.5 > 5.0 mg/kg SCH 23 390). **B** Mean cumulative movement counts accumulated over 2 h (± SEM, $n = 4$) of MPTP-treated common marmosets following IP administration of vehicle, 0.31, 1.25 or 5.0 mg/kg raclopride. Locomotor activity was decreased ($P < 0.05$, Page test, ordered alternative: vehicle > 0.31 > 1.25 > 5.0 mg/kg raclopride)

Table 1. Disability scores prior to and at peak effect of various drug treatments

Treatment	Pre	Post (70 min)
SCH 23390 (5 mg/kg IP)	10.0 (3)	12.5 (2)*
Raclopride (5 mg/kg IP)	10.5 (4)	14.0 (3)**
SKF 38393 (5 mg/kg IP)	10.5 (3)	11.5 (2)
Quinpirole (0.3 mg/kg IP)	10.0 (3)	3.0 (1)*
+ SCH 23390 (5 mg/kg IP)	9.0 (4)	5.0 (9)
+ Raclopride (5 mg/kg IP)	6.5 (3)	15.5 (3)**
+ SKF 38393 (20 mg/kg IP)	10.5 (5)	2.5 (5)
Apomorphine (0.5 mg/kg SC)	9.5 (3)	2.5 (3)*
+ SCH 23390 (5 mg/kg IP)	9.5 (4)	14.0 (1)**
+ Raclopride (5 mg/kg IP)	11.0 (8)	12.5 (6)
+ SKF 38393 (5 mg/kg IP)	9.5 (5)	7.0 (8)

Behavioural scores are represented as the median scores of four animals per treatment group with the range in parenthesis. Statistical differences between pre and post treatment values were calculated by the Mann–Witney U test (*: $P < 0.05$, **: $P < 0.01$)

Effects of SCH 23390 or raclopride on motor behaviour induced by quinpirole or apomorphine

Quinpirole (0.3 mg/kg IP) caused an increase of locomotor activity (Fig. 2) and reversed motor deficits with the appearance of some stereotyped behaviour. The disability scores were significantly reduced (Table 1). Administration of SCH 23390 (1.25 –5.0 mg/kg IP) produced a slight but significant decrease in quinpirole–induced motor activity (Fig. 4A); and attenuated the effect of quinpirole disability scores at the highest dose of SCH 23390 tested (5.0 mg/kg IP). Subjectively the movements were rated to be slower and less well coordinated when compared to quinpirole alone. In contrast, raclopride (0.31–5.0 mg/kg) completely antagonized the improvement in motor function produced by quinpirole (Fig. 4A), resulting in reduced vigilance, complete akinesia and increased motor disability (Table1).

The stimulation of locomotor activity and improvement of motor deficits induced by apomorphine (0.5 mg/kg SC) were reversed by both SCH 23390 (1.25–5.0 mg/kg IP) and raclopride (0.31–5.0 mg/kg IP) (Fig. 4B). Administration of both antagonists augmented the MPTP-induced disability even in the presence of apomorphine although the effect of raclopride was not statistically significant (Table 1). Convulsions were seen in two animals following 0.5 mg/kg apomorphine IP. These were readily antagonized by diazepam IM. Both animals were excluded from analysis and replaced by two animals which had no such a response following identical treatments.

Effects of SKF 38393 on motor behaviour

Administration of SKF 38393 (1.25–5.0 mg/kg IP) caused a dose related decrease in locomotor activity in MPTP-treated common marmosets (Fig. 5) and a tendency to an increase in motor disability (Table 1). The effect of SKF 38393 took the form of an inhibition of locomotor activity, reduced vigilance in the highest dose tested (5 mg/kg

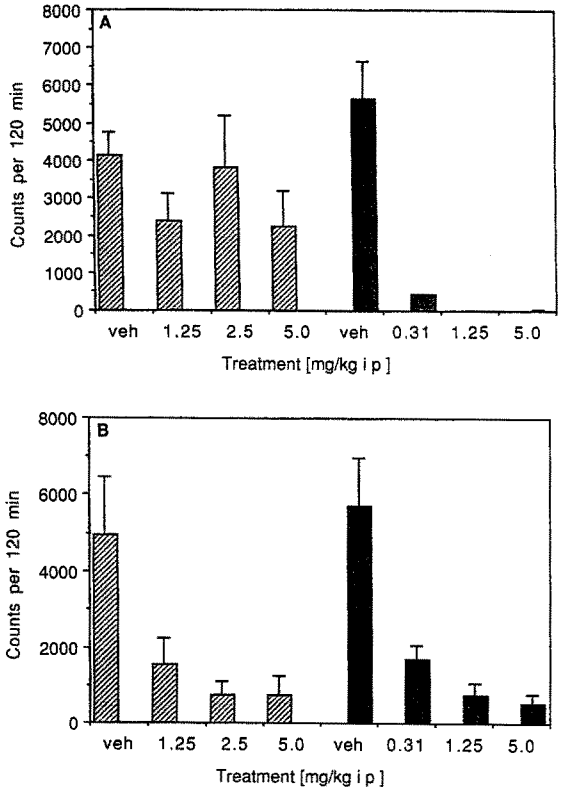


Fig. 4A, B. The effect of pretreatment with raclopride or SCH 23390 on locomotor activity induced by quinpirole or apomorphine in MPTP-treated common marmosets. Mean cumulative movement counts accumulated over 2 h (± SEM, $n = 4$) of MPTP-treated common marmosets pretreated with domperidone (2 mg/kg PO) 15 min prior to administration of vehicle or SCH 23390 (1.25, 2.5 or 5.0 mg/kg IP, *hatched bars*) or raclopride (0.31, 1.25 and 5.0 mg/kg IP, *grey bars*) and challenged with 0.3 mg/kg IP quinpirole (**A**) or 0.5 mg/kg SC apomorphine (**B**) 15 min later. Locomotor stimulation induced by quinpirole was decreased by raclopride ($P < 0.01$, Page test, ordered alternative: vehicle > 0.31 > 1.25 > 5.0 mg/kg raclopride) and Sch 23390 ($P < 0.05$, Page test, ordered alternative: vehicle > 1.25 > 2.5 > 5.0 mg/kg SCH 23 390). Locomotor stimulation induced by apomorphine was decreased by SCH 23390 ($P < 0.05$, Page test, ordered alternative: vehicle > 1.25 > 2.5 > 5.0 mg/kg SCH 23 390) and raclopride ($P < 0.01$, Page test, ordered alternative: vehicle > 0.31 > 1.25 > 5.0 mg/kg raclopride)

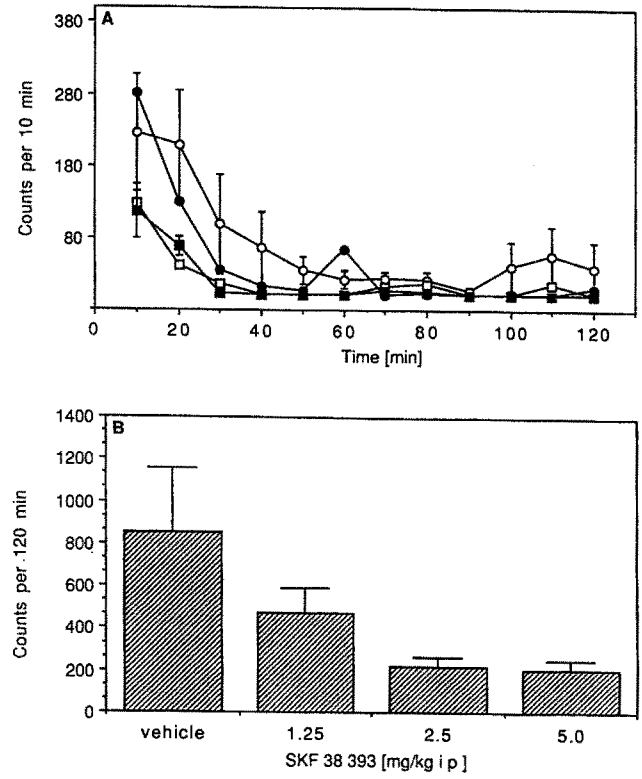


Fig. 5A, B. The effect of SKF 38393 on motor activity in MPTP-treated common marmosets. **A** Mean cumulative movement counts accumulated in 10 min intervals over 2 h (± SEM, $n = 4$) of MPTP-treated common marmosets following intraperitoneal administration of vehicle (-○-) or 1.25 (-●-), 2.5 (-□-) or 5.0 (-■-) mg/kg SKF 38393. *Error bars* for the lower doses of SKF 38393 are omitted for clarity but were in the same range as those shown for the vehicle and SKF 38 393 5.0 mg/kg IP treatment. **B** Mean cumulative movement counts accumulated over 2h (± SEM, $n = 4$) for the data shown in **A**. Locomotor activity was decreased by SKF 38393 ($P < 0.01$, Page test, ordered alternative: vehicle > 1.25 > 2.5 > 5.0 mg/kg SKF 38393)

IP). These effects were apparent within 10 min and lasted for up to 120 min. Animals did not exhibit stereotyped movements, purposeless chewing or other oral movements, dyskinesias, dystonia or increased grooming behaviour. No nausea or vomiting was observed.

Effects of quinpirole or apomorphine in combination with SKF 38393 on motor behaviour

Administration of quinpirole (0.3 mg/kg IP) reversed motor deficits (Table 1) and increased locomotor activity, with some stereotypies (Fig. 2). Administration of SKF 38393 (1.25–5 mg/kg IP) with quinpirole did not qualitatively or quantitatively alter the motor response to quinpirole (Fig. 6A) although the animals were somewhat less active. The incidence of stereotyped movements and grooming behaviour was not altered by SKF 38393. Dystonia, dyskinesia or purposeless chewing were not observed.

SKF 38393 when administered in higher doses (5.0–20.0 mg/kg IP) dose dependently antagonized the stimulation of locomotor activity induced by quinpirole (0.3 mg/kg IP) (Fig. 7). The effects of quinpirole on alertness and vigilance and overall on motor disability scores were not reversed by SKF 38393 (5–20 mg/kg) (Table 1). In contrast to the previous experiment, grooming and purposeless chewing were occasionally observed with 5.0 and 10.0 mg/kg SKF 38393 IP but these did not occur at the highest dose tested.

Administration of apomorphine (0.5 mg/kg IP) reversed motor deficits and induced an increase in locomotor activity and some stereotyped behaviour (Fig. 1). SKF 38393 qualitatively altered the response to apomorphine in a way that the animals were less active (Fig. 6B); disability scores were only marginally reduced mainly due to a failure of apomorphine to reverse the impairment of

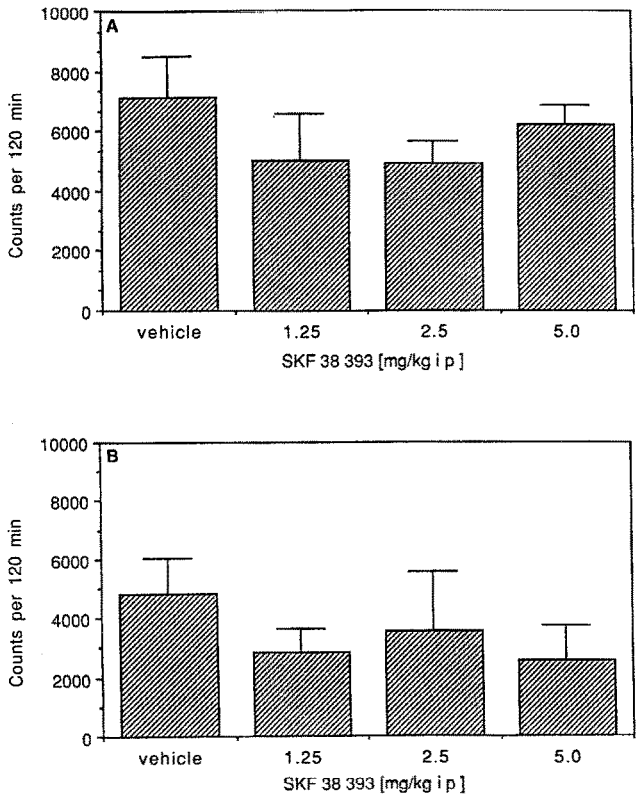


Fig. 6A, B. The effect of quinpirole or apomorphine in combination with SKF 38393 on motor activity in MPTP-treated common marmosets. **A** Mean cumulative movement counts accumulated over 2 h (± SEM, $n = 4$) of MPTP-treated common marmosets pretreated with domperidone (2 mg/kg PO) 30 min prior to administration of quinpirole (0.3 mg/kg IP) alone or in combination with 1.25, 2.5 or 5.0 mg/kg IP. SKF 38393 administered 15 min previously. Locomotor activity was not altered by SKF 38 393 administration. **B** Mean cumulative movement counts accumulated over 2 h (± SEM, $n = 4$) of MPTP-treated common marmosets pretreated with domperidone (2 mg/kg PO) 30 min prior to administration of apomorphine (0.5 mg/kg SC) alone or in combination with 1.25, 2.5 or 5.0 mg/kg IP SKF 38393 administered 15 min previously. Locomotor activity was decreased ($P < 0.01$, Page test, ordered alternative: vehicle > 1.25 > 2.5 > 5.0 mg/kg SKF 38393)

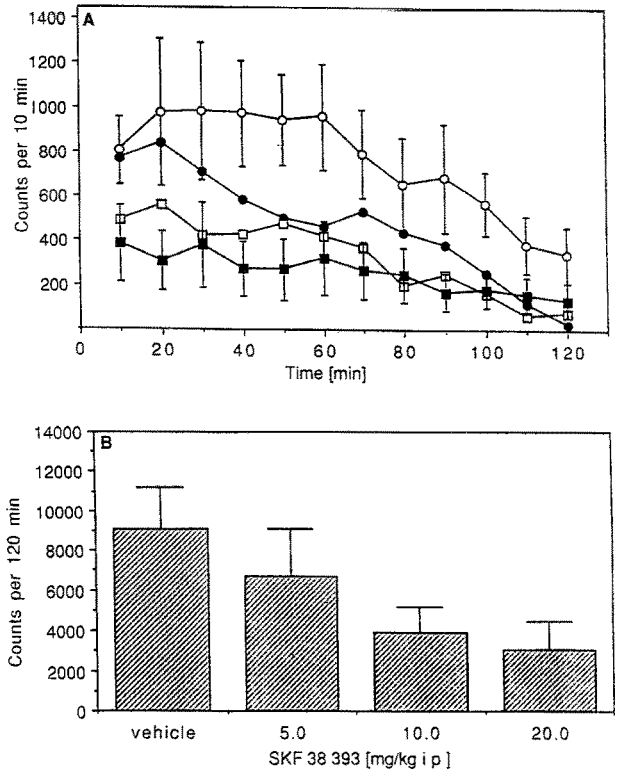


Fig. 7A, B. The effect of quinpirole in combination with SKF 38393 on motor activity in MPTP-treated common marmosets. **A** Mean cumulative movement counts accumulated in 10 min intervals over 2 h (± SEM, $n = 4$) of MPTP-treated common marmosets pretreated with domperidone (2 mg/kg PO) 30 min prior to administration of quinpirole (0.3 mg/kg IP) alone (–○–) or in combination with 5.0 (–●–), 10.0 (–□–), or 20.0 (–■–) mg/kg IP SKF 38393 administered 15 min previously. *Error bars* for the lower doses of SKF 38393 are omitted for clarity but were in the same range as those shown for the vehicle and SKF 38 393 20.0 mg/kg IP treatment. **B** Mean cumulative movement counts accumulated over 2 h (± SEM, $n = 4$) of MPTP-treated common marmosets pretreated with domperidone (2 mg/kg PO) 30 min prior to administration of quinpirole (0.3 mg/kg IP) alone or in combination with 5.0, 10.0 or 20.0 mg/kg IP SKF 38393 administered 15 min previously. Locomotor activity was decreased ($P < 0.01$, Page test, ordered alternative: vehicle > 5.0 > 10.0 > 20.0 mg/kg SKF 38393

coordination. The incidence of stereotyped movements as well as grooming behaviour was not altered by SKF 38393. Dystonia, dyskinesia or purposeless chewing were not observed.

Discussion

At this time the MPTP-treated monkey appears to be the most suitable pharmacological model of Parkinson's disease currently available. However, despite a vast literature on the function and interaction between D-1 and D-2 sites in rodents (for review see Clark and White 1987: LeWitt and Galloway 1987; Waddington and O'Boyle 1987), until now little is known of the role of these receptors in primates.

Both the D-2 agonist quinpirole and the D-1/D-2 agonist apomorphine reversed motor deficits and stimulated locomotor activity in MPTP-treated common marmosets. They also induced stereotyped behaviour when higher doses were administered. These effects are consistent with their effects in rats with 6-OHDA lesions, but contrary to what occurs in dopamine depleted mice where D-2 agonists alone do not stimulate motor activity without concurrent D-1 receptor stimulation. These data might suggest that in MPTP-treated marmoset there is sufficient endogenous dopamine remaining to produce D-1 tone.

Although basal locomotor activity was low following MPTP treatment, both SCH 23390 and raclopride depressed it further. This suggests that either both D-1 and D-2 systems control motor activity or that SCH 23390 is able to reduce it through a D-1/D-2 receptor interaction. The latter seems less likely, since the effects of quinpirole were potently and completely inhibited by raclopride but

only partially and inconsistently by SCH 23390. This suggests that the locomotor effect produced by quinpirole is mediated by D-2 receptors, and that D-1 systems have relatively little ability to manipulate this D-2 mediated behaviour. However, D-1 systems appear to be able to influence locomotor activity induced by the mixed D-1/D-2 agonist apomorphine. Thus, the ability of both SCH 23390 and raclopride to potently but incompletely block apomorphine-induced motor activity supports the concept that in MPTP-treated primates both D-1 and D-2 systems can initiate locomotor activity but independently of one another. Such a conclusion is in good agreement with data generated from rodent studies.

The concept of D-1 involvement in enhancing motor function is not supported by the actions of SKF 38393 in the MPTP-treated marmoset. In contrast to its effects in rodents, the D-1 agonist SKF 38393 did not stimulate locomotor activity in the MPTP-treated animals, but weakly inhibited movement and marginally increased the severity of the motor deficits. There was no evidence at any of the doses employed that SKF 38393 alone could induce novel behaviours or enhance the normal repertoire of behaviour of these animals, such as checking or grooming which have been described in rats (Molloy and Waddington 1987). Similarly, in combination with quinpirole there was a dose-related inhibition of motor activity by SKF 38393 although this effect was partial and was only obvious at the higher doses used (10 and 20 mg/kg). These effects are in agreement with previous findings in primates (Nomoto et al. 1985; Bédard and Boucher 1989) but in contrast with the ability of SKF 38393 to facilitate D-2 mediated motor behaviour in rodents (Braun and Chase 1986) However, the weakness of the effect observed with SKF 38393 suggests that, if this is due to a D-1 mediated action, there is only minor control of D-2 initiated motor activity by D-1 systems in this model. In contrast, SKF 38393 was more effective in inhibiting the actions of apomorphine which appear from the effects of SCH 23390 to be partially mediated through the D-1 system. So, there is no clear explanation for the effect of SKF 38393 in primate species but these may relate to differences in the metabolism of SKF 38393 in vivo leading to the formation of a dopamine antagonist metabolite (Breese et al. 1990) in primates and humans but which does not occur in rodents. Alternatively, the difference may relate to the partial agonist activity of SKF 38393 which could result in functional D-1 antagonist activity depending on the extent of endogenous dopamine tone in marmosets following MPTP treatment. Indeed, a recent report demonstrates that the ability of SKF 38393 to stimulate adenylate cyclase in primate brain is lower than in rat tissue (Pifl et al. 1991). However, another partial D-1 agonist CY 208–243 does produce a reversal of motor deficits and an increase in motor activity in MPTP treated common marmosets. This compound appears to be a typical D-1 agonist in rodent studies indistinguishable from SKF 38393 (Abbott et al. 1991 and own observations). Clarification of the role of the D-1 receptor will have to await the examination of a centrally active full D-1 agonist drug in primate species.

The present experiments therefore only relate to the actions of SKF 38393 which was employed as the standard D-1 agonist used to study the role of the D-1 receptor and its interaction with D-2 sites in rodents. Based on the effects of SKF 38393 and the other selective agents employed a number of tentative conclusions can be reached on the actions of D-1 and D-2 drugs in MPTP-treated marmosets compared to the rat. First, D-2 agonist drugs alone are capable of stimulating motor function without the need for enhanced D-1 receptor tone. Second, the administration of SKF 38393 neither led to the expression of novel D-1 mediated behaviour, or to the facilitation of D-2 mediated behaviour. Finally, there was some evidence of separate involvement of D-1 and D-2 systems in the production of motor behaviours based on the differential ability of SCH 23390 and raclopride to inhibit quinpirole and apomorphine mediated motor activation.

Table 2. Qualitative comparison of effects upon locomotor activity in normal and MPTP-treated common marmosets

Treatment	Normal	MPTP
Raclopride	− − −	− − −
SCH 23390	− − −	− − −
SKF38393	− −	− −
Quinpirole	+ + +	+ + +
+ Raclopride	− − −	− − −
+ SCH 23390	−	−
+ SKF 38393	−	0/− −[a]
Apomorphine	+ + +	+ + +
+ Raclopride	− − −	− − −
+ SCH 23390	0	− − −
+ SKF 38393	0	− −

[a]Inhibition following 5–20 mg/kg SKF 38393 IP

Stimulation of locomotor activity:	+ + +
Complete inhibition of locomotor activity:	− − −
Partial inhibition of locomotor activity:	− −
Weak inhibition of locomotor activity:	−
No effect:	0

A further important comparison to make is the differences in drug response in the normal marmoset compared to MPTP-treated animals (see Table 2). In normal marmosets both quinpirole and apomorphine stimulate motor activity but there was a major difference in the response to antagonists compared to MPTP-treated animals. In normal marmosets the effect of quinpirole was markedly reduced by raclopride and less so by SCH 23390 but this latter effect was more consistent than in MPTP-treated animals. In addition, in normal marmosets the effects of apomorphine were again inhibited by raclopride but, unlike the MPTP-treated animals, not by SCH 23390. These data would suggest that in the normal animals locomotor responses are largely mediated by D-2 systems but that there is some evidence for linkage between these receptor systems. Further, in normal marmosets, SKF 38393 again inhibited motor function but it is considerably more potent in inhibiting the actions of quinpirole than in MPTP-treated animals again suggesting some form of linkage.

The conclusion from our studies in both normal and MPTP-treated animals is that the nature of the relationship between D-1 and D-2 systems in marmosets is different from that occurring in rodents. However, it is the

primate model which appears predictive of drug action in man since SKF 38393 did not improve motor symptoms in Parkinson's disease when administered alone or in conjunction with L-dopa (Braun et al. 1987).

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