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Original investigations

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

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Abstract. In normal common marmosets administration of the D-1/D-2 agonist apomorphine or the selective D-2 agonist quinpirole caused a dose-dependent increase in motor activity and induced stereotyped behaviour. Both the selective D-2 antagonist raclopride and the selective D-1 antagonist SCH 23390 inhibited normal locomotor activity and induced catalepsy. Quinpirole- and apomorphine-induced motor activity were potently inhibited by pretreatment with raclopride. The effects of quinpirole, but not apomorphine, were weakly inhibited by SCH 23390. The selective D-1 partial agonist SKF 38393 decreased motor activity and did not induce grooming, oral movements or other behaviours. SKF 38393 inhibited motor activity induced by the administration of quinpirole but did not alter apomorphine-induced motor behaviour. Locomotor activity in normal common marmosets appears to be mediated mainly via D-2 systems. In contrast to rodents, administration of SKF 38393 does not induce behavioural activation and there does not appear to be a facilitating effect of D-1 systems on D-2 function in the normal common marmoset. However, the ability of both SKF 38393 and SCH 23390 to inhibit quinpirole locomotor activity suggests some interaction between D-1 and D-2 systems to occur in this species.

Key words: D-1 receptors – D-2 receptors – Functional interaction – Locomotor activity – Common marmosets

Brain dopamine receptors are divided into D-1 adenylate cyclase linked sites and D-2 sites (Kebabian and Calne 1979); some of the latter are negatively linked to adenylate cyclase (Stoof and Kebabian 1981). Studies in rodents have shown specific behaviours related to each receptor population, but also indicate a functional linkage between the D-1 and D-2 sites in the intact animal (for review see Clark and White 1987; Waddington and O'Boyle 1987). For example, the D-2 agonist quinpirole and the mixed D-1/D-2 agonist apomorphine, but not the D-1 agonist SKF 38393, are able to induce locomotor hyperactivity and stereotypies in rats and mice. The administration of SKF 38393, however, does cause an increase in non-stereotyped grooming, sniffing and vacuous chewing (Molloy and Waddington 1984, 1987). Also, administration of SKF 38393 potentiates the ability of D-2 agonists such as Ru 24296 (Mashurano and Waddington 1986) or bromocriptine (Jackson et al. 1988) to induce stereotypy. Stimulation of both D-1 and D-2 receptors appears necessary for the induction of some oral components of stereotypy such as licking and gnawing.

D-1 receptor activation in rodents may therefore play a facilitating or permissive role in D-2-mediated behaviours. A similar relationship can be observed using selective D-1 and D-2 antagonist drugs. Thus, administration to rats of the D-1 antagonist SCH 23390 will induce catalepsy identical to that produced by selective D-2 antagonist drugs (Hoffman and Beninger 1985). In addition, both D-1 antagonists and D-2 antagonist drugs, like raclopride (Ögren et al. 1986), can inhibit stereotypy induced by D-2 agonists.

In normal rodents, D-2 receptors also manipulate D-1-mediated behaviours, but in a complex manner. For example, the grooming produced by SKF 38393 can be inhibited by both D-1 and D-2 antagonists (Murray and Waddington 1989a). In contrast, vacuous chewing induced by SKF 38393 is potentiated by selective D-2 antagonists such as sulpiride, presumably by reducing D-2 inhibitory tone (Murray and Waddington 1989b).

All these data point clearly to a mutual interaction between D-1 and D-2 receptors which can influence motor behaviours in rodents. The functional outcome of manipulating brain dopamine receptors appears to depend on the resulting balance between D-1 and D-2 systems. Such results may be of importance in designing new drug therapies for both neurological and psychotic

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disease in man. However, it is unknown whether a similar relationship exists between D-1 and D-2 receptors in man or non-human primates, or whether selective D-1 or D-2 drugs produce similar behavioural effects to those observed in rodents. Consequently, in this investigation we have studied the effect of manipulating D-1 and D-2 receptors on the motor activity of a primate species, namely the common marmoset, seeking to undertake the same series of experiments on which the roles of D-1 and D-2 sites in motor behaviour in rats were established.

Materials and methods

Animals. Common marmosets *(Callithrix jacchus)* of either sex, weighing 280–420 g and aged 2–10 years at the beginning of the study, were used. 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.

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 acclimatise 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. Motor behaviour was rated qualitatively to determine the presenced or absence of stereotypy, co-ordination of movement, the degree of stimulation or inhibition, incidence of head twitches, wet dog shakes or grooming, oral movements and other obvious motor signs in 5-min intervals for 75 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 motor behaviour.

Drug solutions. The following compounds were employed: SKF 38393 (2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine hydrochloride; Research Biochemicals Inc., USA), SCH 23390 (2-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(3,4-g)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 (Janssen, 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 a few drops of ethanol (70%) and diluted to volume (2 ml/kg body weight) with 10% sucrose/water solution and administered by oral gavage.

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 experiments. Individual animals were maximally employed in two 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 (0.18, 0.75, 1.5 mg/kg or vehicle) or intraperitoneal (IP) administration of quinpirole (0.15, 0.3, 0.6 mg/kg or vehicle) to prevent nausea or vomiting. 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 (0.31, 1.25, 5.0 mg/kg IP or vehicle) or raclopride (1.25, 5.0, 20.0 mg/kg IP or vehicle) were examined in an identical manner, except that pretreatment with domperidone was not employed. To assess whether effects of SKF 38393 were affected by domperidone treatment, a group of four animals was treated with either vehicle or SKF 38393 (5 mg/kg IP) alone or pretreated with domperidone (2 mg/kg PO) 30 min prior to administration of SKF 38393 (5 mg/kg IP).

Interaction studies. Animals were pretreated with domperidone (2 mg/kg PO) 15 min prior to the administration of either SKF 38393 (1.25, 2.5, 5.0 mg/kg or vehicle IP) or SCH 23390 (0.31, 1.25, 5.0 mg/kg IP). A further 15 min later apomorphine (1.5 and 0.75 mg/kg SC combined with SKF 38393) or quinpirole (0.6 mg/kg IP) were administered. Raclopride (0.31, 1.25, 5.0 mg/kg IP or vehicle) was administered 15 min prior to the administration of apomorphine (1.5 mg/kg SC) or quinpirole (0.6 mg/kg IP).

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.

Results

Effects of apomorphine and quinpirole on motor behaviour

Administration of apomorphine (0.18–1.5 mg/kg SC) or quinpirole (0.15–0.6 mg/kg IP) dose-dependently increased locomotor activity in normal common marmosets (Figs. 1 and 2). The effect of apomorphine was maximal within 10 min of administration and lasted for about 60 min. Increasing doses did not alter the duration of action but increased the intensity of motor activity. Quinpirole produced a more sustained motor effect, particularly at the higher doses employed. The effect of both apomorphine and quinpirole was to produce an increase in motor behaviour which took the form of fast but controlled movements. In the highest doses tested both apomorphine and quinpirole produced some stereotyped movements in the form of repetitive grasping or body waving. Animals did not exhibit dyskinesia or dystonia and increased grooming was not observed.

Effects of raclopride and SCH 23390 on motor behaviour

Administration of raclopride (1.25–20 mg/kg IP) to normal common marmosets decreased locomotor activity in a dose-dependent manner (Fig. 3*A*). Animals became

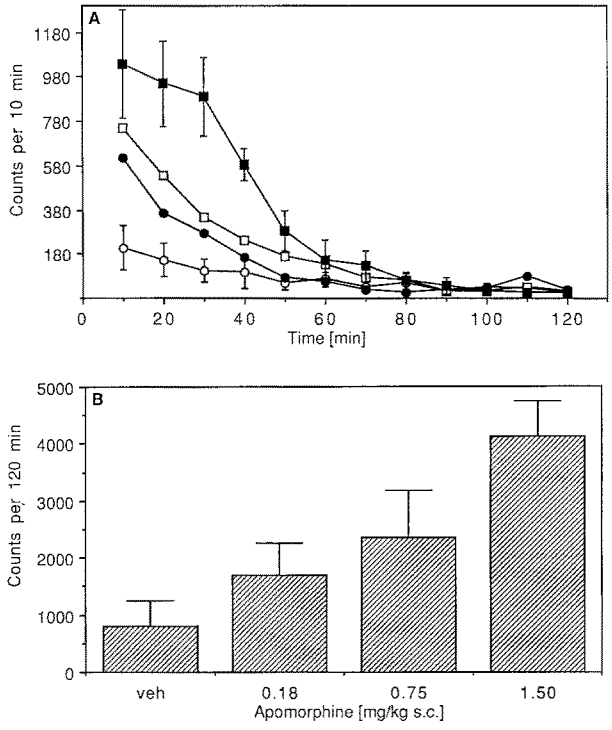

Fig. 1A, B. The effect of apomorphine on motor activity in normal common marmosets. **A** Mean cumulative movement counts accumulated in 10-min intervals over 2 h (±SEM, $n=4$) of common marmosets pretreated with domperidone (2 mg/kg PO) 30 min prior to the subcutaneous administration of vehicle (—○—) or 0.18 (—●—), 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 ($P<0.01$, Page test, ordered alternative: vehicle < 0.18 < 0.75 < 1.5 mg/kg apomorphine)

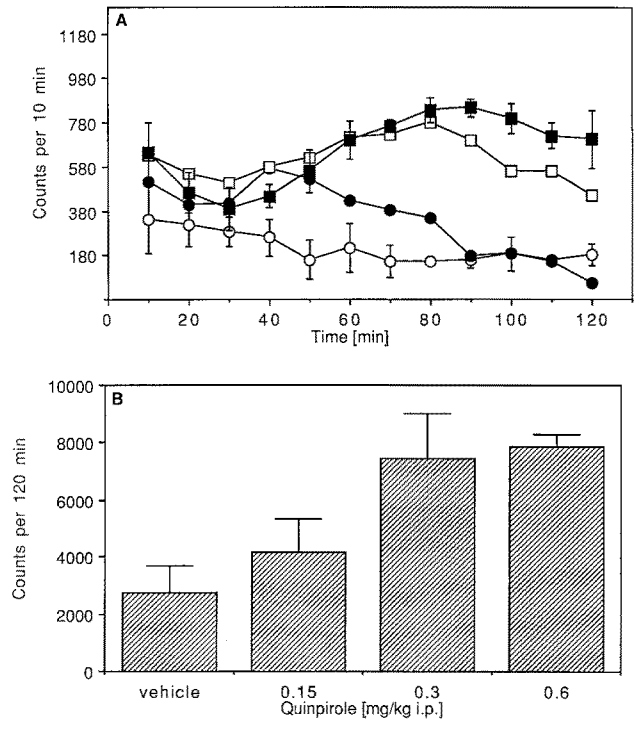

Fig. 2A, B. The effect of quinpirole on motor activity in normal common marmosets. **A** Mean cumulative movement counts accumulated in 10-min intervals over 2 h (±SEM, $n=4$) of common marmosets pretreated with domperidone (2 mg/kg PO) 30 min prior to the intraperitoneal administration of vehicle (—○—) 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 ($P<0.01$, Page test, ordered alternative: vehicle < 0.15 < 0.3 < 0.6 mg/kg quinpirole)

sedated, cataleptic and akinetic after the administration of raclopride. Similarly, SCH 23390 (0.31–5.0 mg/kg IP) also caused a dose-dependent decrease in locomotor activity (Fig. 3*B*). Again, the effects of SCH 23390 were qualitatively identical to those of raclopride.

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

Quinpirole-induced locomotor activity (0.6 mg/kg IP) as well as stereotyped movements were dose-dependently inhibited by pretreatment of animals with SCH 23390 (1.25–5.0 mg/kg IP) or raclopride (0.31–5.0 mg/kg IP) (Fig. 4*A*). The effects of raclopride and SCH 23390 were qualitatively similar, but raclopride had a much more marked effect and induced complete akinesia.

The increase in motor activity and stereotypies produced by apomorphine (1.5 mg/kg SC) was abolished by pretreatment with raclopride (0.31–5.0 mg/kg IP) (Fig. 4*B*). Indeed, treatment with raclopride produced complete akinesia and catalepsy. In contrast, the effect of apomorphine was not inhibited or qualitatively affected by the pretreatment with SCH 23390 (1.25–5.0 mg/kg IP).

Effects of SKF 38393 on motor behaviour

Administration of SKF 38393 (1.25–5.0 mg/kg SC) caused a dose-related decrease in locomotor activity in normal common marmosets (Fig. 5). The effect of SKF 38393 was apparent within 10 min and lasted for up to 120 min. The effect of SKF 38393 took the form of an inhibition of locomotor activity and reduced vigilance, but not catalepsy or complete akinesia. Animals did not exhibit stereotyped movements, purposeless chewing, dyskinesias, dystonia or grooming behaviour.

SKF 38393 (5 mg/kg IP) administered alone (mean counts in 2 h 929 ± 509) or in combination with domperidone (mean counts in 2 h 920 ± 415) reduced locomotor activity to the same extent compared to vehicle-treated animals (mean counts in 2 h 1942 ± 623) ($P < 0.05$). Again, the animals did not exhibit purposeless chewing, tongue protrusions or other oral movements. Retching, vomiting, sialorhea and other signs of gastrointestinal discomfort were not observed.

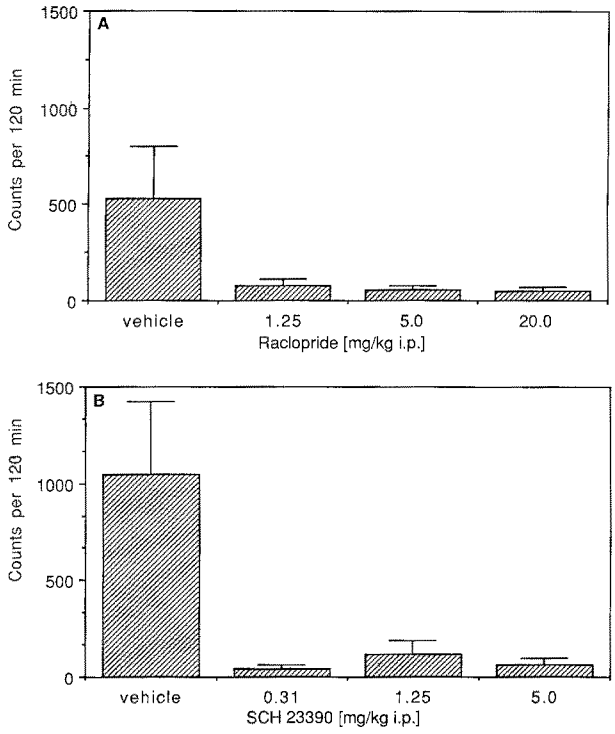

Fig. 3A, B. The effect of raclopride or SCH 23390 on motor activity in normal common marmosets. Mean cumulative movement counts accumulated over 2 h (±SEM, $n=4$) for **A** vehicle, 1.25, 5.0 and 20 mg/kg raclopride IP and **B** vehicle, 0.31, 1.25 and 5.0 mg/kg SCH 23390 IP. Locomotor activity was decreased by raclopride and SCH 23390 ($P<0.05$, Page test, ordered alternative: vehicle > 0.125 > 5.0 > 20 mg/kg raclopride; $P<0.05$, Page test ordered alternative: vehicle > 0.31 > 1.25 > 5.0 mg/kg SCH 23390

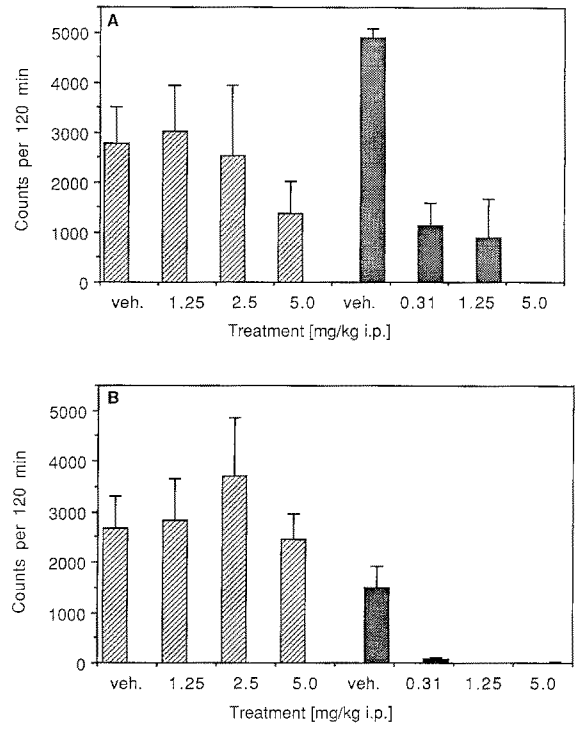

Fig. 4A, B. The effect of pretreatment with raclopride or SCH 23390 on locomotor activity induced by quinpirole or apomorphine in normal common marmosets. Mean cumulative movement counts accumulated over 2 h (±SEM, $n=4$) for animals pretreated with 2 mg/kg domperidone PO 15 min prior to administration of vehicle or SCH 23390 (1.25, 2.5 and 5.0 mg/kg IP, *hatched bars*) or raclopride (0.31, 1.25 and 5.0 mg/kg IP, *grey bars*) and challenged with 0.6 mg/kg quinpirole IP (**A**) or 1.5 mg/kg apomorphine SC (**B**) 15 min later. Locomotor stimulation induced by quinpirole was decreased by SCH 23390 ($P<0.05$ Page test, ordered alternative: vehicle > 1.25 > 2.5 > 5.0 mg/kg SCH 23390) and raclopride ($P<0.01$ Page test, ordered alternative: vehicle > 0.31 > 0.125 > 5.0 mg/kg raclopride). Locomotor stimulation induced by apomorphine was decreased by raclopride ($P<0.01$, Page test, ordered alternative: vehicle > 1.25 > 2.5 > 5.0 mg/kg raclopride)

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

Administration of quinpirole (0.6 mg/kg IP) induced an increase in locomotor activity (Fig. 6*A*). Stereotypies occasionally occurred in the group treated with quinpirole alone. Pretreatment with SKF 38393 (1.25–5.0 mg/kg IP) dose-dependently inhibited the effect of quinpirole. No stereotypies, dyskinesias, dystonia, purposeless chewing or grooming was observed.

Administration of apomorphine (1.5 and 0.75 mg/kg SC) also induced an increase in locomotor activity (Fig. 6*B*), but again in animals treated with 1.5 mg/kg apomorphine alone stereotypies were seen occasionally. Prior administration of SKF 38393 (1.25–5.0 mg/kg IP) did not alter the locomotor response produced by either dose of apomorphine, but SKF 38393 seemed to suppress the occurrence of stereotyped movements. Grooming was seen occasionally, but purposeless chewing or other abnormal movements were not observed.

Discussion

The evidence available from rodent experiments clearly points to a reciprocal interaction between D-1 and D-2 systems in the initiation and control of motor function. In particular, in normal animals D-1 systems act to facilitate D-2 initiated motor behaviours. In the present study we have investigated using the same selective D-1 and D-2 drug combinations whether a similar interaction occurs in a non-human primate species, namely the common marmoset.

Administration of the mixed D-1/D-2 agonist apomorphine or the selective D-2 agonist quinpirole caused an increase in controlled motor activity, increased checking movement of the head and in high doses stereotyped movements of the limbs or the whole body. These effects are identical to those previously reported in normal common marmosets treated with apomorphine (Ridley et al. 1980) and other dopamine agonist drugs (Nomoto et al. 1987). The behavioural changes also correspond to the effect of D-2 and D-1/D-2 agonists reported in rats, namely, increased locomotor activity and stereotypy.

The administration of the D-2 antagonist raclopride or the D-1 antagonist SCH 23390 produced a similar effect on motor behaviour in normal monkeys. Both drugs caused a potent inhibition of all components of locomotor activity and in high doses catalepsy. This

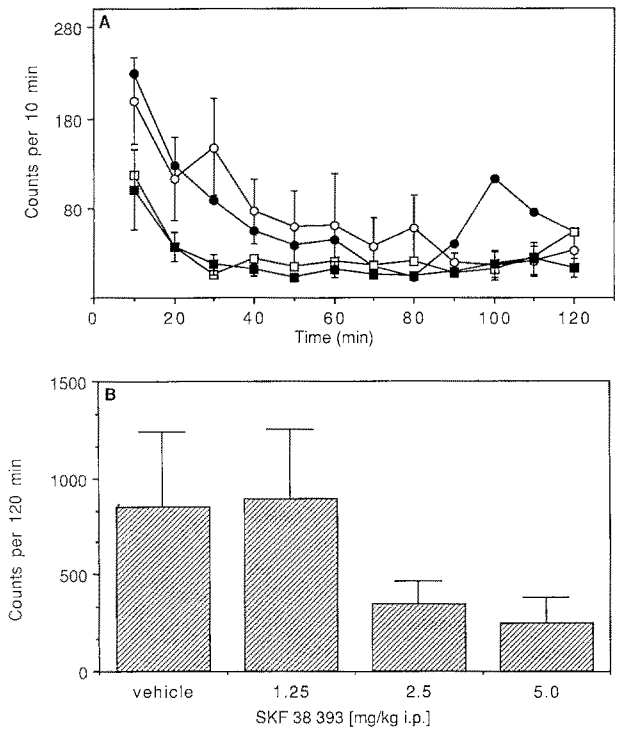

Fig. 5A, B. The effect of SKF 38393 on locomotor activity in normal common marmosets. **A** Mean cumulative movement counts accumulated in 10-min intervals over 2 h (±SEM, $n=4$) of common marmosets following the intraperitoneal administration of vehicle (—○—) or 1.25 (—●—), 2.5 (—□—) or 5.0 (—■—) mg/kg 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 38393 5.0 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 decreased ($P<0.01$, Page test, ordered alternative: vehicle > 1.25 > 2.5 > 5.0 mg/kg SKF 38393)

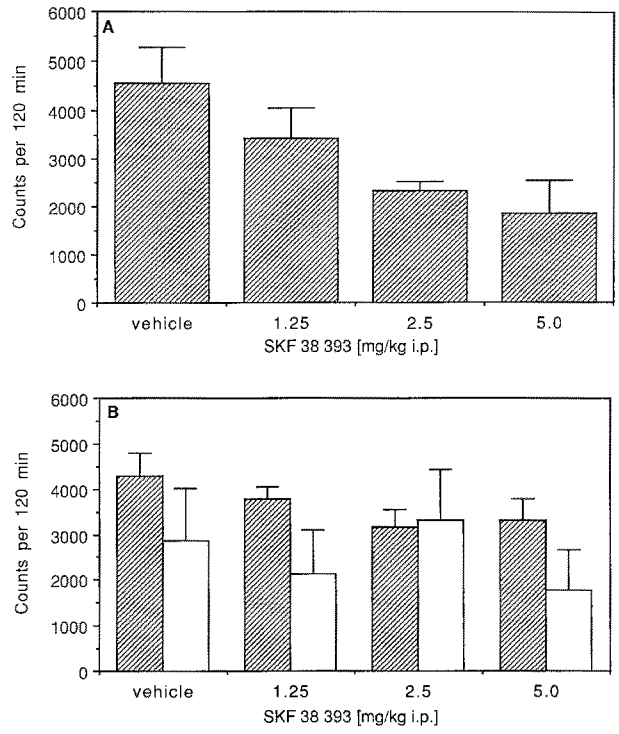

Fig. 6A, B. The effect of apomorphine or quinpirole in combination with SKF 38393 on motor behaviour in normal comon marmosets. **A** Mean cumulative movement counts accumulated over 2 h (±SEM, $n=4$) of common marmosets pretreated with domperidone (2 mg/kg PO) 30 min prior to administration of quinpirole (0.6 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 decreased ($P<0.05$, Page test, ordered alternative: quinpirole > 1.25 > 2.5 > 5.0 mg/kg SKF 38393). **B** Mean cumulative movement counts accumulated over 2 h (±SEM, $n=4$) of common marmosets pretreated with domperidone (2 mg/kg PO) 30 min prior to administration of apomorphine (1.5 mg/kg SC, *hatched bars* or 0.75 mg/kg SC, *open bars*) 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 38393 administration

parallels the ability of both D-1 and D-2 antagonists to inhibit spontaneous locomotor activity and to induce catalepsy in rodents (Christensen et al. 1984). The data support a role for both D-1 and D-2 receptors in mediating basal motor activity in common marmosets.

Both SCH 23390 and raclopride inhibited the motor activity produced by quinpirole but the effect of raclopride was potent and that of SCH 23390 partial and weak. This would suggest a predominant effect of the D-2 system in producing locomotor activity. Indeed, the actions of apomorphine were potently and totally blocked by raclopride but there was no effect of SCH 23390. It therefore appears that D-1 systems play only a minor role in the initiation and control of locomotion induced by these dopamine agonists in normal common marmosets.

In contrast to apomorphine and quinpirole, the administration of the selective D-1 partial agonist SKF 38393 did not stimulate motor behaviour. Rather, the drug caused a partial inhibition of normal motor function without any qualitative changes in its components or the induction of catalepsy. These findings clearly contrast with the effects of SKF 38393 in rats, where increased grooming but no inhibition of locomotor activity is observed (Dall'Olio et al. 1988). It is unlikely that gastrointestinal side effects, which have been reported after higher doses (10 or 30 mg/kg SC) of SKF 38393 in squirrel monkeys (Rupniak et al. 1991), are responsible for the reduction of locomotor activity seen in our experiments. This assumption is based on the observation that the degree of inhibition of locomotor activity as well as the behaviour were not altered by the peripheral D-2 antagonist domperidone. It thus appears that using SKF 38393 to act on D-1 receptors in normal primates results in effects which differ from those in rodents and which do not cause a behavioural activation.

The differences between the effects of D-1 agonists in primates and in rodents were emphasised by the effects of combinations of SKF 38393 with quinpirole or apomorphine. SKF 38393 inhibited the stimulation of motor behaviour produced by quinpirole. This contrasts with the ability of SKF 38393 to enhance and facilitate distinct components of motor activity and stereotypy produced by the stimulation of D-2 receptors in rodents. It is in agreement with the ability of SKF 38393 to inhibit locomotor activity (Nomoto et al. 1985, 1988) and rotational behaviour (Barone et al. 1987) in a variety of

primate species exposed to the selective nigral neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Interestingly, administration of SKF 38393 did not qualitatively or quantitatively alter the motor response to apomorphine. The reasons for this are not clear, but may relate to the potent D-1 receptor agonist activity of apomorphine itself.

On the basis of these results with SKF 38393, it appears that in primate species D-1 receptor activation does not initiate motor behaviour and does not facilitate behaviours induced by D-2 receptor stimulation. Rather, D-1 receptor activation by SKF 38393 serves to depress spontaneous motor behaviour and that induced by the D-2 agonist quinpirole in normal common marmoset.

The administration of D-1 and D-2 agonist and antagonist drugs to common marmosets causes distinct behavioural effects, but these do not completely parallel those observed in rodents. A major difference lies in the effects of SKF 38393 alone and in combination with D-2 agonists. The present results can only be interpreted in terms of the pharmacological actions of SKF 38393, although it is feasible that the drug might exert identical pharmacological effects in different species but which resulted in the initiation of distinct behavioural responses. It may be that in primates SKF 38393 does not exert a selective D-1 dopamine agonist activity. SKF 38393 is a partial D-1 agonist and this may alter the response observed in primates and rodent species, since a high degree of endogenous D-1 tone might result in an antagonist action. Alternatively, SKF 38393 might be metabolised to a D-1 or D-2 antagonist compound in vivo. However, since its behavioural effects were distinct from both those of SCH 23390 and raclopride in not inducing catalepsy, such explanations appear less likely. Certainly in man SKF 38393 does not produce the antiparkinsonian activity that its D-1 agonist effect in rodents would suggest (Braun et al. 1987). The uncertainty over SKF 38393 can only be resolved when further selective D-1 agonists become available. However, in line with this concept are the results obtained with the benzergoline CY 208–243, a compound which has also been characterised as a D-1 receptor partial agonist (Foote et al. 1988). Locomotor activity of the normal common marmosets is stimulated by this drug (Temlett et al. 1988a) and some patients with Parkinson's disease showed improvement (Temlett et al. 1988b). However, at this time it is not known whether the actions of SKF 38393 or CY 208–243 reflect the true effect of D-1 agonist stimulation in a primate species. Until a centrally active full D-1 agonist drug is available this situation will not be resolved.

An alternative explanation may involve a different population of D-1 receptors and the extent to which these are linked to D-2 receptors. There have already been suggestions for different D-1 receptor populations from in vitro ligand binding studies in rats (Wamsley et al. 1989). It remains unresolved whether the behavioural interaction between D-1 and D-2 receptors involves sites located on the same neurones or indeed whether these are even in the same brain area.

Overall, and based on the use of SKF 38393, there does not appear to be a behavioural activation occurring via D-1 sites or a facilitating effect of D-1 systems on D-2 function in the normal common marmoset. However, the weak inhibitory effects of both SKF 38393 and SCH 23390 on D-2 receptor-mediated effects might suggest some linkage between D-1 and D-2 systems. Although no absolute conclusions can be drawn at present on the role of D-1 systems in primates, it is clear that the effects observed in rodents cannot be considered predictive of events occurring in higher species.

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