Psychopharmacology (1995) 117 : 287–297

ORIGINAL INVESTIGATION

Kanna K. Gnanalingham · A. Jackie Hunter
Peter Jenner · C. David Marsden

The differential behavioural effects of benzazepine D_1 dopamine agonists with varying efficacies, co-administered with quinpirole in primate and rodent models of Parkinson's disease.

Received: 20 January 1994 / Final version: 10 June 1994

Abstract The effects of co-administration of quinpirole with benzazepine D_1 dopamine (DA) agonists possessing full/supramaximal (SKF 80723 and SKF 82958), partial (SKF 38393 and SKF 75670) and no efficacies (SKF 83959) in stimulating adenylate cyclase (AC) were investigated in rodent and primate models of Parkinson's disease (PD). In rats with a unilateral 6-hydroxydopamine (6-OHDA) lesion of the medial forebrain bundle, co-administration of SKF 38393 (7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine), SKF 75670 (3-CH_3 analogue), SKF 80723 (6-Br analogue), SKF 83959 (6-Cl, 3-CH_3, 3′-CH_3 analogue) and SKF 82958 (6-Cl, 3-C_3H_5 analogue) strongly potentiated the contralateral circling induced by quinpirole. In MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) treated common marmosets, administration of quinpirole alone increased locomotor activity and reversed motor deficits. Grooming and oral activity were unaltered. Co-administration of SKF 38393 and SKF 75670 inhibited the quinpirole-induced changes in locomotor activity and motor disability. The combined treatment of SKF 80723 or SKF 82958 with quinpirole had no overall effect on locomotor activity or motor disability. In contrast, SKF 83959 extended the duration of the quinpirole-induced increase in locomotor activity with corresponding decreases in motor disability. Co-administration of high doses of SKF 82958 and more especially SKF 83959 and SKF 80723, with quinpirole induced hyperexcitability and seizures. Oral activity and grooming were unaltered following the co-administration of benzazepine derivatives with quinpirole. The ability of some benzazepine D_1 DA agonists to prolong the antiparkinsonian effects of quinpirole in the MPTP-treated marmoset may indicate a role for certain D_1 DA agonists in the clinical treatment of PD. In general, the behavioural responses to the combined administration of benzazepines with quinpirole in the 6-OHDA lesioned rat and more especially the MPTP-treated marmoset failed to correlate with their ability to stimulate AC. These observations further implicate a behavioural role for D_1 DA receptors not linked to AC.

Key words D_1 dopamine agonists · Quinpirole · MPTP Marmoset · Rat · 6-Hydroxydopamine · Behaviour

Kanna K. Gnanalingham · Peter Jenner (✉)
Parkinson's Disease Society Experimental Research Laboratories, Pharmacology Group, Biomedical Sciences Division, King's College London, U.K.

A. Jackie Hunter
SmithKline Beecham Pharmaceuticals, Harlow, U.K.

C. David Marsden
University Department of Clinical Neurology, National Hospital for Neurology, Queen Square, London, U.K.

Introduction

The antiparkinsonian effects of DA agonists in Parkinson's disease (PD) has been largely attributed to D_2 DA receptor stimulation. However, studies in animal models of PD indicate that selective D_1 DA agonists not only have antiparkinsonian effects but also potentiate the effects of selective D_2 DA agonists. Thus, in rats with unilateral 6-OHDA lesions of the nigrostriatal tract, a classical rodent model of PD (Ungerstedt and Arbuthnott 1970), both D_1 and D_2 DA agonists are capable of independently inducing contralateral circling behaviour (Setler et al. 1978; Gower and Marriott 1982; Arnt and Hyttel 1984). Moreover, the combined administration of D_1 and D_2 DA agonists has a powerful synergistic effect on circling (Robertson and Robertson, 1986; Rouillard and Bedard, 1988). Similar effects are seen in bilaterally DA depleted rats (bilateral 6-OHDA lesions or reserpine pretreated animals) (Arnt 1985a, b).

Although, the majority of these studies have utilised the archetypal benzazepine D_1 DA agonist, SKF 38393, other D_1 DA agonists of the benzazepine, isochroman (A77636 and A68930), indolophenanthridine (CY 208–243) and benzophenanthridine (dihydrexidine) classes are also able induce contralateral circling in the 6-OHDA lesioned rat (Weinstock et al. 1985, 1986; Markstein et al. 1988; Lovenberg et al. 1989; DeNinno et al. 1991; Arnt et al. 1992; Kebabian et al. 1992). Interestingly, in this respect similar behavioural responses were seen with benzazepine D_1 DA agonists possessing full/supramaximal (SKF 81297, SKF 80723 and SKF 82958), partial (SKF 38393 and SKF 75670) and no efficacies (SKF 83959) in stimulating AC activity (Weinstock et al. 1985, 1986; O'Boyle et al. 1989; Arnt et al. 1992; Izenwasser and Katz 1993; Gnanalingham et al., submitted). This may indicate a lack of correlation between the behavioural effects of D_1 DA agonists and their ability to stimulate AC activity, as also observed in other experimental paradigms (Arnt et al. 1988, 1992; Murray and Waddington 1989; Johansen et al. 1991; Daly and Waddington 1992; Downes and Waddington 1993). Whether these D_1 DA agonists also synergistically interact with D_2 DA agonists in this rodent model is not known.

In contrast to rodent studies, behavioural interactions between D_1 and D_2 DA receptor stimulation are less well studied in primate models of PD. Mixed D_1/D_2 (e.g. apomorphine) and selective D_2 DA agonists (e.g. PHNO, bromocriptine and quinpirole) exert pronounced antiparkinsonian effects in MPTP-treated monkeys (Nomoto et al. 1985; Bedard and Boucher 1989; Close et al. 1990; Loschmann et al. 1991, 1992; Domino and Sheng 1993). However, SKF 38393 inhibits locomotor activity in this primate model and is also clinically ineffective (Close et al. 1985, 1990; Nomoto et al. 1985; Braun et al. 1987; Bedard and Boucher 1989; Boyce et al. 1990; Loschmann et al. 1991, 1992). Furthermore, SKF 38393 inhibits the locomotor stimulatory effects of quinpirole in the MPTP-treated monkey (Nomoto et al. 1988; Bedard and Boucher 1989; Loschmann et al. 1991, 1992). A similar lack of behavioural synergism has been reported between the benzazepine D_1 DA agonist, SKF 82958 and PHNO (Rupniak et al. 1992). Evidently, behavioural interactions between D_1 and D_2 DA receptor stimulation in the primate may differ from that in the rodent. However, this apparent interspecies difference may also reflect the relative ineffectiveness of both SKF 38393 and SKF 82958 to stimulate locomotor activity in the primate (Loschmann et al. 1992; Rupniak et al. 1992).

In a recent study, we observed that the benzazepine D_1 DA agonists SKF 82958 and more especially SKF 83959 and SKF 80723 exerted pronounced antiparkinsonian effects in the MPTP-treated marmoset (Gnanalingham et al. 1994). SKF 75670, instead mimicked SKF 38393 in worsening the motor deficits in MPTP-treated marmosets. We now report on the behavioural effects of the combined administration of benzazepine D_1 DA agonists with full/supramaximal (SKF 80723 and SKF 82958), partial (SKF 38393, and SKF 75670) and no (SKF 83959) AC efficacies, with quinpirole in the 6-OHDA lesioned rat and in the MPTP-treated common marmoset.

Materials and methods

The studies involving both primates and rodents were carried out in accordance with the requirements of Home Office licences PPL 70/01347 and PPL 70/1348, respectively.

6-Hydroxydopamine lesions in rats

Male Wistar rats (250–350 g) housed in groups of six with free access to food and water, under a 12-h light/dark cycle were used in this study. Thirty minutes prior to surgery, the rats were injected with a preoperative mixture of 15 mg/kg desipramine hydrochloride (noradrenaline uptake blocker) and 5 mg/kg pargyline hydrochloride (IP; monoamine oxidase inhibitor). Under sodium pentobarbitone anaesthesia (60 mg/kg; IP), the animals were positioned in a Kopf stereotaxic frame with the incisor bar at 4.5–5.2 mm below the level of the interaural line. Unilateral intracranial infusions of 6-OHDA hydrobromide (2 mg/ml in 0.9% saline with 1 mg/ml ascorbic acid as an antioxidant; total volume, 4.0 µl at a rate of 0.5 µl/min) were made into the right medial forebrain bundle, through a stainless steel cannula (30 gauge), connected to a Hamilton syringe (10 µl). The stereotaxic co-ordinates used were 1.2 mm posterior to the bregma, 9 mm ventral to the skull surface and 1.5 mm lateral to the midline (Pellegrino et al. 1979). Following delivery, the needle was left in place for a further 4–5 min and then withdrawn. The wound was sutured and the animals were treated with ampicillin (50 mg/kg as a suspension in 0.9% saline; SC).

Behavioural studies in 6-OHDA lesioned rats

Two weeks after surgery, the extent of the 6-OHDA lesion was evaluated by measuring the circling response to apomorphine hydrochloride (0.5 mg/kg in 0.9% sterile saline with 1 mg/kg ascorbic acid as an anti-oxidant; IP) in automated rotometer cages (25 × 23 × 38 cm). The animals were allowed to habituate in the test environment for at least 20 min. The rotometer was programmed to count the number of contralateral turns made every 5 min and rats demonstrating a peak circling rate of 20 or more turns per 5 min were used in subsequent studies.

Three weeks post-lesion, behavioural studies were commenced with various selective D_1 DA agonists (0.75 mg/kg, SKF 38393; 0.5 mg/kg, SKF 80723; 0.2 mg/kg, SKF 83959; 0.5 mg/kg, SKF 82958, and 0.2 mg/kg, SKF 75670 in 1–5% DMSO and 0.9% saline vehicle, except SKF 82958, which was dissolved in 5% DMSO and deionised H_2O), either alone or in combination with quinpirole (0.01 mg/kg in 0.9% saline; IP). In preliminary studies, these doses of benzazepine analogues and quinpirole were the threshold doses needed to induce contralateral turning (Gnanalingham et al. submitted; see also Arnt et al. 1992). The rotometer was programmed to count the number of contralateral turns made every 5 min, for a period of 2.5 h. At the end of this period the animals were taken out of the rotometers and observed in their home cages. At least 4 days separated successive drug challenges, which were allocated in a random fashion.

MPTP treatment of common marmosets

MPTP hydrochloride was administered to ten common marmosets (*Callithrix jacchus*; 4–8 years of age; both male and female) over a 5 to 7-day period (total dose 8–12 mg/kg in 0.9% sterile saline; SC). At the end of the treatment period all animals became hypo/bradykinetic, hypophonic and had developed rigidity (of trunk, limbs and tail). Tremor was less apparent. Although there was some recovery in these behavioural deficits over the following weeks, the MPTP-treated marmosets remained grossly parkinsonian in comparison to untreated animals, at the time of behavioural testing.

Behavioural assessments

The behavioural studies were carried out in automated locomotor activity monitoring cages as described previously (Loschmann et al. 1992, with minor modifications). The monitoring cages were programmed to count the number of interruptions of the photocell beams, every 5 min, for 3 h (starting from the time of administration of the D_1 DA agonist or vehicle).

A number of behavioural parameters were also observer rated every 10 min for a period of 1 h (starting 15 min after the challenge with the D_1 DA agonist): alertness (0 – normal; 1 – reduced from normal; 2 – sleepy), checking movement (0 – present; 1 – reduced from normal; 2 – absent), posture (0 – normal; 1 – abnormal trunk; 2 – abnormal trunk and tail; 3 – abnormal trunk, tail and limbs; 4 – as for 3 with severe flexion of the body), balance/co-ordination (0 – normal; 1 – impaired; 2 – unstable; 3 – falls), reactions (0 – normal; 1 – reduced from normal; 2 – slow; 3 – absent) and vocalisation (0 – normal; 1 – reduced from normal; 2 – absent). Both abnormal oral movements (consisting of abnormal tongue protrusions and vacuous chewing: 0 – absent; 1 – occasional; 2 – frequent) and general grooming of face and body (0 – absent; 1 – occasional; 2 – intermittent and brief episodes; 3 – frequent and intense) were also observer rated. For each animal, the individual scores over the 1-h period were summed to derive an index for disability, oral activity and grooming (maximum scores of 96, 12 and 18 per 60 min, respectively).

Studies with DA agonists

In order to assess the validity of the primate model, approximately 1 month after the last dose of MPTP, all MPTP-treated marmosets were initially challenged with 0.4 mg/kg quinpirole (in 0.9% saline; IP), administered 30 min after pretreatment with domperidone (2 mg/kg; periorally; suspended in a few drops of 70% ethanol and made up to volume in 10% sucrose solution).

A week later, the animals were placed in the monitoring cages and following a habituation period of at least 30 min, they received quinpirole (0.1 mg/kg in 0.9% saline; IP, given 30 min after 2 mg/kg domperidone). A further 20 mins later, the animals received either vehicle or selective D_1 DA agonist treatment (7.5 and 15 mg/kg, SKF 38393; 0.125–1.0 mg/kg, SKF 80723; 0.25–1.0 mg/kg, SKF 83959; 2.0–10.0 mg/kg, SKF 82958 and 2.5–5.0 mg/kg, SKF 75670). In preliminary studies, a dose of 0.1 mg/kg quinpirole was found to be the threshold dose needed to induce behavioural changes in MPTP-treated marmosets. Lower doses of quinpirole induced sedation that was not reversed by the co-administration of benzazepine derivatives (data not shown; see also Loschmann et al. 1992).

The benzazepines were administered intraperitoneally (2 ml/kg), in approximately 1–5% DMSO and 0.9% saline vehicle except SKF 82958 which was dissolved in 5% DMSO and deionised water. At least 1 week separated successive drug challenges, which were allocated in a random fashion. A minimum period of 4 weeks was allowed between successive studies. Diazepam (approximately 1.7 mg/kg; IM) was administered, immediately to animals in which seizures were induced by the combined D_1 and D_2 DA agonist treatments.

Statistics

The data for locomotor activity in the marmosets and circling in the rodents was analysed by ANOVA and Duncan's multiple range test. The behavioural scores were analysed by Kruskal Wallis and Mann-Whitney non-parametric tests.

Materials

Materials used were supplied by the following companies: desipramine hydrochloride, apomorphine hydrochloride, pargyline hydrochloride and 6-OHDA hydrobromide from Sigma, UK; SKF 38393 hydrochloride (MW = 292) and MPTP hydrochloride from Research Biochemicals; SKF 80723 (MW = 415), SKF 83959 (MW = 399), SKF 82958 (MW = 411) (all hydrobromide salts) and SKF 75670 hydrochloride (MW = 309) were prepared as described previously (Weinstock et al. 1985, 1986; greater than 95% purity was achieved) by Dr. D.D. Erol at the Department of Pharmacy, King's College, London. The following drugs were gifts from the respective sources: quinpirole hydrochloride from Eli Lilly, USA and domperidone from Janssen, Belgium. All other chemicals were obtained from standard commercial sources.

Results

Behavioural effects in 6-OHDA lesioned rats

Administration of quinpirole (0.01 mg/kg) alone induced a periodic and low rate of circling (Fig. 1).Co-administration of the benzazepine derivatives potentiated the rate of contraversive circling induced by quinpirole (0.01 mg/kg) (Table 1). The cumulative contralateral turns per 150 min following co-administration was greater than the sum of circling induced by either agonist administered alone. The rank order of potency was SKF 38393 $\gg$ SKF 82958 > SKF 80723 = SKF 83959 = SKF 75670 (Table 1).

All benzazepine derivatives increased both the duration and the peak rate of circling produced by quinpirole in 6-OHDA lesioned rats (Fig. 1). The peak rate of circling was markedly enhanced following the co-administration of quinpirole with SKF 38393 and SKF 82958 (Fig. 1). The duration of response was particularly enhanced in animals given quinpirole and SKF 38393 (the animals continued to circle for over 6 h), SKF 80723 (the animals continued to circle for approximately 3.5 h) or SKF 83959 (the animals were seen to circle for over 8 h compared to 3–4 h following the administration of SKF 83959 alone). Co-adminis-tration of quinpirole and SKF 82958 potentiatedcircling at the start (10–50 min) and at the end (100–200 min approximately) and the animals exhibited a lower rate of circling in the period in between (Fig. 1).

Table 1 The behavioural effects of benzazepine analogues administered (IP) separately or in combination with quinpirole (0.01 mg/kg; IP), in rats with unilateral 6-OHDA lesions of the nigrostriatal tract. Cumulative contralateral turns (over 150 min) are expressed as mean ± SEM ($n = 3$–6)

	(Total contralateral turns/150 min)			Ratio
	A	B	C	C/(A+B)
Benzazepines (mg/kg)	Benzazepines	Quinpirole (0.01 mg/kg)	Benzazepines +Quinpirole (0.01 mg/kg)	
SKF 38393 (0.75)	13 ± 4**	155 ± 36**	824 ± 157	4.9
SKF 75670 (0.2)	139 ± 36**	290 ± 122**	763 ± 69	1.8
SKF 80723 (0.5)	281 ± 97**	194 ± 77**	897 ± 161	1.9
SKF 82958 (0.5)	50 ± 33**	146 ± 64**	481 ± 65	2.5
SKF 83959 (0.2)	345 ± 160**	155 ± 47*	838 ± 137	1.8

*$P<0.05$, **$P<0.01$ compared to co-administration of quinpirole and the benzazepine derivative (one-way ANOVA and post-hoc Duncan's multiple range test)

Behavioural effects in MPTP-treated marmosets

Effects of quinpirole alone on motor activity

Administration of quinpirole alone (0.1 mg/kg) increased locomotor activity and reversed motor disability in MPTP-treated marmosets (Table 2). The locomotor effects were apparent for approximately 60–90 mins (Figs 2 and 3). Well co-ordinated fast leaping movements between perches and the cage walls largely accounted for the increase in locomotor activity in these animals. Alertness, checking movements, posture, balance and speed of reaction were all improved following the challenge with quinpirole. No

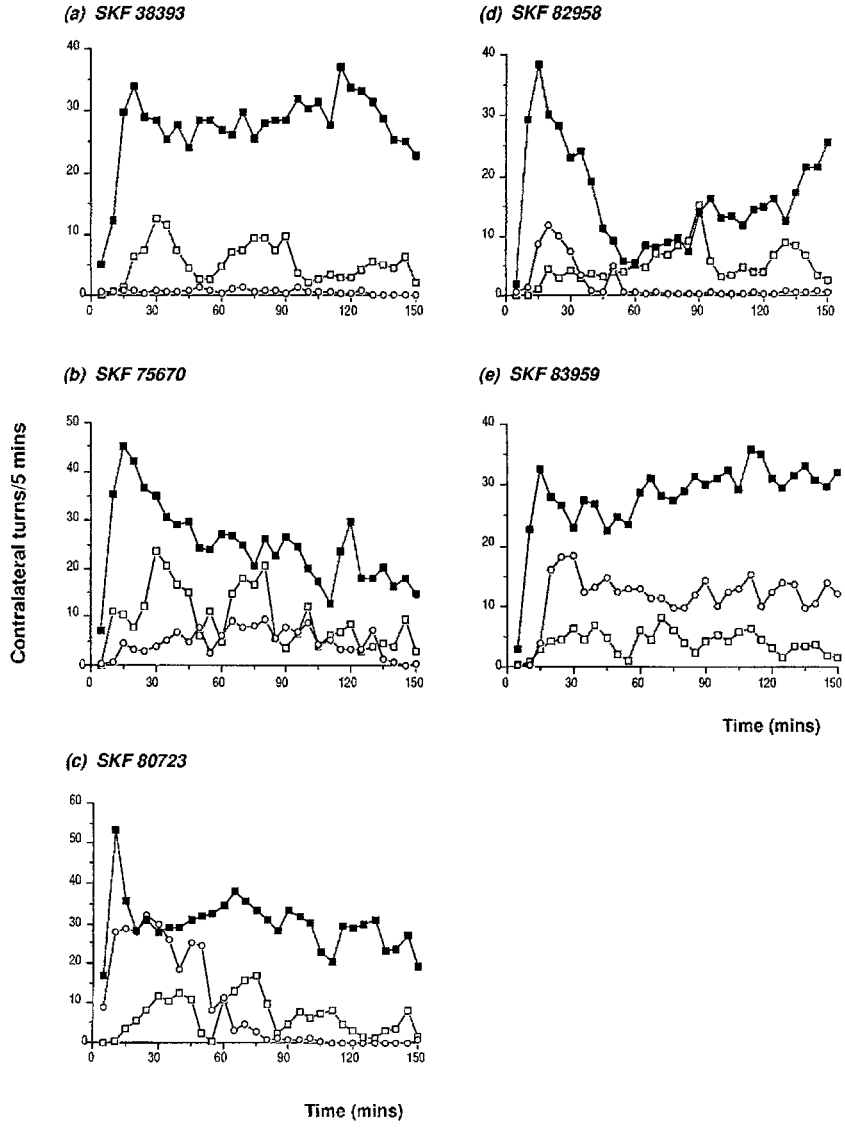

Fig. 1a–e The time course for the behavioural effects of quinpirole (0.01 mg/kg; IP) and benzazepine derivatives administered separately or in combination in rats with unilateral 6-OHDA lesions of the nigrostriatal tract. The following doses of benzazepine derivatives were used: SKF 38393 – 0.75, SKF 75670 – 0.2, SKF 80723 – 0.5, SKF 82958 – 0.5 and SKF 83959 0.2 mg/kg; IP. Contralateral turns per 5 min are shown and for clarity the error bars have been omitted ($n = 3$–6). □ quinpirole, ○ benzazepine, ■ quinpirole + benzazepine

Table 2 The behavioural effects of quinpirole (1.0 mg/kg; IP) in the MPTP-treated marmoset. All animals were pretreated with domperidone (2 mg/kg; PO) 30 min prior to the administration of quinpirole. Cumulative locomotor activity counts (over 120 min), oral activity (vacuous chews and tongue protrusions), grooming and motor disability scores (over 60 min) are expressed as mean ± SEM ($n = 7$).

Drug treatments	Locomotor activity (counts/120 min)	Oral activity (scores/60 min)	Grooming (scores/60 min)	Disability (scores/60 min)
Vehicle	553 ± 145	0.3 ± 0.2	0.6 ± 0.4	66.0 ± 4.7
Quinpirole (0.1 mg/kg; IP)	3613 ± 828**	0.4 ± 0.3	2.4 ± 1.1	30.1 ± 4.0**

**$P < 0.01$ compared to vehicle treatment; paired Student's t-test and Mann-Whitney U test

obvious dyskinetic/dystonic movements or nausea/emesis were apparent in these animals. Grooming and oral activity were not significantly altered following treatment with quinpirole (Table 2).

Effects of co-administration of benzazepine derivatives and quinpirole on motor activity

SKF 38393. Administration of SKF 38393 (7.5 and 15.0 mg/kg) inhibited the quinpirole-induced increase in locomotor activity (5–60 min post injection; $P < 0.05$) and decrease in motor disability ($P < 0.05$; Fig. 2). The animals appeared sedated and were largely still, either on the floor or perches. The combination of SKF 38393 and quinpirole did not significantly alter either oral movements or grooming (Fig. 2).

SKF 75670. Co-administration of SKF 75670 reversed the quinpirole-induced locomotor stimulation in the MPTP-treated marmosets (2.5 and 5.0 mg/kg, 5–60 min post-injection; $P < 0.05$; Fig. 3). There were corresponding increases in disability scores (2.5 and 5.0 mg/kg; $P < 0.05$; Fig. 4) in these animals. The animals became less mobile and appeared sedated. Co-administration of SKF 75670 and quinpirole failed to affect either oral activity (Fig. 5) or grooming (Fig. 6).

SKF 80723. In contrast, SKF 80723 (0.125 and 0.25 mg/kg) failed to affect locomotor activity in MPTP-treated marmosets, pretreated with quinpirole (Fig. 3). However, in two out of the four animals, SKF 80723 appeared to potentiate quinpirole-induced locomotor activity, which accounts for the large standard errors seen in Fig. 3b. Likewise, motor disability, oral activity and grooming were unaffected in these animals (Figs 4, 5 and 6). Co-administration of higher doses of SKF 80723 (0.5 and 1.0 mg/kg) and quinpirole induced hyperexcitability, loss of co-ordination/balance and seizures (one out of four animals).

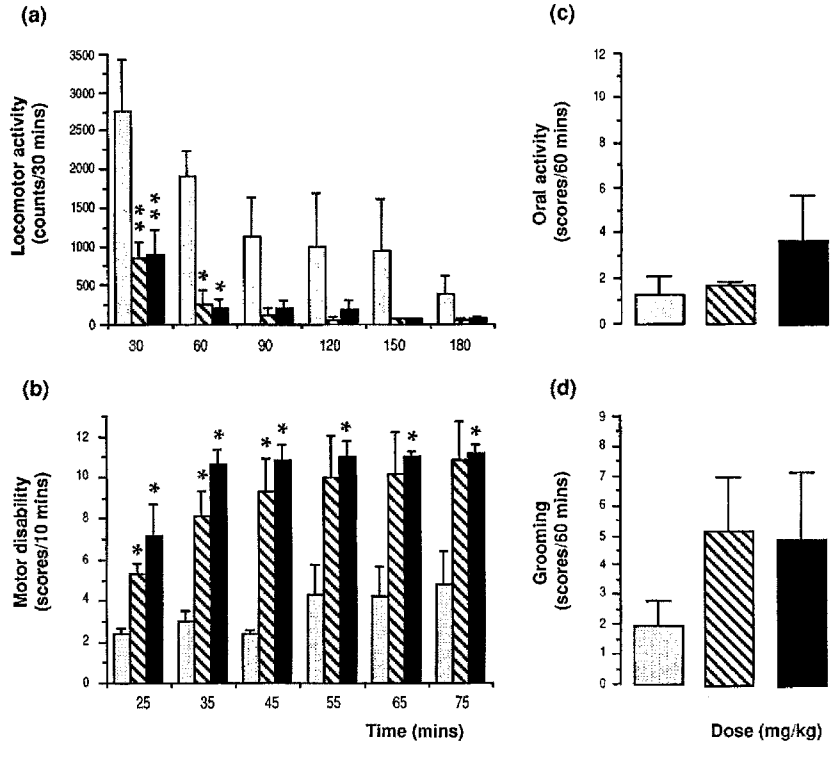

Fig. 2 The behavioural effects of the co-administration of SKF 38393 (7.5 and 15 mg/kg; IP) and quinpirole (0.1 mg/kg; IP) on **a** locomotor activity (counts per 30 min), **b** motor disability (scores/10 min), **c** oral activity (scores/60 min) and **d** grooming (scores/60 min) in MPTP-treated marmosets. The data are expressed as mean ± SEM; $n = 5$. *$P < 0.05$, **$P < 0.01$ compared to vehicle treatment; two-way ANOVA and post-hoc Duncan's multiple range test or Kruskal Wallis and Mann-Whitney U test. □ vehicle, ▨ 7.5, ■ 15.0

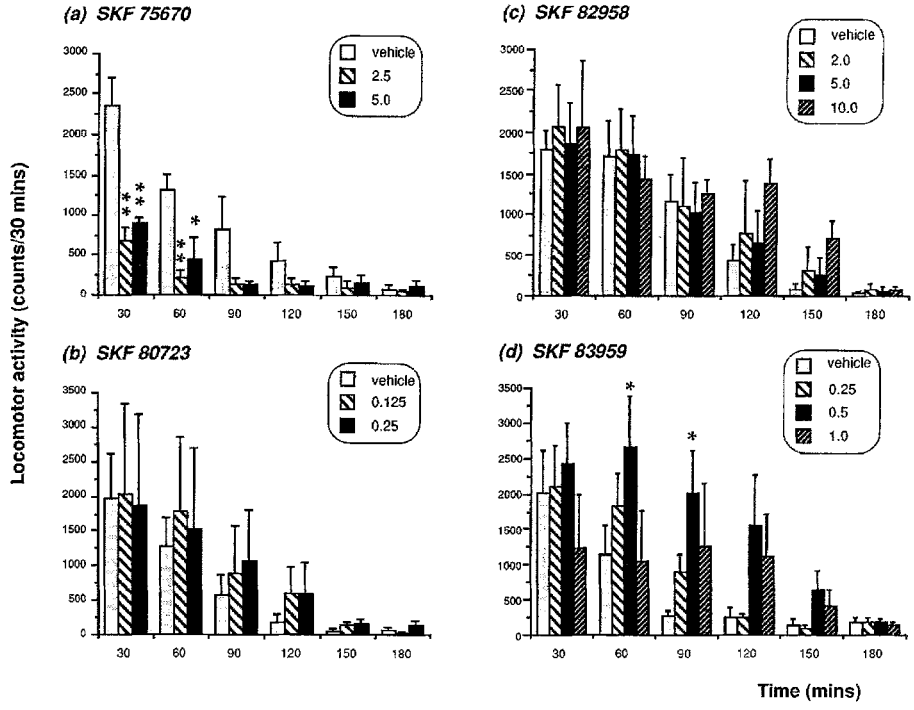

Fig. 3a–d The behavioural effects of the co-administration of benzazepine derivatives (0.125–10 mg/kg; IP; $n = 4$–5) and quinpirole (0.1 mg/kg; IP) on locomotor activity in MPTP-treated marmosets. The data are expressed as mean ± SEM locomotor counts per 30 min. $^{*}P < 0.05$, $^{**}P < 0.01$ compared to vehicle treatment; two-way ANOVA and post-hoc Duncan's multiple range test

SKF 82958. Co-administration of SKF 82958 and quinpirole (0.1 mg/kg) did not alter either the peak rate or the duration of locomotor stimulation (Fig. 3). Although, 10 mg/kg SKF 82958 appeared to potentiate the locomotor response between 90 and 150 min, this failed to be significant. Moreover, at this dose of SKF 82958, hyperexcitability, loss of balance and seizures were observed in one of the five animals.

Motor disability, oral activity and grooming were not significantly affected by the combined treatment of SKF 82958 and quinpirole (Figs 4, 5 and 6), although a dose-dependent decrease in grooming activity was

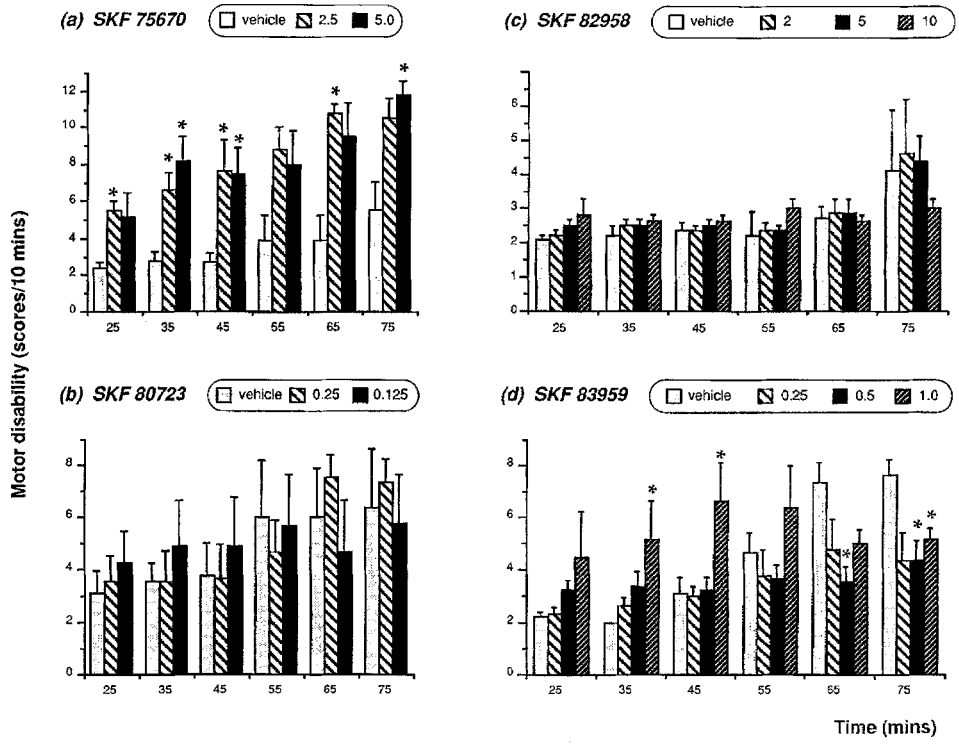

Fig. 4a–d The behavioural effects of the co-administration of benzazepine derivatives (0.125–10 mg/kg; IP; $n = 4$–5) and quinpirole (0.1 mg/kg; IP) on motor disability in MPTP-treated marmosets. The data are expressed as mean ± SEM disability scores per 10 min. $^{*}P < 0.05$, compared to vehicle treatment; Kruskal Wallis and Mann-Whitney U test

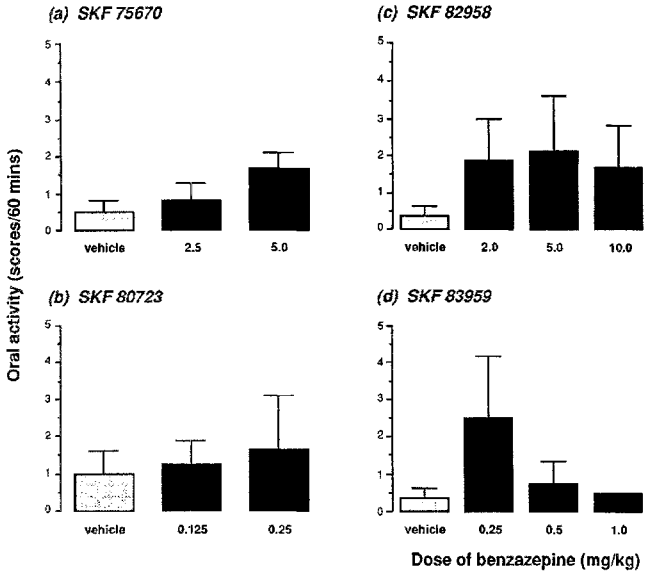

Fig. 5a–d The behavioural effects of the co-administration of benzazepine derivatives (0.125–10 mg/kg; IP; $n = 4$–5) and quinpirole (0.1 mg/kg; IP) on oral activity (vacuous chews and tongue protrusions) in MPTP-treated marmosets. Oral activity was unchanged. The data are expressed as mean ± SEM cumulative oral activity scores over 60 min

apparent with increasing doses of SKF 82958 (at 10 mg/kg SKF 82958, $P = 0.11$).

SKF 83959. Co-administration of SKF 83959 and quinpirole extended the duration of response to quinpirole in MPTP-treated marmosets (Fig 3). The peak rate of locomotor activity was not altered. The increase in the duration of response, although evident at 0.25 mg/kg SKF 83959, was significant between 30 and 90 min after the administration of 0.5 mg/kg SKF 83959 ($P < 0.05$). Correspondingly, SKF 83959 (0.5 mg/kg) reduced the motor disability scores in MPTP-treated marmosets that also received quinpirole pretreatment (between 55 and 75 mins; $P < 0.05$; Fig 4).

Although quinpirole-induced locomotor activity appeared to be also increased (between 60 and 150 min) in animals treated with 1.0 mg/kg SKF 83959, this was not significant. However, 1.0 mg/kg SKF 83959 induced a significant decrease in motor disability between 65 and 75 min ($P < 0.05$), although at the same dose of SKF 83959 there was an initial increase in motor disability (25–45 min; $P < 0.05$; Fig 4). This dose of SKF 83959 also induced hyperexcitability, loss of balance and seizures (two out of four animals) in animals pretreated with quinpirole. Oral activity and grooming were not significantly affected by the combined treatment of SKF 83959 and quinpirole (Figs 5 and 6).

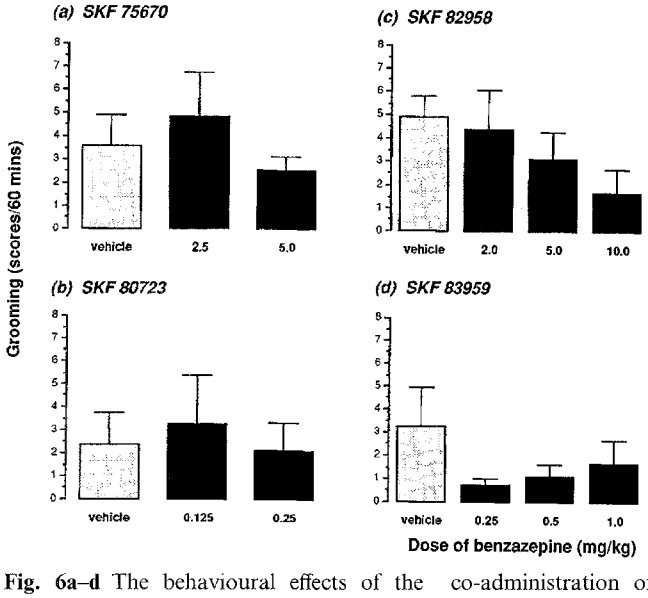

Fig. 6a–d The behavioural effects of the co-administration of benzazepine derivatives (0.125–10 mg/kg; IP; $n = 4$–5) and quinpirole (0.1 mg/kg; IP) on grooming in MPTP-treated marmosets. Grooming behaviour was not significantly altered. The data are expressed as mean ± SEM cumulative grooming scores over 60 min

Discussion

Behavioural effects in 6-OHDA lesioned rats

Although the archetypal benzazepine D_1 DA agonist SKF 38393 has been shown to synergistically enhance D_2 DA agonist mediated contraversive circling in the 6-OHDA lesioned rat, whether this is a response typical of D_1 DA agonists was hitherto unknown (Robertson and Robertson 1986; Rouillard and Bedard 1988).

The present study establishes that not only SKF 38393 and but other benzazepine derivatives such as SKF 75670, SKF 80723, SKF 82958 and SKF 83959 are also able to potentiate the contralateral circling induced by quinpirole in the 6-OHDA lesioned rat. In this respect, SKF 82958 and SKF 38393 were found to be the most potent. All compounds, in particular SKF 38393 and SKF 83959, increased both the peak rate and duration of turning. The rapid onset of the synergistic response, evident within 5–10 min of the co-administration of the benzazepine analogues and quinpirole, suggests that active metabolites of the benzazepine derivatives are unlikely to be involved. However, an exception may be SKF 82958, which exhibited a biphasic synergism with quinpirole. The second phase of the potentiation in the circling response (approximately 2–3.5 h) may indicate the involvement of a metabolite. Indeed, *N*-demethylation of SKF 82958 would yield SKF 80723 (see Weinstock et al. 1985).

Our findings in the unilaterally DA denervated rat model are in agreement with similar studies carried out in both intact and hemitransected rats. Indeed, co-administration of SKF 38393, SKF 75670, SKF 80723

Table 3 Qualitative comparison of the behavioural effects of the co-administration of benzazepine D_1 DA agonists and quinpirole in the 6-OHDA lesioned rat (contralateral circling) and MPTP-treated marmoset (locomotor effects). These effects are compared to the biochemical effects of the benzazepines in the rodent striatum ++++ very high, +++ high, ++ moderate, + low, 0 no effect, − inhibition

D_1 DA agonists	Potentiation of the effects of quinpirole?		Biochemical effects of benzazepines
	MPTP-treated marmoset[a] (locomotor)	6-OHDA lesioned rat[b] (circling)	maximal AC stimulation[c]
SKF 80723	0	++	+++
SKF 82958	0	+++	++++
SKF 38393	−	++++	++
SKF 75670	−	++	+
SKF 83959	++	++	+/0

[a] From Figs 2 and 3
[b] From Table 1
[c] Maximal AC activity in the intact rodent striatum DA (in relation to DA = +++) (from Weinstock et al. 1985, 1986; O'Boyle et al. 1989; Arnt et al. 1992)

and SKF 83959 with quinpirole potentiates stereotypy (intact animal) and ipsilateral circling (hemitransected model), with similar maximum effects and rank order of potencies (Barone et al. 1986; Mashurano and Waddington 1986; Arnt et al. 1988; 1992; Dall'Olio et al. 1988).

Behavioural effects in MPTP-treated marmosets

In contrast, the benzazepine D_1 DA agonists produced a variety of behavioural effects when co-administered with quinpirole in the MPTP-treated marmoset. Concordant with previous findings, acute administration of SKF 38393 inhibited the quinpirole-induced increase in locomotor activity and reversal of motor disability (Nomoto et al. 1988; Bedard and Boucher 1989; Loschmann et al. 1991, 1992). Although, in this respect, SKF 75670 mimicked the effects of SKF 38393, the combined administration of SKF 80723 or SKF 82958 with quinpirole had no overall effect on locomotor activity and motor disability (see also Rupniak et al. 1992). In contrast, doses of SKF 83959 that do not affect locomotor activity when given alone (unpublished observations) were able to extend the duration of the antiparkinsonian effects of quinpirole. However, at higher doses SKF 83959 (as well as SKF 80723 and SKF 82958) tended to produce hyperexcitation, loss of co-ordination and seizures in some animals, when co-administered with quinpirole. Indeed, this (i.e. the poor co-ordination and balance) accounted for the initial increase in motor disability seen in the MPTP-treated marmosets given high doses of SKF 83959 and quinpirole.

Co-administration of the benzazepine derivatives and quinpirole had no significant effect on either oral activity or grooming. However, the doses of SKF 38393 (7.5 and 15.0 mg/kg), SKF 83959 (0.5 and 1.0 mg/kg) and SKF 82958 (10 mg/kg) used in this study can increase oral activity (all compounds) and grooming (SKF 82958 only), when administered alone in MPTP-treated marmosets (unpublished observations; see also Bedard and Boucher 1989; Loschmann et al. 1992; Gnanalingham et al. 1994). Therefore, co-administration of quinpirole may attenuate the effects of SKF 38393, SKF 83959 and SKF 82958 on oral activity and that of SKF 82958 on grooming.

Contrary to the present findings with SKF 38393, concurrent administration of SKF 38393 and quinpirole has been previously reported to potentiate oral dyskinesias in both normal and MPTP-treated cynomolgus monkeys (Bedard and Boucher 1989). Although the reasons for this are unclear, differences in the dose and route of administration of the DA agonists may underly this discrepancy. However, inhibitory effects of quinpirole on D_1 DA agonist-induced oral dyskinesias have been reported in monkeys withdrawn from chronic neuroleptic treatment (Peacock et al. 1990). Moreover, in intact rodents, co-administration of both D_1 and D_2 DA agonists, while potentiating stereotypy, suppress grooming, perioral dyskinesias and vacuous chewing behaviours (Mashurano and Waddington 1986; Rosengarten et al. 1986; Johannson et al. 1987; Dall'Olio et al. 1988; Collins et al. 1991). These findings are consistent with the present observations in the MPTP-treated marmoset and suggest an antagonistic relationship between D_1 and D_2 DA agonists on grooming and oral activity.

Lack of correlation with adenylate cyclase activity (see Table 3)

In the 6-OHDA lesioned rats, the ability of all benzazepine derivatives (notably SKF 38393 and SKF 82958) to potentiate quinpirole-induced contraversive circling is surprising, particularly in view of the fact that these benzazepines stimulate AC activity to varying extents. The rank order of AC efficacy in control rat striatal tissue is SKF 82958 ≥ DA = SKF 80723 > SKF 38393 > SKF 75670 ≫ SKF 83959 (see Itoh et al. 1984; Weinstock et al. 1985, 1986; O'Boyle et al. 1989; Arnt et al. 1992). Moreover, we have also observed a similar rank order of AC efficacy in striatal tissue from the 6-OHDA lesioned rat, although there is a general increase in the stimulation of AC activity by these benzazepines in the DA denervated striatum (Gnanalingham et al., submitted). It is therefore apparent that the degree of potentiation of quinpirole-induced circling does not relate to the AC efficacy in the DA denervated striatum. For example, SKF 38393 despite demonstrating partial AC efficacy (with respect

to DA), was the most effective benzazepine in potentiating the circling response to quinpirole in the 6-OHDA lesioned rat.

The behavioural potency of the D_1 DA agonists is also dependent upon other factors, including D_1 DA receptor affinity/selectivity and penetration across the blood-brain barrier. However, the penetrability of the benzazepines into the brain does not seem to be a critical factor, since potentiation of circling was evident within 5–10 min following the administration of quinpirole and the benzazepine D_1 DA agonists. Moreover, there is no clear relationship with the receptor binding characteristics of the benzazepine derivatives, since with the exception of SKF 82958 (D_1 DA receptor affinity, $K_i = 236$ nM; D_1 DA receptor selectivity = 8 fold), all the other benzazepines exhibit similar high affinities (nM range) and selectivities (approximately 100 fold or more) for the D_1 DA receptor (Gnanalingham et al. 1994; Arnt et al. 1992).

The discrepancy between the behavioural effects of the benzazepine derivatives, when co-administered with quinpirole and their ability to stimulate AC, was more evident in the MPTP-treated marmoset. Thus, while the inefficacious benzazepine D_1 DA agonist, SKF 83959 was able to prolong the antiparkinsonian effects of quinpirole in the MPTP-treated marmoset, other benzazepines with partial (SKF 38393 and SKF 75670) and full/supramaximal AC efficacies (SKF 80723 and SKF 82958) either inhibited or did not alter the effects of quinpirole. Indeed, the fact that both SKF 38393 and SKF 75670 inhibit the antiparkinsonian effects of quinpirole in this primate model indicates that these compounds do get into the brain, and suggests that differences in penetrability into the brain cannot explain their locomotor inhibitory effects. Furthermore, evidence to date indicates that the benzazepine derivatives retain their D_1 DA receptor selectivity in the primate striatum and that their AC efficacies in the primate brain tissue are comparable or lower than that in the rodent brain (O'Boyle and Waddington 1987; Madras et al. 1988; Pifl et al. 1991; Izenwasser and Katz 1993; Watts et al. 1993). Thus, while we cannot rule out some complex interaction between D_1 DA receptor binding, penetrability into the brain and AC efficacy of the benzazepines, the observations of the present study indicate a lack of correlation between the behavioural effects of the benzazepines and their ability to stimulate AC.

Similar discrepancies between the AC stimulation and the behavioural effects of benzazepine D_1 DA agonists have been observed in the MPTP-treated marmoset (Gnanalingham et al. 1994) and in intact, hemitransected and DA denervated rodents (Murray and Waddington 1989; Arnt et al. 1992; Daly and Waddington 1992; Downes and Waddington 1993; Gnanalingham et al. submitted). These behavioural studies, together with the biochemical observations of a mismatch between D_1 DA receptor binding and AC activity (Battaglia et al. 1986; Mailman et al. 1986; Hess et al. 1987; Schoors et al. 1991), further implicate a behavioural role for D_1 DA receptors utilising transduction systems other than AC.

Although, D_1 DA receptors are also known to affect Ca^{2+} mobilisation, inositol phosphate formation, arachidonic acid release and the activity of the Na^+/K^+ ATPase, the behavioural significance of these systems is not clear (Bertorello et al. 1990; Mahan et al. 1990; Undie and Friedman 1990; Piomelli et al. 1991). Interestingly, D_1 and D_2 DA receptors synergistically interact in inhibiting the Na^+/K^+ ATPase and stimulating the release of arachidonic acid (Bertorello et al. 1990; Piomelli et al. 1991). These biochemical effects are therefore in keeping with synergistic interaction between D_1 and D_2 DA receptors seen behaviourally. Moreover, recent in situ hybridisation studies have reported the existence of multiple DA receptor types which may be grouped into "D_1 like" (D_1 and D_5) and "D_2 like" (D_2, D_3 and D_4) DA receptor families (see Sibley and Monsma 1992 for review). In this respect, it is worth noting that, although SKF 38393 exhibits similar affinities for D_1 and D_5 DA receptor subtypes (Sunahara et al. 1991), whether this is true of other benzazepine D_1 DA agonists is not known. Consequently, differences in the behavioural effects of the benzazepine D_1 DA agonists observed may reflect a preference for one or more D_1 DA receptor subtypes.

In the present study, quinpirole was utilised to investigate D_1 and D_2 DA receptor interactions in both rodent and primate models of PD. Although quinpirole is selective for the "D_2 DA receptor family", it has greater affinity for the D_3 DA receptor subtype (Sokoloff et al. 1990). However, this is unlikely to have influenced the findings of this study, since similar results are observed in both primate (Rupniak et al. 1992) and rodent studies following the acute administration of D_1 agonists and a variety of D_2 DA agonists with similar affinities for D_2 and D_3 DA receptor subtypes (Mashurano and Waddington 1986; Robertson and Robertson 1986; Rouillard and Bedard 1988).

Concluding remarks

To date, clinical trials with D_1 DA agonists such as SKF 38393, either alone or in conjunction with levodopa, have proved disappointing (Braun et al. 1987). Moreover, although CY 208–243 exerts mild antiparkinsonian actions in parkinsonian patients, it does not potentiate the effects of bromocriptine (Emre et al. 1992).

The present study demonstrates that the benzazepine D_1 DA agonists can potentiate the behavioural effects of quinpirole not only in 6-OHDA lesioned rats, but also that the benzazepine SKF 83959 is able to prolong

the antiparkinsonian effects of quinpirole in the MPTP-treated marmoset. While this may indicate a role for some D_1 DA agonists as an adjunctive therapy to levodopa in PD, great care is required in selecting the D_1 DA agonist and its dose. Interestingly, chronic administration of behaviourally ineffective doses of SKF 38393 can prevent the onset of tolerance to bromocriptine in the MPTP-treated cynomolgus monkey (Rouillard et al. 1990). Thus, low doses D_1 DA agonists may also be of use, especially in patients who have become tolerant ("wearing off" effect) to levodopa and DA agonist therapy. Additionally, the findings of this study further highlight the behavioural and biochemical (AC efficacy) mismatch of the benzazepine D_1 DA agonists in both animal models. Consequently, even D_1 DA agonists with *partial or no* AC efficacy may prove to possess useful antiparkinsonian activity in the clinical setting.

Acknowledgements This work was supported by the Parkinson's Disease Society and the Medical Research Council. We thank Dr. D.D. Erol and Professor R.C. Hider (Dept of Pharmacy, King's College, London) for synthesising benzazepine analogues. The expert technical assistance of Dr. L.A. Smith and M. Jackson is gratefully acknowledged. K. K. Gnanalingham is a SERC CASE student in conjunction with SmithKline Beecham.

References

Arnt J (1985a) Behavioural stimulation is induced by separate dopamine D_1 and D_2 receptors in reserpine-pretreated but not in normal rats. Eur J Pharmacol. 113:79–88

Arnt J (1985b) Hyperactivity induced by stimulation of separate dopamine D_1 and D_2 receptors in rats with bilateral 6-OHDA lesions. Life Sci 37:717–723

Arnt J, Hyttel J (1984) Differential inhibition by dopamine D_1 and D_2 antagonists of circling behaviour induced by dopamine agonists in rats with unilateral 6-hydroxydopamine lesions. Eur J Pharmacol 102:349–354

Arnt J, Bogeso KP, Hyttel J, Meier E (1988) Relative dopamine D_1 and D_2 receptor affinity and efficacy determine whether dopamine agonists induce hyperactivity or oral stereotypy in rats. Pharmacol Toxicol 62:121–130

Arnt J, Hyttel J, Sanchez C (1992) Partial and full dopamine D_1 receptor agonists in mice and rats: relation between behavioural effects and stimulation of adenylate cyclase activity in vitro. Eur J Pharmacol 213:259–267

Barone P, Davis TA, Braun AR, Chase TN (1986) Dopaminergic mechanisms and motor function: characterisation of D_1 and D_2 dopamine receptor interactions. Eur J Pharmacol 123:109–114

Battaglia G, Norman AB, Hess EJ, Creese I (1986) Functional recovery of D_1 dopamine receptor mediated stimulation of rat striatal adenylate cyclase activity following irreversible modification by *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ): evidence for spare receptors. Neurosci Lett 69: 290–295

Bedard PJ, Boucher R (1989) Effect of D_1 receptor stimulation in normal and MPTP monkeys. Neurosci Lett 104:223–228

Bertorello AM, Hopfield JF, Aperia A, Greengard P (1990) Inhibition by dopamine of (Na^+/K^+) ATPase activity in neostriatal neurones through D_1 and D_2 dopamine receptor synergism. Nature 347:386–388

Boyce S, Rupniak NMJ, Steventon MJ, Iversen SD (1990) Differential effects of D_1 and D_2 agonists in MPTP-treated primates: functional implications for Parkinson's disease. Neurology 40: 927–933

Braun A, Fabbrini G, Mouradian MM, Serrati C, Barone P, Chase TN (1987) Selective D_1 dopamine agonist treatment of Parkinson's disease. J Neural Transm 68:41–50

Close SP, Marriott AS, Pay S (1985) Failure of SKF 38393-A to relieve parkinsonian symptoms induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in the marmoset. Br J Pharmacol 85: 320–322

Close SP, Elliott PJ, Hayes AG, Marriott AS (1990) Effects of classical and novel agents in a MPTP-induced reversible model of Parkinson's disease. Psychopharmacology 102:295–300

Collins P, Broekkamp CLE, Jenner P, Marsden CD (1991) Drugs acting at D_1 and D_2 dopamine receptors induce identical purposeless chewing in rats which can be differentiated by cholinergic manipulation. Psychopharmacology 103:503–512

Dall'Olio R, Gandolfi O, Vaccheri A, Roncada P, Montanaro N (1988) Changes in behavioural responses to the combined administration of D_1 and D_2 dopamine agonists in normosensitive and D_1 supersensitive rats. Psychopharmacology 95:381–385

Daly SA, Waddington JL (1992) D_1 dopamine receptors and the topography of unconditioned motor behaviour: studies with the selective, "full efficacy" benzazepine D_1 agonist SKF 83189. J Psychopharmacol 6:50–60

DeNinno MP, Schoenleber R, MacKenzie R, Britton DR, Asin KE, Briggs C, Trugman JM, Ackerman M, Artman L, Bednarz L, Bhatt R, Curzon P, Gomez E, Kang CH, Stitts J, Kebabian JW (1991) A68930: a potent agonist selective for the dopamine D_1 receptor. Eur J Pharmacol 199:209–219

Domino EF, Sheng J (1993) Relative potency and efficacy of some dopamine agonists with varying selectivities for D_1 and D_2 receptors in MPTP-induced hemiparkinsonian monkeys. J Pharmacol Exp Ther 265:1387–1391

Downes RP, Waddington JL (1993) Grooming and vacuous chewing induced by SKF 83959 and agonist of dopamine "D_1 like" receptors that inhibits dopamine sensitive adenylyl cyclase. Eur J Pharmacol 234:135–136

Emre M, Rinne UK, Rascol A, Lees A, Agid Y, Lataste X (1992) Effects of a selective partial D_1 agonist, CY 208–243, in de novo patients with Parkinson's disease. Mov Disord 7:239–243

Gnanalingham KK, Erol DD, Hunter AJ, Smith LA, Jenner P, Marsden CD (1994) The differential antiparkinsonian effects of benzazepine D_1 dopamine agonists with varying efficacies in the MPTP-treated marmoset. Psychopharmacology

Gower AJ, Marriott A (1982) Pharmacological evidence for the subclassification of central dopamine receptors in the rat. Br J Pharmacol 77:185–194

Hess EJ, Battaglia G, Norman AB, Creese (1987) Differential modification of striatal D_1 dopamine receptors and effector moieties by *N*-ethoxycarbonyl-2-thoxy-1,2-dihydroquinoline in vivo and in vitro. J Pharmacol Exp Ther 31:50–57

Itoh Y, Beaulieu M, Kebabian J (1984) The chemical basis for the blockade of the D_1 dopamine receptor by SCH 23390. Eur J Pharmacol 100:119–122

Izenwasser S, Katz J (1993) Differential efficacies of dopamine D_1 receptor agonists for stimulating adenylyl cyclase in squirrel monkey and rat. Eur J Pharmacol - [Mol Pharmacol] 246:39–44

Johansen PA, Hu X-T, White FJ (1991) Relationship between D_1 dopamine receptors, adenylate cyclase and the electrophysiological responses of rat nucleus accumbens neurones. J Neural Transm 86:97–113

Johansson P, Levin E, Gunne L, Ellison G (1987) Opposite effects of D_1 and D_2 agonist on oral movements in rats. Eur J Pharmacol 134:83–88

Kebabian JW, Britton DR, DeNinno MP, Perner R, Smith L, Jenner P, Schoenleber R, Williams M (1992) A77636: A potent

and selective dopamine D_1 receptor agonist with antiparkinsonian activity in marmosets. Eur J Pharmacol 229:203–209

Loschmann PA, Smith LA, Lange KW, Jaehnig P, Jenner P, Marsden CD (1991) Motor activity following the administration of selective D_1 and D_2 dopaminergic drugs to normal common marmosets. Psychopharmacology 105:303–309

Loschmann PA, Smith LA, Lange KW, Jaehnig P, Jenner P, Marsden CD (1992) Motor activity following the administration of selective D_1 and D_2 dopaminergic drugs to MPTP-treated common marmosets. Psychopharmacology 109:49–56

Lovenberg TW, Brewster WK, Mottola DM, Lee RC, Riggs RM, Nichols DE, Lewis MH, Mailman RB (1989) Dihydrexidine, a novel selective high potency full dopamine D_1 receptor agonist. Eur J Pharmacol 166:111–113

Madras BK, Fahey MA, Canfield DR, Spealman RD (1988) D_1 and D_2 dopamine receptors in caudate-putamen of non-human primates (*Macaca fascicularis*). J Neurochem 51:934–943

Mahan LC, Burch RM, Monsma FJ, Sibley DR (1990) Expression of striatal D_1 dopamine receptors coupled to inositol phosphate production and Ca^{2+} mobilisation in *Xenopus* oocytes. Proc Natl Acad Sci 87:2196–2200

Mailman RB, Schulz DW, Kilts CD, Lewis MH, Rollema H, Wyrick S (1986) The multiplicity of the D_1 dopamine receptor. Neurobiology of central D_1 dopamine receptors. In: Breese GR, Creese I (eds) Adv Exp Med Biol 204:53–72

Markstein R, Seiler NP, Vigouret JM, Urwyler S, Enz A, Dixon K (1988) Pharmacological properties of CY 208–243, and normal D_1 agonists, In Sandler M. ed. Proceedings of XIth international catecholamine symposium Part B: Central aspects. Alan R Liss, New York, pp 59–64

Mashurano M, Waddington JL (1986) Stereotyped behaviour in response to the selective D_2 dopamine agonist RU 24213 is enhanced by pretreatment with the selective D_1 agonist SK&F 38393. Neuropharmacology 25:947–949

Murray AM, Waddington JL (1989) The induction of grooming and vacuous chewing by a series of selective D_1 dopamine agonists: two directions of D_1:D_2 interaction. Eur J Pharmacol 160: 377–384

Nomoto M, Jenner P, Marsden CD (1985) The dopamine D_2 agonist LY 141865, but not the D_1 agonist SKF 38393 reverses parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in the common marmoset. Neurosci Lett 57:37–41

Nomoto M, Jenner P, Marsden CD (1988) The D_1 agonist SKF 38393 inhibits the antiparkinsonian activity of the D_2 agonist LY 171555 in the MPTP-treated marmoset. Neurosci Lett 93: 275–280

O'Boyle KM, Waddington JL (1987) [^{3}H]-SCH 23390 binding to human putamen D_1 dopamine receptors: stereochemical and structure-affinity relationships among 1-phenyl-1H-3-benzazepine derivatives as a guide to D_1 receptor topography. J Neurochem 48:1039–1042

O'Boyle KM, Gaitanopoulos DE, Brenner M, Waddington JL (1989) Agonist and antagonist properties of benzazepine and thienopyridine derivatives at the D_1 dopamine receptor. Neuropharmacology 28:401–405

Peacock L, Lublin H, Gerlach J (1990) The effects of dopamine D_1 and D_2 receptor agonists and antagonists in monkeys withdrawn from long-term neuroleptic treatment. Eur J Pharmacol 186: 49–59

Pellegrino LJ, Pellegrino AS, Cushman AJ (1979) A stereotaxic atlas of the rat brain. Plenum Press, London

Pifl C, Reither H, Hornykiewicz O (1991) Lower efficacy of the dopamine D_1 agonist, SKF 38393, to stimulate adenylyl cyclase activity in primate than in rodent striatum. Eur J Pharmacol 202:273–276

Piomelli D, Pilon C, Giros B, Sokoloff P, Martes M-P, Schwartz J-C (1991) Dopamine activation of the arachidonic acid cascade as a basis for D_1/D_2 receptor synergism. Nature 353:164–167

Robertson GS, Robertson HA (1986) Synergistic effects of D_1 and D_2 dopamine agonists on turning behaviour in rats. Brain Res 384:387–390

Rosengarten H, Schweitzer JW, Friedhoff AJ (1986) Selective dopamine D_2 receptor reduction enhances a D_1 mediated oral dyskinesia in rats. Life Sci 39:29–35

Rouillard C, Bedard PJ (1988) Specific D_1 and D_2 dopamine agonists have synergistic effects in the 6-hydroxydopamine circling model in the rat. Neuropharmacology 27:1257–1264

Rouillard C, Bedard PJ, Di Paolo T (1990) Effects of chronic treatment of MPTP monkeys with bromocriptine alone or in combination with SKF 38393. Eur J Pharmacol 185:209–215

Rupniak NMJ, Boyce S, Steventon M, Iversen SD (1992) Weak antiparkinsonian activity of the D_1 agonist C-APB (SKF 82958) and lack of synergism with a D_2 agonist in primates. Clin Neuropharmacol 15:307–309

Schoors DF, Vauquelin GP, Vos HD, Smets G, Velkeniers B, Vanhaelst L, Dupont AG (1991) Identification of a D_1 dopamine receptor, not linked to adenylate cyclase, on lactotroph cells. Br J Pharmacol 103:1928–1934

Setler PE, Sarau HM, Zirkle CL, Saunders HL (1978) The central effects of a novel dopamine agonist. Eur J Pharmacol 50: 419–430

Sibley DR, Monsma FJ (1992) Molecular biology of dopamine receptors. Trends Pharmacol Sci 13:61–69

Sokoloff P, Giros B, Martres M-P, Bouthenet M-L, Schwartz J-C (1990) Molecular cloning and characterisation of a novel dopamine receptor (D_3) as a target for neuroleptics. Nature 34:146–151

Sunahara RK, Guan H-C, O'Dowd BF, Seeman P, Laurier LG, Ng G, George SR, Torchia J, Van Tol HHM, Niznik HB (1991) Cloning of the gene for a human dopamine D_5 receptor with high affinity for dopamine than D_1. Nature 350:614–619

Undie AS, Friedman E (1990) Stimulation of a dopamine D_1 receptor enhances inositol phosphates formation in rat brain. J Pharmacol Exp Ther 253:987–992

Ungerstedt U, Arbuthnott GW (1970) Quantitative recording of rotational behaviour in rats after 6-hydroxydopamine lesions of the nigrostriatal system. Brain Res 14:461–471.

Watts VJ, Lawler CP, Gilmore JH, Southerland SB, Nichols DE, Mailman RB (1993) Dopamine D_1 receptors: efficacy of full (dihydrexidine) vs. partial (SKF 38393) agonists in primates vs. rodents. Eur J Pharmacol 24:165–172

Weinstock J, Hieble JP, Wilson JW (1985) The chemistry and pharmacology of 3-benzazepine derivatives. Drugs Future 10: 645–696

Weinstock J, Ladd DL, Wilson JW, Brush CK, Yim NCF, Gallagher G, McCarthy ME, Silvestri J, Sarau HM, Flaim KE, Ackerman DM, Setler PE, Tobia AJ, Hahn RA (1986) Synthesis and renal vasodilator activity of some dopamine agonist 1-aryl-2,3,4,5-tetrahydro-1H-3-benzazepine-7,8-diols: halogen and methyl analogues of fenoldopam. J Med Chem 29:2315–2325