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Effect of 5-$HT_{1B/D}$ receptor agonist and antagonist administration on motor function in haloperidol and MPTP-treated common marmosets

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Abstract

An interaction between brain serotonergic and dopaminergic systems involving 5-HT_{1B} receptors may contribute to motor complications arising from the drug treatment of neurological and psychiatric disorders. This study assessed the effects of treatment with a non-selective 5-$HT_{1B/D}$ receptor agonist and a selective 5-HT_{1B} receptor antagonist on akinesia induced in marmosets by long-term treatment with haloperidol and on motor disability and L-3, 4-dihydroxyphenylalanine (L-DOPA)-induced dyskinesia in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated marmosets. In marmosets treated chronically with haloperidol, the 5-HT_{1B} agonist SKF-99101-H reduced locomotor activity and induced motor disability, whereas the 5-HT_{1B} antagonist SB-224289-A had no effect on motor behaviour. Haloperidol administration induced a suppression of locomotor activity which was not reversed by co-administration of either SKF-99101-H or SB-224289-A. In MPTP-treated common marmosets, neither SKF-99101-H nor SB-224289-A induced any significant change in motor function. However, SKF-99101-H inhibited L-DOPA-induced dyskinesia and the reversal of motor deficits whereas SB-224289-A was without effect. The results of this study indicate that the 5-HT_{1B} receptor appears not to be an appropriate target for the treatment of Parkinson's disease (PD) or for the control of drug-induced motor complications developed as a tong-term consequence of neuroleptic or L-DOPA treatment.

Keywords: 5-HT_{1B} receptors; Agonist; Antagonist; SB-224289-A; SKF-99101-H; L-DOPA; Haloperidol; Dyskinesia; Marmoset

1. Introduction

In Parkinson's disease (PD), dopamine replacement therapy using L-3, 4-dihydroxyphenylalanine (L-DOPA) and to a lesser extent dopamine agonists induces chorea, dystonia and athetosis (Marconi et al., 1994; Nutt, 1990; Olanow and Obeso, 2000). Similarly, the chronic treatment of schizophrenia with classical dopamine antagonists, such as haloperidol, is accompanied by the onset of extra-pyramidal side effects (EPS) including acute dystonia and tardive dyskinesia (Baldessarini, 1980; Glazer, 2000; Marsden et al., 1975). In both cases, the development of dyskinesia can reduce the effective use of the treatment. In contrast, newer atypical antipsychotics such as olanzapine, risperidone and seroquel are less likely to induce EPS (Glazer, 2000). The mechanism of action for this effect is unclear but may reflect the antagonism of serotonergic receptors. Olanzapine has high affinity for 5-HT_{2A}, 5-HT_{2C} and 5-HT_3 receptors, risperidone has high affinity for 5-HT_{2A} and seroquel high affinity for 5-HT_3 receptors (Tazari et al., 2002). There is also evidence that risperidone and olanzapine act as inverse-agonists at 5-HT_{2C} receptors (Rauser et al., 2002).

Further evidence that serotonergic mechanisms may be involved in the induction or control of dyskinesia is that both the selective serotonin uptake inhibitor (SSRI) fluoxetine and the 5-HT_{1A} receptor agonists sarizotan and tandospirone reduce L-DOPA-induced involuntary move-

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ments in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated primates and patients with PD (Bibbiani et al., 2001; Durif et al., 1995; Kannari et al., 2002).

A possible target in the human and primate brain by which to investigate the treatment of motor abnormalities is 5-HT_{1B} receptors which are abundant in the substantia nigra, ventral pallidum, globus pallidus, nucleus accumbens and caudate nucleus (Bruinvels et al., 1992; Varnas et al., 2001). 5-HT_{1B} receptors are located presynaptically on serotonergic neurones where they function as autoreceptors controlling 5-HT release (Hoyer et al., 1994). In addition, evidence from several studies indicates that there is a large population of 5-HT_{1B} heteroreceptors located on cholinergic, glutamatergic, GABAergic and dopaminergic neurones where they serve to modulate neurotransmitter release (Chadha et al., 2000; Galloway et al., 1993; Maroteaux et al., 1992). At present, there is no detailed evidence of the 5-$HT_{1D/B}$ receptor profile in the brain of the common marmoset. However, it has been shown that there are differences in 5-HT_1 receptor distribution between human, Old World primate and common marmosets in the striate cortex and frontal cortex (Gebhard et al., 1993, 1995) Whereas, there is greater similarity of 5-HT_1 receptor distribution between human and common marmoset in the hippocampus than that found between human and rat (Kramer et al., 1995).

Agonist activity at 5-HT_{1B} receptors indicates that they play a role in the control of motor behaviour. The 5-HT_{1B} receptor agonist, anpirtoline, increases locomotion in rats and mice, and both the 5-HT_1 agonist sumatriptan and the 5-$HT_{1B/D}$ receptor agonist SKF-99101-H induce locomotor activity in guinea pigs (O'Neill and Parameswaran, 1997; Higgins et al., 1991; O'Neill et al., 1997). The effects of anpirtoline and SKF-99101-H are blocked by co-administration of the 5-$HT_{1B/D}$ antagonist GR 127935 (O'Neill et al., 1997, 2000). To determine whether drugs acting on 5-HT_{1B} receptors can modulate the motor abnormalities associated with PD, chronic neuroleptic treatment and L-DOPA-induced dyskinesia in PD, we used chronically haloperidol-treated and MPTP-treated common marmosets. Administration of haloperidol to common marmosets induces a temporary syndrome of akinesia, rigidity, absence of vocalisation and somnolence, similar to the EPS observed in patients receiving antipsychotic treatment (Fukuoka et al., 1997). MPTP induces a chronic syndrome of motor deficits that is reversible by the administration of L-DOPA or dopamine agonists (Jenner et al., 1984; Pearce et al., 1998; Smith et al., 1997). Dyskinesia similar to that observed in PD patients can be induced in MPTP-treated marmosets by the chronic administration of L-DOPA and once primed with L-DOPA, dyskinesia can subsequently be provoked by acute treatment with L-DOPA and dopamine agonists (Pearce et al., 1995). We now investigate the effects of SKF-99101-H, a potent, 5-$HT_{1B/D}$ receptor agonist and SB-224289-A, a potent and selective, 5-HT_{1B} receptor antagonist, both of which penetrate into brain in these models (Cilia et al., 1998; Gaster et al., 1998; Hagan et al., 1997; Hagan et al., 1995).

2. Materials and methods

The study was carried out in the UK in accordance with the Animals (Scientific Procedures Act) 1986.

2.1. Animals

Adult common marmosets (n=32) of either sex weighing 320–450 g, aged 3–10 years were obtained from UK Home Office approved breeding and supply establishments. Animals were housed singly or in pairs under standard conditions at a temperature of 24±2 °C and relative humidity of 50%, employing a 12-h light–dark cycle, with free access to food and water.

2.2. Drugs

To induce parkinsonian motor deficits 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (MPTP HCl, Research Biochemicals, USA) was dissolved in sterile 0.9% saline and administered subcutaneously (sc) once a day for 5 days at a dose of 2.0 mg/kg (Loschmann et al., 1992; Smith et al., 1996). During and for 6–8 weeks following MPTP treatment, the animals were hand fed with liquidised food until able to feed themselves and maintain body weight. At this stage, the animals exhibited a marked reduction in locomotor activity, poor co-ordination and balance, abnormal posture and reduced head checking movements. Haloperidol base (Sigma) was ground in a pestle and mortar with a few drops 5% gum arabic solution, made up to the required volume with 10% sucrose solution and administered orally at a dose of 0.25–2.0 mg/kg. SB-224289-A, (5)1′ -methyl-5-[[2′ -methyl-4′ -(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]carbonyl]-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4′ -piperidine] hydrochloride, was prepared as a suspension in 1% methylcellulose and administered by oral gavage at a dose of 5.0 mg/kg. This dose was selected from studies carried out in guinea pigs showing it to be a potent antagonist of terminal 5-HT1B autoreceptor function in both in-vitro and in-vivo (Gaster et al., 1998).

SKF-99101-H,3-(2-dimethylaminoethyl)-4-chloro-5-propoxyindolehemifumarate, was dissolved in 20 μL glacial acetic acid, neutralised (target pH 6–7) with 80–100 μL of NaOH (2 M solution) and made up to volume with phosphate buffered saline (0.1 M, pH 7.4) and administered by subcutaneous injection (0.3, 1.0 and 3.0 mg/kg). Previous studies have shown that SKF-99101-H induces hypothermia in marmosets (0.3–3.0 mg/kg sc) and informal observations indicate a syndrome of behavioural quiescence (Cilia et al., 1998). From this data, a dose (1.0 mg/kg sc) was selected that caused moderate hypothermia as evidence of agonist activity. A dose response experiment using SKF-

99101-H (0.3, 1.0 and 3.0 mg/kg) was also carried out in a group of MPTP-treated, non L-DOPA-primed marmosets. Carbidopa (Merck, Sharp and Dohme, Rahway, NJ, USA) was prepared as a suspension in a 10% sucrose solution and administered orally at 12.5 mg/kg. L-3,4-dihydroxyphenylalanine (L-DOPA; Merck, Sharp and Dohme) was prepared as a suspension in a 10% sucrose solution and administered orally doses of 2.5, 5.0 and 12.5 mg/kg.

2.3. Administration of SB-224289-A and SKF-99101-H to haloperidol-treated common marmosets

Drug naïve common marmosets (n=4) were treated with haloperidol (0.25–2.0 mg/kg po) on a chronic intermittent basis for a period of approximately 2 years prior to commencing the current study. During this 2 years, treatment consisted of once daily dosing for 5 consecutive days, with week-ends being drug free, and occasional drug free "holiday" periods of 2–4 weeks at approximately 6-month intervals. Following this 2-year chronic treatment with haloperidol, a drug-free period of approximately 1 week was allowed prior to the administration of SB-224289-A (5.0 mg/kg po) for 5 consecutive days. One week alter the fifth administration of SB-224289-A (5.0 mg/kg po), a combination of SB-224289-A (5.0 mg/kg po) and haloperidol (0.25 mg/kg po) was administered. On completion of experiments with SB-224289-A (5.0 mg/kg po), a drug-free period of 1 month was allowed prior to the administration of SKF-99101-H (1.0 mg/kg sc.). Due to the marked suppression of normal behaviour, SKF-99101-H (1.0 mg/kg sc.) was administered for a 2-day period only. This was followed by a single administration of haloperidol (0.25 mg/kg po) in combination with SKF-99101-H (1.0 mg/kg sc.). Drug naive, common marmosets (n=4) were used as a control group-receiving vehicle only.

2.4. Administration of SB-224289-A and SKF-99101-H to MPTP-treated common marmosets

Common marmosets (n=4) were treated with MPTP approximately 3 months prior to the investigation. The animals received no other drug treatment prior to the start of the current study. A single daily dose of SB-224289-A (5.0 mg/kg po) was administered for a period of 5 consecutive days. Following a 10-day drug-free washout period, a single daily dose of SKF-99101-H (1.0 mg/kg sc.) was administered for a period of 5 consecutive days. MPTP-treated, drug naive common marmosets (n=4) were used as a control group-receiving vehicle only. Data for these experiments are not shown.

The dose effect of SKF-99101-H (0.3, 1.0 and 3.0 mg/kg sc.) was investigated in marmosets (n=4) which had been treated with MPTP 12–18 months previously. These animals were not primed to exhibit dyskinesia by chronic administration of L-DOPA, but were not drug naïve having previously received acute administrations of L-DOPA and various antiparkinsonian drugs. However, a wash-out period of approximately 3–4 months, during which no drugs were administered, was allowed before the commencement of the current study. A different group of marmosets (n=4) treated with MPTP at a similar time and with a comparable drug history was used as a vehicle control group.

2.5. Administration of SB-224289-A, SKF-99101-H and L-DOPA to MPTP-treated, L-DOPA-primed common marmosets

Common marmosets (n=4) underwent MPTP treatment and were primed to exhibit dyskinesia by chronic administration of L-DOPA (12.5 mg/kg po plus carbidopa 12.5 mg/kg po bid for 30 days), 2–3 years prior to the study. These animals then received a number of acute antiparkinsonian treatments. However, a 6-week washout period, during which time no drugs were given, was allowed prior to the current investigation. All animals had reduced locomotor activity, abnormal posture, poor co-ordination and balance and reduced head checking movements at the start of the study. A single daily dose of L-DOPA (12.5 mg/kg po plus carbidopa 12.5 mg/kg po) was administered for 4 days to assess consistency of the dyskinetic response exhibited by these animals. The animals were then drug free for 2 days prior to the administration of SB-224289-A (5.0 mg/kg po) in combination with L-DOPA (12.5 mg/kg po plus carbidopa 12.5 mg/kg po). To assess whether SB-224289-A (5.0 mg/kg po) would enhance or reduce the effects of a sub maximal dose of L-DOPA, studies with L-DOPA (2.5 and 5.0 mg/kg plus carbidopa 12.5 mg/kg po) alone and in combination with SB-224289-A (5.0 mg/kg po) were carried out (data not shown for experiments using L-DOPA 2.5 and 5.0 mg/kg).

Following a washout period of approximately 1 month, a single dose of L-DOPA (12.5 mg/kg po plus carbidopa 12.5 mg/kg po) was administered daily for 3 days to assess the dyskinetic response. The animals were drug free for 2 days prior to commencing the administration of SKF-99101-H (1.0 mg/kg sc.) in combination with L-DOPA (12.5 mg/kg po plus carbidopa 12.5 mg/kg po). Subsequently, to assess whether SKF-99101-H (1.0 mg/kg sc.) inhibition of L-DOPA-induced activity was due to altered absorption from the gastro-intestinal tract, SKF-99101-H (1.0 mg/kg sc.) was administered at the time of peak effect of L-DOPA (12.5 mg/kg po plus carbidopa 12.5 mg/kg po), approximately 60 min following administration. MPTP-treated, L-DOPA-primed common marmosets (n=4) were used as a control group-receiving vehicle and L-DOPA (12.5 mg/kg po plus carbidopa 12.5 mg/kg po).

2.6. Assessment of locomotor activity

Common marmosets were placed individually into activity cages (50×60×70 cm) fitted with a clear perspex door to allow greater visibility for observation. Each cage

was equipped with eight horizontally orientated infrared photocell emitters and corresponding detectors arranged to permit maximum assessment of movement. Locomotor activity was assessed as the number of light beam interruptions accumulated in 10-min intervals for up to 6 h. The animals were weighed, where necessary pretreated with carbidopa and allowed a 45–60-min acclimatisation period in the activity cages before administration of drug and start of monitoring.

2.7. Rating of disability and dyskinesia

Animals were observed through a one-way mirror by blinded observers and rated for the degree of motor dysfunction and occurrence of dyskinesia. Motor dysfunction was scored on a disability rating scale; alertness (normal=0, reduced=1, sleepy=2); checking (present=0, reduced=1, absent=2); posture (normal=0, abnormal trunk 1, abnormal tail plus 1, abnormal limbs plus 1, flexed=4); balance (normal=0, impaired=1, unstable=2, spontaneous falls=3); reaction to stimuli (normal=0, reduced=1, slow=2, absent=3) vocalisation; (normal=0, reduced=1, absent=2); motility (normal=bradykinesia or hyperkinesia=1, akinesia or severe hyperkinesia=2). These values were summed to give a maximum score of 18. Dyskinesia was described according to recognised criteria: chorea-rapid random flicking limb movements; athetosis-sinuous writhing limb movements; dystonia-abnormal sustained posturing; stereotypy-repetitive purposeless or semi purposive movement. The presence and severity of dyskinesia was scored on a semi-quantitative dyskinesia rating scale: 0=Absent; 1=Mild: fleeting and rare dyskinetic postures; 2=Moderate: more prominent abnormal movements, but not interfering significantly with normal behaviour; 3=Marked: frequent and at times continuous dyskinesias intruding upon normal repertoire of activity; 4=Intense: virtually continuous dyskinetic activity, impairing the animal's normal behaviour. Observation was carried out for up to 6 h with ratings of disability and dyskinesia at 15-min intervals.

2.8. Statistical analysis

Statistical analysis was carried out for the period corresponding to the observed duration of drug effect. Total locomotor activity counts and disability scores over 4 h for haloperidol treated marmosets were compared to a control group of normal marmosets using the Kruskal–Wallis one-way analysis of variance followed where appropriate by the Mann–Whitney U test (probability set at $p<0.05$). Total locomotor activity counts and disability scores for all animals, and dyskinesia scores for L-DOPA primed animals for up to 4 h were compared to a control group of MPTP-treated marmosets using the Kruskal–Wallis one-way analysis of variance followed where appropriate by the Mann–Whitney U test (probability set at $p<0.05$).

3. Results

3.1. Effect of SB-224289-A and SKF-99101-H administration in haloperidol-treated common marmosets

Chronic administration, daily for approximately 2 years, of haloperidol (0.25–2.0 mg/kg po) induced akinesia and bradykinesia that lasted for approximately 4–6 h following each dose. The animals would remain in fixed, often abnormal postures and exhibited limited response to external stimuli. No dyskinesia was observed during the chronic dosing phase. Once drug effect had expired and on

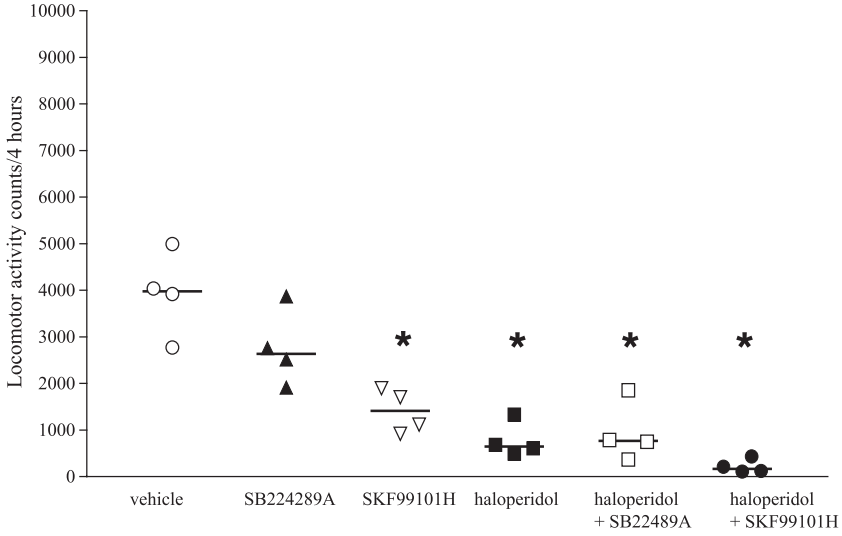

Fig. 1. Effect of SK-F99101-H and SB-224289-A alone and in combination with haloperidol on locomotor activity in common marmosets previously treated chronically with haloperidol. Locomotor activity expressed as median of total scores over 4 h. * Indicates values significantly different to vehicle ($p<0.05$ Mann–Whitney test). Haloperidol dose=0.25 mg/kg po, SKF-99101-H dose=1.0 mg/kg sc, SB-224289-A dose=5.0 mg/kg po.

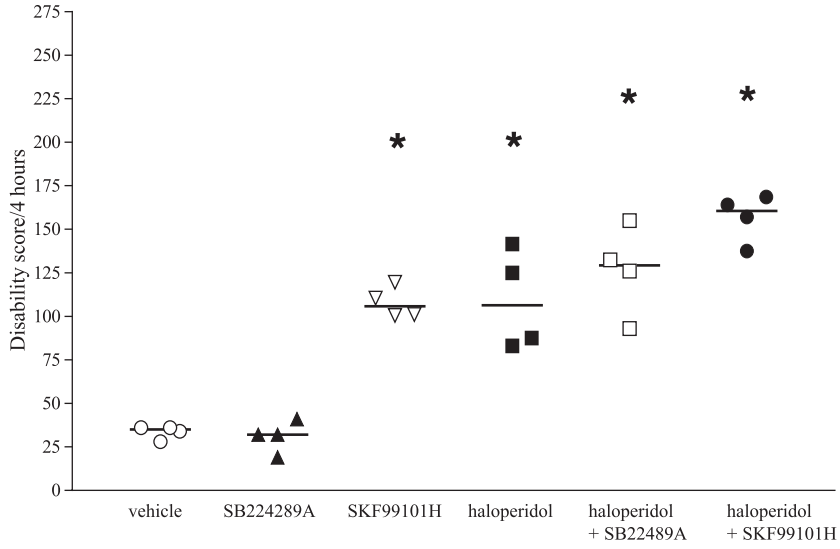

Fig. 2. Effect of SKF-99101-H and SB-224289-A alone and in combination with haloperidol on disability in common marmosets previously treated chronically with haloperidol. Disability rating expressed as median of total scores over 4 h. * Indicates values significantly different to vehicle ($p<0.05$ Mann–Whitney test). Haloperidol dose=0.25 mg/kg po, SKF-99101-H dose=1.0 mg/kg sc, SB-224289-A dose=5.0 mg/kg po.

non-drug days, the animals displayed the normal range of behaviour. Daily haloperidol (0.25–2.0 mg/kg po) dosing was stopped prior to starting the administration of 5-$HT_{1B/D}$ receptor antagonist and agonist.

Administration of SB-224289-A (5.0 mg/kg po) alone to previously haloperidol-treated marmosets did not effect locomotor activity or induce other changes in motor behaviour. When given in combination, SB-224289-A (5.0 mg/kg po) did not affect the motor disability induced by administration of haloperidol (0.25 mg/kg po) (Figs. 1 and 2) which was significantly different to vehicle.

SKF-99101-H (1.0 mg/kg sc) administration caused a reduction in total locomotor activity over a 4-h period and induced motor disability (Figs. 1 and 2). All of the animals exhibited akinesia or bradykinesia. When movement occurred, it was slow with trunk and limb rigidity. Occasional dystonic movements were observed including leg elevations and torticollis. SKF-99101-H (1.0 mg/kg sc) did not reverse haloperidol (0.25 mg/kg po) induced motor deficits when given in combination rather there was a trend toward increasing motor deficits (Figs. 1 and 2).

3.2. Effect of SB-224289-A and SKF-99101-H administration in MPTP-treated common marmosets

Prior to commencing the experiment, the animals exhibited stable motor deficits with reduced locomotor activity, abnormal posture, poor co-ordination and reduced

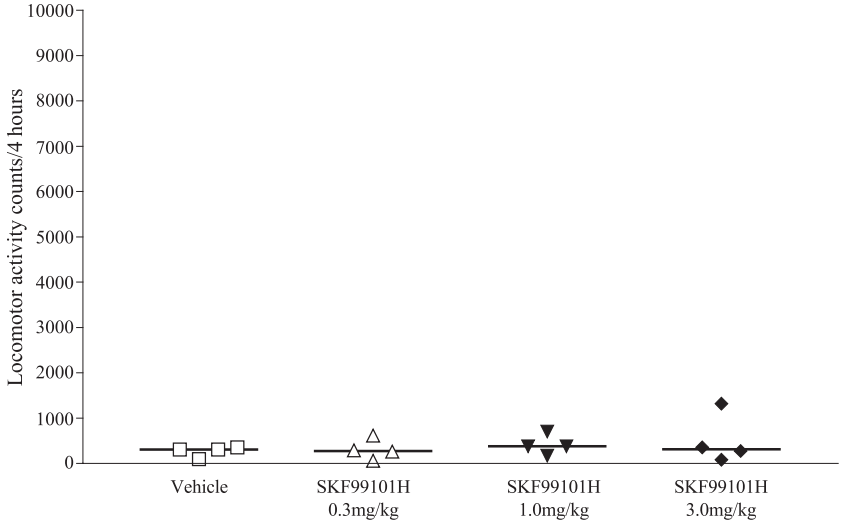

Fig. 3. Effect of SKF-99101-H on locomotor activity in MPTP-treated, non L-DOPA-primed marmosets. Locomotor activity expressed as median of total scores over 4 h. SKF-99101-H dose=0.3, 1.0 and 3.0 mg/kg sc.

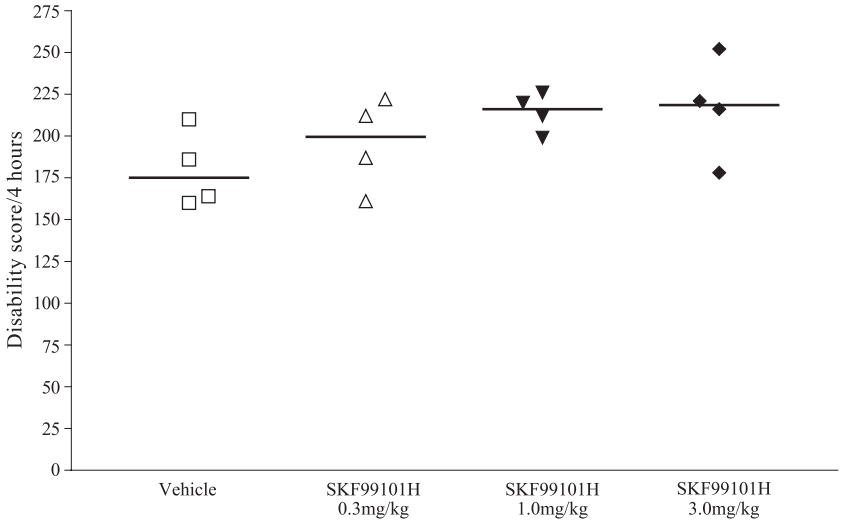

Fig. 4. Effect of SKF-99101-H on reversal of disability in MPTP-treated, non L-DOPA-primed marmosets. Disability rating expressed as median of total scores over 4 h. SKF-99101-H dose=0.3, 1.0 and 3.0 mg/kg sc.

head checking movements. Treatment of drug naïve, MPTP-treated marmosets with SB-224289-A (5.0 mg/kg po) did not improve or worsen locomotor activity or motor disability. The administration of SKF-99101-H (1.0 mg/kg sc) induced a slight increase in locomotor activity, but exacerbated motor disability, however, these were not significantly different compared to vehicle administration. Data for these experiments are not shown. The dose response effect of SKF-99101-H (0.3, 1.0, 3.0 mg/kg sc) was investigated in MPTP-treated, non-L-DOPA-primed marmosets that had previously received acute administrations of L-DOPA and other antiparkinsonian drugs. SKF-99101-H (0.3, 1.0, 3.0 mg/kg sc) had no significant effect on locomotor activity in these animals. Posture and movement appeared very rigid and checking behaviour was reduced. This slightly increased motor disability scores in a dose dependent manner, but these were not significantly different to vehicle (Figs. 3 and 4).

3.3. Effect of SB-224289-A and SKF-99101-H administration on L-DOPA in MPTP-treated, L-DOPA-primed common marmosets

Administration of L-DOPA (2.5, 5.0 and 12.5 mg/kg po plus carbidopa 12.5 mg/kg po) increased locomotor activity, reduced motor disability and induced dyskinesia in a dose related manner (data not shown for experiments using L-DOPA 2.5 and 5.0 mg/kg). L-DOPA (12.5 mg/kg po plus carbidopa 12.5 mg/kg po) reversed motor deficits for approximately 3–4 h. Dyskinesia including chorea and

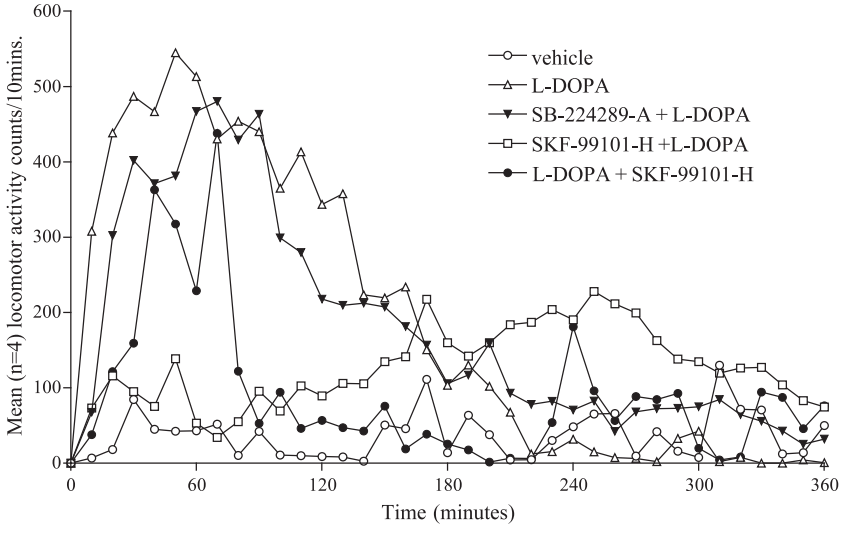

Fig. 5. Time course of locomotor activity following administration of L-DOPA. L-DOPA 12.5 mg/kg alone (△), in combination with SB-224289-A 5.0 mg/kg (▼), in combination with SKF-99101-H 1.0 mg/kg (□) as pre-treatment to SKF-99101-H 1.0 mg/kg (●) and vehicle control (○). Locomotor scores expressed as mean (n=4) counts per 10 min.

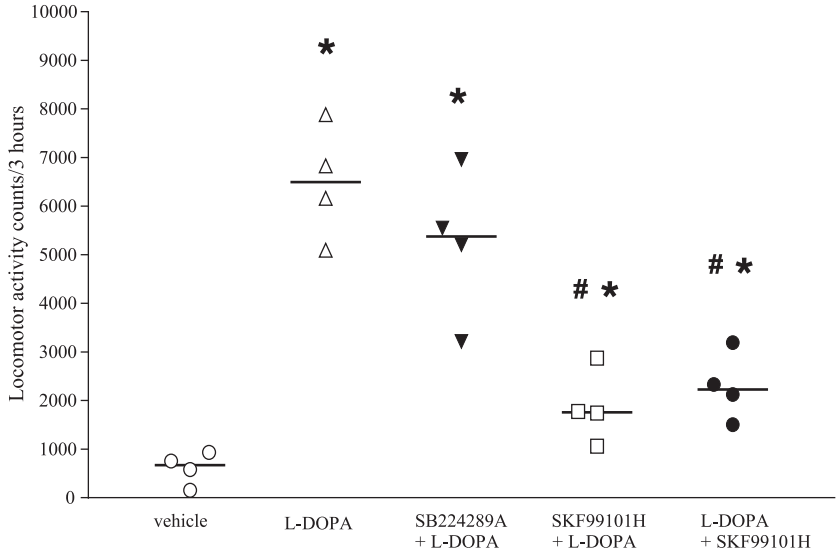

Fig. 6. Effect of SKF-99101-H and SB-224289-A on L-DOPA-induced locomotor activity in MPTP-treated, L-DOPA-primed common marmosets. Locomotor activity expressed as median of total scores over 3 h. * Indicates values significantly different to vehicle, # indicates values significantly different to L-DOPA ($p<0.05$ Mann–Whitney test). L-DOPA dose=12.5 mg/kg po, SKF-99101-H dose=1.0 mg/kg sc, SB-224289-A dose=5.0 mg/kg po.

dystonia of the limbs and trunk were induced that reached a peak approximately 75 min after dosing. Administration of SB-224289-A (5.0 mg/kg po) did not alter the L-DOPA (12.5, 5.0 and 2.5 mg/kg po plus carbidopa 12.5 mg/kg po) induced increase in locomotor activity, reversal of motor disability or intensity of dyskinesia (Figs. 5–8).

Administration of SKF-99101-H (1.0 mg/kg sc) inhibited the L-DOPA (12.5 mg/kg po plus carbidopa 12.5 mg/kg po) induced increase in locomotor activity, reversal of motor disability and dyskinesia induction in the first 3 h following L-DOPA administration (Figs. 5–8). Locomotor activity and dyskinesia increased slowly and only became maximal at approximately 4 h following L-DOPA administration (Fig. 5). The dyskinesia observed was both choreic and dystonic in form but less severe than those observed following administration of L-DOPA (12.5 mg/kg po plus carbidopa 12.5 mg/kg po) alone.

To assess whether SKF-99101-H (1.0 mg/kg sc.) altered L-DOPA plus carbidopa absorption, L-DOPA (12.5 mg/kg po plus carbidopa 12.5 mg/kg po) was administered 1 hour prior to SKF-99101-H (1.0 mg/kg sc). Administration of SKF-99101-H (1.0 mg/kg sc) caused a reduction in L-DOPA (12.5 mg/kg po plus carbidopa 12.5 mg/kg po) induced locomotor activity and reversal of motor disability (Figs. 5–7).

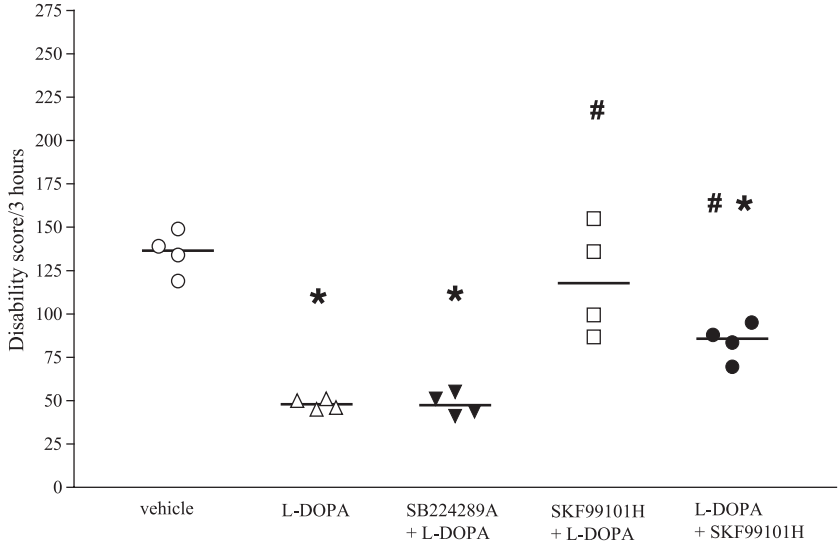

Fig. 7. Effect of SKF-99101-H and SB-224289-A on L-DOPA-induced reversal of disability in MPTP-treated, L-DOPA-primed common marmosets. Disability rating expressed as median of total scores over 3 h. * Indicates values significantly different to vehicle, # indicates values significantly different to L-DOPA ($p<0.05$ Mann–Whitney test). L-DOPA dose=12.5 mg/kg po, SKF-99101-H dose=1.0 mg/kg sc, SB-224289-A dose=5.0 mg/kg po.

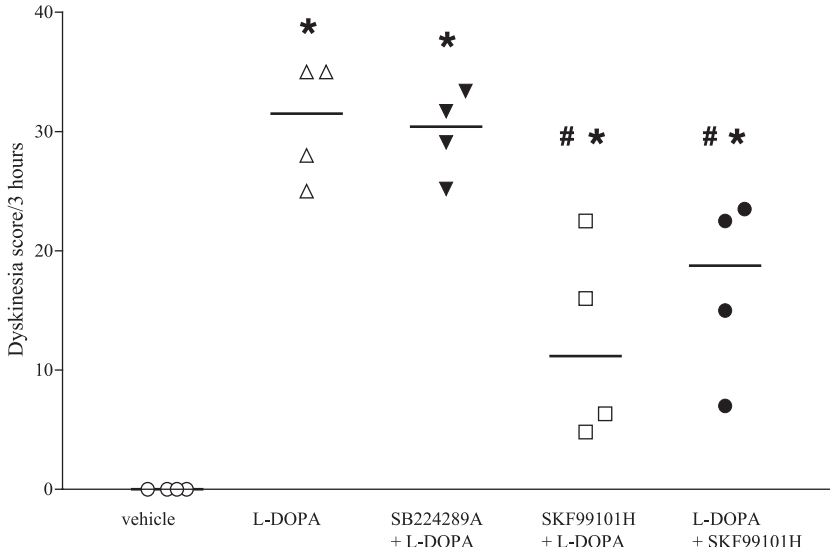

Fig. 8. Effect of SKF-99101-H and SB-224289-A on L-DOPA-induced dyskinesia in MPTP-treated, L-DOPA-primed common marmosets. Dyskinesia rating expressed as median of total scores over 3 h. * Indicates values significantly different to vehicle, # indicates values significantly different to L-DOPA ($p<0.05$ Mann–Whitney test). L-DOPA dose=12.5 mg/kg po, SKF-99101-H dose=1.0 mg/kg sc, SB-224289-A dose=5.0 mg/kg po.

Dyskinesia was reduced for the remainder of the duration of L-DOPA's effect.

4. Discussion

Dyskinesia is a treatment limiting side effect of some antipsychotic therapies and of L-DOPA treatment of Parkinson's disease (Glazer, 2000; Nutt, 1990; Olanow and Obeso, 2000). There is a need to establish the underlying mechanism of dyskinesia induction and to develop treatments that have a lower propensity to initiate dyskinesia or that are able to reduce the intensity of established involuntary movements.

The localisation and density of 5-HT_{1B} receptors in the human substantia nigra, ventral pallidum, globus pallidus, nucleus accumbens and caudate nucleus suggest that they play a role in the regulation of motor function (Varnas et al., 2001). Consequently, 5-HT_{1B} receptors may be a potential therapeutic target for the treatment of motor abnormalities associated with the chronic treatment of Parkinson's disease and schizophrenia. Some support for this concept comes from the ability of the 5-HT_{1B} agonist, anpirtoline, to produce locomotion in rats and mice that is attenuated by administration of the 5-$HT_{1B/D}$ antagonist GR127935 (O'Neill and Parameswaran, 1997; O'Neill et al., 1997) Similarly, the 5-$HT_{1B/D}$ agonist, SKF-99101-H, induces locomotor activity in guinea pigs that is blocked by GR127935 (O'Neill et al., 2000). Dopamine release in the prefrontal cortex and striatum may also be affected by 5-HT_{1B} receptor activation since 5-HT_{1B} agonists and the SSRI, fluoxetine, increase dopamine levels as measured by in vivo microdialysis (Benloucif et al., 1993; Galloway et al., 1993; Matsumoto et al., 1999; Sarhan et al., 1999). Hence, $5HT_{1B}$ agonists should increase locomotor activity in normal and MPTP-treated common marmosets, reverse the motor deficits induced by haloperidol and enhance the effects of L-DOPA.

Haloperidol is a dopamine D2 receptor antagonist which has low affinity for 5-$HT_{1B/D}$ receptors in rats with Ki values of 6950 nM for $5HT_{1D}$ receptors and <50% at 10,000 nM for $5HT_{1B}$ receptors (Bymaster et al., 1996). In this study, chronic administration of haloperidol induced a temporary akinetic/cataleptic syndrome, lasting for 4–6 h. However, in contrast to other reports in common marmosets and different primate species, neither dystonia nor tardive dyskinesia was observed. Surprisingly, in marmosets previously receiving chronic haloperidol treatment, the 5-$HT_{1B/D}$ receptor agonist, SKF-99101-H, suppressed locomotor activity and induced infrequent mild dystonia. Similarly, treatment with SKF-99101-H following acute haloperidol re-treatment tended to further reduce locomotor activity and worsen disability. Administration of the 5-HT_{1B} antagonist SB-224289-A did not alter the basal activity of previously haloperidol-treated marmosets or alter the response to acute haloperidol administration. These findings are in agreement with the inability of the 5-$HT_{1B/D}$ receptor antagonist GR127935 to induce catalepsy and to inhibit dopamine D_2 receptor antagonist induced catalepsy in rats (Kalkman et al., 1997). So, overall these data suggest that activation of 5-$HT_{1B/D}$ receptors in normal common marmosets causes a reduction in locomotor activity and induces a temporary syndrome of motor deficits.

The administration of SKF-99101-H to both drug naïve and non-drug naïve MPTP-treated marmosets did not significantly alter basal motor disability in contrast to its effects in normal marmosets. A slight exacerbation of motor disability was induced with a further reduction of alertness and a pronounced rigidity that was observed when the

animals moved. However, MPTP-treated marmosets are markedly akinetic or bradykinetic and any worsening of motor disability would be difficult to detect. As with normal marmosets, administration of the 5-HT_{1B} antagonist SB-224289-A did not alter motor behaviour in MPTP-treated animals. L-DOPA reverses motor disability in MPTP-treated common marmosets and administered chronically, induces choreic and dystonic dyskinesia (Pearce et al., 1995). Once established dyskinesia can be induced by acute administration of L-DOPA and dopamine agonists. The administration of SKF-99101-H to marmosets primed to exhibit dyskinesia markedly altered the motor response to L-DOPA. There was an initial abolition of dyskinesia, but this was however accompanied by a reduction in the reversal of motor disability. When administered prior to L-DOPA the inhibitory effect of SKF-99101-H lasted for several hours after which L-DOPA-induced activity and dyskinesia was again apparent. Delaying the administration of SKF-99101-H until the peak of L-DOPA's effect reduced locomotor activity and dyskinesia to basal levels at which they remained for the duration of the test. Since L-DOPA is administered orally, this suggests that SKF-99101-H did not alter its absorption from the gastro-intestinal tract, but inhibited the L-DOPA response by action on central 5-$HT_{1B/D}$ receptors. The experiment also suggests that the return of L-DOPA-induced motor activity and dyskinesia after pre-treatment with SKF-99101-H was a reflection of its pharmacokinetic profile rather than a component of its pharmacodynamic action. A similar effect in MPTP-treated common marmosets was produced by the mixed 5-$HT_{1A/B}$ agonist RU24969, which reduced the increase in motor activity and dyskinesia induced by L-DOPA (Iravani et al., 2003). However, RU24969 has a high affinity for 5-HT_{1A} and 5-HT_{1B} receptors, and has some activity on 5-HT_3 and 5-HT_{2A} receptors and the locomotor activity induced in rats is thought to be mediated by its actions on both 5-HT_{1A} and 5-HT_{1B} receptors (O'Neill and Parameswaran, 1997). Consistent with its lack of effect in haloperidol-treated and non-primed MPTP-treated marmosets, administration of the 5-HT_{1B} receptor antagonist SB-224289-A did not alter motor activity or the intensity of dyskinesia in MPTP-treated, L-DOPA-primed animals.

In conclusion, in the common marmoset, activation of 5-$HT_{1B/D}$ receptors induces motor deficits and inhibits the motor response to L-DOPA, whereas blockade of 5-HT_{1B} receptors has no observable effects on motor behaviours. These data suggest that neither stimulation nor blockade of 5-HT_{1B} receptors will be therapeutically beneficial in the treatment of Parkinson's disease or in the treatment of drug-induced dyskinetic syndromes.

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