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Chronic treatment with the D_1 receptor antagonist, SCH 23390, and the D_2 receptor antagonist, raclopride, in cebus monkeys withdrawn from previous haloperidol treatment

Extrapyramidal syndromes and dopaminergic supersensitivity

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Abstract. The effects of chronic treatment with dopamine (DA) D_1 and D_2 receptor antagonists were evaluated in eight *cebus apella* monkeys with mild oral dyskinesia after previous haloperidol treatment. SCH 23390 (D_1 antagonist) was given daily to investigate the direct behavioural effect during long-term treatment and the subsequent supersensitivity to DA agonists. Raclopride (D_2 antagonist) was investigated for comparison. All drugs were given subcutaneously. SCH 23390 and raclopride induced dystonic syndromes, catalepsy, sedation and reduced locomotor activity. The monkeys developed marked tolerance to the dystonic effect of SCH 23390, while they showed increased sensibility to the dystonic effect of raclopride. Baseline oral dyskinesia (24 h after injection) remained unchanged during D_1 antagonist treatment, while it increased during D_2 antagonist treatment. SCH 23390 induced supersensitivity to the oral dyskinesia- and grooming-inducing effects of SKF 81297 (D_1 agonist) after 9 weeks, while the subsequent treatment with raclopride induced supersensitivity to the reactivity- and stereotypy-inducing effects of quinpirole (D_2 receptor agonist) after 3 weeks. Because of the possibility of a carry-over effect (SKF 81297-induced oral hyperkinesia and grooming), other changes in raclopride-induced behaviours cannot be ruled out. The development of tolerance to the dystonic effect of SCH 23390 and the unchanged baseline oral dyskinesia during SCH 23390 treatment indicate an advantageous profile of side effects of DA D_1 receptor blockade.

Key words: D_1 receptors – D_2 receptors – Extrapyramidal side effects – Dopaminergic supersensitivity – SCH 23390 – Raclopride – SKF 81297 – Quinpirole – Monkeys

All commonly used neuroleptics may cause acute and chronic extrapyramidal syndromes (EPS), such as dystonia, parkinsonism, akathisia and dyskinesia (acute or tardive) (Rupniak et al. 1986; Gerlach and Casey 1988; Adler et al. 1989). EPS are, as the antipsychotic effect thought to be mediated by the dopamine (DA) D_2 receptor subtype (Seeman 1980; Coffin et al. 1989; Hyttel et al. 1989) or after the successful use of recombinant DNA techniques the D_2 receptor subfamily, i.e. DA D_2, D_3 and D_4 receptor subtypes (Sokoloff et al. 1990; Snyder 1990; Van Tol et al. 1991; Sibley and Monsma Jr 1992). Because of the often severe side effects of neuroleptics, there has been a search for new, potential antipsychotic drugs lacking the propensity to induce EPS. The first selective D_1 receptor antagonist, SCH 23390, was described in 1983 (Hyttel 1983; Iorio et al. 1983). SCH 23390 has been proposed as a potential antipsychotic agent, based upon its ability to exert potent effects upon animal behaviours in many models considered predictive of antipsychotic activity (Iorio et al. 1983; for review see Clark and White 1987; Waddington 1988; Andersen et al. 1992; Nielsen and Andersen 1992). Furthermore, its lack of D_2 receptor blocking capacity implies a reduced propensity to produce neurological side effects.

Some animal studies have shown fewer EPS with D_1 blocking drugs such as SCH 23390 when compared to classical neuroleptics (Iorio et al.1983; Creese and Chen 1985; Gerhardt et al. 1985; Coffin et al. 1989), but the results are conflicting. Thus, other studies have shown a similar liability of SCH 23390 to induce EPS as typical neuroleptics (Morelli and Di Chiara 1985; Amalric et al. 1986; Kistrup and Gerlach 1987; Löschmann et al. 1991; Casey 1992).

Chronic neuroleptic treatment blocks and subsequently induces DA supersensitivity of the D_2 receptors in the brain (Seeman 1980). DA supersensitivity has been used to predict the liability of a drug to induce tardive dyskinesia (TD) (Baldessarini et al. 1980; Bernardi et al. 1981; Palermo-Neto 1984; Felicio et al. 1987; Hyttel et al.1989), although newer studies with positron emission tomography of brain of living patients with TD indicate that TD is not related to an increased number of D_2 receptors (Blin et al. 1989; Andersson et al. 1990).

Chronic treatment with SCH 23390 might induce a significant increase in the number of D_1 receptors in the striatum and substantia nigra (Creese and Chen 1985; Hess et al. 1986). In some studies, however, chronic D_1

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antagonist treatment does not produce the subsequent behavioral supersensitivity to DA agonists (e.g., apomorphine, methylphenidate and amphetamine) (Christensen et al. 1984a, 1985), while others have found this to be the case (Hess et al. 1986; Maldonado et al. 1990).

The aim of this study was to investigate the behavioural effects of chronic DA D_1 and D_2 receptor blockade, and the potential development of supersensitivity to DA (D_1 and D_2) receptor agonists.

Material and methods

Subjects. Eight adult *Cebus apella* monkeys, five female and three males, weighing 2.6–4.3 kg, were used. The monkeys had received oral haloperidol 5–10 mg/day for 2 years in order to induce a dyskinetic syndrome. At the time of the study, where the monkeys had not received haloperidol treatment for $1\frac{1}{2}$ years, five monkeys had mild oral dyskinesia. The monkeys have been used and described in previous studies (Lublin and Gerlach 1988; Peacock et al. 1990; Lublin et al. 1992). They had been free of medication for 2 months before the current investigation. The monkeys were housed in separate cages in temperature and humidity regulated rooms with a 12-h light/dark cycle.

Drugs and design. The drugs and doses were: SCH 23390 (R)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepin-7-ol hemimalate (D_1 receptor antagonist) given in individually adjusted subdystonic doses. A subdystonic dose was a dose just below the dose known to produce dystonia in each animal. Raclopride S-(−)-3,5-dichloro-N-[(1-ethyl-2-pyrrolidinyl)methyl]-2-hydroxy-6-methoxy-benzamide L(+)-tartrate (D_2 receptor antagonist) was also given in individually adjusted subdystonic doses. When an antagonist induced dystonia, the same dose was given again the next day. If dystonia was not induced again, the dose was increased the following day. If dystonia was induced on 2 successive days the dose was decreased, and not until after another 7 days, was a new attempt made to increase the antagonist dose.

The DA receptor agonists were SKF 81297, 2,3,4,5-tetrahydro-6-chloro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine (high efficacy D_1 receptor agonist), 0.3 mg/kg, and quinpirole (LY 171555), trans-(−)-4aR-4,4a,5,6,7,8,8a,9-octahydro-5-propyl-1H-pyrazolo [3,4-g] quinoline monohydrochloride (D_2 receptor agonist), 0.1 mg/kg. Saline was given as placebo. The doses of SKF 81297 and quinpirole were based upon experience from previous studies (Lublin and Gerlach 1988; Lublin et al. 1992). The drugs were freshly prepared in saline just before subcutaneous injection.

The drugs were given as indicated in Fig. 1. The antagonists were given daily for variable periods, depending upon the development of supersensitivity to the DA receptor agonists. In the case of SCH 23390, a 3 + 6 week period was required. After a 4-week washout period, raclopride was given for 3 weeks, after which supersensitivity developed.

SKF 81297, quinpirole and saline were given in five test periods (Fig. 1): before (test period T1), between the first and second treatment period with SCH 23390 (test period T2), at the end of treatment with SCH 23390 (test period T3), and before and after treatment with raclopride (test periods T4 and T5). The tests with SKF 81297, saline and quinpirole (in that order) were performed with an interval of 2 days. In all cases, the drugs were given at the same time each day.

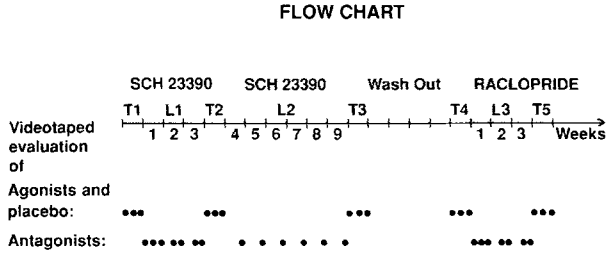

Fig. 1. Flow chart of the study. During the long-term treatment periods (*L*), the monkeys were exposed to SCH 23390 (*L1* and *L2*) or raclopride (*L3*) in increasing doses. During the test periods (*T1–T5*), the monkeys were exposed to single doses of SKF 81297 0.3 mg/kg, saline and quinpirole 0.1 mg/kg with intervals of two days. During the wash-out period, between T3 and T4, the animals were drug-free. The time points of video recordings are shown below

Evaluation. The effects of drugs were evaluated using a rating scale for DA agonist and antagonist behaviour (Table 1) (Korsgaard et al. 1985; Lublin and Gerlach 1988). Locomotor activity, stereotypy, reactivity, sedation, grooming, dystonia and bradykinesia (parkinsonism) were rated on a 7-point scale (0–6). Oral hyperkinesia (tongue protrusions, chewing movements and licking/biting movements) were scored by actual counts/90 s. The behaviour of the monkeys was rated before the injection (baseline) (i.e. 24 h after last drug administration during the antagonist treatments) and at 15-min intervals for a period of 60 min. The monkeys were videotaped for later blind evaluation. The days of evaluation are indicated on Fig. 1.

Statistics. The comparison of drug effects with those of saline, were performed by means of Wilcoxon's signed rank test for paired data. The data from the chronic treatment periods was evaluated by Friedman's test for non-parametric data followed by Wilcoxon's signed rank test for paired data. Comparison between the SCH 23390 and raclopride treatment courses was done with a non-parametric analysis of variance.

Results

Effects of SCH 23390

SCH 23390 induced a dystonic/dyskinetic syndrome in all monkeys, but with great individual variation. The syn-

Table 1. Rating scale for evaluation of dopamine agonist and antagonist behaviour. The scorings were 0 = normal; 1 = doubtful (can be variation of the normal); 2 = mild (behaviour slightly more pronounced than normal); 3 = mild to moderate; 4 = moderate (behaviour pronounced but interrupted); 5 = moderate to severe; 6 = severe (behaviour continuous)

Behaviour rating scale		Score
Locomotor activity	Generalized non-stereotyped movements of the whole body	± 0–6
Stereotypy	Non-oral stereotyped movements of the head, neck, limbs and trunk	0–6
Reactivity	Orientation or aggressiveness towards objects or observer	0–6
Grooming	Nibbling, biting or licking of the fur/or teasing of the fur with the forepaws	0–6
Sedation	Drowsiness/sleepiness	0–6
Dystonia	Tonic contractions, clonic seizures, writhing, flinging of the body, thrusting of the legs, grimacing, gaping, bizarre twisted postures	0–6
Bradykinesia	Slowness of movements, prolonged sustained abnormal posture	0–6

drome varied from mild, brief or intermittent attacks, to prolonged and sustained attacks. The dystonic/dyskinetic syndrome consisted of muscle spasms and abnormal postures, opening of the mouth, biting the air or the cage, torticollis of the neck, torsion, flexion or extension of limbs, twisting and extension of the trunk. Often the monkeys flung themselves about the cage.

All monkeys developed tolerance to the dystonic effect of SCH 23390. Thus, increasing doses were required to produce dystonia (Fig. 2). In most cases, following a dystonic attack, the dystonia could not be induced the next day when the same dose of SCH 23390 was given to the monkey. The mean ($\pm$ SEM) start dose of SCH 23390 was 0.010 mg/kg; the mean dose after 3 weeks was 0.041 $\pm$ 0.004 mg/kg ($P = 0.0107$ compared to the start dose); and the mean end dose was 0.149 $\pm$ 0.041 mg/kg ($P = 0.0115$) corresponding to a 15-fold increase in dose (Fig. 2). In all monkeys, it was possible to gradually increase the dose of SCH 23390 after a dystonic attack without inducing dystonia (range 4–30 fold increase in dose). Thus for the whole treatment period of 9 weeks, no significant increase in the degree of dystonia was found, even though the doses were increased.

During the entire study there were periods where the monkeys were bradykinetic (parkinsonian) with slow movements and often fixed postures (cataleptic). During the treatment course of 9 weeks (with increasing doses) there was a slight and significant increase in bradykinesia ($P < 0.05$) (Fig. 2).

During the treatment with SCH 23390 the monkeys were characterized by reduced locomotor activity and sedation (Fig. 2); they sometimes slept. During the study period, with increasing doses, a decrease in locomotor activity ($P < 0.01$) and an increase in sedation were found over time ($P < 0.01$) (Fig. 2). Although the animals were often sedated before and after dystonia and bradykinesia, the presence of dystonia and/or marked bradykinesia overrode the presence of sedation.

During the entire period of 9 weeks of treatment, SCH 23390 had little effect upon oral hyperkinesia (Figs. 2 and 3), but with individual variations. There were no significant changes in baseline dyskinesia (Fig. 3), but during actual SCH 23390 treatment there was a slight increase in oral hyperkinesia (acute dyskinesia) ($P < 0.01$) (Fig. 2). There was a mild, but significant increase in baseline grooming ($P < 0.05$) (Fig. 3), but no increase in grooming was found during the actual D_1 antagonist treatment.

Effects of raclopride

Raclopride induced dystonia, bradykinesia, sedation and reduced locomotor activity in all monkeys (Fig. 2). The dystonia and bradykinesia after raclopride were identical

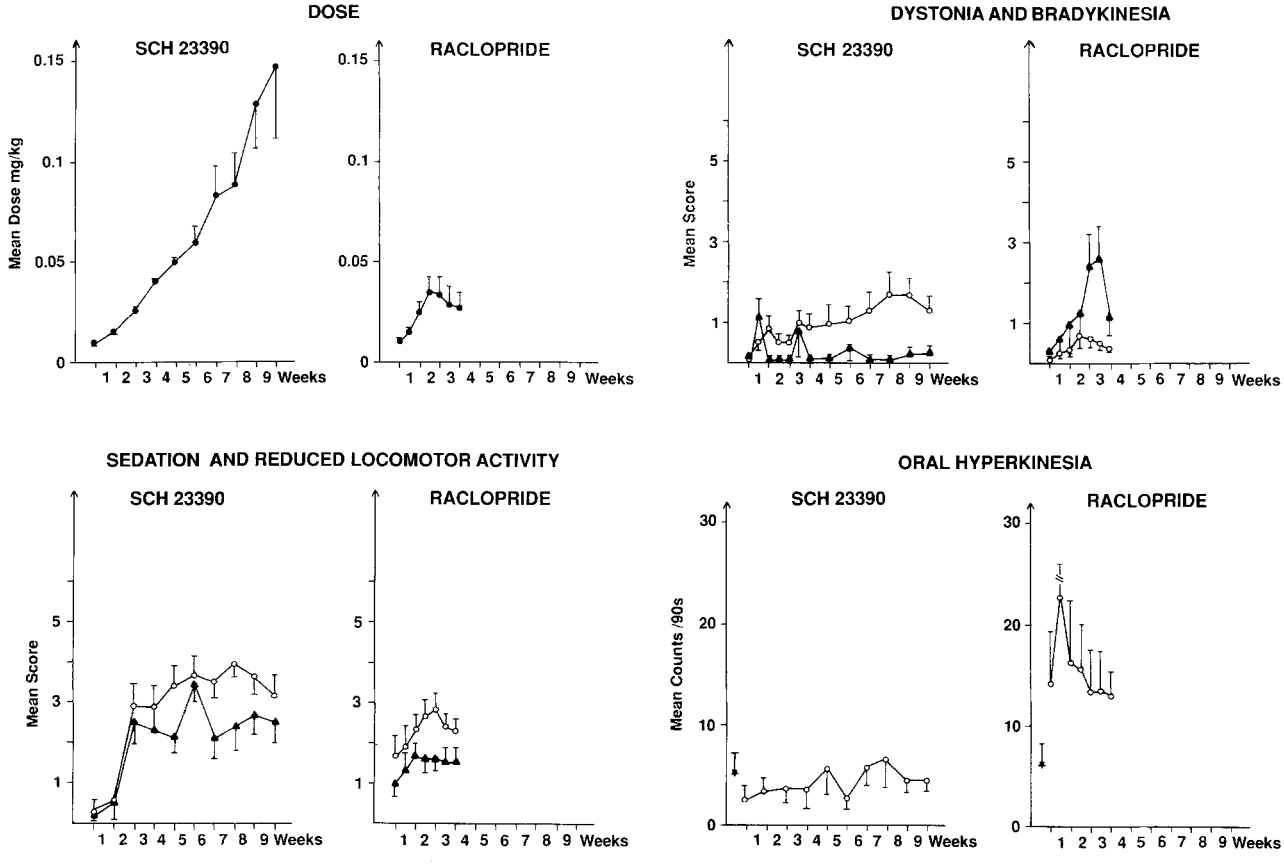

Fig. 2. Dose, dystonia (closed triangle), bradykinesia (open circle), sedation (closed triangle), reduced locomotor activity (open circle) and oral hyperkinesia during treatment with SCH 23390 and raclopride. Each point represents the mean ($\pm$ SEM) of four single determinations of 90 s (15, 30, 45 and 60 min after injection) in each of the 8 monkeys. * indicates the saline values of oral dyskinesia and grooming. Saline values of dystonia, bradykinesia, sedation and reduced locomotor activity (that were about zero) are not indicated

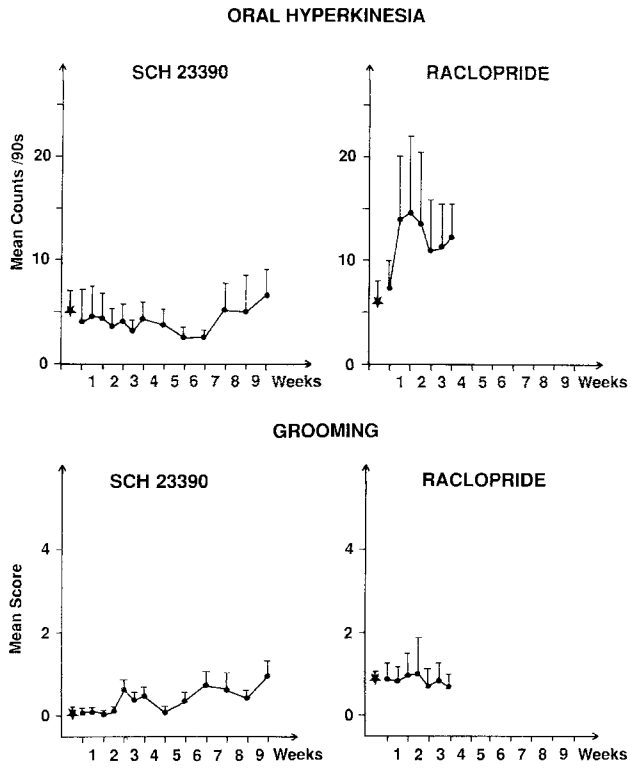

Fig. 3. Baseline oral hyperkinesia and grooming during treatment with SCH 23390 and raclopride. Each point represents the mean ($\pm$ SEM) of 8 monkeys 24 h after drug administration. * indicates the saline values of oral dyskinesia and grooming

to those after SCH 23390, although the dystonia after raclopride was more pronounced (more severe and longer lasting) (compared to SCH 23390 first 3 weeks, $P < 0.01$). During the raclopride treatment there was a significant increase in dystonia ($P < 0.01$) (Fig. 2). Further, there was one remarkable difference in dystonia induced by raclopride as compared to SCH 23390; when raclopride had induced a dystonic attack at a given dose, it was not possible to increase or retain the same dose without inducing dystonia; the dose had to be reduced in order to avoid dystonia (Fig. 2). Thus, the course of dystonia during raclopride treatment was significantly different from that of SCH 23390, with no development of tolerance towards dystonia ($P < 0.01$).The mean dose at the beginning of the study was 0.010 mg/kg and after 3 weeks 0.027 $\pm$ 0.007 mg/kg (NS). The dose of raclopride did not differ significantly from that of SCH 23390 at the beginning of the antagonist treatment periods. At the end of week 3, the dose of raclopride was significantly lower than the dose of SCH 23390 ($P < 0.02$).

The monkeys were sedated ($P < 0.05$) with reduced locomotor activity compared to saline ($P < 0.05$) (Fig. 2). During the long-term treatment period, the changes in bradykinesia, sedation and locomotor activity were maintained, without significant changes over time. There were no significant differences between raclopride and SCH 23390 (first 3 weeks) with regard to bradykinesia, sedation and locomotor activity.

During raclopride treatment there was a small, but significant increase in baseline oral hyperkinesia ($P < 0.01$) (Fig. 3). During actual raclopride treatment, there was also a significant increase in oral hyperkinesia as compared to saline ($P < 0.05$) (Fig. 2), but with great individual variations. Six monkeys showed a large increase in oral hyperkinesia as compared to saline at the beginning of the treatment period (week 1) with a tendency towards a reduction during the remainder of the treatment period. Two monkeys had no changes or a minor decrease in oral hyperkinesia at the beginning of the long-term treatment period as compared to saline, and a tendency towards an increase during the remainder of the treatment period. Raclopride had no significant effect upon grooming behaviour as compared to saline (data not shown), but again, with individual variations.

During raclopride treatment grooming behaviour was scored lower ($P < 0.01$) and oral hyperkinesia was scored higher ($P < 0.01$) as compared to SCH 23390 (first 3 weeks).

Effects of dopamine agonists and saline following withdrawal of antagonists

Effects of saline. Five of the monkeys had spontaneous, mild oral tardive dyskinesia with a characteristic appearance in each animal, varying from slight lip and chewing movements to slight tongue protrusions. Each individual also showed a characteristic pattern of motor and grooming behaviour. After 9 weeks' treatment with SCH 23390, a significant increase in saline-related grooming behaviour as compared to pretreatment values was found (Fig. 4, $P < 0.01$). Otherwise, no significant saline-related changes in any other of the behavioral items were seen after long-term treatment with SCH 23390 or with raclopride.

Effects of SKF 81297. SKF 81297, 0.3 mg/kg, induced a significant increase in *oral hyperkinesia* in all monkeys compared to saline ($P < 0.05$) (Fig. 4). The effect was most pronounced in the monkeys with pre-existing oral dyskinesia, but was clearly seen in all of the monkeys. The oral hyperkinesia during SKF 81297 treatment was much more intense, with a greater amplitude and rapidity of movements, than that seen after saline. SKF 81297 induced tongue protrusions, chewing movements and licking or biting, but with great individual variation. In two of the five monkeys with pre-existing oral dyskinesia, SKF 81297 induced oral hyperkinesia with extreme licking movements and tongue protrusions. In the other monkeys the oral movements increased from a mild to a moderate-severe degree.

After 3 weeks' treatment with SCH 23390, SKF 81297 induced no further changes as compared to week 0. Both the quality and intensity of oral hyperkinesia was unchanged. After 6 weeks' further treatment with SCH 23390, SKF 81297, 0.3 mg/kg, significantly increased the number of counts of oral movements, as compared to the number of counts before SCH 23390 (Fig. 4, $P < 0.01$). The quality of oral movements was unchanged.

In each test period, SKF 81297 induced a significant increase in *grooming behaviour* as compared to saline ($P < 0.05$) (Fig. 4). In some monkeys, the grooming after

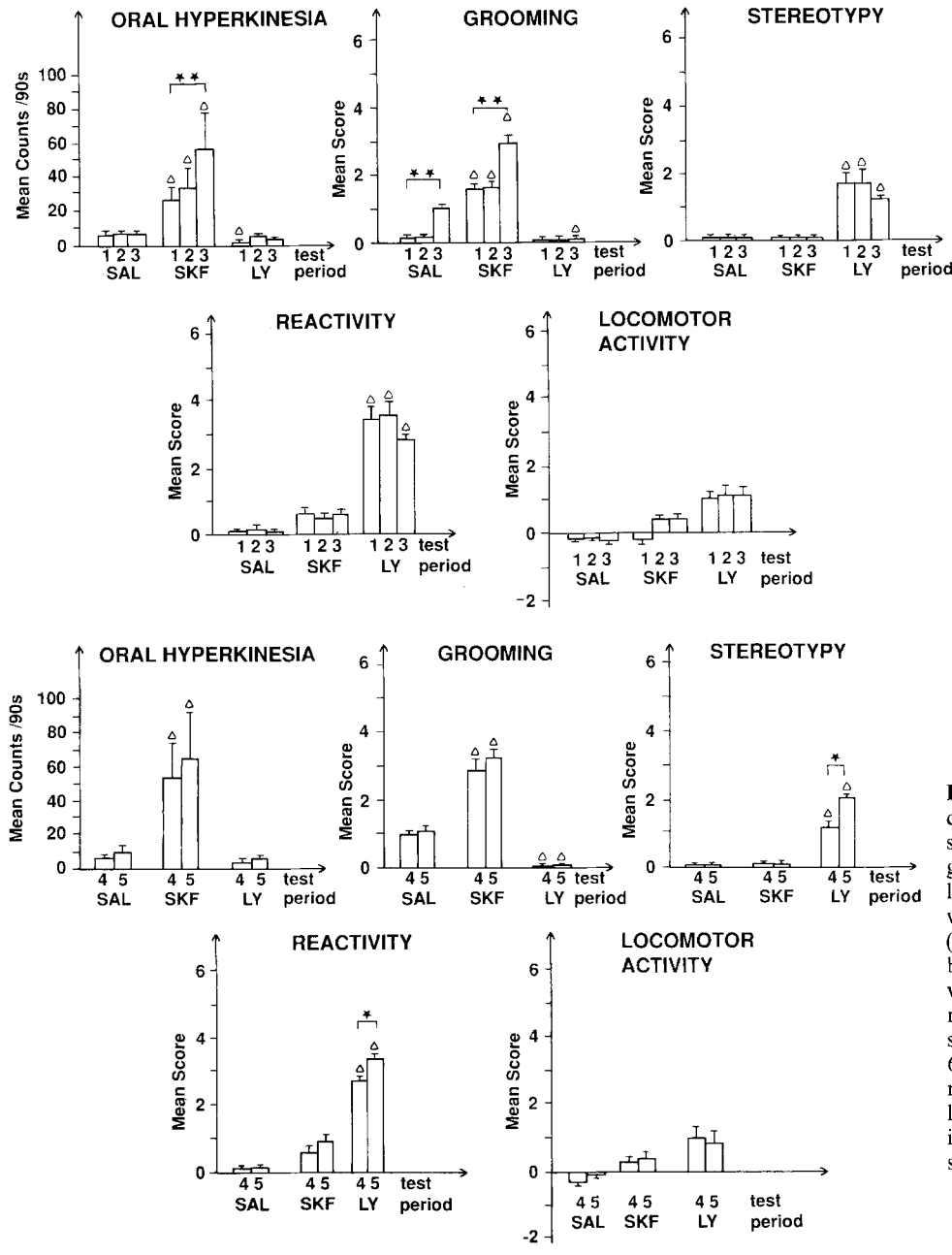

Fig. 4. Effects of SKF 81297 (*SKF*), quinpirole = LY 171555 (*LY*) and saline (*SAL*) upon oral hyperkinesia, grooming, stereotypy, reactivity and locomotor activity before (*T1*), after 3 weeks (*T2*) and 9 weeks of treatment (*T3*) with SCH 23390 (above), and before (*T4*) and after treatment (*T5*) with raclopride (below). Each column represents the mean (± SEM) of four single determinations (15, 30, 45 and 60 min after injection) in each of the 8 monkeys. $*P < 0.05$, $**P < 0.01$, the last test week compared to the first as indicated. $\Delta P < 0.05$, as compared to saline the same week

SKF 81297 had a compulsive character, primarily composed of excesses of licking and biting of the fur and forepaws, as a part of the general picture of increased oral movements. After 9 weeks' treatment with SCH 23390, there was a significant increase in the SKF 81297-induced grooming behaviour, as compared to the grooming score prior to the SCH 23390 treatment (Fig. 4, $P < 0.01$).

Locomotor activity, *reactivity* and *stereotypy* were not significantly changed by SKF 81297 (Fig. 4). In general the monkeys were attentive, but calm.

Chronic treatment with *raclopride* did not induce any significant changes in the effect of SKF 81297 upon any of the behavioral items (Fig. 4). However, it must be noted that SKF 81297-induced oral hyperkinesia and grooming had not returned to baseline values after the wash-out period (Fig. 4). Thus, the effects of raclopride on SKF 81297-induced behaviour must be viewed with caution.

Effects of quinpirole. Quinpirole induced increased *reactivity* and *stereotypy* (Fig. 4). There was no change after treatment with SCH 23390 for 3 (test period T2) or 9 weeks (test period T3) (Fig. 4).

Quinpirole had a tendency to reduce *grooming behaviour*, but only after 9 weeks' treatment with SCH 23390 (test period T3), when grooming was increased, was this behaviour significantly reduced as compared to saline ($P < 0.05$) (Fig. 4). Quinpirole also had a tendency to reduce *oral movements* as compared to saline, but only in test period T1, prior to SCH 23390 treatment, was this reduction significant ($P < 0.05$) (Fig. 4).

After 3 weeks' treatment with raclopride, quinpirole induced a small, but significant increase in *reactivity* and *stereotypy* (test period T5 compared to T4, $P < 0.05$) (Fig. 4). No changes were found in *grooming behaviour*, *oral hyperkinesia* and *locomotor activity* (test period T5 compared with T4)

Discussion

Extrapyramidal symptoms and sedation during antagonist treatment

In the present study, eight monkeys received long-term treatment with the selective D_1 receptor antagonist SCH 23390 and the selective D_2 receptor antagonist raclopride. SCH 23390 induced dystonic attacks that were qualitatively indistinguishable from those induced by raclopride, except that the dystonia was less intense, and of shorter duration. This is in agreement with earlier studies comparing D_1 and D_2 antagonists in non-drug-naive monkeys (Kistrup and Gerlach 1987; Christensen 1990). The most remarkable difference between raclopride and SCH 23390 was the development of a marked tolerance to the dystonic effect of SCH 23390, while the monkeys showed an increasing sensitivity to the dystonic effect of raclopride. All of the monkeys had dystonic attacks during both treatments, but in the case of SCH 23390 it was possible to increase the dose above the dose at which the dystonia originally appeared, without inducing dystonia. During treatment with raclopride, such an increase of the dose was not possible. On the contrary, the dose had to be reduced in order to avoid dystonia. The dystonic effect of the *D_2 receptor antagonist* in the present study is in agreement with the findings of many other studies with both drug-naive and non-drug-naive animals (Weiss and Santelli 1978; Liebman and Neale 1980; Christensen 1990; for review see Rupniak et al. 1986), including the increasing sensibility to EPS in monkeys having D_2 receptor antagonists (Coffin et al. 1989).

In the present study the DA receptor antagonists were given in individually adjusted subdystonic doses. The mean end doses were for SCH 23390 0.041 mg/kg (week 3) and 0.149 mg/kg (week 9) and for raclopride 0.027 mg/kg (week 3). In studies using oral administration of these drugs, much higher doses have been used (Neale et al. 1982; Coffin et al. 1989; McHugh and Coffin 1991). In the study by Casey (1990) tolerance developed to the dystonic effect of both SCH 23390 and haloperidol. In that study, constant and dystonic doses of the antagonists were given (0.025 mg/kg IM) for 31 days. In the present study, variable doses of the antagonists were given throughout study, because the intention was to give a subdystonic dose. In order to comply with this intention, the dose of SCH 23390 had to be increased throughout the study period, while the dose of raclopride had to be reduced during the last part of the study (Fig. 2). In a recently completed study in another group of neuroleptic sensitized *Cebus* monkeys, tolerance to the dystonic effect of raclopride (0.01 mg/kg SC) was induced, but only after a treatment period of 8 weeks (Lublin et al., to be published). Tolerance may develop to the dystonic effect of D_2 receptor antagonists, but high and possibly dystonic doses, and long treatment periods may be needed. (Neale et al. 1982; Casey 1990; Lublin et al., to be published).

In the present investigation, the study animals were *Cebus apella* monkeys, which had previously received haloperidol for a period of 2 years. In all eight monkeys, SCH 23390 induced dystonia, but only during the first weeks of the chronic treatment period. Furthermore, in spite of increasing doses of SCH 23390, the liability to induce dystonia decreased or disappeared, which is in agreement with the findings of Christensen (1990) and McHugh and Coffin (1991) in non-drug-naive monkeys. In the study of Coffin et al. (1989) peroral SCH 23390 only induced dystonia in monkeys after chronic treatment with haloperidol for more than half a year. These results might indicate that neuroleptic-sensitized monkeys have a markedly different sensitivity to drugs than drug-naive monkeys (Coffin et al. 1989). However, in another study, it has been shown that acute and intramuscular SCH 23390 at doses of 0.10 and 0.25 mg/kg was able to induce dystonia in drug-naive Cebus monkeys (Casey 1992). Thus, the findings regarding the ability of D_1 receptor antagonists to induce EPS in drug-naive monkeys are conflicting. In the present study the drugs were administered subcutaneously, while the drugs were administered perorally in the studies of Coffin et al. (1989) and McHugh and Coffin (1991). The route of drug administration may be an important factor determining the effects of D_1 antagonists, a peroral route of administration resulting in a lower bioavailability of the drug and thus a lesser effect than a parenteral route of administration (Christensen et al. 1984b).

SCH 23390 induced bradykinesia (parkinsonism)/catalepsy, sedation and reduced locomotor activity as did raclopride. The changes in locomotor activity paralleled the sedation. Regarding the ability of SCH 23390 to induce parkinsonism or catalepsy, the results of other studies are conflicting. Induction of catalepsy has been found in rodents in some studies (Christensen et al. 1984b; Morelli and Di Chiara 1985; Amalric et al. 1986), but not in others (Iorio et al. 1983; Maldonado et al. 1990). In monkeys, some have found a very low incidence of EPS, including catalepsy (Iorio et al. 1983; Coffin et al. 1989) or EPS only after pretreatment with a D_2 receptor antagonist (Gerhardt et al. 1985; Coffin et al. 1989). The induction of bradykinesia during D_1 receptor antagonist treatment in the present study, is in agreement with the results of other studies with non-drug-naive monkeys (Kistrup and Gerlach 1987; Coffin et al. 1989; Christensen 1990).

The sedative effect of SCH 23390 has been noted in earlier studies, in both rodents (Christensen et al. 1984b; Starr and Starr 1986) and monkeys (Kistrup and Gerlach 1987; Coffin et al. 1989; Christensen 1990; McHugh and Coffin 1991). In an acute single dose study, no sedative effect of SCH 23390 was found (Casey 1992). In the paper by McHugh and Coffin (1991) it was demonstrated that rapid tolerance developed to D_1 receptor antagonist-induced dystonia but not to sedation. In the study of Christensen (1990) utilizing vervet monkeys, no sedation was induced by SCH 23390 during the acute phase of the trial where dystonia, catalepsy and akathisia predominated, whereas a significant increase of sedation was found

during the long-term phase of the study, where EPS decreased. The presence of EPS, especially dystonia, during acute administration of SCH 23390 may override the sedation. In our study, sedation might be present prior to or after a dystonic attack or marked bradykinesia/catalepsy, but never during these behaviours.

During treatment with SCH 23390 baseline grooming behaviour increased, while baseline oral dyskinesia remained unchanged. During raclopride treatment the opposite was found, baseline oral dyskinesia increased, while baseline grooming was unchanged. The increased baseline dyskinesia during raclopride might indicate a relationship between D_2 antagonism and dyskinesia. The potential clinical relevance of the increase of grooming during D_1 antagonist treatment is unknown.

Dopaminergic supersensitivity following antagonistic treatment

One of the primary aims of the present study was to examine the potential development of DA supersensitivity during DA antagonist treatment. It was decided to stop treatment when withdrawal supersensitivity was produced. Supersensitivity to the D_2 receptor agonist LY 171555 was produced after 3 weeks' treatment of raclopride, while supersensitivity to the D_1 receptor agonist SKF 81297 was first induced after 9 weeks' treatment with SCH 23390.

Chronic treatment with raclopride did not induce any further changes in the response to SKF 81297, but the results must be viewed with caution. Although the effects of saline remained at baseline after chronic SCH 23390 treatment and after the subsequent wash-out period, the effects of SKF 81297 had not returned to baseline. Thus, some effects of chronic raclopride treatment may have been masked by the earlier treatment with SCH 23390.

Chronic treatment with DA antagonists may up-regulate DA receptors. It has been shown that daily administration of haloperidol increases DA D_2 receptors (Memo et al. 1987), just as chronic treatment with the D_1 antagonist SCH 23390 increases D_1 receptors (Porceddu et al. 1985; Hess et al. 1986; Memo et al. 1987). Some changes in behaviour (e.g. increased effect of DA agonists) during and after chronic DA antagonist treatment may reflect changes in the densities of the receptor subtypes, but do not explain the differences in regards to the liability to induce EPS (Gerhardt et al. 1985; Coffin et al. 1989; McHugh and Coffin 1991; present study). These differences may instead be due to differences in the action of DA receptor subtypes (see also Neale et al. 1982; Coffin et al. 1989; Casey 1992).

Christensen et al. (1984a, 1985) did not find any behavioral supersensitivity after chronic treatment with SCH 23390, while this has been found in other studies (Hess et al. 1986; Smialowski and Bijak 1989; Maldonado et al. 1990).

Chronic treatment with SCH 23390 for 9 weeks did not change the effect of the D_2 receptor agonist quinpirole upon any behavioral item. The unchanged effects of the D_2 agonist must be viewed with caution. In many rodent studies a permissive or a synergistic effect has been found between the D_1 and D_2 receptor agonists in rats (Mashurano and Waddington 1986; Arnt et al. 1987; Longoni et al. 1987; Dreher and Jackson 1989). Thus, an increased effect of both D_1 and D_2 receptor agonists has been demonstrated after chronic treatment with SCH 23390 in rats (Hess et al. 1986; Maldonado et al. 1990). In other studies, antagonistic relations between D_1 and D_2 receptor agonists have been shown (Starr and Starr 1986; Ellison et al. 1988; Lublin and Gerlach 1988; Peacock et al. 1990). Probably many types of D_1/D_2 interaction exist, depending upon the behaviour (Murray and Waddington 1989a, b; Williams et al. 1990), species of animal or the drug treatment history of the study animals (Hess et al. 1986; Pich et al. 1987; Braun and Chase 1988; Pitts et al. 1989; Wilcox et al. 1990).

The results of chronic raclopride treatment in the present investigation demonstrate the development of D_2 receptor supersensitivity. Treatment with the D_2 receptor antagonist raclopride for 3 weeks induced an increased response to the D_2 receptor agonist quinpirole both in regards to stereotypy and reactivity. No changes in the effects of SKF 81297 were found. However, the effects of SKF 81297 upon grooming and oral hyperkinesia did not return to baseline values after the wash-out period. Thus, the long-term effects of raclopride must be viewed with caution. Other effects of chronic raclopride treatment cannot be ruled out.

The results of the present investigation indicate that chronic treatment with the D_1 receptor antagonist SCH 23390 induces supersensitivity to the D_1 receptor agonist, but not to the D_2 receptor agonist. However, the development of supersensitivity during the D_1 antagonist treatment may be slow. Thus the behavioural D_1 receptor supersensitivity could not be demonstrated after treatment for 3 weeks. It cannot be excluded that both D_1 *and* D_2 receptor supersensitivity may develop after chronic D_1 *or* D_2 antagonist treatment if the antagonist treatments are continued for a longer period.

An antipsychotic effect of SCH 23390 has been proposed. Many studies have shown that SCH 23390 induces behavioural effects in animals predictive of antipsychotic activity in humans, e.g. reduction of stereotypy and locomotor activity induced by DA agonists (Iorio et al. 1983; Christensen et al. 1984b; Kistrup and Gerlach 1987), suppression of conditioned avoidance response in monkeys and rats (Iorio et al. 1983), and disruption of operant behaviour (Sanger 1987; for review see Clark and White 1987). There have been findings suggesting that SCH 23390 (and other selective D_1 receptor antagonists) have fewer side-effects than ordinary neuroleptics (Iorio et al. 1983; Coffin et al. 1989). The results of the present study indicate that SCH 23390, in non-drug-naive monkeys, induces EPS similar to that of clinically utilized neuroleptics, but that these side-effects are less pronounced, and that tolerance develops (at least to the dystonic effect). No increase of spontaneous oral movements was demonstrated during chronic treatment with SCH 23390, suggesting that D_1 antagonism may be less liable to induce tardive dyskinesia and other EPS than conventional neuroleptics. With this background, further animal and human studies evaluating the liability of D_1 receptor

antagonists to induce EPS and tardive dyskinesia are warranted.

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