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European Journal of Pharmacology 308 (1996) 235–241

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Behavioural effects of 7-OH-DPAT are solely due to stimulation of dopamine D_2 receptors in the shell of the nucleus accumbens; turning behaviour

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Received 1 February 1996; revised 11 April 1996; accepted 12 April 1996

Abstract

The goal of this study was to determine whether the dopamine D_3 receptor in limbic structures plays a role in the shell-specific and dopamine-dependent display of turning behaviour in rats. When combined with the dopamine D_1 receptor agonist (±)-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine-7,8-diol (SKF-38393, 5 μg), the putative dopamine D_3 receptor agonist (±)-7-hydroxy-*N,N*-di-*n*-propyl-2-aminotetralin (7-OH-DPAT, 1, 5 and 10 μg) elicited contralateral turning in a dose-dependent manner following unilateral injection into the shell, but not the core, of the nucleus accumbens. The turning pattern displayed was identical to that reported previously after intra-accumbens administration of the cocktail of SKF-38393 and the dopamine D_2 receptor agonist quinpirole. The behaviour under study was dose-dependently attenuated by local administration of the dopamine D_1 receptor antagonist *R*(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SCH 23390: 10 and 100 ng), the dopamine D_2 receptor antagonist domperidone (25 and 50 ng) or the dopamine $D_{2/3}$ receptor antagonist *l*-sulpiride (5 and 25 ng). Combined blockade of both dopamine D_1 and D_2 receptors in the shell with *a* dose of either antagonist alone that produced just a moderate reduction (10 ng SCH 23390 and 50 ng domperidone) completely antagonized the turning behaviour elicited by the cocktail of SKF-38393 and 7-OH-DPAT. Replacing 7-OH-DPAT by another putative dopamine D_3 receptor agonist, *S*(+)-(4*aR*,10*bR*)-3,4,4*a*,10*b*-tetrahydro-4-propyl-2*H*,5*H*-[1]benzopyrano[4,3-*b*]-1,4-oxazin-9-ol (PD 128,907, 10 μg), in the cocktail did produce no turning behaviour at all. It is concluded that mesolimbic dopamine D_3 receptors play no role in the dopamine-dependent and shell-specific turning behaviour: the contribution of 7-OH-DPAT in the cocktail of SKF-38393 and 7-OH-DPAT to the display of turning behaviour is solely due to its ability to activate dopamine D_2 receptors.

Keywords: Accumbal shell; Accumbal core; Turning behavior; Dopamine D_1/D_2 receptor interaction; Dopamine D_1/D_3 receptor interaction; (Rat)

1. Introduction

7-OH-DPAT ((±)-7-hydroxy-*N,N*-di-*n*-propyl-2-aminotetralin) has been found to act as a selective agonist at dopamine D_3 receptors in a variety of studies (biochemical studies: Rivet et al., 1994; Sokoloff et al., 1990; electrophysiological studies: Kreiss et al., 1995; behavioural studies: Daly and Waddington, 1993; Damsma et al., 1993; Svensson et al., 1994; Waters et al., 1993). However, later studies have demonstrated that 7-OH-DPAT may be less selective than originally claimed (biochemical studies: Gonzalez and Sibley, 1995; electrophysiological studies: Freedman et al., 1994; Liu et al., 1994; behavioural studies: Koshikawa et al., 1996b; Large and Stubbs, 1994). Apart from the accompanying paper, in which the effects of intra-accumbens injections of 7-OH-DPAT on jaw movements were studied (Koshikawa et al., 1996b), all remaining studies on the behavioural function of dopamine D_3 receptors are limited to studies in which 7-OH-DPAT and other putative, selective dopamine D_3 receptor agents are systemically applied. Dopamine D_3 receptors are abundantly concentrated in limbic structures, such as the nucleus accumbens (Bouthenet et al., 1991; Lévesque et al., 1992), and evidence has been presented that a subpopulation of dopamine D_3 receptors is located on neurons which serve as a major output route of the shell, but not the core, of the nucleus (Diaz et al., 1995). In our accompanying

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PII S0014-2999(96)00302-0

paper we provide evidence that the contribution of 7-OH-DPAT in the cocktail of SKF-82958 ((±)-6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine) and 7-OH-DPAT to the display of jaw movements is solely due to its ability to activate dopamine D_2 receptors. Moreover, we provide evidence that mesolimbic dopamine D_3 receptors play no role in dopamine-dependent and shell-specific jaw movements. Given these findings, the question arose whether the same holds true for other dopamine-specific and shell-specific behaviours.

We have recently shown that unilateral administration of a highly specific dose combination of the dopamine D_1 receptor agonist (±)-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine-7,8-diol (SKF-38393, 5 μg) and the dopamine D_2 receptor agonist quinpirole (10 μg) into the shell, but not the core, of the nucleus accumbens is required for the elicitation of a highly characteristic turning behaviour in rats. Since this behaviour is inhibited by the intra-accumbens administration of either the dopamine D_1 receptor antagonist *R*(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SCH 23390) or the dopamine D_2 receptor antagonist *l*-sulpiride (Cools et al., 1995; Koshikawa et al., 1996a), it has been suggested that dopamine D_1 and D_2 receptors play a role in the expression of these behaviours. However, a role of dopamine D_3 receptors could not be excluded: quinpirole has a high affinity not only at the dopamine D_2 receptor (Stoof and Kebabian, 1981), but also at the dopamine D_3 receptor (Sokoloff et al., 1990), and *l*-sulpiride has only a marginal lower affinity at the dopamine D_3 receptor than at the dopamine D_2 receptor (Sokoloff et al., 1990). Accordingly, we investigated the behavioural role of dopamine D_3 receptors in dopamine-dependent and shell-specific turning. For that purpose, we replaced quinpirole in the SKF-38393–quinpirole cocktail by the putative dopamine D_3 receptor agonist 7-OH-DPAT and studied the effects of intra-accumbens administration of this cocktail upon turning behaviour.

Given the lack of available dopamine D_3 receptor antagonists at the moment, the following strategy was used to assess the specificity of the effects elicited. First, the effects following administration of the cocktail into the shell were compared with those following its administration into the core, an area containing far less dopamine D_3 receptors than the shell. Second, we investigated to what extent the effects elicited by this cocktail could be antagonized by the dopamine D_1 receptor antagonist SCH 23390, the dopamine D_2 receptor antagonist domperidone or the dopamine $D_{2/3}$ receptor antagonist *l*-sulpiride. Third, the effect of a mixture of SCH 23390 and domperidone upon the effects elicited by the cocktail was analysed. Finally, the effect of the cocktail was compared to that of a cocktail, in which 7-OH-DPAT was replaced by another putative dopamine D_3 receptor agonist, viz. *S*(+)-(4*aR*,10*bR*)-3,4,4*a*,10*b*-tetrahydro-4-propyl-2*H*,5*H*-[1]benzopyrano[4,3-*b*]-1,4-oxazin-9-ol (PD 128,907). The binding profile of PD 128,907 for dopamine D_3 receptors relative to dopamine D_2 receptors is reported to be more selective (54-fold) than that of 7-OH-DPAT (7-fold) (Sautel et al., 1995).

2. Materials and methods

2.1. Surgical procedures

Male Wistar rats weighing 200–250 g were used throughout the experiments. They were housed in a temperature-controlled environment and under a light (07:00–19:00 h)/dark (19:00–07:00 h) cycle with free access to food and water. Behavioural testing was performed between 10:00 h and 15:00 h. For stereotactic implantation of cannulas, the rats were anaesthetized with sodium pentobarbitone (50 mg/kg i.p.) and mounted in a stereotactic apparatus (Narishige, Japan). Guide cannulas (0.5 mm o.d., 0.3 mm i.d., 6.0 mm length) were implanted into the shell or into the core of the nucleus accumbens according to previously described procedures (Prinssen et al., 1994; Koshikawa et al., 1996a). The coordinates based on the atlas of Paxinos and Watson (1986) were: anterior = 10.6 mm, vertical = 8.0 mm, lateral = 0.5 mm (shell); anterior = 10.6 mm, vertical = 7.0 mm, lateral = 1.2 mm (core). The cannulas directed at the shell were angled 21°, and cannulas directed at the core were angled 18° from the mid-sagittal plane to avoid the ventricular system. Damage to the target site was minimized by implanting the tips of the guide cannulas 1.2 mm (for the core) or 2.0 mm (for the shell) above the desired injection site. Wire stylets were placed in the guide cannulas to prevent occlusion. The animals were allowed at least 1 week post-operative recovery before behavioural testing and were used only once. All experiments were performed according to institutional and national guideline of animal experimentation.

2.2. Intracerebral microinjection and drugs

The animals ($n = 6–10$ per experiment) received unilateral injection of the dopamine D_1 receptor agonist SKF-38393 (5 μg; (±)-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine-7,8-diol hydrochloride; Research Biochemicals International), the putative dopamine D_3 receptor agonist 7-OH-DPAT (1, 5 or 10 μg; (±)-7-hydroxy-*N*,*N*-di-*n*-propyl-2-aminotetralin hydrobromide; Research Biochemicals International) or their combination (cocktail). In a separate set of experiments another putative dopamine D_3 receptor agonist PD 128,907 (10 μg; *S*(+)-(4*aR*,10*bR*)-3,4,4*a*,10*b*-tetrahydro-4-propyl-2*H*,5*H*-[1]benzopyrano[4,3-*b*]-1,4-oxazin-9-ol hydrochloride; Research Biochemicals International) was tested. Control animals received the solvent of the drugs. In additional sets of experiments the dopamine D_1 receptor antagonist SCH 23390 (10, 100 or 500 ng; *R*(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-

2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride; Research Biochemicals International) and/or the dopamine D_2 receptor antagonist domperidone (25, 50 or 100 ng; Research Biochemicals International), or the dopamine $D_{2/3}$ receptor antagonist *l*-sulpiride (5, 25 or 50 ng; Ravizza) were given into the shell 10 min prior to the agonists injection. Domperidone and *l*-sulpiride were dissolved in a few drops of diluted acetic acid and then diluted with saline (0.9% w/v NaCl solution) for injection. All remaining drugs were dissolved in saline immediately before use. For the unilateral intracerebral microinjection, the rat was held manually while the stylet was removed and the injection needle (31 gauge) was lowered through the guide cannula until it protruded 1.2 mm (core) or 2.0 mm (shell) beyond the tip. The needle was connected to a Hamilton syringe and the injection was made slowly in a volume of 0.5 μl over 30 s, after which the needle was left in place for a further 30 s. Doses and time schedule were based on previous studies (Saigusa et al., 1993, 1995; Cools et al., 1995; Koshikawa et al., 1996a).

2.3. Behavioural methods

The rats were placed individually in a circular chamber (60 cm diameter) with 30-cm high Perspex sides at least 1 h before the start of the experiment. To allow detailed observation of the turning behaviour, limb stepping patterns and spinal curvature, a mirror was mounted underneath the chamber at an angle of 30° and the image was recorded on videotape for off-line analysis. Contralateral and ipsilateral turnings (defined as complete 360° turns) were counted visually by a trained observer who had no prior knowledge of the drug treatment. Description of the stepping pattern involved analysis of the presence/absence of the following items: (1) lateral head movements, defined as lateral movements of the head in relation to the upper torso; (2) lateral torso movements, defined as lateral movements of the upper torso in relation to the lower torso; (3) lateral pelvic movements, defined as lateral movements of the lower torso in relation to the hindquarters; (4) normal hindlimb stepping during turning, characterized by the sequential occurrence of two forward steps (hindlimb forward steps: Cools and Jongen-Rêlo, 1991); (5) apomorphine-induced hindlimb stepping, characterized by the sequential occurrence of a closing and an open step (hindlimb doublet: Cools and Jongen-Rêlo, 1991); (6) normal forelimb stepping during turning, characterized by the sequential occurrence of a closing and an open step (forelimb doublet: Cools and Jongen-Rêlo, 1991); (7) dexamphetamine-induced forelimb stepping, characterized by the sequential occurrence of a crossing and an open step (forelimb crossing step: Cools and Jongen-Rêlo, 1991); (8) pivoting, characterized by turning around one leg (Szechtman et al., 1985); (9) uncoupling of lateral movements of the torso and the limbs, causing the legs to lag behind (dragging). Observations were made during consecutive 5-min periods for 90–120 min, starting immediately after the injection.

2.4. Histology

At the end of each experiment, the rats were deeply anaesthetized with sodium pentobarbitone and perfused transcardially with 10% of formalin. The brains were removed, sectioned (50 μm) and stained with Cresyl violet to visualize the injection site.

2.5. Data analysis

All values are expressed as means ± S.E.M. and analysed using either one-way analysis of variance (ANOVA) or two-way ANOVA (group × time) followed by a post-hoc Newman-Keuls test, where appropriate. Differences were considered significant when $P < 0.05$.

3. Results

3.1. Effects of combined injection of SKF-38393 and 7-OH-DPAT into the core and the shell of the nucleus accumbens

Fig. 1 gives a survey of the core and shell region in which the injection sites were located; data of rats with injection sites outside the region were discarded in the analysis ($n = 49$).

When combined with SKF-38393 (5 μg) unilateral injections of 7-OH-DPAT (1 μg, $n = 6$; 5 μg, $n = 10$; 10 μg, $n = 9$) into the shell of the nucleus accumbens dose-dependently elicited contralateral turnings (Fig. 2), viz. turning directed away from the injection site in all tested rats. Ipsilateral turning rarely occurred (data not shown). When given alone, SKF-38393 (5 μg, $n = 6$) and 7-OH-

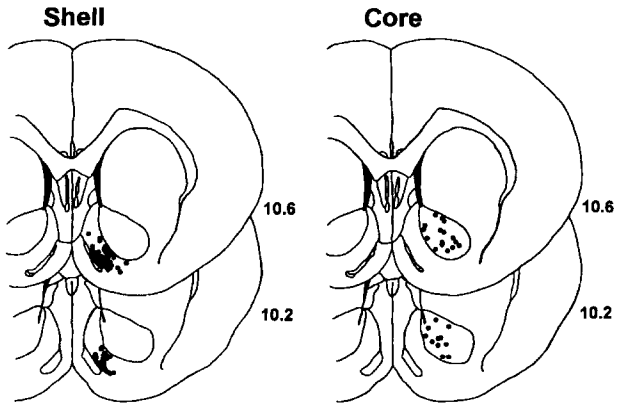

Fig. 1. All injection sites found in the shell (left) and the core (right) of the nucleus accumbens. Planes are modified to a series of 2 or 3 sections for each brain area from the atlas of Paxinos and Watson (1986); approximate coordinates indicated are in mm anterior to the interaural line.

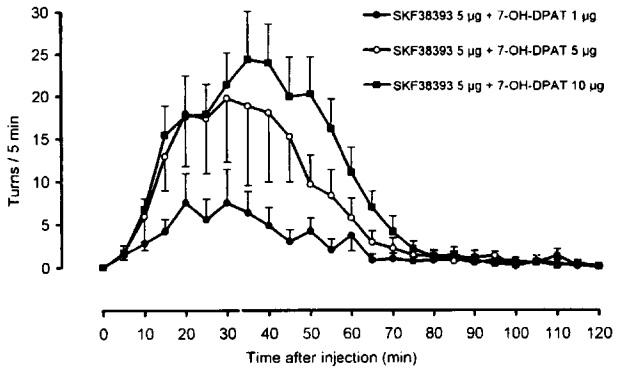

Fig. 2. Effects of unilateral injection of a combination of 7-OH-DPAT (1 μg ●, 5 μg ○ or 10 μg ■) and SKF-38393 (5 μg) into the shell of the nucleus accumbens on production of contraversive turning. The data are expressed as the mean number of turns occurring in 5-min observation periods ($n = 6$–10). Vertical bars indicate S.E.M.

DPAT (10 μg, $n = 6$) remained ineffective following injections into the shell: the number of turns in the SKF-38393-treated and the 7-OH-DPAT-treated rats, respectively, did not significantly differ from that found in solvent-treated rats ($n = 6$). Comparing the effects of the combined treatment with the effects of each single drug resulted in a highly significant difference (overall $F(3,23) = 21.42$, $P < 0.001$; Newman-Keuls, $P < 0.01$ vs. SKF-38393, 7-OH-DPAT or solvent, respectively; Fig. 3, upper part).

In contrast, the combined administration of SKF-38393 and 7-OH-DPAT ($n = 9$) was less effective when injected unilaterally into the core, although the effects were significantly greater than those found after the administration of each drug alone or the solvent (overall $F(3,23) = 3.36$, $P < 0.05$; Newman-Keuls, $P < 0.05$ vs. SKF-38393 ($n = 6$), 7-OH-DPAT ($n = 6$) or solvent ($n = 6$), respectively; Fig. 3, lower part).

Analysis of the stepping pattern induced by unilateral injections of the SKF-38393 and 7-OH-DPAT mixture into the shell showed that the rats displayed a characteristic stepping pattern that was highly comparable with that induced by unilateral injections of SKF-38393 and quinpirole mixture into the nucleus (cf. Saigusa et al., 1993, 1995; Koshikawa, 1994). In short, while turning around the contralateral hindlimb, the rats first made a tight contralateral turn by stepping backwards with the hindlimb followed by one step forwards with the ipsilateral hindlimb, then made another turn by stepping backwards with the contralateral hindlimb. Apart from the occurrence of a small number of forelimb crossing steps (Cools and Jongen-Rêlo, 1991), the rats displayed normal forelimb doublets. Although no hindlimb doublets (Cools and Jongen-Rêlo, 1991) were seen, the ipsilateral hindlimb was dragged, while the animal was pivoting contralaterally

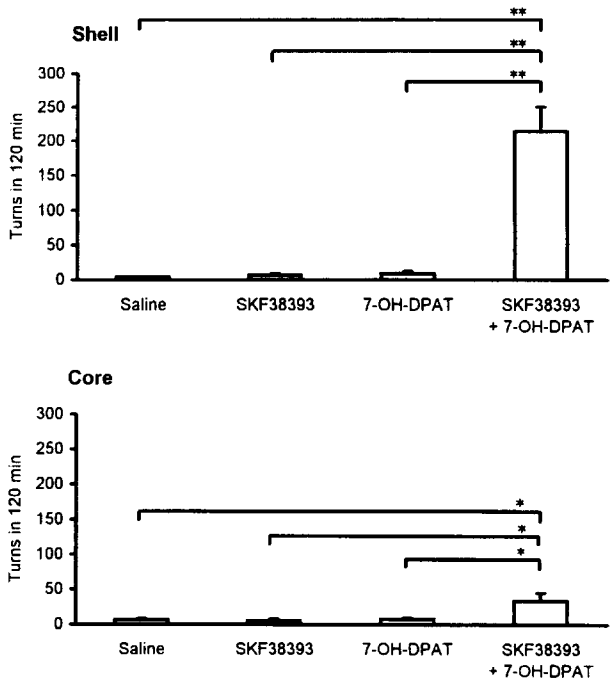

Fig. 3. Effects of unilateral injection of saline, 5 μg SKF-38393, 10 μg 7-OH-DPAT and the mixture of 5 μg SKF-38393 and 10 μg 7-OH-DPAT into the shell (upper part) and the core (lower part) of the nucleus accumbens (0.5 μl) on production of contraversive turning. The data are expressed as the mean number of total turns occurring in a 120-min observation period after injection ($n = 6$–9). Vertical bars indicate S.E.M. * $P < 0.05$, ** $P < 0.01$.

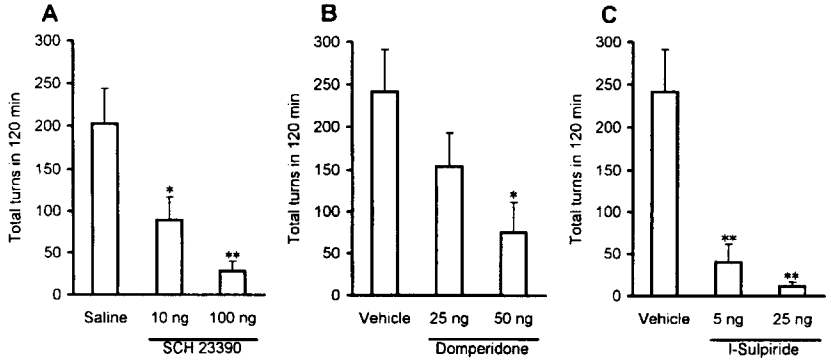

Fig. 4. Effects of SCH 23390 (10 or 100 ng/0.5 μl, A), domperidone (25 or 50 ng/0.5 μl, B) and l-sulpiride (5 or 25 ng/0.5 μl, C) given 10 min prior to the mixture of SKF-38393 (5 μg) and 7-OH-DPAT (10 μg): all injections were made into the shell of the nucleus accumbens. The data are expressed as the mean number of total turns occurring in a 120-min observation period ($n = 6$–10). Vertical bars indicate S.E.M. Control = effects of the mixture of SKF-38393 and 7-OH-DPAT. * $P < 0.05$, ** $P < 0.01$.

around its contralateral hindlimb. The overall result was a severe head-to-tail curvature during turning and/or sitting.

3.2. Effects of SCH 23390, domperidone and l-sulpiride on turning elicited by the combined administration of SKF-38393 and 7-OH-DPAT into the shell

When given into the shell of the nucleus accumbens, SCH 23390 (10 and 100 ng; $n = 6$ in each group) dose-dependently suppressed the contralateral turning induced by unilateral injections of SKF-38393 (5 μg) and 7-OH-DPAT (10 μg) mixture into the shell [saline pretreatment, 10 min before ($n = 6$) vs. 10 ng SCH 23390: $F(1,10) = 5.26$, $P < 0.05$, saline pretreatment vs. 100 ng SCH 23390: $F(1,10) = 16.48$, $P < 0.003$; Fig. 4A]. A similar dose-dependent inhibition was observed with domperidone (25 ng, $F(1,14) = 1.49$, $P = 0.24$; 50 ng, $F(1,14) = 5.55$, $P < 0.04$; $n = 6$ in each group; Fig. 4B) and *l*-sulpiride (5 ng, $n = 6$, $F(1,14) = 8.99$, $P < 0.01$; 25 ng, $n = 7$, $F(1,15) = 14.62$, $P < 0.002$; Fig. 4C): they all significantly reduced the response to the mixture, although this reduction required higher doses of domperidone than of *l*-sulpiride (Fig. 4B,C). Although higher doses of these antagonists were tested, their effects were not included in Fig. 4, since these doses produced a behavioural instead of pharmacological inhibition. So, 500 ng SCH 23390 affected the neck joint in some rats, preventing these rats from displaying normal forelimb stepping and pure contralateral head movements. When the head was moved laterally, the torso simultaneously moved laterally: the head appeared to be fixed to the torso. Consequently, these rats had difficulties with executing turning. Higher doses of both *l*-sulpiride (50 ng) and domperidone (100 ng) affected the mixture-induced turning in a different manner. These drugs disturbed the hindlimb stepping; there was an uncoupling between lateral movements of the torso and those of the hindlimbs, resulting in dragging of these limbs when the head and torso were completely rotated towards the contralateral side. Furthermore, the rats often had splayed hindlimbs. Overall, the highest doses of these drugs affected the turning by deficient hindlimb stepping.

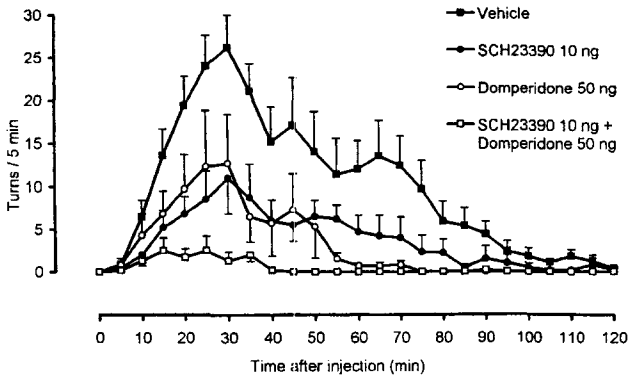

Fig. 5. Effects of SCH 23390 (10 ng, ●), domperidone (50 ng, ○) or the mixture (□) of SCH 23390 and domperidone given 10 min prior to the mixture of SKF-38393 (5 μg) and 7-OH-DPAT (10 μg): all injections were made into the shell of the nucleus accumbens (0.5 μl). The data are expressed as the mean number of turns occurring in 5-min observation periods ($n = 6$–10). Vertical bars indicate S.E.M. Control (■) = effects of the mixture of SKF-38393 and 7-OH-DPAT.

3.3. Effects of combined injection of SCH 23390 and domperidone on turning elicited by administration of SKF-38393 and 7-OH-DPAT mixture into the shell

Simultaneous blockade of both dopamine D_1 and D_2 receptors in the shell of the nucleus accumbens, achieved by the focal injection of a mixture of doses of SCH 23390 (10 ng) and domperidone (50 ng) which per se produced only a partial reduction, completely abolished the contralateral turning induced by the SKF-38393 (5 μg) and 7-OH-DPAT (10 μg) mixture ($F(1,14) = 12.40$, $P < 0.004$; Fig. 5).

3.4. Effects of administration of the cocktail of SKF-38393 and PD 128,907 into the shell

Injection of SKF-38393 (5 μg) and the putative dopamine D_3 receptor agonist PD 128,907 (10 μg) into the shell of the nucleus accumbens remained ineffective. The total number of turns elicited during a 120-min observation period being 8.0 ± 9.4 (mean ± S.E.M., $n = 6$); [$F(1,10) = 4.7$, $P > 0.05$] compared to 3.7 ± 0.3 after saline.

4. Discussion

The present study and the one reported in the accompanying paper (Koshikawa et al., 1996b) intended to provide evidence that dopamine D_3 receptors play a role in mediating functions of mesolimbic structures as has been suggested before (Diaz et al., 1995; Sokoloff et al., 1990). For that purpose, we focused our attention on a brain structure in which these receptors are abundantly concentrated, viz. the shell of the nucleus accumbens (Bouthenet et al., 1991; Diaz et al., 1995; Lévesque et al., 1992) and chose two behaviours, viz. turning behaviour (present study) and jaw movements (accompanying paper: Koshikawa et al., 1996b). These behaviours are known to be dopamine-dependent and specific for the shell region of the nucleus accumbens (Cools et al., 1995; Koshikawa et al., 1996a). The present study on turning behaviour confirms and extends the conclusions put forward in our accompanying paper: the putative dopamine D_3 receptor agonist 7-OH-DPAT is rather a dopamine D_2 receptor agonist than a dopamine D_3 receptor agonist, at least in our in vivo studies, and the dopamine D_3 receptor is certainly not involved in the limbic functions under study. Below, the data giving rise to these conclusions concerning the turning behaviour are discussed.

The present study shows that the cocktail of the putative dopamine D_3 receptor agonist 7-OH-DPAT (1, 5 and 10 μg) and the dopamine D_1 receptor agonist SKF-38393 (5 μg), like the cocktail of the dopamine $D_{2/3}$ receptor agonist quinpirole and the dopamine D_1 receptor agonist SKF-38393 (5 μg) (Koshikawa et al., 1996a), elicited turning behaviour in a dose-dependent manner, when administered unilaterally into the shell of the nucleus accumbens; administration of this combination into the core was far less effective. Comparison of the effects of the two cocktails with 7-OH-DPAT and quinpirole, respectively, reveals two phenomena: first, there was virtually no difference between the stepping patterns elicited by these cocktails; second, the peak of the time-response curve of the cocktail with 7-OH-DPAT appeared approximately 30 min earlier than that of the cocktail with quinpirole. Although these data are not yet sufficient to draw a definite conclusion about the ability of 7-OH-DPAT to interact with dopamine D_2 or D_3 receptors, the following data are conclusive in this respect. First, both the dopamine D_1 receptor antagonist (SCH 23390), the dopamine D_2 receptor antagonist domperidone and the dopamine $D_{2/3}$ receptor antagonist *l*-sulpiride dose-dependently attenuated the effects of the cocktail of SKF-38393 and 7-OH-DPAT. Second, combining a partially effective dose of the dopamine D_1 receptor antagonist SCH 23390 (10 ng) with a partially effective dose of the dopamine D_2 receptor antagonist domperidone (50 ng) completely inhibited the effects of the cocktail of SKF-38393 and 7-OH-DPAT. Third, combination of SKF-38393 and another putative dopamine D_3 receptor agonist PD 128,907, which was reported to be far more selective for dopamine D_3 receptors than 7-OH-DPAT (Akunne et al., 1994; Sautel et al., 1995), had no effect at all, when injected unilaterally into the shell in a dose (10 μg) that 7-OH-DPAT was found highly effective.

All these data together give rise to two conclusions. First, the contribution of 7-OH-DPAT in the cocktail of SKF-38393 and 7-OH-DPAT to the display of turning behaviour is solely due to its ability to activate dopamine D_2 receptors. This conclusion fits in with earlier reports showing that this drug behave similarly to dopamine D_2 receptor agonists (Caine et al., 1995; Freedman et al., 1994; Gonzalez and Sibley, 1995; Large and Stubbs, 1994; Liu et al., 1994; Starr and Starr, 1995). The present study, however, shows that this holds also true for intracerebrally administered 7-OH-DPAT, confirming and extending thereby the findings reported in our accompanying paper (Koshikawa et al., 1996b). Second, the dopamine-dependent and shell-specific turning behaviour is just mediated by stimulation of dopamine D_1 and D_2 receptors.

In summary, it was already known that 7-OH-DPAT behaves similarly to the dopamine $D_{2/3}$ receptor agonist quinpirole in various rodent paradigms (see above). Both the present study and the accompanying paper (Koshikawa et al., 1996b) provide direct evidence that the same holds true for 7-OH-DPAT when its effect on shell-specific behaviours, such as turning behaviour and jaw movements, are studied. All these data together show that a thorough reevaluation of the dopamine D_3 receptor specificity of 7-OH-DPAT is required. In addition, both the present study and the accompanying paper (Koshikawa et al., 1996b) provide direct evidence that mesolimbic dopamine D_3 receptors play no role in the dopamine-dependent and shell-specific turning behaviour and jaw movements. In other words, there is ample evidence that the mesolimbic dopamine D_3 receptors play no role in a series of well-known motor functions of limbic structures. Thus, the role of dopamine D_3 receptors in mesolimbic functions needs to await further investigations.

Acknowledgements

This work was supported by the Sato Fund (Japan).

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