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Motor actions of 7-OH-DPAT in normal and reserpine-treated mice suggest involvement of both dopamine D_2 and D_3 receptors

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Abstract

In non-habituated mice, 7-hydroxy-*N*,*N*-di-*n*-propylaminotetralin (7-OH-DPAT, 0.04–10 mg/kg s.c.) potently and rapidly suppressed species-typical behaviours and induced frozen postures, with only occasional evidence of weak behavioural stimulation occurring at 5–10 mg/kg. This inhibitory effect was reversed by the dopamine D_1 receptor agonist 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine hydrochloride (SKF 38393, 10 mg/kg i.p.). 7-OH-DPAT (3–10 mg/kg) did not reinstate locomotion in 4 h habituated mice, either when administered alone or in conjunction with a threshold dose of SKF 38393 (3 mg/kg). By contrast, 7-OH-DPAT (0.2–10 mg/kg) dose-dependently reversed the akinesia of 24 h reserpine-treated mice. This response was blocked by the dopamine D_2 receptor antagonist raclopride (10 mg/kg i.p.), but not by the dopamine D_1 receptor antagonist (*R*)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepine-7-ol hemimaleate (SCH 23390, 0.05 mg/kg i.p.), and was potentiated synergistically by coinjection of SKF 38393 (3 mg/kg). These and earlier data suggest the motor inhibitory effects of 7-OH-DPAT (low doses) in normal animals are mediated by dopamine autoreceptors (D_2 and/or D_3), whilst its motor stimulant actions in normal (high doses) and in dopamine-depleted, supersensitive animals, are mediated by dopamine D_2 receptors.

Keywords: Dopamine D_3 receptor; 7-OH-DPAT (7-hydroxy-*N*,*N*-di-*n*-propylaminotetralin); SKF 38393; Motor behavior; Reserpine; (Mouse)

1. Introduction

The discovery of dopamine D_3 receptors and their selective expression by the ventral striatum has fuelled speculation of a specialised role for these receptors in limbic functions (Lévesque et al., 1992; Sokoloff et al., 1990). Autoradiographic studies have also revealed the presence of dopamine D_3 receptors in the striatum, as well as a pocket of dopamine D_3 receptors in the substantia nigra pars compacta, leading to the suggestion that somatodendritic, and possibly axon terminal dopamine D_3 receptors, may be autoreceptors (Gehlert et al., 1992). Since the nigrostriatal dopamine pathway is believed to modulate the expression of motor responses (Graybiel, 1990), whilst the mesoaccumbens dopamine pathway is more concerned with their initiation (LeMoal and Simon, 1991), it follows that dopamine D_3 receptors could play an important role in motor control.

Various investigators have attempted to demonstrate such a role in behavioural experiments, by injecting animals with compounds which have been shown to bind preferentially to cloned human dopamine D_3 receptors in vitro. One such compound is 7-hydroxy-*N*,*N*-di-*n*-propylaminotetralin (7-OH-DPAT), an agonist which displays a 78-fold greater affinity for dopamine D_3 over dopamine D_2 receptors in transfected Chinese hamster ovary cells, and a dopamine 'D_3-like' binding profile in the rat olfactory tubercle (Lévesque et al., 1992). These same authors reported that 7-OH-DPAT exhibited insignificant binding to dopamine D_1 and D_4 receptors, giving 7-OH-DPAT the appearance of being a highly specific pharmacological tool with which to investigate the behavioural properties of dopamine D_3 receptors. Whether this is strictly true is open to debate, as Large and Stubbs (1994) have emphasised that the conditions which prevail in vivo are likely to favour

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a much stronger attachment of 7-OH-DPAT to dopamine D_2 receptors than is indicated by in vitro binding experiments.

This uncertainty is evident in other published data. For instance, biochemical measurements of dopamine synthesis (Meller et al., 1993) and release (Damsma et al., 1993) have uncovered an inhibitory action of 7-OH-DPAT, consistent with the stimulation of striatal dopamine D_3 (or possibly D_2) autoreceptors. A presynaptic localization of dopamine D_3 receptors could also explain the inhibition of locomotion and induction of yawning by 7-OH-DPAT in behavioural studies in rats (Ahlenius and Salmi, 1994; Daly and Waddington, 1993). By contrast, another research group has discovered that selective dopamine D_3 receptor ligands can alter motor behaviour independently of dopamine release (Svensson et al., 1994; Waters et al., 1993). Consequently, whether the dopamine receptors that regulate motor behaviour are presynaptic autoreceptors (Stähle, 1992), or a discrete population of inhibitory postsynaptic dopamine 'D_2-like' receptors (Costall et al., 1981), remains an open question.

Considerations of motor behaviour should not ignore the part played by dopamine D_1 receptors, which have traditionally come to be viewed as being functionally coupled to dopamine D_2 receptors (Clark and White, 1987). This coupling usually takes the form of positive cooperativity, in the sense that locomotion and stereotyped activities are greatly facilitated if both D_1 and D_2 receptors are stimulated simultaneously (Braun and Chase, 1986; Clark and White, 1987). Little is known about the functional relationship that may exist between dopamine D_1 and D_3 receptors. Daly and Waddington (1993) were able to block the motor stimulant effects of 7-OH-DPAT with BW 737C, a dopamine D_1 receptor-selective antagonist, while Waters et al. (1993) noticed a 'behavioural activation' occurred with a combination of the dopamine D_3 receptor-preferring ligand U-99194A and the dopamine D_1 receptor agonist SKF 38393 in reserpine-treated rats. Both of these findings are suggestive of a form of receptor synergism, but it is not clear if this was because 7-OH-DPAT was engaging dopamine D_2 receptors in these experiments.

The present study considers the extent to which the behavioural effects of 7-OH-DPAT are attributable to the stimulation of dopamine D_2 or D_3 receptors, and how these are influenced by the concomitant activation of dopamine D_1 receptors with SKF 38393 in the dopamine-intact and reserpine-treated mouse.

2. Materials and methods

2.1. Animals and treatment

Male albino mice (TO strain strain, Tuck), weighing 25–35 g at the start of the experiments, were housed in groups of 20 at $22 \pm 1°$ C, under fluorescent lighting from 07:00 to 17:00 h, and allowed free access to laboratory chow and tap water. Experiments were conducted between 10:00 and 15:00 h, and each animal was used once only.

Normal mice were injected with drugs or vehicle and immediately placed onto the floor of a clear Perspex container ($29 \times 26 \times 21$ cm high), with (4 h) or without prior acclimatization, and their motor activity recorded every 10 min for up to 2 h. Other behaviours were noted by an experienced observer, but were not quantified. Motor activity, expressed as arbitrary motor counts, was measured by a Radiospares 8960 Microwave Doppler Module, connected to a combined amplifier, timer and LED display unit constructed in this laboratory to our own design. The sensitivity of the Doppler unit was adjusted to record large movements of the body (principally locomotion, but also some rearing).

In other experiments, mice were first injected with reserpine (5 mg/kg i.p.), returned to their home cage and maintained at a room temperature of $28 \pm 1°$ C to prevent hypothermia. Twenty-four hours later, the mice were injected with drugs or vehicle and their motor activity recorded every 10 min for 1 h, as described above.

2.2. Statistics

Cumulative 1 h (reserpine-treated mice) or 2 h (normal mice) motor counts were determined and the significance of drug effects determined by one-factor analysis of variance (ANOVA). Post-hoc analyses were made with Dunnett's t-test. Significance levels were set at $P < 0.05$.

2.3. Drugs

The selective dopamine D_1 receptor agonist 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine hydrochloride (SKF 38393), the dopamine $D_{2/3}$ receptor-selective agonists *trans*-(+)-4,4*a*,5,6,7,8,8*a*,9-octahydro-5-propyl-2*H*-pyrazolo-(3,4-*g*)quinoline hydrochloride (LY 171555) and 7-hydroxy-*N*,*N*-di-*n*-propylaminotetralin (7-OH-DPAT; Lévesque et al., 1992) were obtained from Research Biochemicals, Natick, USA. Reserpine was obtained from Sigma, while the dopamine D_2 receptor antagonist raclopride (Astra) and the dopamine D_1 receptor antagonist (*R*)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepine-7-ol hemimaleate (SCH 23390; Schering) were supplied as gifts. All drugs were dissolved in distilled water (reserpine and raclopride with the aid of a minimum quantity of glacial acetic acid), and administered in a dose volume of 5 ml/kg.

3. Results

3.1. Effects of SKF 38393 and LY 171555 on locomotor activity of non-habituated mice

Mice injected with distilled water (5 ml/kg i.p.) and placed immediately into a novel environment exhibited fast exploratory locomotor activity, rearing and sniffing for 40–60 min, interspersed by steadily increasing periods of whole body grooming and stillness (Fig. 1).

The partial dopamine D_1 receptor agonist SKF 38393 had no effect on motor activity at 3 mg/kg or 10 mg/kg, but significantly increased motor counts at 20 mg/kg i.p. (drug main effect by ANOVA $F(3,30) = 12.99$, $P < 0.0001$; Fig. 1). These animals moved continuously around the test arena for the whole of the 2 h observation period, stopping only to sniff, rear or to engage in bouts of vigorous whole-body grooming.

By contrast, the dopamine $D_{2/3}$ receptor-selective agonist LY 171555, 0.5–2.5 mg/kg s.c., strongly inhibited all motor activity within 1–2 min of injection (drug main effect by ANOVA $F(2,22) = 20.97$, $P < 0.0001$; Fig. 1). LY 171555-treated mice remained quiescent with their eyes open, and appeared to be alert but not sedated. Other species-typical behaviours such as rearing, sniffing and grooming were also strongly suppressed.

3.2. Effects of 7-OH-DPAT on locomotor activity in non-habituated mice

Following subcutaneous injection (0.04–10 mg/kg), 7-OH-DPAT induced almost instantaneous stillness (Fig. 2). Mice displayed a brief flurry of activity for 1–2 min after entering the observation box, then assumed a stationary position which was effectively maintained for the next 2 h (drug main effect by ANOVA $F(5,33) = 25.57$, $P < 0.0001$). Rearing and grooming were also greatly reduced.

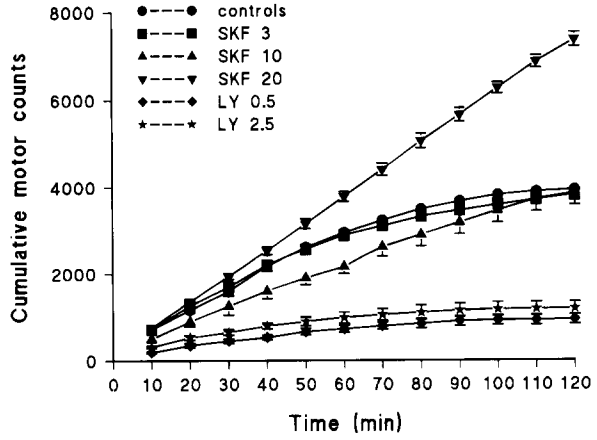

Fig. 1. Effects of SKF 38393 and LY 171555 on motor activity in non-habituated mice. Animals were injected with drugs as indicated, then placed singly onto the floor of a Perspex test box without prior acclimatisation. Locomotion was measured with a Doppler probe every 10 min, for a total period of 2 h. Each value is the mean ± S.E.M. of at least six determinations.

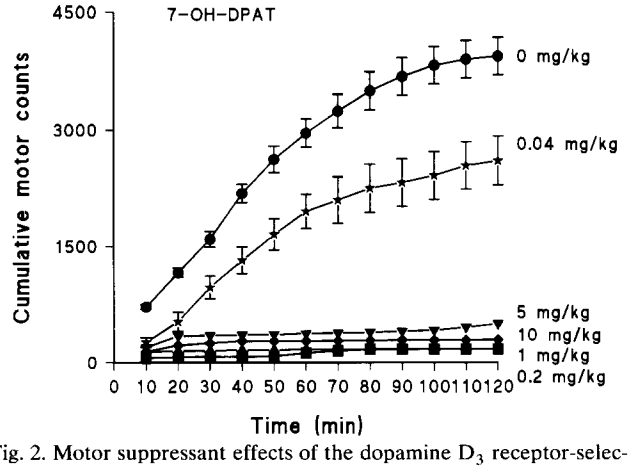

Fig. 2. Motor suppressant effects of the dopamine D_3 receptor-selective agonist 7-OH-DPAT in non-habituated mice. Experimental details as for Fig. 1. Each value is the mean ± S.E.M. of at least six determinations.

At the higher doses especially (5–10 mg/kg s.c.) some mice briefly adopted abnormal frozen postures when placed in the test arena. There was evidence of slight behavioural stimulation in the second hour after 5 mg/kg 7-OH-DPAT, and after 5–10 min with 10 mg/kg 7-OH-DPAT in most animals. This consisted of slow, head-down forward walking, attempted rearing and much sniffing, but in all but one animal this stimulation was short-lived and the animals resumed their hypoactive pose after 5–10 min. One mouse treated with 5 mg/kg s.c. 7-OH-DPAT became hyperactive at 70 min post-injection, and displayed perseverative forward walking and floor sniffing for the remainder of the experiment.

3.3. Effect of SKF 38393 on motor responses to 7-OH-DPAT in normal mice

To determine the nature of any behavioural interaction between dopamine D_1 and D_3 receptor stimulation in dopamine-intact mice, SKF 38393 (3–10 mg/kg i.p.) was coinjected with 7-OH-DPAT (0.04–10 mg/kg s.c.). The dopamine D_1 receptor agonist failed to modify motor counts in non-habituated controls, or in animals receiving a threshold inhibitory dose of 7-OH-DPAT (0.04 mg/kg; Fig. 3). Hypoactivity induced by 0.2 mg/kg or 10 mg/kg 7-OH-DPAT was significantly reversed by 10 mg/kg (but not 3 mg/kg) SKF 38393 (Fig. 3).

The dopamine D_3 receptor agonist caused instant akinesia, whilst signs of dopamine D_1 receptor-dependent motor activation appeared 3–5 min later. Be-

havioural stimulation comprised slow and persistent forward walking, with head-down posture and exaggerated sniffing of the floor and sides of the container. There was much rearing, sometimes perseverative with animals becoming fixed in an upright position against the container wall (reminiscent of a high dose of apomorphine), and in later stages often vigorous whole body grooming and stereotyped licking. Similar levels of motor activation occurred with mice which had been acclimatised to the test arena for 4 h, then administered 10 mg/kg SKF 38393 alone, except that these did not exhibit stereotypy (i.e. licking or biting), and rearing was not perseverative (Fig. 3).

In further experiments with acclimatised animals, control mice which had been exposed to the test box for 4 h and then injected with water (5 ml/kg i.p.) became transiently active before resuming a still posture (mean 2 h cumulative counts = 288.5 ± 21.7, n = 6). SKF 38393 reinstated locomotion in habituated mice at 10 mg/kg i.p. (mean counts = 2464.3 ± 425.7, $n = 6$, $P < 0.001$; Fig. 3) but not at 3 mg/kg i.p. (mean counts = 343.5 ± 31.4, $n = 6$). 7-OH-DPAT did not increase motor activity at 3 or 10 mg/kg s.c., either when administered alone (mean counts = 376.5 ± 55.0 and 252.3 ± 41.1 respectively, $n = 6$) or in conjunction with 3 mg/kg i.p. SKF 38393 (mean counts = 345.0 ± 51.6 and 182.7 ± 34.9 respectively, $n = 6$).

3.4. Effect of 7-OH-DPAT on locomotor activity in reserpine-treated mice

Twenty-four hours after injection of 5 mg/kg i.p. reserpine mice were totally akinetic (Fig. 4). 7-OH-DPAT (0.2–5 mg/kg s.c.) dose-dependently restored

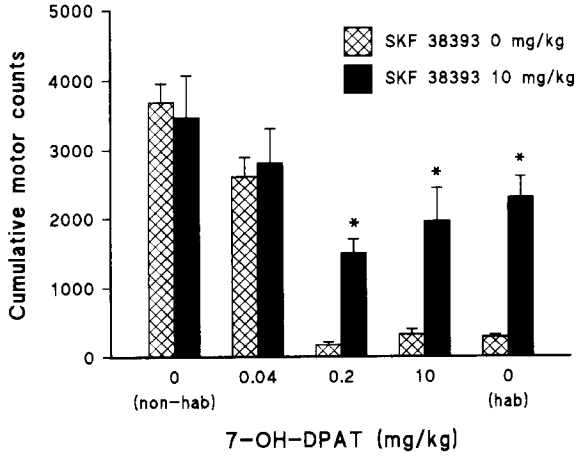

Fig. 3. Effects of dopamine D_1 receptor stimulation with SKF 38393 on the motor suppression induced by 7-OH-DPAT or habituation in mice. Habituation (hab) involved leaving the mice in the test box for 4 h prior to drug treatment. Other details as for Fig. 1. non-hab = non-habituated. Each value is the mean ± S.E.M. of at least six determinations.

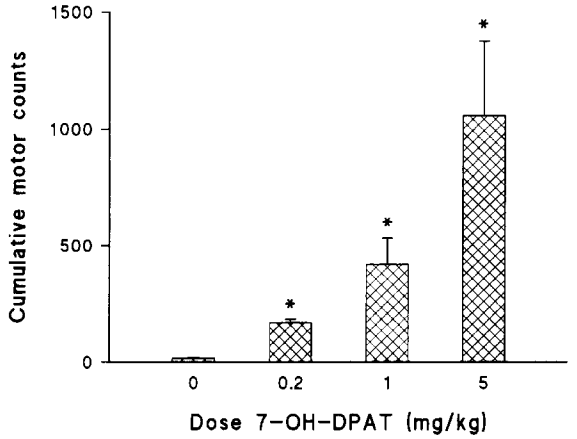

Fig. 4. Dose-dependent motor stimulant effect of 7-OH-DPAT in 24 h reserpine-treated mice. Mice were injected with reserpine (5 mg/kg i.p.), and again 24 h later with 7-OH-DPAT, then placed immediately into the test box (no prior acclimatisation) and their motor activity recorded every 10 min for 1 h. Each value is the mean ± S.E.M. of at least six determinations. * $P < 0.001$ versus vehicle-injected controls by Dunnett's t-test.

locomotion (drug main effect by ANOVA $F(3,23) = 8.56$, $P < 0.005$; Fig. 4). Lower doses of 7-OH-DPAT were not effective. Recovery was rapid (1–2 min) and was typified by fast walking, head-down posture, sniffing and biting directed at the container. Rearing was abundant and often perseverative at the higher drug doses.

The behavioural stimulation induced by 5 mg/kg s.c. 7-OH-DPAT was abolished by cotreatment with the dopamine D_2 receptor-selective antagonist raclopride (10 mg/kg i.p.), but not by the dopamine D_1 receptor-selective antagonist SCH 23390 (0.05 mg/kg i.p.; Fig. 5).

As noted previously (Starr and Starr, 1993), 3 mg/kg i.p. SKF 38393 was a threshold dose of the dopamine D_1 receptor agonist for inducing locomotion in reserpine-treated mice (Fig. 6). A combination of this dose of SKF 38393 and a threshold dose of 7-OH-DPAT (0.2 mg/kg s.c.), gave rise to a profound and synergistic increase in locomotion (Fig. 6). Fluent locomotion was reinstated by 10 mg/kg i.p. SKF 38393, but this was not affected by subthreshold doses of 7-OH-DPAT (0.01–0.1 mg/kg s.c.; data not shown).

4. Discussion

The discovery of dopamine D_3 receptors, with a discrete localisation in limbic brain areas associated with motor 'drive' (Mogenson et al., 1993) and novelty-induced locomotion (Pierce et al., 1990), and a capacity to function as autoreceptors suppressing dopamine release (Tang et al., 1994), has generated much speculation as to their possible inhibitory role in the expres-

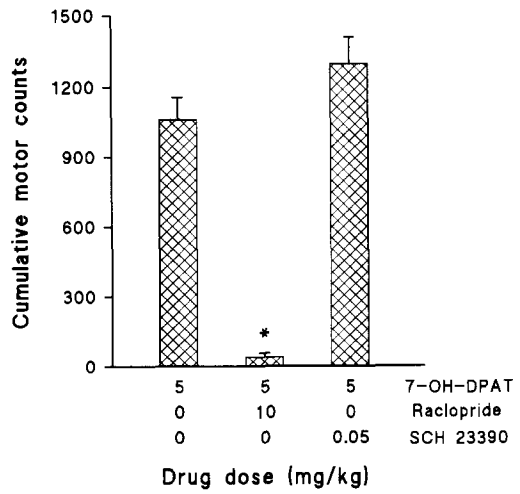

Fig. 5. Effects of dopamine antagonists on the motor response to 7-OH-DPAT in 24 h reserpine-treated mice. Twenty-four hours after receiving reserpine (5 mg/kg i.p.) mice were injected with 7-OH-DPAT plus either vehicle (5 ml/kg i.p. water), the dopamine D_1 receptor antagonist SCH 23390 (0.05 mg/kg i.p.) or the dopamine D_2 receptor antagonist raclopride (10 mg/kg i.p.). Motor activity was then recorded every 10 min for 1 h. Each value is the mean ± S.E.M. of at least six determinations. * $P < 0.001$ versus controls by Dunnett's t-test.

sion of motor activity. Much of the research in this area has centred on the use of the aminotetralin 7-OH-DPAT, an old drug (e.g. Feenstra et al., 1983) with a recently discovered preference for binding to transfected dopamine D_3 receptors in vitro, and to limbic brain regions in vivo (Herroelen et al., 1994; Lévesque et al., 1992; Sokoloff et al., 1990). The abolition of all species-typical behaviours and the adoption of frozen postures we observed with 7-OH-DPAT in non-habituated mice are comparable to that described in the rat (Ahlenius and Salmi, 1994; Daly and Waddington, 1993; Svensson et al., 1994), and bears a close resemblance to the behavioural profile described for the preferential dopamine $D_{2/3}$ receptor agonist LY 171555 (Eilam and Szechtman, 1989; Jackson et al., 1989; see also Fig. 1). Previous authors have cited this depression of motor activity as evidence of dopamine D_3 autoreceptor activation by 7-OH-DPAT (Ahlenius and Salmi, 1994; Gilbert and Cooper, 1995; Gilbert et al., 1995), although simultaneous microdialysis has failed to reveal a concomitant reduction in endogenous dopamine release (Svensson et al., 1994). Nevertheless, there is a growing body of evidence supporting the autoreceptor hypothesis of 7-OH-DPAT's motor depressant action.

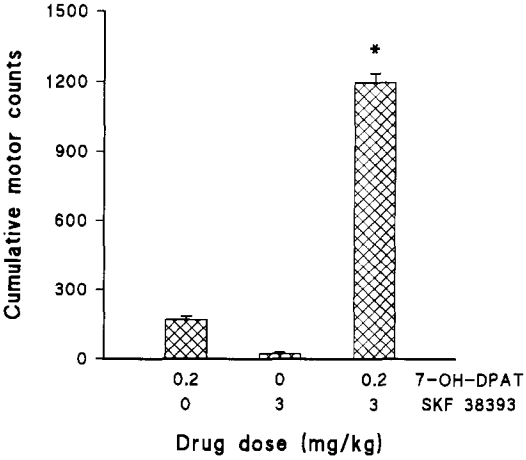

Fig. 6. Synergistic interaction between SKF 38393 and 7-OH-DPAT in reserpine-treated mice. Twenty-four hours after receiving reserpine (5 mg/kg i.p.) mice were injected with 7-OH-DPAT and SKF 38393, either alone or concurrently, and their motor activity measured every 10 min for 1 h. Each value is the mean ± S.E.M. of at least six determinations. * $P < 0.001$ versus other columns.

For instance, Gilbert and Cooper (1995) noted that intraccumbens infusion of 7-OH-DPAT dose-dependently induced profound hypolocomotion, whilst voltammetric recording revealed that the output of dopamine in the nucleus accumbens, in response to electrical stimulation of the ventral tegmentum, was rapidly and potently suppressed by 7-OH-DPAT administered systemically (Gilbert et al., 1995). These authors detected a close temporal and potency correlation between the behavioural depressant and dopamine release-inhibiting properties of 7-OH-DPAT, although this result is at variance with the findings of Svensson et al. (1994). The disparity between these two experimental approaches requires clarification, and we cannot ignore the possibility of a population of postsynaptic dopamine D_3 receptors that inhibit locomotion (Svensson et al., 1994; Waters et al., 1993).

In behavioural experiments, conditions that lead to a reduction in synaptic dopamine concentration, and hence a diminution in the tonic activation of postsynaptic dopamine D_1 receptors, disclose a potent motor excitant action of dopamine D_1 receptor agonists such as SKF 38393. Such conditions include depleting dopamine stores with reserpine (Starr et al., 1987), destroying the dopamine neurones with a neurotoxin (Rouillard and Bédard, 1988), or simply habituating the animal to the test environment (Molloy and Waddington, 1984), as exemplified by the fact that rats trained to walk in circles release less dopamine in the 'hypoactive' as compared to the 'hyperactive' hemisphere (Yamamoto et al., 1982). This would explain why SKF 38393, 10 mg/kg i.p., promoted locomotion in habituated and not non-habituated mice (Fig. 3). This argument can be extended to the akinesia elicited by low ('autoreceptor') doses of the dopamine agonists apomorphine (Starr and Starr, 1987) and LY 171555 (Jackson et al., 1989), since these drugs have been observed in dialysis experiments to cause a rapid and long-lasting decrease in the efflux of endogenous dopamine (e.g. Imperato and Di Chiara, 1988). Jackson

et al. (1989) hypothesised that SKF 38393 reversed this akinesia by restoring postsynaptic dopamine D_1 receptor activity. If this is the case, then the ability of SKF 38393 to counteract the hypolocomotion induced by 7-OH-DPAT in the present study would also be consistent with the notion of the aminotetralin acting presynaptically to inhibit dopamine release (Gilbert and Cooper, 1995; Gilbert et al., 1995). We would point out, however, that exactly the same behavioural profile is exhibited by bromocriptine (Jackson et al., 1988), which has equal affinity for dopamine D_2 and D_3 receptors (Sokoloff et al., 1990), both of which inhibit dopamine efflux (Tang et al., 1994). Thus while a strong case can be made for 7-OH-DPAT depressing motor activity in naive animals via autoreceptors, it is not clear if these belong to the dopamine D_2 or D_3 subtype, or both.

Other investigators have reached a similar conclusion, stating that 7-OH-DPAT appeared no different from dopamine D_2/D_3 receptor unselective dopamine agonists in terms of its activity on body temperature, motor function and dopamine synthesis (Ahlenius and Salmi, 1994; Booth et al., 1994). This theme was taken up by Large and Stubbs (1994), who posited that the high dopamine $D_3:D_2$ receptor selectivity claimed for 7-OH-DPAT is illusory, and an artefact of non-physiological binding conditions. We would agree with this sentiment, since signs of postsynaptic dopamine D_2 receptor stimulation are clearly evident in the behavioural profile of 7-OH-DPAT, albeit with higher doses, which is entirely in keeping with the lower sensitivity of postsynaptic versus presynaptic dopamine receptors recorded in electrophysiological experiments (Skirboll et al., 1979). For example, in reversing the hypokinesia induced by 7-OH-DPAT (10 mg/kg i.p.) in non-habituated mice, SKF 38393 additionally evoked oral stereotypy and perseverative rearing, whereas no such stereotyped activity occurred when SKF 38393 reinstated locomotion in habituated animals. These findings are reminiscent of the behaviour one sees with a high dose of the mixed dopamine $D_1/D_2/D_3$ agonist apomorphine (Starr and Starr, 1986), and of the behavioural synergism that occurs when dopamine D_1 and D_2 receptors are stimulated simultaneously (Braun and Chase, 1986), suggesting to us that an element of postsynaptic dopamine D_2 receptor agonism occurs when doses of > 1 mg/kg 7-OH-DPAT are used. This would also explain the transitory increase in locomotion and sniffing we sometimes saw with 7-OH-DPAT (5–10 mg/kg s.c.) administered on its own to non-habituated mice, and the more robust motor excitation reported with similar high-dose treatment in the rat (Ahlenius and Salmi, 1994; Daly and Waddington, 1993). A switch from low-dose inhibition to high-dose stimulation of motor activity has also been observed with the dopamine $D_{2/3}$ receptor-preferring agonist LY 171555 (Eilam and Szechtman, 1989). With both 7-OH-DPAT and LY 171555, the emergence of behavioural excitant effects at doses approximately 100 times greater than the threshold for inducing hypokinesia in all likelihood reflects the stimulatory actions of the drugs at postsynaptic dopamine D_2 receptors. This is difficult to verify behaviourally with selective dopamine D_1 and D_2 receptor antagonists in naive animals, since these compounds strongly inhibit exploratory motor activity by themselves, most probably because they interfere with the ongoing actions of endogenously released dopamine (Starr and Starr, 1986).

A more obvious interaction of 7-OH-DPAT with postsynaptic dopamine D_2 receptors is apparent in mice pretreated with reserpine, which induces functional sensitisation of dopamine D_1 and D_2 receptors (Butkerait and Friedman, 1993). We found that 7-OH-DPAT potently reversed the attendant akinesia of these animals, as reported recently for the rat (Ahlenius and Salmi, 1994), and that this activity was markedly potentiated by concomitant administration of SKF 38393. These actions of 7-OH-DPAT can be attributed to an enhanced effect of the drug at supersensitive postsynaptic dopamine D_2 receptors, as the motor response to 7-OH-DPAT alone was abolished by the dopamine D_2 receptor antagonist raclopride and not by the dopamine D_1 receptor antagonist SCH 23390. The cooperative interaction between SKF 38393 and 7-OH-DPAT then becomes a straightforward case of dopamine D_1/D_2 receptor synergism, which persists in an altered form in dopamine-depleted animals (Rouillard and Bédard, 1988; Starr et al., 1987).

Finally, we find it interesting that doses of 7-OH-DPAT which evoked prominent akinesia in non-habituated, dopamine-intact mice, were completely ineffective at reducing SKF 38393-induced locomotion in reserpine-treated animals. If, as has been proposed (Svensson et al., 1994; Waters et al., 1993), the motor inhibitory dopamine D_3 receptors engaged by 7-OH-DPAT are located postsynaptically, we might reasonably have expected the functional opposition between low doses of 7-OH-DPAT and SKF 38393 to be just as operative in dopamine-depleted as in dopamine-intact mice. The lack of any such depressant action of 7-OH-DPAT in the reserpine model therefore tends to argue against the postsynaptic localisation of these motor-inhibiting dopamine D_2/D_3 receptors. Unless, of course, the reserpine treatment down-regulated the dopamine D_3 receptors, as has been reported to occur with the dopaminergic neurotoxin 6-hydroxydopamine (Sokoloff et al., 1993).

In summary, the most parsimonious interpretation of these and earlier findings with 7-OH-DPAT is that low doses of the aminotetralin stimulate dopamine autoreceptors (either D_2 or D_3) in dopamine-intact

animals, and that consequent suppression of dopamine release contributes to the profound inhibition of exploratory motor behaviour. At high doses, and in dopamine-depleted animals, this action is supplanted by an appreciable interaction of the drug with behaviourally excitant dopamine D_2 receptors, most probably at postsynaptic sites. A possible interaction of 7-OH-DPAT with dopamine D_2 receptors should therefore be borne in mind when attempting to use this compound to define the behavioural functions of dopamine D_3 receptors.

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