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Locomotor Behaviour of Selective Dopamine Agonists in Mice: Is Endogenous Dopamine the Only Catecholamine Involved?

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Abstract—The purpose of the study was to determine the effect alone and in combination of the selective dopamine (DA) agonists SKF 38393 (D_1-) and B-HT 920 (D_2-) on the locomotor activity of reserpine pretreated mice (5 mg kg^{-1} i.p.). After 4 h, reserpine–B-HT 920 (up to 20 mg kg^{-1} s.c.) did not induce locomotor activity whereas SKF 38393 was markedly effective at high doses ($\geq$ 30 mg kg^{-1} s.c.). In contrast, at 24 h, reserpine–B-HT 920 (0·2–6 mg kg^{-1} s.c.) elicited considerable locomotor activity and SKF 38393 (1–100 mg kg^{-1} s.c.) was effective at lower doses when compared with the corresponding 4 h reserpine experiments. When, however, these animals additionally received α-methyl-*p*-tyrosine (αMPT; 300 mg kg^{-1} i.p., at 4 h before the DA agonists) neither B-HT 920 (0·2–20 mg kg^{-1} s.c.) nor SKF 38393 (1–100 mg kg^{-1} s.c.) had an effect of their own. When B-HT 920 was tested in the presence of a fixed-dose of SKF 38393 (10 or 3 mg kg^{-1} s.c., combination experiments) B-HT 920 (0·6–20 mg kg^{-1} s.c.) induced considerable locomotor activity at 4 h post reserpine. At 24 h post reserpine the dose-response curve of B-HT 920 (0·06–20 mg kg^{-1} s.c.) was shifted to the left and the maximum effect was greatly increased. When additional αMPT was given, the dose response curve was the same but the maximum effect was markedly reduced. When SKF 38393 was tested in the presence of a fixed-dose of B-HT 920 (2 mg kg^{-1} s.c.; combination experiments) this resulted in a dose response curve in the range of 0·3–10 mg kg^{-1} s.c. at 4 h post reserpine. At 24 h post reserpine the curve shifted to the left by approximately a factor of 30 (0·1–3 mg kg^{-1} s.c.) and the maximum effect was markedly increased. Additional αMPT shifted the curve to the right by a factor of approximately 30 without a substantial change in the maximum effect. It is concluded that simultaneous stimulation of D_1- and D_2- receptors is necessary to elicit locomotor activity in mice. From dose response analysis of experiments with additional αMPT it is furthermore concluded that endogenous noradrenaline may play an additional modulatory role.

Dopaminomimetic drugs are classified according to their agonistic action on D_1- and D_2-dopamine (DA) receptors (Stoff & Kebabian 1984). Originally, the classical unconditioned behaviour as induced by DA agonists was assumed to be mediated predominantly by D_2-receptors (Creese et al 1983). Subsequently, a functional dependence of D_2-agonists on D_1-receptor stimulation was suggested (Gershanik et al 1983; Barone et al 1986; Walters et al 1987). In normosensitive animals, D_1/D_2 interdependence is obligatory. However, when receptors are rendered supersensitive, as for instance in 6-hydroxydopamine-lesioned animals or in animals with prolonged reserpine pretreatment, behavioural stimulation appears to be induced by either D_1 or D_2 receptor stimulation (Arnt & Hyttel 1984; Arnt 1985). These findings are, however, in contrast with a study by Gershanik et al (1983) who suggested D_1/D_2 interdependence even for supersensitive conditions.

B-HT 920, as a strong DA autoreceptor agonist (Andén et al 1983), has selective D_2-receptor agonist properties (Jennewein et al 1986; Arnt et al 1988). Unlike other selective D_2-agonists, such as quinpirole or RU 24926 (Tsuruta et al 1981; Euvrard et al 1979), B-HT 920—when given alone to normosensitive animals—does not produce the classical effects of postsynaptic DA receptor stimulation such as locomotion or stereotypic behaviour (Andén et al 1983; Hinzen et al 1986). Similarly, the selective D_1-receptor agonist SKF 38393 fails to produce locomotor effects in naive animals (Setler et al 1978). B-HT 920 does, however, induce such effects under supersensitive conditions in a variety of species (Hinzen et al 1986), or when the drug is given in combination with the D_1-agonist SKF 38393 in reserpine-treated (Andén & Grabowska-Andén 1987; Hjorth & Carlsson 1987) or naive rodents (Pifl & Hornykiewicz 1988). These and other studies have already demonstrated the importance of D_1-receptor stimulation in facilitating B-HT 920 or other selective D_2-receptor agonist-induced behaviour in naive or reserpine-treated animals with or without pretreatment with the catecholamine synthesis inhibitor α-methyl-*p*-tyrosine (Starr et al 1987; Rubinstein et al 1988). The purpose of the present study was to investigate D_1/D_2 interactions by a complete dose response analysis of the effect of B-HT 920 and/or SKF 38393 on locomotor activity in the absence and presence of additional treatment with α-methyl-*p*-tyrosine. This classical instrument of pharmacology revealed that the α-methyl-*p*-tyrosine-induced effects cannot be explained by the inhibition of DA synthesis alone.

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Materials and Methods

Male mice, 20–24 g, of the Chbb: NMRI strain, according to the International Index of Laboratory Animals, 3rd ed. 1975, Med. Res. Council, Labor. Animal Centre, UK, were used.

Locomotor activity was measured in a 24 × 48 × 8 cm

observation cage with an infrared photoelectric barrier connected with a counter. Groups of 6 mice were placed into the observation cage, and the number of infrared beam crossings within 5 min was counted ("crossing counts"). The animals received either (a) 4 h reserpine or (b) 24 h reserpine or (c) 24 h reserpine plus 300 mg kg^{-1} α-methyl-*p*-tyrosine (αMPT) i.p. at 4 h pre-injection of test substances. The dose of reserpine was 5 mg kg^{-1} i.p. in all animals. To prevent exsiccosis, 24 h pretreated mice received 3 times 2 mL s.c. of 5% glucose in Tyrode solution. Animals were kept at approximately 25°C. The test substances were given s.c. to each of the groups of 6 mice at 30 min before the activity test. Where not stated otherwise, n = 3–6 groups of animals were used per dose. In combination experiments one drug was injected after the other.

Injection volume was 0·1 mL/10 g. The putative D_2-selective agonist B-HT 920 (6-allyl-2-amino-5,6,7,8-tetrahydro-4H-thiazolo-[4,5-d]azepine dihydrochloride) and the D_1-selective agonist SKF 38393 (1-phenyl-2,3,4,5-tetrahydro(1H)-3-benzazepine-7,8-diol hydrochloride) were dissolved in saline, α-methyl-*p*-tyrosine-methylester was dissolved in distilled water. Reserpine was dissolved in warm distilled water containing 20% ascorbic acid. Results are presented as means ± s.e.

Results

Control animals, which underwent the same pretreatments, but were injected with saline instead of the test substances at 30 min before the activity test, were found to be completely akinetic (n > 10 groups each).

Locomotor effects of B-HT 920 alone (Fig. 1a)

In the animals with 4 h reserpine pretreatment B-HT 920 had no effect of its own on motor behaviour over the dose range 0·2–20 mg kg^{-1} s.c. (filled circles, solid line in Fig. 1a). Upon extension of reserpine pretreatment to 24 h, B-HT 920 did, however, evoke locomotor activity over the dose range 0·2–6 mg kg^{-1} s.c., a maximum of crossing counts (56 ± 6·4/5 min, n = 6) being observed at 2 mg kg^{-1} (halved circles, broken line in Fig. 1a). When, however, the animals received αMPT in addition to 24 h reserpine pretreatment, B-HT 920 (0·2–20 mg kg^{-1} s.c.) was again totally ineffective (open circles, Fig. 1a).

Locomotor effects of SKF 38393 alone (Fig. 1b)

In the animals with 4 h reserpine pretreatment SKF 38393 (3 and 10 mg kg^{-1} s.c.) had no effect of its own on motor behaviour. When, however, the dose was increased to 30 and 100 mg kg^{-1} s.c., SKF 38393 did stimulate locomotor activity, a maximum of crossing counts (81 ± 3·7/5 min, n = 3) being observed at the highest dose (filled squares, solid line in Fig. 1b). Upon extension of reserpine pretreatment to 24 h, SKF 38393-induced activity (1–100 mg kg^{-1} s.c.) was further increased, a plateau of about 80 crossings/5 min being reached at 10 mg kg^{-1} (halved squares; broken line in Fig. 1b). When, however, the animals received αMPT in addition to 24 h reserpine, SKF 38393 (1–100 mg kg^{-1} s.c.) was totally ineffective (open squares in Fig. 1b).

Locomotor effects of B-HT 920 in the presence of a fixed dose of SKF 38393 (Fig. 2a)

At 4 h, reserpine with B-HT 920, in the presence of 10 mg kg^{-1} SKF 38393 s.c., was found to elicit motor activity over the dose range 0·6–20 mg kg^{-1} s.c., the dose response curve being bell shaped with a maximum of crossing counts (115·7 ± 18/5 min, n = 3) being observed at 6 mg kg^{-1} (filled circles, solid line in Fig. 2a).

At 24 h reserpine the dose-response curve of B-HT 920 (0·06–20 mg kg^{-1} s.c.) in the presence of 3 mg kg^{-1} SKF 38393 s.c. was markedly shifted to the left, a maximum of crossing counts (232 ± 26/5 min, n = 3) being observed at 20 mg kg^{-1} (halved circles, broken line in Fig. 2a). In the

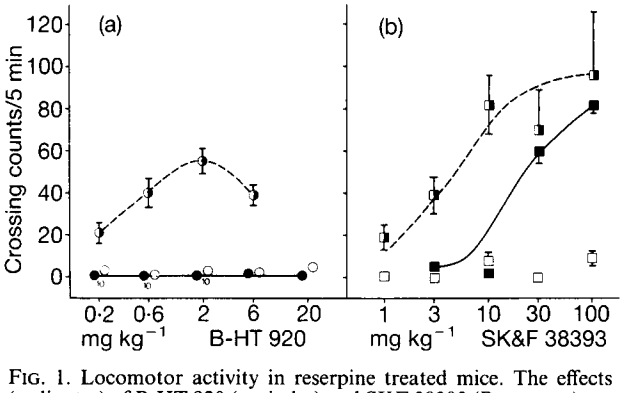

FIG. 1. Locomotor activity in reserpine treated mice. The effects (ordinates) of B-HT 920 (a, circles) and SKF 38393 (B, squares) are shown. Doses are given at the abscissae in a logarithmic scale. Filled symbols (solid line) indicate experiments with 4 h reserpine pretreatment; halved symbols and broken lines indicate experiments with 24 h reserpine. Experiments with 24 h reserpine + 4 h αMPT pretreatment are illustrated by open symbols. If not stated otherwise (small numbers within plot) all values are given as means ± s.e. of n = 3–6 groups; when less than 2·5 units, s.e. is not given. Test substances were injected s.c. 30 min before the test.

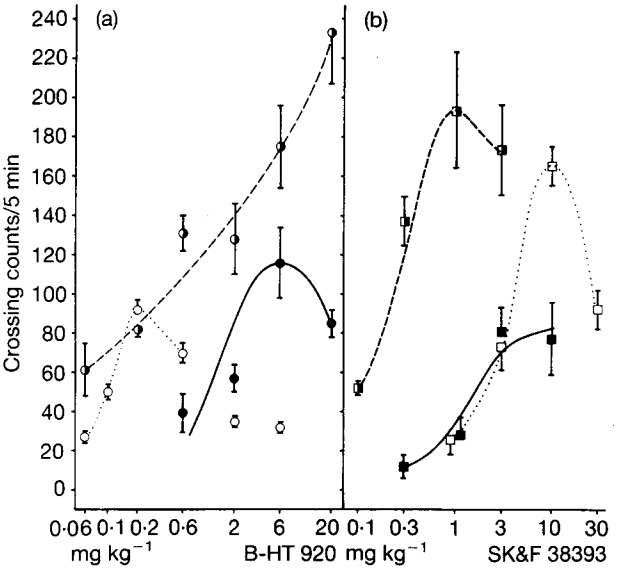

FIG. 2. Locomotor activity in reserpine treated mice. The results of combination experiments are shown. Dose response curves of B-HT 920 (a, circles) in the presence of coadministered SKF 38393 (3 mg kg^{-1} in 24 h reserpine treated animals; 10 mg kg^{-1} in 4 h reserpine-treated animals) and of SKF 38393 (b, squares) in the presence of B-HT 920 (2 mg kg^{-1}). For futher details see legend of Fig. 1. Dotted lines connect open symbols (= 24 h reserpine + 4 h αMPT pretreatment).

animals with 24 h reserpine plus αMPT (4 h), B-HT 920 in the presence of 3 mg kg^{-1} SKF 38393 s.c. was effective over the dose range 0·06–6 mg kg^{-1} s.c., the dose-response curve being bell-shaped with a maximum number of crossing counts (91·7 ± 1/5 min, n = 6) at 0·2 mg kg^{-1}.

Locomotor activity of SKF 38393 in the presence of a fixed dose of B-HT 920 (Fig. 2b)

At 4 h, reserpine—SKF 38393 in the presence of 2 mg kg^{-1} B-HT 920 s.c. elicited locomotor activity over the dose range 0·3–10 mg kg^{-1} s.c., a plateau of about 80 crossing counts/5 min being reached at a dose of 3 mg kg^{-1} (full squares, solid line in Fig. 2b). At 24 h reserpine the SKF-induced effect was markedly increased over the dose range 0·1–3 mg kg^{-1} s.c., the dose-response relationship being bell-shaped with a maximum of crossing counts (193 ± 29·5/5 min, n = 3) being observed at 1 mg kg^{-1} (halved squares, broken line in Fig. 2b). In the animals with 24 h reserpine plus αMPT, similar effects were obtained but at higher doses (1–30 mg kg^{-1} s.c.), a maximum number of crossing counts (165·3 ± 9·5/5 min, n = 3) being observed at 10 mg kg^{-1} (open squares, dotted line in Fig. 2b).

Discussion

In acutely (4 h) reserpine-treated mice the D_2-agonist B-HT 920 was unable to reverse akinesia over a dose range of two orders magnitude (0·2–20 mg kg^{-1} s.c.). In contrast, in the 24 h reserpine-treated animals the smallest dose (0·2 mg kg^{-1}) caused locomotion, the maximum activity being elicited with the 10-fold dose (2 mg kg^{-1}).

In contrast, the D_1-agonist SKF 38393 reversed akinesia both in acutely (4 h) and chronically (24 h) reserpine-treated animals. Again, the effect was investigated over a dose range of two orders of magnitude, starting with a dose of 1 mg kg^{-1} s.c. which was already sufficient to elicit locomotor behaviour in the 24 h reserpine-treated animals. Apparently, the dose-response curve for the 24 h reserpine-treated animals underwent a marked shift to the left when compared with that for the 4 h pretreated animals. Interestingly—with the exception of Andén & Grabowska-Andén (1987) who used 12 mg kg^{-1} s.c.—other authors who used only low doses of SKF 38393 did not observe locomotor effects in acutely reserpine-treated animals (Starr et al 1987; Rubinstein et al 1988).

When the 24 h reserpine-treated animals received additional αMPT neither of the two dopamine agonists had an effect of its own. This finding may be explained by the hypothesis that selective dopamine agonists can elicit locomotor activity only if catecholamine synthesis facilitates endogenous dopamine induced stimulation of the complementary dopamine receptor (Braun & Chase 1986; Mashurano & Waddington 1986). Nevertheless, the question remains obscure why in 4 h reserpine-treated mice B-HT 920 was ineffective. Two explanations appear plausible. First, it could be that by its action on dopamine autoreceptors B-HT 920 inhibits dopamine synthesis in 4 h pretreated mice (Andén et al 1983), thereby preventing a postsynaptic, agonistic effect of its own. In contrast, in the 24 h reserpine-treated animals, dopamine synthesis is disinhibited (Carlsson & Lindquist 1976) and hence B-HT 920 might not be capable of inhibiting endogenous dopamine synthesis, and hence of preventing D_1-receptor stimulation. An alternative explanation may be that the increased D_1- receptor sensitivity in the 24 h reserpine-treated animals (Kumakura et al 1976) may counteract the effect of B-HT 920 on dopamine synthesis. The D_1- receptors would then be stimulated by minimal amounts of endogenous dopamine. On the other hand DA-synthesis cannot be inhibited by D_1-receptor stimulation (Brown et al 1985). Therefore the D_1-agonist might well be capable of eliciting locomotor activity in 4 h reserpine treated mice. The shift to the left of the dose response curve for SKF 38393 at 24 h reserpine (see Fig. 1b) might then simply be explained by the increased receptor sensitivity 1 day post-injection of reserpine (Kumakura et al 1976).

In combination with a fixed dose of their respective complementary dopamine agonist, both B-HT 920 and SKF 38393 dose-dependently affected locomotor activity in the 4 h reserpine-treated mice. When these combination experiments were performed in 24 h-treated mice, not only was there a shift in the dose response curve to the left but at the same time the maximum effect was markedly increased. Here it is interesting to note that these phenomena were observed for B-HT 920 even when the SKF 38393 dose in the 24 h-treated animals was reduced to 3 mg kg^{-1} s.c. (in the corresponding experiment in 4 h reserpine-treated animals the SKF 38393 dose was 10 mg kg^{-1}). Furthermore, comparison of the maximum effects in 24 h reserpine-treated animals as elicited by each agonist alone (Fig. 1) or a combination thereof (Fig. 2) reveals that even under supersensitive conditions the effect of one agonist is potentiated by the other, a finding which is in contrast to the results by Starr et al (1987).

Inhibition of catecholamine synthesis as induced by additional pretreatment with αMPT in 24 h reserpine-treated mice had different effects on the dose-response curves of the combination experiments. After catecholamine synthesis inhibition the dose-response curve for SKF 38393, when given in the presence of 2 mg B-HT 920, was shifted to the right without changing the maximum effect (Fig. 2b). Conversely, when B-HT 920 was given in the presence of 3 mg kg^{-1} SKF 38393, the additional αMPT did not result in a shift of the curve but dramatically reduced the maximum effect (Fig. 2a).

Only in the first case, i.e. when B-HT 920 was given in the presence of 3 mg SKF 38393 (Fig. 2a), can the additional αMPT-induced effect be explained by dopamine-synthesis inhibition. In Fig. 1b this dose of SKF 38393 appears to be submaximal and consequently, in the 24 h reserpine-treated animals without αMPT the additional effect may have been facilitated by endogenous dopamine. However, it also appears possible that noradrenaline depletion may have decreased the maximum effect. Studies by Andén et al (1973) revealed that stimulation of α_1-adrenoceptors amplifies the maximum locomotor stimulation as evoked by the mixed D_1-/D_2-agonist apomorphine in reserpine-treated mice. Similarly, the selective α_1-adrenoceptor agonist St 587 (2-(2-chloro-5-trifluoromethyl phenylimino)imidazolidine) (De Jonge et al 1981; Pichler & Kobinger 1985) was found to potentiate the effect of B-HT 920 in 24 h reserpine-treated mice (Pichler, unpublished observation). Consequently, in αMPT-pretreated animals a loss in adrenergic tonus might

well impair the maximum effect as elicited by the D_2-agonist B-HT 920 in the presence of a fixed dose of the D_1-agonist SKF 38393.

In contrast, the αMPT-induced shift to the right of the dose response curve for SKF 38393 in combination with a fixed dose of B-HT 920 cannot be explained by dopamine synthesis inhibition. As the complementary (D_2-) receptor had already been maximally stimulated by the 2 mg kg^{-1} B-HT 920, the shift to the right, which suggests a loss in hypersensitivity of the D_1-receptor, might have been facilitated by inhibition of noradrenaline synthesis. Recently, Tassin et al (1986) showed that lesions in the noradrenergic innervation may abolish the D_1-receptor supersensitivity, which in 20 h reserpine-treated mice was found to be characterized by an increase in affinity (Tonon et al 1979).

From these data it is concluded that the selective D_1- and D_2-receptor agonists SKF 38393 and B-HT 920 both have locomotor stimulating effects in supersensitive mice provided that concomitant stimulation of the respective complementary DA receptor is present. However, the experiments with additional αMPT-pretreatment suggest that inhibition of catecholamine synthesis may influence the postsynaptic behavioural effects both by dopamine and noradrenaline depletion.

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