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Inhibitory role of D-1 dopamine receptors for the jerks induced by B-HT 920 in rats

M. GRABOWSKA-ANDÉN, N.-E. ANDÉN*, *Department of Pharmacology, Karolinska Institute, Box 60400, S-104 01 Stockholm, Sweden*

Jerks of the head and upper trunk produced by the dopamine agonist B-HT 920 in reserpine-treated rats were abolished by the D-1 dopamine receptor agonist SKF 38393. The combined treatment with SKF 38393 and B-HT 920 instead resulted in stereotypies and locomotion. B-HT 920 also caused jerks when given after the D-1 receptor antagonist SCH 23390 to rats not pretreated with reserpine. The results indicate that B-HT 920 induces jerks by stimulation of postsynaptic D-2-like dopamine receptors provided that the D-1 receptors are not activated.

* Correspondence.

The dopamine autoreceptor agonist B-HT 920 causes jerks but not stereotypies or locomotion in rats treated 6 h earlier with reserpine (Grabowska-Andén & Andén 1983). A low dose of apomorphine produces a similar although weaker effect. The B-HT 920-induced jerks are not observed if the postsynaptic dopamine receptors are stimulated by a high dose of apomorphine or blocked by haloperidol. These paradoxical effects were explained by the existence of two kinds of postsynaptic dopamine receptors: one of them stimulatory and the other one inhibitory with regard to jerks. The stimulatory receptors should be selectively activated by B-HT 920 (Grabowska-Andén & Andén 1983). The inhibitory dopamine receptors might be identical with the D-1 dopamine receptors stimulating the enzyme adenylate cyclase (Kebabian & Calne 1979). This hypothesis was tested in the present work by giving B-HT 920 in combination with the D-1 receptor agonist, SKF 38393, or the D-1 receptor antagonist, SCH 23390 (Setler et al 1978; Iorio et al 1983; Hyttel 1983; Stoof & Kebabian 1984).

Materials and methods

Male Sprague-Dawley rats, about 200 g, were used. Care was taken to keep the rectal temperature at 37 °C. Immediately after the injection of B-HT 920, the rats were placed in plastic cylinders (diameter 50 cm). The rats were observed for jerks and stereotypies during 1 h.

The following drugs were used: B-HT 920 (2-amino-6-allyl-5,6,7,8-tetrahydro-4*H*-thiazolo[5,4-*d*]azepine 2 HCl; Boehringer Ingelheim, Ingelheim am Rhein), SKF 38393 ((±)-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine HCl; Research Biochemicals, Wayland, MA), SCH 23390 ((R)-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine maleate; Schering, Kenilworth, NJ), reserpine (CIBA-Geigy, Mölndal). The doses refer to the forms indicated.

Results

The reserpine-treated rats responded to 1 mg kg^{-1} of B-HT 920 with jerks of the head and upper trunk. Usually the forepaws were lifted from the ground during these jerks which in some cases were so powerful that the rats jumped using all four legs. The number of jerks produced by B-HT 920 is presented in Table 1. The B-HT 920-induced jerks were inhibited by SKF 38393 in a dose-dependent manner (Table 1). Following 2 mg kg^{-1} of SKF 38393, practically no jerks were seen after the injection of B-HT 920. Instead the rats displayed very pronounced stereotypies such as sniffing, licking and, particularly, gnawing with short, intervening bursts of locomotor activity. Pretreatment with SCH 23390 (5 mg kg^{-1}) blocked the effects of SKF 38393, i.e., the B-HT 920-treated rats jerked (Table 1) but did not show any sign of stereotypy.

In rats not pretreated with reserpine, administration of 1 mg kg^{-1} of B-HT 920 resulted in no or only a few jerks (Table 2). B-HT 920 produced jerks, however, if it was given in combination with SCH 23390. The number of jerks caused by B-HT 920 was lower following SCH 23390 than reserpine (cf. Table 1). No stereotypies were induced by SCH 23390 plus B-HT 920.

Discussion

B-HT 920 produced jerks when given after treatment with reserpine or SCH 23390. It can be assumed that in both cases there was no stimulation of the postsynaptic D-1 dopamine receptors due to complete inhibition of the dopamine release by reserpine and to direct

Table 1. Number of jerks in rats after treatment with B-HT 920 (1 mg kg^{-1} i.p. at the start of the recording), different doses of SKF 38393 (s.c. 30 min before the start), SCH 23390 (5 mg kg^{-1} i.p. 45 min before the start) and reserpine (5 mg kg^{-1} s.c. 6 h before the start).

Treatment	Jerks*	Difference†
A. Reserpine + B-HT 920	265 ± 18·3 (5)	
B. Reserpine + SKF 38393, 0·4 mg kg^{-1} + B-HT 920	175 ± 51·4 (5)	B–A: $P > 0.05$
C. Reserpine + SKF 38393, 0·9 mg kg^{-1} + B-HT 920	140 ± 41·7 (5)	C–A: $P < 0.05$
D. Reserpine + SKF 38393, 2 mg kg^{-1} + B-HT 920	2 ± 0·6 (5)	D–A: $P < 0.001$
E. Reserpine + SCH 23390 + SKF 38393, 2 mg kg^{-1} + B-HT 920	157 ± 38·7 (5)	E–A: $P < 0.05$ E–D: $P < 0.01$

* Mean ± s.e.m. (*n*).
† Statistical significances by one-way analysis of variance followed by *t*-test.

Table 2. Number of jerks in rats after treatment with B-HT 920 (1 mg kg^{-1} i.p. at the start of the recording) and different doses of SCH 23390 (i.p. 30 min before the start).

Treatment	Jerks*	Difference†
A. B-HT 920	11 ± 8·0 (5)	
B. SCH 23390, 0·04 mg kg^{-1} + B-HT 920	38 ± 9·9 (5)	B–A: $P > 0·05$
C. SCH 23390, 0·2 mg kg^{-1} + B-HT 920	120 ± 18·2 (5)	C–A: $P < 0·01$
D. SCH 23390, 1 mg kg^{-1} + B-HT 920	124 ± 17·7 (5)	D–A: $P < 0·01$
E. SCH 23390, 5 mg kg^{-1} + B-HT 920	129 ± 48·7 (5)	E–A: $P < 0·01$

* Mean ± s.e.m. (n).
† Statistical significances by one-way analysis of variance followed by *t*-test.

blockade of the D-1 receptors by SCH 23390. The number of B-HT 920-induced jerks was somewhat higher following reserpine than SCH 23390. This difference might be the result of a reserpine-induced supersensitivity of postsynaptic dopamine receptors (Arnt 1985) including the B-HT 920-sensitive ones. Another possibility is that SCH 23390 slightly blocks the B-HT 920-sensitive receptors since the D-2 dopamine receptors might be blocked by very high concentrations of SCH 23390 (O'Boyle & Waddington 1984; Christensen et al 1984; Plantjé et al 1984).

The jerks caused by B-HT 920 in the reserpine-treated rats were eliminated by the D-1 receptor agonist SKF 38393. The effect of SKF 38393 was abolished by the D-1 receptor antagonist SCH 23390. These findings give further evidence for an inhibitory role of the D-1 receptors in the B-HT 920-induced jerks.

B-HT 920 and SKF 38393 given in combination to reserpine-treated rats led to marked stereotypies as seen following stimulation of both D-1 and D-2 dopamine receptors by apomorphine or SKF 38393 plus a D-2 receptor agonist (Arnt 1985; Mashurano & Waddington 1986; Braun & Chase 1986). The similar effects of B-HT 920 and the D-2 receptor agonists might indicate that these agents act at the same receptor.

B-HT 920 (1 mg kg^{-1}) produced no or only a few jerks in rats not pretreated with reserpine. This dose of B-HT 920 suppresses the spontaneous motor activity of rats by only 60% (Andén et al 1983). Therefore, it is likely that the D-1 receptors are still activated in this condition though to a lesser degree than normal. This small D-1 dopamine receptor stimulation might be sufficient in order to prevent the appearance of jerks.

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