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Stimulation of postsynaptic DA_2 receptors produces jerks in reserpine-treated rats

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The azepine derivative B-HT 920 reduces the synthesis and turnover of dopamine in the mouse and rat brain by a mechanism sensitive to haloperidol, but it does not produce stereotyped behaviour or increased locomotion. Therefore, this drug was considered as a selective agonist at dopamine autoreceptors (Andén et al 1982, 1983). Unexpectedly, we observed a kind of hyperactivity in reserpine-treated rats given B-HT 920 and placed in motor activity meters. This behaviour was qualitatively different from that usually seen after stimulation of postsynaptic dopamine receptors. In the present work, this effect was studied after administration of B-HT 920 and some other dopamine receptor agonists.

Methods

Male Sprague-Dawley rats, about 200 g, were pretreated with reserpine, 5 mg kg^{-1} i.p. and 6 h later were injected with a dopamine receptor agonist and placed singly in a plastic cage (20 × 32 × 20 cm) for observation of behaviour. The rectal temperature was maintained at 37 °C.

In other rats, B-HT 920 and apomorphine were injected bilaterally into the brain of conscious animals via injection cannulae introduced by means of guide cannulae stereotaxically implanted under anaesthesia one day before the experiment (Stock et al 1973). According to the atlas of König & Klippel (1963), the injections into the nucleus accumbens and into the corpus striatum were made at the coordinates A 9·4, L 1·0, V-0·9 and A 7·4, L 2·5 and V + 1·0, respectively. The rats were pretreated with reserpine and placed in observation cages as described above.

The following drugs were used: B-HT 920 (2-amino-6-allyl-5,6,7,8-tetrahydro-4H-thiazolo-[4,5-d]-azepine 2 HCl; Boehringer Ingelheim*, Ingelheim am Rhein), apomorphine HCl.½H_2O (Sandoz, Basle), bromocriptine mesylate (Sandoz*, Stockholm), piribedil (Servier*, Suresnes), (+)-3-PPP ((+)-3-(hydroxyphenyl)-*N*-n-propylpiperidine HCl; Astra*, Södertälje), clonidine HCl (Boehringer Ingelheim*, Stockholm), haloperidol (Leo*, Helsingborg), pimozide (Janssen*, Beerse), (±)-sulpiride (Delagrange*, Paris), prazosin HCl (Pfizer*, Sandwich, Kent), reserpine (CIBA-Geigy*, Mölndal), desipramine HCl (CIBA-Geigy*, Västra Frölunda), 6-hydroxydopamine HCl (Sigma, St Louis, MO). The doses refer to the forms indicated.

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Results

The behaviour induced by B-HT 920 consisted mainly of jerks of the head and the upper part of the 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. Sometimes, very slight backward movements occurred after the jerks, particularly in the early phase of action of B-HT 920. Between the jerks, the rats sat with the hindlegs stretched out. This position was maintained for some time after the disappearance of the jerks. No stereotypies such as gnawing were seen after B-HT 920.

The jerks produced by B-HT 920 were counted and their total number is presented in Table 1. The effect was dose-dependent with a peak following 1 mg kg^{-1}. This appeared within 5 min and lasted up to 45 min. At 3 mg kg^{-1}, B-HT 920 caused only few jerks. The dopamine receptor blocking agent haloperidol inhibited the jerks and its effect was significant after 0·125 mg kg^{-1} ($P < 0·05$) and virtually complete after 0·5 mg kg^{-1} or higher doses. Pimozide and sulpiride also markedly antagonized the effect of B-HT 920.

No inhibition of the jerks produced by B-HT 920 was observed after treatment with 6-hydroxydopamine (250 μg bilaterally in the lateral ventricles 2 weeks before the experiment and 30 min after desipramine, 25 mg kg^{-1} i.p.), rather the drug's effect was potentiated ($P < 0·025$). In rats not treated with reserpine, 6-hydroxydopamine lowered the concentration of dopamine in the corpus striatum and the limbic system by 60–95 per cent (data not shown).

Apomorphine alone (after reserpine) produced jerks after low doses (0·05–0·1 mg kg^{-1}). After 0·5 mg kg^{-1}, very few jerks were observed but stereotyped behaviour with a slight locomotion appeared. This dose also blocked the jerks seen after B-HT 920. The apomorphine-induced jerks were markedly antagonized by haloperidol, pimozide and sulpiride.

The dopamine receptor agonists bromocriptine, piribedil and (+)-3-PPP given alone (after reserpine) also produced jerks. Their peak effects and those of apomorphine were smaller than that of B-HT 920. The highest doses of bromocriptine and piribedil, but not that of (+)-3-PPP, caused stereotyped behaviour.

The α-adrenoceptor agonist clonidine did not produce jerks. The α_1-adrenoceptor blocking agent prazosin did not change the jerks induced by B-HT 920.

Bilateral injection of B-HT 920 or apomorphine into

the nucleus accumbens resulted in jerks of about the same number as seen maximally after systemic treatment with B-HT 920 (Table 2). The effect of B-HT 920 was almost completely inhibited by haloperidol. Similar injections into the corpus striatum led to no jerks after apomorphine and to a smaller number of jerks after B-HT 920 ($P < 0.005$ cf. nucleus accumbens). These jerks appeared only about 15 min after the application to the corpus striatum whereas they were seen almost immediately after the application to the nucleus accumbens.

Table 1. Number of jerks in rats after treatment with B-HT 920 (i.p. at the start of the recording), apomorphine (s.c. at the start), bromocriptine (i.p. at the start), piribedil (i.p. at the start), (+)-3-PPP (s.c. at the start), halperidol (i.p. 2 h before the start), pimozide (1 mg kg^{-1} i.p. 1 h before the start), sulpiride (30 mg kg^{-1} i.p. 30 min before the start), 6-hydroxydopamine (250 µg in each lateral ventricle after desipramine, 25 mg kg^{-1} i.p. 2 weeks before), prazozin (10 mg kg^{-1} i.p. 30 min before the start), clonidine (i.p. at the start). All the rats were pretreated with reserpine (5 mg kg^{-1} i.p. 6 h before the start of the recording).

Treatment	Jerks*†
1. B-HT 920, 0·1 mg kg^{-1}	81 (5)
2. B-HT 920, 0·3 mg kg^{-1}	155 (6)
3. B-HT 920, 1·0 mg kg^{-1}	252 (4)
4. B-HT 920, 3·0 mg kg^{-1}	10 (3)
5. Haloperidol, 0.125 mg kg^{-1} + B-HT 920, 1 mg kg^{-1}	202 (3)
6. Haloperidol, 0·25 mg kg^{-1} + B-HT 920, 1 mg kg^{-1}	89 (3)
7. Haloperidol, 0·5 mg kg^{-1} + B-HT 920, 1 mg kg^{-1}	20(3)
8. Haloperidol, 1·0 mg kg^{-1} + B-HT 920, 1 mg kg^{-1}	6 (3)
9. Haloperidol, 2·0 mg kg^{-1} + B-HT 920, 1 mg kg^{-1}	6 (4)
10. Pimozide + B-HT 920, 1·0 mg kg^{-1}	50 (3)
11. Sulpiride + B-HT 920, 1·0 mg kg^{-1}	57 (3)
12. 6-OH-dopamine + B-HT 920, 0·3 mg kg^{-1}	201 (4)
13. Apomorphine, 0·5 mg kg^{-1} + B-HT 920, 0·3 mg kg^{-1}	18(3)
14. Apomorphine, 0·01 mg kg^{-1}	9 (3)
15. Apomorphine, 0·05 mg kg^{-1}	67 (3)
16. Apomorphine, 0·1 mg kg^{-1}	114 (3)
17. Apomorphine, 0·5 mg kg^{-1}	11 (3)
18. Haloperidol, 2·0 mg kg^{-1} + apomorphine 0·1	2 (3)
19. Pimozide + apomorphine 0·1 mg kg^{-1}	4 (3)
20. Sulpiride + apomorphine 0·1 mg kg^{-1}	18 (3)
21. Bromocriptine, 0·5 mg kg^{-1}	13 (3)
22. Bromocriptine, 2·5 mg kg^{-1}	49 (3)
23. Bromocriptine, 5·0 mg kg^{-1}	57 (3)
24. Bromocriptine, 10·0 mg kg^{-1}	54 (3)
25. Piribedil, 1·0 mg kg^{-1}	10 (3)
26. Piribedil, 2·5 mg kg^{-1}	42 (3)
27. Piribedil, 5·0 mg kg^{-1}	78(3)
28. Piribedil, 10·0 mg kg^{-1}	96 (2)
29. (+)-3-PPP, 1.0 mg kg^{-1}	12(3)
30. (+)-3-PPP, 3·0 mg kg^{-1}	77 (4)
31. (+)-3-PPP, 10·0 mg kg^{-1}	45 (3)
32. Clonidine, 0·03 mg kg^{-1}	0 (3)
33. Clonidine, 0·1 mg kg^{-1}	3 (3)
34. Prazosin + B-HT 920, 1·0 mg kg^{-1}	248 (3)

* Mean with number of experiments in parentheses.
† Statistical significances by one-way analysis of variance followed by *t*-test (F = 19·988, d.f. within groups = 76, variance within groups = 877·776).

Table 2. Number of jerks in rats after bilateral application of B-HT 920 or apomorphine to the nucleus accumbens or the corpus striatum. All the rats were pretreated with reserpine (5 mg kg^{-1}, i.p. 6 h before the start of the recording). One group was also treated with haloperidol (2 mg kg^{-1}, i.p. 2 h before the start).

Treatment	Jerks*†
1. 2 × 1 µl‡ 0·9% NaCl, nucleus accumbens	0 (3)
2. 2 × 1µg‡ B-HT 920, nucleus accumbens	78 (3)
3. 2 × 3 µg B-HT 920, nucleus accumbens	139 (3)
4. 2 × 10 µg B-HT 920, nucleus accumbens	242 (3)
5. Haloperidol + 2 × 10 µg B-HT 920, nucleus accumbens	6 (3)
6. 2 × 1 µg apomorphine, nucleus accumbens	252 (3)
7. 2 × 10 µg B-HT 920, corpus striatum	100 (3)
8. 2 × 1 µg apomorphine, corpus striatum	2 (3)

* Means with number of experiments in parentheses.
† Statistical significances by one-way analysis of variance followed by *t*-test (F = 12·114, d.f. within groups = 16, variance within groups = 2605·67).
‡ 1 µl or 1 µg on each side.

Discussion

Qualitatively, the behaviour described differed from the normal activity as well as from the increased activity and the stereotypies induced by high doses of apomorphine. The jerks might resemble those seen after low doses of seizure-producing drugs. It is not likely, however, that the present behaviour was connected to seizures since it occurred only within a narrow dose range of B-HT 920 or apomorphine and it disappeared when the doses of these drugs were increased. Furthermore, haloperidol, pimozide and sulpiride blocked the jerks produced by B-HT 920 and apomorphine despite the fact that neuroleptic drugs by themselves reduce the seizure threshold.

The jerks observed should be the result of a stimulation of dopamine receptors since they were antagonized by the dopamine receptor blocking agent haloperidol in a dose-dependent manner. Other dopamine receptor blocking agents, with different chemical structures, such as pimozide and sulpiride also inhibited the jerks. The α-adrenoceptors do not seem to be implicated since the α-adrenoceptor agonist clonidine did not cause the jerks and the α_1-adrenoceptor blocking agent prazosin did not inhibit the jerks induced by B-HT 920.

The dopamine receptors involved in the jerks are probably located postsynaptically since the effect was not reduced after 6-hydroxydopamine-induced degeneration of the dopamine nerves. Actually, the effect was somewhat potentiated, perhaps due to denervation supersensitivity. The jerks appeared to be evoked from the nucleus accumbens. The effect of

B-HT 920 applied to the corpus striatum might be the result of diffusion to the nucleus accumbens since it occurred after some latency and the response was smaller.

Apomorphine at a dose of 0·5 mg kg^{-1} produced stereotyped behaviour and locomotion, in all probability as a result of stimulation of postsynaptic dopamine receptors (Ernst 1967). This effect appears to interfere with the jerks since they were not observed after 0·5 mg kg^{-1} apomorphine alone or with B-HT 920. Thus, stimulation of postsynaptic dopamine receptors seems both to evoke and block the jerks. This paradox can be explained if there are two types of postsynaptic dopamine receptors stimulating and inhibiting the jerks, respectively. The dopamine receptor antagonists used, and most dopamine receptor agonists, seem to act on both dopamine receptor types. B-HT 920 and (+)-3-PPP induced only jerks, and might be selective at one of the receptor types. The absence of jerks after B-HT 920 or (+)-3-PPP in rats not treated with reserpine might be due to stimulation of the other dopamine receptor type by the small amount of dopamine still released from the nerves. However, in combination with reserpine the two drugs completely inhibited the release of dopamine. B-HT 920 and (+)-3-PPP are also potent agonists at dopamine autoreceptors (Andén et al 1982, 1983; Hjorth et al 1983). Therefore, the postsynaptic dopamine receptors mediating the jerks might be pharmacologically identical to the dopamine autoreceptors. In the noradrenaline neurotransmission, α_2-receptors occur mainly as autoreceptors but apparently also at some postsynaptic sites together with the more common α_1-receptors (Timmermans & van Zwieten 1981; Langer 1981; McGrath 1982). Analogously, the dopamine autoreceptors and the dopamine receptors mediating the jerks might be called DA_2 receptors whereas the stereotyped behaviour, the locomotion and the jerk-inhibitory effect might be evoked via DA_1 receptors.

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