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Dopamine-mediated behaviour following chronic treatment with B-HT 920

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Abstract—Following subchronic (5-day) dosing with B-HT 920 (2-amino-6-allyl-5,6,7,8-tetrahydro-4*H*-thiazolo(4,5-*d*)azepine (1 mg kg^{-1} day^{-1} i.p.) in rats there was a significant increase in both apomorphine-induced motor activity and stereotypy. On continued B-HT 920 treatment, however, the enhancement of apomorphine motor activity faded into insignificance but the increase in stereotypy persisted beyond 15 days. The results are discussed in terms of dopamine autoreceptor tolerance, postsynaptic D_2 supersensitivity and possible differential effects in different brain loci on the above two receptor sub-classes.

B-HT 920 is an azepine derivative shown to have agonist effects on central and peripheral α_2-adrenoceptors causing hypotension and bradycardia (Kobinger & Pichler 1980; Pichler & Kobinger 1981). B-HT 920 also produces a decrease in motor activity in mice and this is thought to be a consequence of α_2-adrenoceptor activation. However, subsequent studies (Anden et al 1982, 1983) have revealed that, in addition, B-HT 920 possesses central dopamine (DA) agonist activity with marked selectivity for autoreceptors at low doses. B-HT 920 at such dose levels not only inhibits locomotion in mice but also decreases the firing rate in dopaminergic neurons (Eriksson et al 1985). Furthermore, it produces a dose-dependent retardation of α-methyl-*p*-tyrosine-induced reduction of DA content in rat brain and inhibition of γ-butyrolactone-stimulated DA synthesis in rat corpus striatum. These effects are antagonized by spiperone and haloperidol (Brown et al 1984; Mierau & Schingnitz 1987). There is no effect, however, upon DA-sensitive adenylate cyclase, suggesting that B-HT 920 does not act at D_1-receptors. Indeed its pharmacological effects are characteristic of a dopamine D_2-autoreceptor agonist (Brown & Mitchell 1985). However, if the presynaptic dopaminergic terminals have degenerated, additional postsynaptic effects of B-HT 920 emerge and become predominant (Mierau & Schingnitz 1987). Grabowska-Anden & Anden (1987) have also demonstrated a direct action of B-HT 920 on postsynaptic D_2 receptors (head jerks) when D_1 receptors are antagonized by SCH 23390. Following low chronic dosing, the autoagonistic effects of B-HT 920 may lead to postsynaptic D_2-receptor supersensitivity arising from prolonged inhibition of dopamine release. This study was therefore undertaken to investigate the chronic effects of B-HT 920 on apomorphine-induced motor activity and stereotypy as behavioural measures of dopamine receptor sensitivity.

Materials and methods

Male Wistar rats (150 g) were housed on a 12 h light- 12 h dark cycle and allowed free access to food and water. The animals were dosed daily with either B-HT 920 (1 mg kg^{-1} i.p. n = 6) or 0·9% NaCl (saline) (n = 6) for periods of 5 and 15 days. The experiments were carried out 36 h after the last dose. One hour after habituation to test environment the animals received apomorphine (0·5 mg kg^{-1} i.p.). Then, cumulative motor activity was measured via electronic counters every 10 min for a period of 1 h using photocell cages measuring 48 × 26 × 26cm. Paired cages were fitted with three light beams (one along the long axis and two equally spaced along the short axis of the oblong floor space. Single animals (test and control) were studied concurrently and simultaneously stereotyped behaviour was observed and assessed for 2 min in each 10 min period using the scoring system employed by Creese & Iversen (1973). Statistical analysis of difference between means was determined using Student's *t*-test.

The drugs used were: apomorphine hydrochloride HCl (Sigma), B-HT 920 (2-amino-6-allyl-5,6,7,8-tetrahydro-4*H*-thiazolo(5,4-*d*)azepine 2HCl (Boehringer Ingelheim).

Results

In subchronic studies (5 days treatment) B-HT 920 caused a significant increase ($P < 0.02$) in motor activity between the 10-20 min time period, the motor activity count being 174·8% of saline-pretreated controls, and this effect persisted throughout the experiment. In chronic studies (15 days treatment) no such locomotor change ($P > 0.05$) was observed between B-HT 920 and controls at any time period after apomorphine injection (Fig. 1).

In subchronically B-HT 920-treated rats, a significant increase (160% $P < 0.04$) in stereotyped behaviour was seen between 10 and 20 min. However, in 15 day chronically treated animals the increase in stereotyped behaviour persisted up to 50 min after apomorphine injection compared with saline-pretreated controls (50–78·5%, $P < 0.03$) (Fig. 2).

Discussion

Creese & Iversen (1973) provided behavioural evidence for post-synaptic supersensitivity following biochemical disruption of dopamine neuronal terminals using 6-hydroxydopamine. Since B-HT 920, at low doses through its autoreceptor action, inhibits the release of dopamine from presynaptic terminals, it should also cause a similar post-synaptic supersensitivity on repeated dosage to that described above. This is evidenced by increased apomorphine-induced locomotor activity and stereotyped behaviour after five daily treatments with the dopamine autoreceptor agonist in our study. However, if the drug dosing regimen is extended to 15 days, the increase in sensitivity to apomorphine locomotor activity fades into insignificance. This loss of dopamine supersensitivity between 5 and 15 day B-HT 920 treatment

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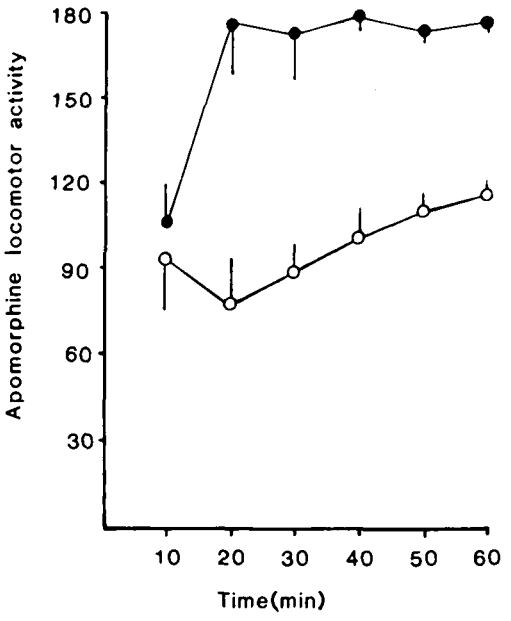

FIG. 1. Effects of 5 and 15 daily treatments with B-HT 920 (1 mg kg^{-1} day^{-1} i.p.) on apomorphine-induced cumulative locomotor activity (counts taken as percent of respective saline pretreated controls). ● = 5 days B-HT 920 pre-treatment. ○ = 15 days B-HT 920 pretreatment. Each point is a group mean value ± s.e.m. (n = 6).

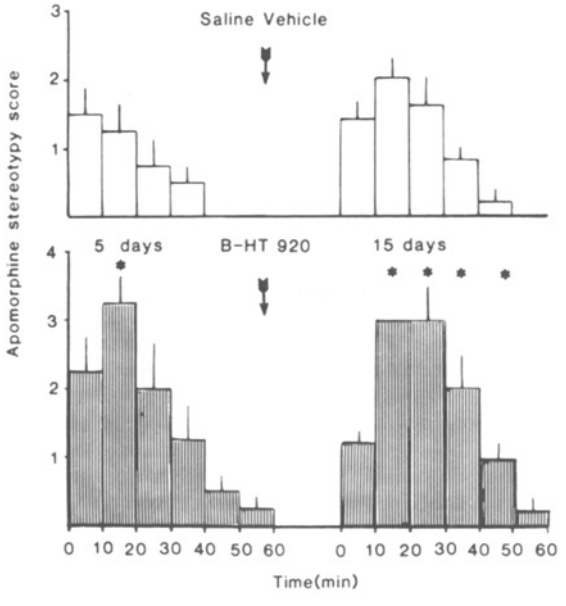

FIG. 2. Effects of 5 and 15 daily treatments with B-HT 920 (1 mg kg^{-1} day^{-1} i.p.) on apomorphine-induced stereotypies recorded for 2 min in each 10 min period. Open columns = control, hatched columns = B-HT 920 pretreated. (*$P < 0.004$. Student's t-test). Each bar represents the group mean value ± s.e.m. (n = 6).

may be attributable to a tolerance effect at dopamine autoreceptors, which would allow postsynaptic D_2 receptors to revert to a basal level of sensitivity. At the same time B-HT 920 may build up to levels capable of having inherent agonistic effects on postsynaptic D_2 receptors which may also contribute to their down regulation towards a normosensitive state. This possibility remains speculative since, to our knowledge, pharmacokinetic data are not available in rodents.

However, unlike locomotor activity, the effect of B-HT 920 on apomorphine-induced stereotyped behaviour persists beyond 15 days of treatment, although the peak effect at 5 days is subsequently reduced. This difference in locomotor activity and stereotyped behaviour may be due to the fact that these behavioural effects are produced by different centres in the brain (Creese & Iversen 1974). 6-Hydroxydopamine and electrolytic lesions of the ascending dopaminergic systems have convincingly implicated dopamine in both stereotypical and locomotor stimulant effects (Costall et al 1975; Kelly et al 1975). More selective terminal lesions have suggested that the stereotypy may be mediated via dopamine release in the caudate nucleus while locomotor stimulation and exploratory sniffing involves the accumbens-olfactory tubercle (Costall et al 1975, 1977). It may be that B-HT 920 produces differential effects on auto and postsynaptic D_2 receptors located in different parts of the CNS and/or its distribution may vary in the aforementioned brain loci. These factors may explain the differing time-course of locomotor and stereotypy effects produced by apomorphine after subchronic and chronic B-HT 920 treatment.

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