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Dopamine Receptor Mediated Hypothermic Action of B-HT 920 in Rats

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Abstract—The hypothermic action of the thiazoloazepine derivative B-HT 920, an α_2-adrenoceptor agonist has been investigated in rats. B-HT 920 (6-allyl-2-amino-5,6,7,8-tetrahydro-4H-thiazolo-(4,5-d)-azepine dihydrochloride) (0·25–1·0 mg kg^{-1} i.p.) induced a dose-dependent hypothermia. The peak effect was seen within 60–90 min and lasted up to 120 min. Its action was potentiated by the selective D_1-dopamine agonist SKF 38393 and inhibited by the D_2-anatagonists haloperidol (1 mg kg^{-1}) and sulpiride (100 mg kg^{-1}). The hypothermic action of B-HT 920 was centrally mediated; i.c.v. administration of 10 μg produced a significant fall in rectal temperature which was sensitive to blockade by haloperidol. B-HT 920 also potentiated the hypothermic action of apomorphine (0·1 and 0·5 mg kg^{-1}) in a haloperidol sensitive manner. Reserpine (5 mg kg^{-1} i.p.) pretreatment reduced the hypothermic response of B-HT 920 (0·5 mg kg^{-1}) but sensitized the response due to the combination of B-HT 920 (0·5 mg kg^{-1}) and apomorphine (0·1 mg kg^{-1}). Neither the selective α_2-adrenoceptor antagonists, yohimbine (1 mg kg^{-1}) or idazoxan (1 mg kg^{-1}), the histamine antagonist mepyramine (10 mg kg^{-1}) nor the 5-HT antagonist cyproheptadine (5 mg kg^{-1}) inhibited B-HT 920-induced hypothermia. Similarly, the selective α_1-antagonist prazosin (1 mg kg^{-1}) and the β-antagonist propranolol (10 mg kg^{-1}) failed to modify the hypothermic action of B-HT 920. These observations demonstrated hypothermia induced by B-HT 920 is mediated by postsynaptic D_2-receptors and D_1- and D_2-receptor interplay is essential for the full expression of hypothermia in rats.

A role of brain dopamine has been suggested in thermoregulation and apomorphine, a mixed type dopamine agonist produces hypothermia through its dopaminergic action (Clark & Lipton 1985; Lee et al 1985; Meller et al 1989). Several recent studies have examined the involvement of dopamine receptor subtypes, D_1 or D_2 (Stoof & Kebabian 1984) in the hypothermic action (Menon et al 1988; Carboni et al 1986). However, there is no unanimity on the participation of the exact receptor subtype in the observed response, as opposing effects have been reported in the literature (Kulkarni 1980; Iorio et al 1983; Carboni et al 1986).

Recently much research has been focused on central D_1- and D_2-receptor mechanisms and their interplay. Following concomitant administration of D_1- and D_2-agonists, a synergistic functional interaction between D_1- and D_2-receptors has been described for various functional responses (Braun & Chase 1986; Mashurano & Waddington 1986; Arnt et al 1987; Pifl & Hornykiewicz 1988). Several studies have shown that pharmacological and behavioural effects of selective D_2-agonists are weaker when given alone, but become fully manifested in the presence of a D_1-agonist (Barone et al 1986; Hjorth & Carlsson 1987). B-HT 920 (6-allyl-2-amino-5,6,7,8-tetrahydro-4H-thiazolo-(4,5-d)-azepine hydrochloride) is reported to be a dopamine autoreceptor agonist (Anden et al 1983) but some of the recent studies have described postsynaptic D_2-dopaminergic actions of B-HT 920 (Hsu et al 1986; Pifl & Hornykiewicz 1988). Therefore, in the present study the hypothermic action of B-HT 920 and its modification by concomitant administration of the D_1-agonist SKF 38393 was examined in rats.

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Materials and Methods

Wistar albino rats of either sex (bred in Panjab University), 200–250 g, were housed under standard laboratory conditions, maintained on rat chow (Hindustan Lever Products) and had free access to water. Food and water were withdrawn 12 h before the experiment. Animals were acclimatized to the laboratory conditions and all the experiments were carried out between 1000 and 1700 h. Animals were selected at random for the study.

Recording of rectal temperature

The animals were restrained in a rat restrainer and the variation in rectal temperature was recorded using a telethermometer (Yellow Springs Instrument Co., Inc., USA) by inserting the thermistor probe to a depth of 2–3 cm into the rectum. Rectal temperature of each animal was recorded just before drug administration and 15, 30, 60, 90 and 120 min after drug administration. Temperature of each animal was recorded for 1 min. The ambient temperature was 25 ± 0.5°C and the rectal temperature recorded at zero time served as control for each animal in addition to a separate control group being included in the study.

Drugs

Various doses of B-HT 920 (0·025–1·0 mg kg^{-1}) and apomorphine (0·1–1·0 mg kg^{-1}), respectively, were administered 15 min before recording rectal temperature. In combination studies B-HT 920 (0·5 mg kg^{-1}) was administered with apomorphine (0·1 and 0·5 mg kg^{-1}). SKF 38393 (5 mg kg^{-1}) was given in combination with B-HT 920 (0·1, 0·25 and 0·5 mg kg^{-1}) or apomorphine (1·0 mg kg^{-1}). The antagonists were administered 30 min before the agonists. The effect of clonidine (0·1 mg kg^{-1}) and its combination with B-HT 920 (0·5 mg kg^{-1}) in control and yohimbine (1·0 mg kg^{-1})

pretreated rats was studied. To avoid stimulation of dopamine receptors by endogenous dopamine, reserpine (5 mg kg^{-1}) was administered 24 h before the experiment. B-HT 920 (0·5 mg kg^{-1}) or B-HT 920 (0·5 mg kg^{-1}) plus apomorphine (0·1 mg kg^{-1}) was administered to reserpinized rats.

All drugs were administered i.p. in a constant volume of 0·5 mL/100 g of body weight. The selection of doses was based on earlier reports from our laboratory. For intracerebroventricular (i.c.v.) administration, chronic implantation of a polyethylene cannula was as reported by Noble et al (1967). A dose of 10 μg in 20 μL was slowly administered using a Hamilton microsyringe. Each group comprised 4–7 animals. B-HT 920 (Boehringer-Ingelheim, Germany), apomorphine (Sigma, St Louis, MO), SKF 38393 (1-phenyl-2,3,4,5-tetrahydro-(1H)-3-benzazepine-7,8-diol hydochloride; Research Biochemicals Inc., MA), SCH 23390 (8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepine-7-ol; Schering Plough Co., Bloomfield, NJ), idazoxan (Reckitt & Colman, Hull, UK), haloperidol (Searle, Skokie, IL), cyproheptadine (MSD, USA), mepyramine (Mallinicrodt Inc., USA), clonidine hydrochloride (Boehringer-Ingelheim, Germany), yohimbine hydrochloride (E. Merck, Darmstadt, Germany) and propranolol (Sigma, USA) were dissolved in distilled water. Reserpine (Loba Chemicals, Bombay, India) and sulpiride (Delagrange, Paris, France) were dissolved in a few drops of glacial acetic acid, volume was made-up with distilled water and pH adequately adjusted. Prazosin (Pfizer, Kent) was dissolved in a minimum of lactic acid (0·04 M) and the volume was made-up with distilled water.

Statistics

The data are expressed as mean (°C ± s.e.m.) change in rectal temperature as compared with the respective control groups. The difference in body temperature was assessed by employing ANOVA plus Student's *t*-test. $P < 0.05$ was considered statistically significant.

Results and Discussion

The lower doses (0·025–0·1 mg kg^{-1}) of B-HT 920 did not reduce a hypothermic response whilst the higher doses (0·25–1·0 mg kg^{-1}) produced a dose-dependent fall in rectal temperature (Table 1). This effect was sensitive to reversal by the D_2-antagonists, haloperidol and sulpiride and was potentiated by SKF 38393, a D_1-agonist (Setler et al 1978; Stoof & Kebabian 1981, 1984) (Tables 1, 3). B-HT 920 also increased apomorphine-induced hypothermia; an effect that was blocked by haloperidol (Table 2). The present findings are, therefore, consistent with the recent suggestions that D_1- and D_2-receptor interplay is essential in the full expression of dopamine-dependent behavioural patterns such as locomotion and stereotypy (Jackson & Hashizume 1986; Barone et al 1986; Arnt & Perregaard 1987). The need for concurrent D_1- and D_2-receptor stimulation can also explain the antago-

Table 1. Effect of various doses of B-HT 920 on rectal temperature of rats.

Group	Treatment (mg kg^{-1} i.p.)		n	Mean fall in rectal temperature (°C ± s.e.m.)
1	B-HT 920	(0·025)	5	0·12 ± 0·10
2	B-HT 920	(0·1)	5	0·25 ± 0·12
3	B-HT 920	(0·5)	7	1·57 ± 0·13***
4	B-HT 920	(1·0)	5	2·0 ± 0·25***
5	Haloperidol	(1·0)	5	0·75 ± 0·25*
	+			
	B-HT 920	(0·5)		

The peak effect was observed between 60–90 min. The dose-dependent hypothermic effect of B-HT 920 was sensitive to blockade by haloperidol. Statistical significances were calculated by ANOVA and compared using Student's *t*-test. *$P < 0.05$, ***$P < 0.001$ compared with respective control values. F-ratio (27, 108) = 29·41, $P < 0.05$.

Table 2. Effect of B-HT 920 on apomorphine-induced hypothermia in control and haloperidol pretreated rats. The response was recorded at peak effect (15–30 min) after drug administration.

Group	Treatment (mg kg^{-1} i.p.)		n	Mean fall in rectal temperature (°C ± s.e.m.)
1	Apomorphine	(0·1)	6	0·16 ± 0·09
2	Apomorphine	(0·5)	6	0·9 ± 0·18**
3	B-HT 920	(0·5)	7	1·57 ± 0·13***
4	B-HT 920	(0·5)	7	2·5 ± 0·26***
	+			
	apomorphine	(0·1)		
5	B-HT 920	(0·5)	5	3·1 ± 0·25***
	+			
	apomorphine	(0·5)		
6	Haloperidol	(1·0)	5	1·0 ± 0·10***
	+			
	B-HT 920	(0·5)		
	+			
	apomorphine	(0·1)		

The dose-dependent increase in apomorphine-induced hypothermia following concomitant administration of B-HT 920 and apomorphine was blocked by haloperidol. * F-ratio (27,108) = 29·41, $P < 0.05$. All values are given as mean ± s.e.m. **$P < 0.01$, ***$P < 0.001$, compared with respective control groups.

Table 3. Effect of SKF 38393 on B-HT 920- and apomorphine-induced hypothermia in rats. SCH 23390 blocked the response of the combination of SKF 38393 plus B-HT 920. The response was recorded at peak effect.

Group	Treatment (mg kg^{-1} i.p.)		n	Mean fall in rectal temperature (°C ± s.e.m.)
1	B-HT 920	(0·1)	4	0·25 ± 0·12
2	B-HT 920	(0·25)	5	1·0 ± 0·28*
3	B-HT 920	(0·5)	7	1·57 ± 0·126***
4	Apomorhphine	(1·0)	5	2·17 ± 0·55*
5	SKF 38393	(5·0)	5	1·4 ± 0·35*
	+			
	B-HT 920	(0·1)		
6	SKF 38393	(5·0)	5	2·4 ± 0·22**
	+			
	B-HT 920	(0·25)		
7	SKF 38393	(5·0)	4	4·5 ± 0·25***
	+			
	B-HT 920	(0·5)		
8	SCH 23390	(1·0)	4	1·5 ± 0·25***
	+			
	SKF 38393	(5·0)		
	+			
	B-HT 920	(0·5)		
9	SKF 38393	(5·0)	5	2·10 ± 0·5
	+			
	apomorphine	(1·0)		

All values are given as means ± s.e.m. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ compared with respective control values. F-ratio (27,108) = 29·41, $P < 0.05$.

Table 4. Effect of reserpine pretreatment (24 h before) on the hypothermic effect of B-HT 920 alone and the combination of B-HT 920 plus apomorphine. The response was recorded at peak effect.

Group	Treatment (mg kg^{-1} i.p.)		n	Mean fall in rectal temperature (°C ± s.e.m.)
1	Reserpine	(5·0)	5	1·0 ± 0*
2	Reserpine	(5·0)	5	0·8 ± 0·25*
	+			(1·57 ± 0·13)
	B-HT 920	(0·5)		
3	Reserpine	(5·0)	5	5·0 ± 0·16**
	+			(2·5 ± 0·26)
	B-HT 920	(0·5)		
	+			
	apomorphine	(0·1)		

*$P < 0.05$, **$P < 0.01$ compared with respective control values in naive animals given in parenthesis. Reserpine alone showed significant hypothermia.

nism of the effect of the combination of SKF 38393 plus B-HT 920 by the D_1-antagonist, SCH 23390 (Hyttel 1983).

Since endogenous dopamine is probably available for the stimulation of D_1- and/or D_2-receptors, rats were pretreated with reserpine 24 h before the experiment to deplete catecholamine stores and sensitize dopamine receptors. B-HT 920 alone produced a mild hypothermia in reserpinized rats. B-HT 920, produced a lower response compared with that in naive rats with normosensitive dopamine receptors. Reserpinization, however, sensitized the response of B-HT 920 and apomorphine given in combination (Table 4). A minor contribution from postsynaptic dopamine receptor sensitization in the present study cannot be entirely ruled out. Diminished D_1-receptor tone due to endogenous amine depletion by reserpine might explain the reduction in hypothermic response of B-HT 920 in reserpinized rats. Postsynaptic behavioural effects of D_2-agonists have been

Table 5. Modulation of rectal temperature by various drugs in rats. The response was recorded at peak effect.

Group	Treatment (mg kg^{-1} i.p.)		n	Mean fall in rectal temperature (°C ± s.e.m.)
1	B-HT 920	(0·5)	4	3·25 ± 0·14***
2	Clonidine	(0·1)	4	3·5 ± 0·30
3	B-HT 920	(0·5)	5	4·9 ± 0·33
	+			
	clonidine	(0·1)		
4	Yohimbine	(1·0)	4	3·3 ± 0·55
	+			
	clonidine	(0·1)		
	+			
	B-HT 920	(0·5)		
5	Sulpiride	(100)	4	1·5 ± 0·30**
	+			
	B-HT 920	(0·5)		
6	Mepyramine	(10)	6	3·25 ± 0·31
	+			
	B-HT 920	(0·5)		
7	Prazosin	(1·0)	4	3·0 ± 0·35
	+			
	B-HT 920	(0·5)		
8	Propranolol	(10)	6	1·0 ± 0·12**
9	Propranolol	(10)	6	2·96 ± 0·21
	+			
	B-HT 920	(0·5)		

All values are mean ± s.e.m. **$P < 0.01$, ***$P < 0.001$ compared with B-HT 920 treatment. F-ratio (27,108) = 29·41, $P < 0.05$.

Table 6. Effect of α_2- and 5-HT-receptor antagonists on the B-HT 920-induced hypothermia in rats.

Group	Treatment (mg kg^{-1} i.p.)		n	Mean fall in rectal temperature (°C ± s.e.m.)
1	B-HT 920	(0·5)	7	1·0 ± 0·07***
2	Idazoxan	(1·0)	4	1·36 ± 0·08
	+			
	B-HT 920	(0·5)		
3	Yohimbine	(1·0)	4	1·38 ± 0·18
	+			
	B-HT 920	(0·5)		
4	Cyproheptadine	(5·0)	4	1·9 ± 0·33
	+			
	B-HT 920	(0·5)		

None of the antagonists blocked the hypothermic response of B-HT 920. ***$P < 0.001$.

similarly reported to be facilitated by concomitant D_1-receptor activation in naive (Pifl & Hornykiewicz 1988; Meltzer et al 1988; Chopra & Kulkarni 1988) as well as reserpinized rodents (Braun & Chase 1986; Hjorth & Carlsson 1987; Anden & Grabowska-Anden 1989). Contrary to this finding Cox & Tha (1975) reported reversal of reserpine-induced hypothermia in mice by high doses (5–20 mg kg^{-1}) of apomorphine.

The effect of combined treatment with SKF 38393 and B-HT 920 was of the same intensity as the effect of a high dose of apomorphine, a mixed D_1-/D_2-agonist (Arnt & Hyttel 1985; Andersen & Nielsen 1986). Further evidence for comparable D_1-/D_2-receptor stimulation with apomorphine was provided by the lack of influence of SKF 38393 on the hypothermic response of apomorphine.

Reserpine alone produced hypothermia which could be attributed to its ability to deplete monoamines. Since virtually all monoamines are involved in thermoregulation, their depletion may interfere with peripheral temperature lowering mechanisms. However, neither the α_1-antagonist prazosin nor the β-blocker propranolol blocked the hypothermic action of B-HT 920 (Table 5). A role of 5-HT (particularly 5-HT_1) and histaminergic receptors has also been ruled out because of the inability of cyproheptadine and mepyramine, respectively, to modify B-HT 920-induced hypothermia (Tables 5, 6).

B-HT 920 has been characterized as an α_2-agonist (Mottram 1983). α_2-Receptor involvement in the hypothermic action of B-HT 920 was evaluated from a study of the combined effect of clonidine, another α_2-agonist and B-HT 920. Yohimbine, an α_2-blocker, reversed only the clonidine response but not the response due to B-HT 920 when both drugs were administered simultaneously (Table 5). Furthermore, the hypothermic response of B-HT 920 was more pronounced in α_2-antagonist (yohimbine or idazoxan)-treated animals indicating an unmasking effect of α_2-receptors on the preferential action of the drug on D_2-receptors (Table 6). In the dose employed, haloperidol (1 mg kg^{-1}) exhibits some degree of blockade at α_2-adrenoceptors. However, the inability of α_2-antagonists to modify B-HT 920 responses argues against the possibility of participation of α_2-receptors in the observed response.

The hypothermic action of B-HT 920 is centrally mediated. I.c.v. administration of a low dose (10 μg)

Table 7. Effect of intracerebroventricular (i.c.v.) administration of B-HT 920 and its modification by an α_2-adrenoceptor antagonist and a dopamine antagonist on rectal temperature in rats. The response was recorded at peak effect.

Group	Treatment (dose)	n	Mean fall in rectal temperature (°C ± s.e.m.)
1	B-HT 920 (10 μg i.c.v.)	5	2·7 ± 0·26**
2	Yohimbine (1 mg kg^{-1} i.p.) + B-HT 920 (10 μg i.c.v.)	4	2·5 ± 0·22
3	Haloperidol (1 mg kg^{-1} i.p.) + B-HT 920 (10 μg i.c.v.)	5	1·2 ± 0·18**

Statistical significances were calculated by ANOVA and compared using Student's t-test. ** $P < 0·01$ compared with respective control values. F-ratio (27,108) = 29·41, $P < 0·05$.

produced a significant fall in body temperature in a haloperidol-sensitive manner (Table 7). The thermogenic response to B-HT 920 was more rapid in onset and the agonist was 10-fold more potent than when injected i.p. These observations extend the concept of an enabling effect of D_1-receptor agonists on D_2-receptor mediated behaviour including the hypothermic response.

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