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The role of α_2-adrenoceptors in the hypothermic effect of clonidine in the rat

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Clonidine induces a decrease in body temperature in rats (Laverty & Taylor 1969; Maj et al 1975; Bugajski & Zacny 1979). Our previous experiments indicate that the clonidine-induced hypothermia seems to be due to central α-adrenergic mechanisms since this effect was antagonized by a central injection of phentolamine but not by propranolol (Bugajski et al 1980).

Recent results show that clonidine has a high affinity for α_2-adrenoceptors (Starke & Altmann 1973; Miach et al 1978; U'Prichard & Snyder 1979) which mediate the inhibition of noradrenaline release from sympathetic neuron terminals (Langer 1974). Clonidine hypothermia in mice was prevented by presynaptic α-adrenoceptor blocking agents (Von Voigtlander et al 1978). However, larger doses of clonidine can act postsynaptically (Maj et al 1972; Andén et al 1976).

The aim of the present study was to determine which type of adrenoceptors, α_1 or α_2, mediates clonidine-induced hypothermia in rats. Clonidine was used in combination with yohimbine and tolazoline which have a high affinity for α_2-adrenoceptors (Borowski et al 1976; Miach et al 1978), and phenoxybenzamine (PBZ) preferentially blocks α_1-adrenoceptors (Cubeddu et al 1974; Doxey et al 1977).

Methods

The experiments were carried out on male Wistar rats, 200–250 g. The oesophageal temperature was measured using an Ellab TE-3 thermometer at an ambient temperature of 21 ± 1 °C. The exact experimental procedure was as described by Bugajski et al (1980).

Yohimbine was dissolved in distilled water and injected i.p. 30 min before the clonidine injection, tolazoline in 0·9% NaCl and administered i.p. 60 min before clonidine. PBZ was homogenized in 3% solution of Tween 80 and injected i.p. 60 min before clonidine. PBZ was also given into the lateral cerebral ventricle (i.c.v.) through a cannula stereotaxically implanted. The original solution of PBZ was dissolved in distilled water and injected in doses of 10 and 50 μg in a volume of 10 μl per rat, 30 min before clonidine (for details see Bugajski et al 1980).

Drugs used were: clonidine HCl (Boehringer), yohimbine HCl (Polfa), tolazoline HCl (Pridazol, Polfa), phenoxybenzamine HCl (Smith, Kline and French). One-way analysis of variance and Student's *t*-test was used for a statistical analysis.

Results

Clonidine (50 μg kg^{-1} i.p.) induced a significant fall in body temperature to a maximum of 1·4 ± 0·05 °C at 60 min after administration. Yohimbine in doses of 0·5; 1 and 2 mg kg^{-1} reduced the clonidine-induced hypothermia by about 80% (Fig. 1). 0·5 and 1 mg kg^{-1} doses of yohimbine alone did not affect body temperature but a higher dose of 2 mg kg^{-1} produced a slight decrease (−0·6 ± 0·05 °C), which was statistically significant ($P < 0·05$).

Tolazoline (1, 5 and 10 mg kg^{-1}) antagonized the clonidine hypothermia (Fig. 2). The least antagonizm was observed with the 10 mg kg^{-1} dose which by itself significantly diminished body temperature.

In contrast to yohimbine and tolazoline, PBZ administered i.p. in thermoneutral doses (1 and 5 mg kg^{-1}) did not influence the hypothermic action of clonidine. Also, the central injection of PBZ, 10 μg, did not reduce this hypothermia. Larger doses (10 mg kg^{-1} i.p. and 50 μg i.c.v.) were not tested with clonidine because PBZ in these doses induced marked changes by itself (Table 1).

Discussion

The present data indicate that the hypothermia induced by clonidine is due to its agonistic effect on α_2-adrenoceptors. In this study clonidine was used in a small dose (50 μg kg^{-1}) which according to Andén (1976) has a presynaptic effect; a larger dose is necessary to stimulate postsynaptic α-adrenoceptors. In the present experiments, the α_2-adrenoceptor antagonists, yohimbine and tolazoline used in thermoneutral doses significantly antagonized the hypothermic effect of clonidine. Lack of a dose-response relationship may be due to the fact that larger doses of these

Table 1. Effect of phenoxybenzamine on clonidine hypothermia. The means are for the maximum change in body temperature occurring within 60 min of injection. PBZ pretreatment time was 60 min for i.p. and 30 min for i.c.v. injection. The number of rats are given in parentheses.

Drug	Dose	Mean change in body temperature (°C ± s.e.m.)
Clonidine	50 μg kg^{-1} i.p.	−1·3 ± 0·08 (10)
Clonidine + PBZ	1 mg kg^{-1} i.p.	−1·27 ± 0·09 (9)
Clonidine + PBZ	5 mg kg^{-1} i.p.	−1·23 ± 0·10 (8)
PBZ	10 mg kg^{-1} i.p.	−1·4 ± 0·05 (7)
Clonidine	50 μg kg^{-1} i.p.	−1·2 ± 0·10 (8)
Clonidine + PBZ	10 μl/rat i.c.v.	−0·95 ± 0·15 (9)
PBZ	50 μg/rat i.c.v.	+1·6 ± 0·10 (3)

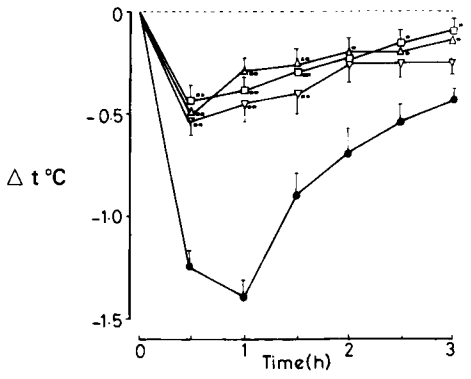

FIG. 1. Influence of yohimbine pretreatment on clonidine hypothermia. Yohimbine was injected 30 min before the agonist. ● Clonidine (50 μg kg^{-1}) alone; △ 0·5 mg kg^{-1} yohimbine + clonidine; ▽ 1 mg kg^{-1} yohimbine + clonidine; □ 2 mg kg^{-1} yohimbine + clonidine. In Figs 1 and 2 each point represents a mean change in body temperature (△ t °C) for at least 7 animals. Vertical lines show ± s.e.m. Significance of difference from control, $^{*}P < 0{\cdot}05$; $^{**}P < 0{\cdot}001$. Abscissa: time (h) after clonidine injection.

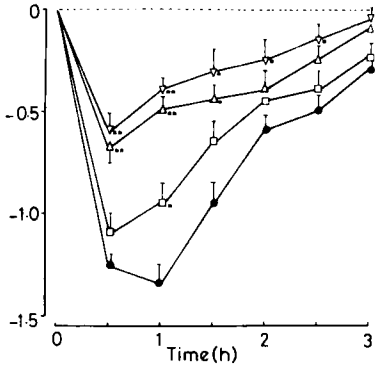

FIG. 2. Influence of tolazoline pretreatment on clonidine hypothermia. Tolazoline was injected 60 min before the agonist. ● Clonidine (50 μg kg^{-1}) alone; △ 1 mg kg^{-1} tolazoline + clonidine; ▽ 5 mg kg^{-1} tolazoline + clonidine; □ 10 mg kg^{-1} tolazoline + clonidine. Abscissa: time (h) after clonidine injection. Symbols as in Fig. 1.

drugs produced a hypothermic effect by themselves. Conversely, pretreatment with PBZ, either i.p. or i.c.v., in doses which themselves had no effect on the body temperature, failed to alter the hypothermic response to clonidine. However, Zebrowska-Lupina (1976) has reported that PBZ in the dose used in our study (10 μg i.c.v.) was effective in blocking postsynaptic α-adrenoceptors. Therefore, it may be assumed that the hypothermia induced by a small dose of clonidine is connected with a decrease in the release of noradrenaline in the central nervous system as a result of the action of clonidine on α_2-adrenoceptors.

Recently, Drew et al (1979) demonstrated that the hypothermic effect of clonidine was not antagonized by piperoxan and yohimbine and was not consistently antagonized by phentolamine injected i.c.v. However, these experiments were carried out on rats weighing 40–70 g, the drugs were administered by the free-hand method under anaesthesia and changes in body temperature were measured only 20 min after the clonidine injection. We have previously observed (Bugajski et al 1980) that the peak of the hypothermic effect of clonidine occurred approximately 60 min after i.p. administration. For those reasons these results can hardly be compared.

Many data indicate that the behavioural and metabolic effects of clonidine can be antagonized by typical α_2-adrenoceptor blocking drugs. Franklin & Herberg (1977) have reported that the depression of self-stimulation, evoked by low doses of clonidine, can be antagonized by piperoxan, but not by PBZ. Also tolazoline, yohimbine and piperoxan prevent the inhibition of exploration induced by clonidine (Delini-Stula et al 1979). The present data corroborate the assumption that clonidine-induced hypothermia is also medicated by α_2-adrenoceptors.

Clonidine hypothermia is one of the pharmacological tests used for studying antidepressant drugs (Von Voigtlander et al 1978; Górka & Zacny 1981), so an explanation of the mechanism of the hypothermic action of clonidine may help in the understanding of the action of antidepressants.

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