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Evidence for the presence of α-adrenoceptors in the central thermoregulatory mechanism of rabbits

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Summary

1. The effects of intracerebroventricular administration of some α- and β-adrenoceptor stimulants and antagonists on the body temperature of rabbits were investigated.

2. Noradrenaline produced a dose dependent rise in body temperature. Other catecholamines were less active.

3. The noradrenaline response was blocked by α-adrenoceptor blocking agents while β-adrenoceptor antagonists had no effect.

4. α-Methyl-noradrenaline and metaraminol had some hyperthermic effect, but significantly reduced the response of noradrenaline.

5. The possible presence of α-adrenoceptors in the central thermoregulatory mechanisms is suggested.

Introduction

Intracerebroventricular (i.c.v.) administration of catecholamines changes normal and elevated body temperatures (Feldberg & Myers, 1963, 1964). In the cat, dog and monkey catecholamines produce hypothermia (Feldberg & Lotti, 1967), but in rabbit and sheep they increase body temperature (Cooper, Cranston & Honour, 1965). In the rat the response is dose dependent (Feldberg & Lotti, 1967). Catecholamines produce these effects by their action on the anterior hypothalamus (Feldberg & Myers, 1965), which is the site of regulation of body temperature (Hardy, 1961). The rostral hypothalamus, in the region of the thermoregulatory centres, contains relatively high concentrations of catecholamines (Lomax, Foster & Kirkpatrick, 1969) and noradrenaline-containing neurones may be concerned with thermoregulation (Corrodi, Fuxe & Hökfelt, 1967). No information is available, however, regarding the nature of adrenoceptors in the central thermoregulatory loci. The present investigation was undertaken to elucidate the nature of these receptors. A preliminary report of part of this work has appeared (Dua & Dhawan, 1970).

Methods

Forty albino rabbits weighing 2·5–3 kg were used. A Collison cannula (Feldberg & Sherwood, 1953) was aseptically implanted into the left lateral cerebral ventricles of the brain under pentobarbitone and paraldehyde anaesthesia. The cannula was inserted at right angles to the bone, 7–8 mm deep according to the parameters described by Jancović, Draškoci & Isaković (1961). After the cannula had been

screwed into the skull and communication with the ventricular fluid established, it was fixed to the bone with dental acrylate and skin sutures were applied. The incision area was sealed with tincture benzoin. One week later the stitches were removed and the animals were ready for the experiment. At least five animals were used for each dose level of each drug.

The rectal temperature was measured by a thermistor probe, inserted 3–4 cm into the rectum and held in position by adhesive tape wrapped around the tail. The temperature was recorded at hourly intervals by telethermometer. All experiments were conducted at a room temperature of $25 \pm 1°$ C.

The following compounds were used: (−)-adrenaline bitartrate, α-methyl-noradrenaline hydrochloride, dibenamine hydrochloride, (−)-1-(4-nitrophenyl)-2-isopropylaminoethanol hydrochloride (D-(−)-INPEA), dopamine hydrochloride, (−)-isoprenaline hydrochloride, metaraminol bitartrate, (±)-4-(2-isopropylamino-1-hydroxyethyl) methane-sulphonanilide hydrochloride (MJ-1999), (−)-noradrenaline bitartrate and tolazoline hydrochloride. Solutions of all the drugs were prepared in pyrogen-free normal saline and the volume of the fluid injected never exceeded 0·25 ml. Control intracerebroventricular administration of 0·25 ml saline (thirty animals) was without any significant effect on body temperature. All syringes and needles were sterilized.

Results

Effect of noradrenaline

Intracerebroventricular administration of noradrenaline produced a dose dependent rise of body temperature (Fig. 1). With a dose of 150 μg (thirty animals), the effect appeared within an hour, a peak was reached at about 3 h and the effect lasted

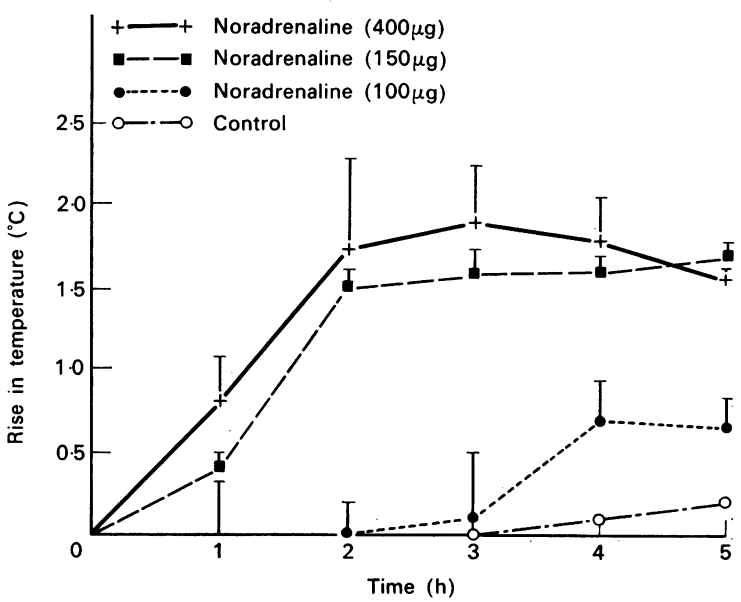

FIG. 1. Effect of noradrenaline (100, 150 and 400 μg given intracerebroventricularly) on normal body temperature control in rabbits. Each point in this and subsequent figures represents data from five animals except 150 μg of noradrenaline and controls where thirty animals were used in each case. The vertical lines indicate standard deviations of the means.

for more than 4 hours. The hyperthermic response to noradrenaline (150 μg) was considered adequate and was used where drug interactions were studied.

Effect of other catecholamines

To elucidate the mechanism of the hyperthermic response to noradrenaline some other catecholamines were also investigated. (−)-Adrenaline (100 μg or 150 μg) produced a rise in body temperature which was less marked than that of corres-

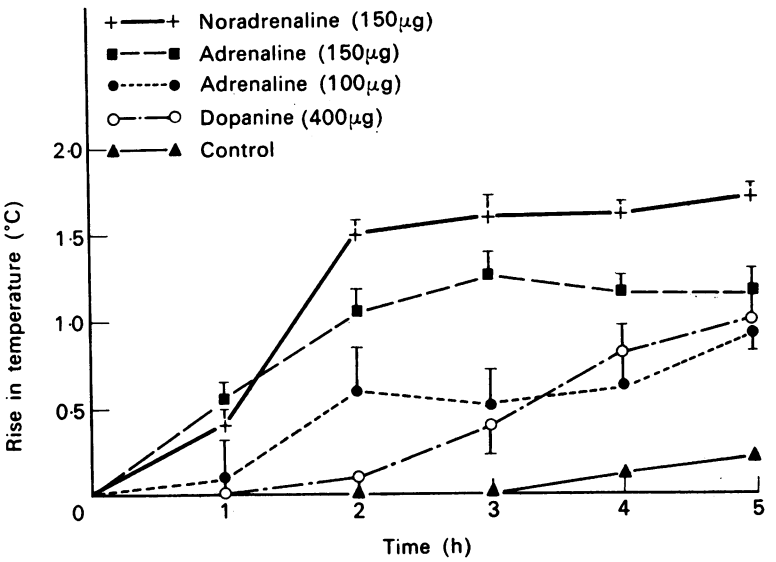

FIG. 2. Effect of intracerebroventricular administration of noradrenaline (150 μg), adrenaline (100 and 150 μg), and dopamine (400 μg) on the normal body temperature of rabbits. The vertical lines represent the standard deviations of the means.

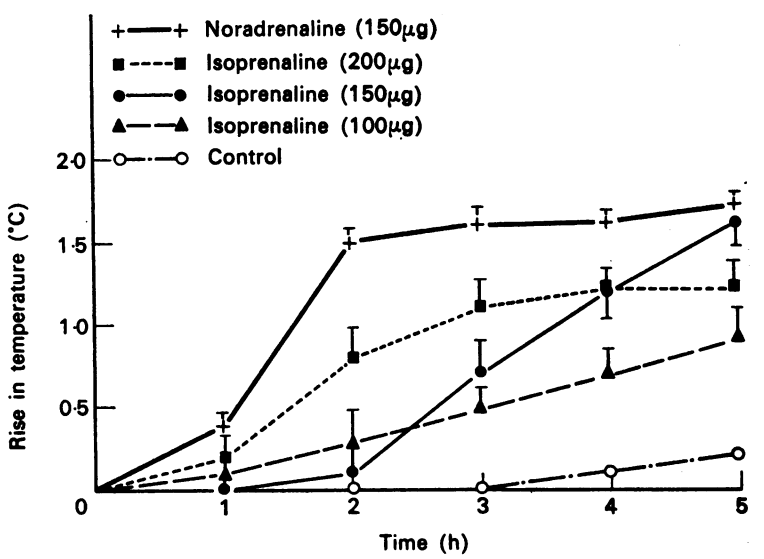

FIG. 3. Effect of isoprenaline (100, 150 and 200 μg) and noradrenaline (150 μg) given intracerebroventricularly on the normal body temperature in rabbits. The vertical lines represent the standard deviations of the means.

ponding amounts of noradrenaline. Dopamine (even up to 400 μg), produced only an insignificant increase in body temperature. The results are shown in Fig. 2. The effect of various doses of isoprenaline are shown in Fig. 3, from which it is evident that it had a weaker effect than noradrenaline even at a dose of 200 μg.

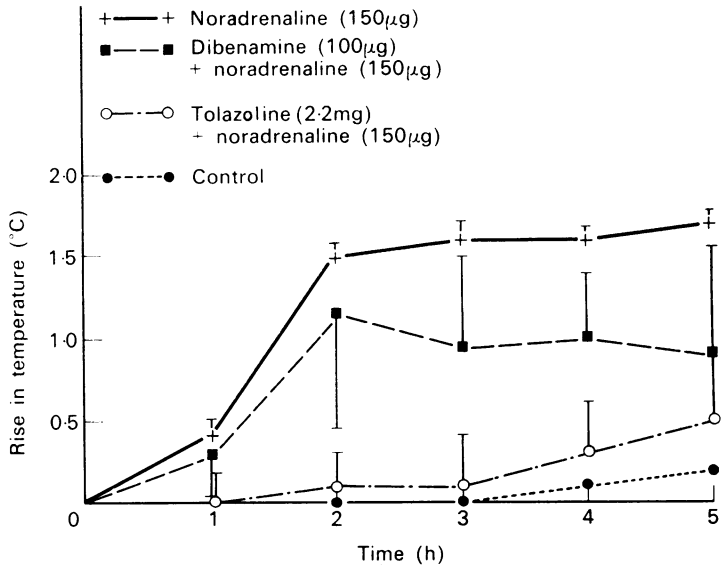

FIG. 4. Effect of the α-adrenoceptor blocking agents dibenamine (100 μg) and tolazoline (2 mg) on the hyperthermic response to noradrenaline in rabbit. The vertical lines represent the standard deviations of the means.

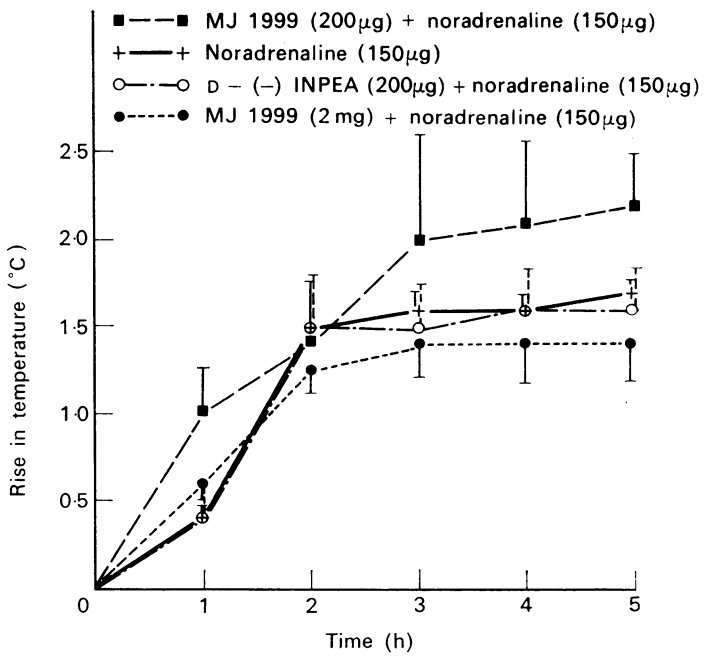

FIG. 5. Effect of the β-adrenoceptor blocking agents MJ-1999 (2 mg and 200 μg) and D-(–)-INPEA (200 μg) on the hyperthermic response to noradrenaline in rabbit. The vertical lines represent the standard deviations of the means.

Effect of α-adrenoceptor blocking agents on the hyperthermic response to noradrenaline

Two α-adrenoceptor blocking agents, dibenamine (100 μg) and tolazoline (42·2 mg) were studied. They were also given intracerebroventricularly and produced no significant effect on body temperature when administered alone. Both these agents, however, significantly reduced the effect of noradrenaline given 1 h later (Fig. 4). The more marked effect of tolazoline may have been due to the higher dose used.

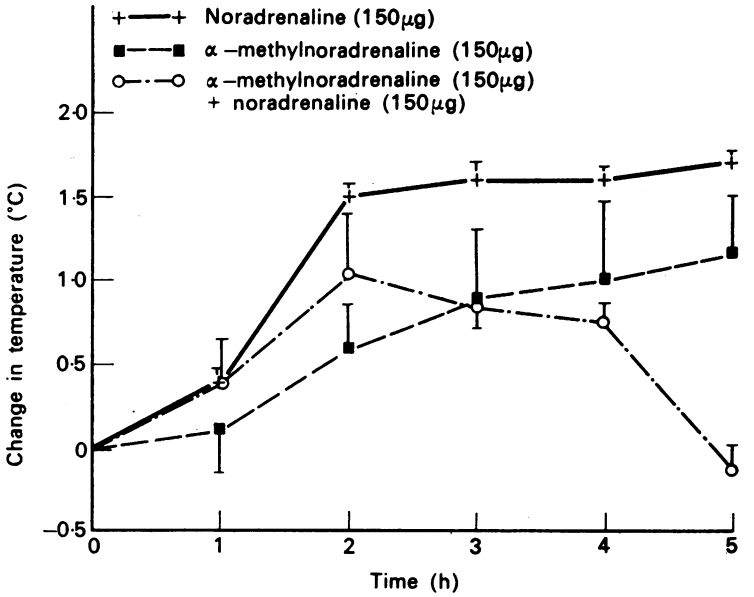

FIG. 6. Effect of α-methyl noradrenaline (150 μg, i.c.v.) on normal body temperature and its antagonism of the noradrenaline hyperthermic response in rabbit. The normal response to noradrenaline alone has also been shown. The vertical lines are the standard deviations of the means.

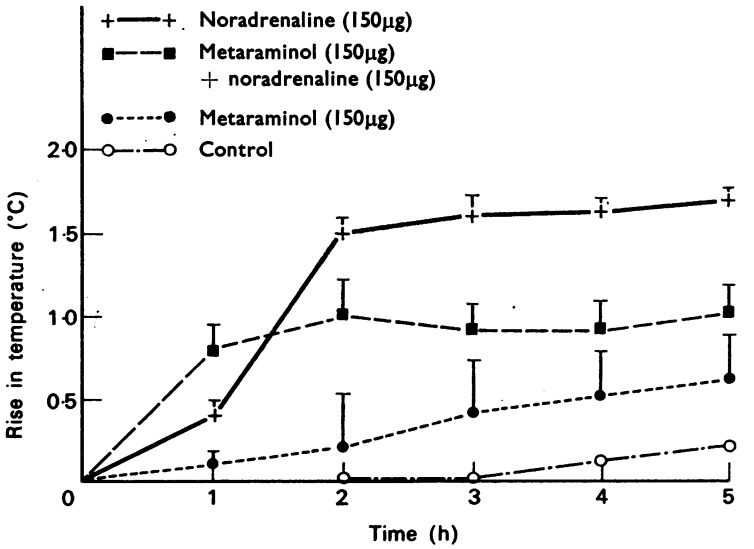

FIG. 7. Effect of metaraminol (150 μg) on normal body temperature and its antagonism of the hyperthermic response to noradrenaline (150 μg) in rabbit. The standard deviations of the means are represented by vertical bars.

Effect of β-adrenoceptor blocking agents on the hyperthermic response to noradrenaline

Neither of the two β-adrenoceptor blocking agents used, D-(−)-INPEA or MJ-1999 (200 μg i.c.v. in each case), antagonized the noradrenaline-induced rise of body temperature (Fig. 5). There was actually a potentiation of the response with MJ-1999. Even higher dose (2 mg) of MJ-1999 failed to reduce the noradrenaline response. The potentiation of noradrenaline response was, however, not obtained when the high dose of MJ-1999 was used.

Effect of α-methyl noradrenaline and metaraminol on the hyperthermic response of noradrenaline

The results with α-methyl-noradrenaline (150 μg) are shown in Fig. 6. The compound had a weak hyperthermic activity but it effectively suppressed the response to subsequently administered noradrenaline. Metaraminol had even weaker hyperthermic activity and its antagonism of noradrenaline also was less marked (Fig. 7).

Discussion

The results obtained with intracerebroventricular administration of noradrenaline in rabbits in this investigation are in agreement with the earlier published report of Cooper *et al.* (1965). A comparison of the results obtained with the various catecholamines shows that (−)-noradrenaline is the most potent agent of those tested in this regard even though all produced some effect. Dopamine produced a delayed response (Fig. 2) which may have been the result of its partial conversion to noradrenaline.

One feature of this investigation was the ability of the α-adrenoceptor blocking agents, dibenamine and tolazoline to suppress the hyperthermic response to noradrenaline (Fig. 4) and the inability of β-adrenoceptor blocking agents MJ-1999 and D-(−)-INPEA to reduce it even slightly. These results strongly suggest that α-adrenoceptors are involved in mediation of the hyperthermic response to noradrenaline and other catecholamines. These findings are in agreement with the reported presence of α-adrenoceptors in the spinal cord (Dhawan & Sharma, 1970), medulla (Bradley, Wolstencroft, Hösli & Avanzino, 1966) and cerebral cortex (Johnson, Roberts, Sobieszek & Straughan, 1969) of cat, olfactory bulb of rabbit (Salmoiraghi, Bloom & Costa, 1964) and hypothalamic centres regulating oestrous cycle in mouse and rabbit (Bhargava, 1970). It is possible that the hyperthermic effect of the other catecholamines is weaker because they have a less marked effect on the α-adrenoceptors.

α-Methyl-noradrenaline and metaraminol simulate the effects of noradrenaline peripherally (Day & Rand, 1963 ; Crout & Shore, 1964) as well as centrally (Dhawan & Sharma, 1970). The weak hyperthermic effect of these compounds is also easily explainable on this basis. Both of these compounds block the effect of noradrenaline on spinal cord adrenoceptors (Dhawan & Sharma, 1970) and α-methyl noradrenaline has a similar action on brain stem neurones as well (Boakes, Candy & Wolstencroft, 1968).

There is indirect evidence that rabbit pyrexia induced by lysergic acid diethylamide is adrenergically mediated centrally (Bapat, Chandra, Jauhari, Ansari & Dhawan, 1970 ; Dhawan, 1959). It would be interesting to find out if these adreno-

ceptors are also of the α-type, in which case both catecholamines and LSD-25 may be acting on the same set of receptors in the central nervous system.

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