

## Effects of adrenoceptor blocking agents on body temperature

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### Summary

1. The effect on rectal temperature of adrenoceptor blocking agents, injected through a cannula chronically implanted into a lateral cerebral ventricle, was examined in unanaesthetized rabbits, cats and rats, kept at room temperature (19–22° C).
2. In rabbits, the  $\alpha$ -adrenoceptor blocking agent phenoxybenzamine (50 or 100  $\mu$ g) produced marked hypothermia when injected intraventricularly but not when injected intravenously. In some rabbits as little as 1  $\mu$ g was effective on intraventricular injection. Phentolamine and ergotamine, the other  $\alpha$ -adrenoceptor blocking agents examined, had a much weaker hypothermic action when injected intraventricularly, whereas the  $\beta$ -adrenoceptor blocking agents propranolol, pronethalol and Trasacor had no effect.
3. In rabbits in which the noradrenaline stores of the hypothalamus were depleted by intraventricular injections of reserpine, the hypothermic effect of phenoxybenzamine was abolished and remained abolished for a few days.
4. In cats, an intraventricular injection of phenoxybenzamine (200  $\mu$ g) produced long-lasting hyperthermia, but not in all cats, and only with the first, or the first two or three injections. Injected intraperitoneally, this dose had no effect on temperature. Phentolamine (100 or 200  $\mu$ g) had a very weak hyperthermic effect and phentolamine (500  $\mu$ g), a hypothermic effect, but only on intraventricular injection, whereas ergotamine (100 and 200  $\mu$ g) had a weak hyperthermic effect both on intraventricular and intraperitoneal injection. Propranolol and Trasacor had no effect on temperature when injected intraventricularly.
5. In rats, phenoxybenzamine (5 or 20  $\mu$ g) produced long-lasting hypothermia on intraventricular injection.
6. Some of the temperature effects produced by intraventricular injections of the  $\alpha$ -adrenoceptor blocking agents are explained on the assumption that they prevent the effect on temperature produced by a continuous release of noradrenaline from adrenergic neurones innervating the anterior hypothalamus.

### Introduction

Whenever a drug injected into the cerebral ventricles, or directly into the anterior hypothalamus, produces changes in body temperature, and these changes are the opposite in rabbits from those in cats, the possibility has to be considered that the drug acts not directly on the cells of the anterior hypothalamus, but by interference with monoamines released from monoaminergic fibres innervating these cells.

In rabbits, the two catecholamines, noradrenaline and adrenaline, raise temperature, but in cats they lower it when acting on the anterior hypothalamus. These pharmacological effects are thought to imitate central transmitter functions of adrenergic fibres ending on cells in this part of the brain. On the assumption of a continuous release of noradrenaline or adrenaline from these fibres, temperature should be affected by either an  $\alpha$ - or a  $\beta$ -adrenoceptor blocking agent, and the effect should be different in rabbits and cats.

We have therefore examined the effect on body temperature of  $\alpha$ - and  $\beta$ -adrenoceptor blocking agents injected into the cerebral ventricles, in these two species. In rabbits the effect of one  $\alpha$ -adrenoceptor blocking agent, phenoxybenzamine, was examined also after the hypothalamus was depleted of its catecholamines, a condition brought about by injections of reserpine into the cerebral ventricles (Cooper, Cranston & Honour, 1967). A few experiments were carried out on rats as well in which hyper- and hypothermic responses are obtained with the catecholamines when applied by the intraventricular route (Feldberg & Lotti, 1967) or by microinjection into the anterior hypothalamus (Lomax, Foster & Kirkpatrick, 1969). Some of the results have been communicated to the Physiological Society (Feldberg & Saxena, 1971).

## Methods

In rabbits, cats and rats, a cannula was implanted in an aseptic operation under pentobarbitone sodium anaesthesia into the left (rabbit, cat) or right (rat) lateral ventricle. After recovery, injections were made through the cannula usually once or twice a week, without anaesthesia, whilst rectal temperature was recorded.

Albino New Zealand rabbits of either sex weighing 2.5–4 kg were used. For cannulating the left lateral ventricle, a Collison cannula with a 4 mm shaft was screwed into the skull at a point 7 mm lateral to the midpoint of the sagittal suture. The tip of the shaft then lay in the lateral ventricle. The total length of the cannula with its shaft, measured 16 mm. The shaft, made of stainless steel tubing (19 gauge), was continued through the head of the cannula to its upper end; the space between tubing and wall of the cannula head was filled with Araldite. Between injections, the lumen of the steel tubing was filled with a stilette which was removed for the injections after removing the cap. For the injection, a 16 mm long needle (22 gauge) filled with the fluid to be injected and connected to a 1 ml syringe was used. After unscrewing the cap of the Collison cannula, the tip of the needle was pierced through the rubber diaphragm of the cap and inserted into the steel tubing. The cap was then screwed on and the needle passed through the whole length of the shaft before the injection was made. The volume of fluid injected was 0.2 ml.

Male cats weighing 2.5–3.5 kg were used. For cannulating the left lateral ventricle a Collison cannula with a shaft length of 12 mm was screwed into the skull at a point 3 mm lateral to the midline and 7 mm posterior to the coronal suture. The tip of the shaft then lay in the lateral ventricle. The total length of the cannula with its shaft, but without the cap, measured 22 mm. It was filled with a stilette. Before the injections, the cap was unscrewed and the stilette removed. The injections were made with a 23 mm long needle, filled with the fluid to be injected and connected to a 1 ml syringe, was used. A 1 mm thick disk of rubber was pierced

in the centre by the needle and placed where the needle meets the hub. The needle was passed through the whole length of the shaft. The rubber disk prevented any leakage of fluid during the injection. The volume of fluid injected was 0.2 ml.

Sprague-Dawley rats of either sex weighing 250 to 280 g were used. The method for cannulation of the right lateral ventricle and for the intraventricular injection was that described elsewhere (Feldberg & Lotti, 1967) except that in between the injections the lumen of the cannula was filled with a stilette. The volume of fluid injected was 10  $\mu$ l; it was injected with a Hamilton microlitre syringe (N.710).

Rectal temperature was recorded at room temperature (19–22° C) with a thermistor probe (Yellow Spring Instrument Co.) inserted into the rectum about 10 cm deep in rabbits and cats, and about 6 cm deep in rats. The probe was held in position by adhesive tape which was attached to its protruding end and gently wrapped around the base of the tail. Temperature was monitored continuously by a Kent multichannel recorder, and the figures given in this paper were plotted directly from the tracings obtained in this way. During recording of the temperature the cats were allowed to move freely in their cages, whereas the rabbits were placed into an open box, 16 cm wide 40 cm long 10 cm high, but otherwise restrained as little as possible. The rats were placed in a tunnel shaped container made from a piece of wire mesh, 19 cm long and 15 cm wide, attached to a flat 5 cm wide base of cork, closed at the front by a piece of cork, and at the back by a removable rubber bung with a hole for the tail and thermistor probe. For the injections, the rats were removed from the container.

### *Drugs*

Phenoxybenzamine hydrochloride, kindly supplied by Smith, Kline and French Laboratories. According to Harvey & Nickerson (1955) its solubility in water is so low that only nanogrammes dissolve in 1 ml. This low solubility was confirmed when either 0.9% NaCl or the artificial cerebrospinal fluid (c.s.f.) of Merlis (1940) was used as solvent, but in distilled water at least 2 mg could be dissolved in 1 ml at 37° C. Phentolamine mesylate (Rogitine, Ciba); ergotamine tartrate (Burroughs Wellcome); propranolol HCl (Inderal, I.C.I.); pronethalol HCl (Alderlin, I.C.I.); I-isopropyl-amino-2-hydroxy-3-(O-allyloxy-phenoxy)-propane hydrochloride (Trasicor, Ciba); reserpine phosphate, kindly supplied by Dr. A. J. Plummer, Ciba Pharmaceutical Co., Summit, New York. All doses refer to the salts. All solutions, glassware, syringes and tubing used for the injections were sterile, and the solutions and glassware were pyrogen-free as well.

## **Results**

### *Rabbits*

#### *Phenoxybenzamine*

Its injection into the lateral ventricle in a dose of 50 or 100  $\mu$ g regularly produced a fall in rectal temperature associated with skin vasodilatation and pronounced tachypnoea. Temperature began to fall within a few minutes of the injection whilst the ears became hot. Tachypnoea began several minutes later whilst temperature continued to fall. Temperature fell 1.2–2.3° C (mean fall in seven experiments 1.9° C) within 1.5 h and returned to normal after 3 to 3.5 hours. On intravenous injection these doses of phenoxybenzamine had no effect on temperature. In rabbit

1 of Fig. 1 this difference in the effect between the two kinds of injection is illustrated for 50  $\mu$ g. The threshold dose for intraventricular injection varied in different rabbits; in some, as little as 1  $\mu$ g produced a fall of about a quarter of a degree, whereas in others, as much as 10  $\mu$ g had no effect on temperature. Tachyphylaxis did not develop. When, after an effective dose of phenoxybenzamine, temperature had returned to its preinjection level, a further injection again lowered temperature, as shown in rabbit 3 of Fig. 1 for three successive injections of decreasing doses of phenoxybenzamine, that is for 10, 5 and 2  $\mu$ g.

#### *Phenoxybenzamine after reserpine*

After two or more intraventricular injections of reserpine phosphate (0.75 mg), given at 24 h intervals, phenoxybenzamine no longer lowered temperature. This condition lasted a few days.

The reserpine itself affected temperature. Its first intraventricular injection, and sometimes the second as well, produced a rise, followed after some hours by a prolonged fall so that the temperature was often low on the next day. With subsequent injections the initial rise was no longer obtained but a late fall still occurred, often followed by a rise.

Figure 2 illustrates the effect of phenoxybenzamine before and after reserpine in two rabbits. Before the reserpine an injection of phenoxybenzamine (50  $\mu$ g) produced a pronounced fall in temperature in both rabbits, greater in rabbit 1 than in

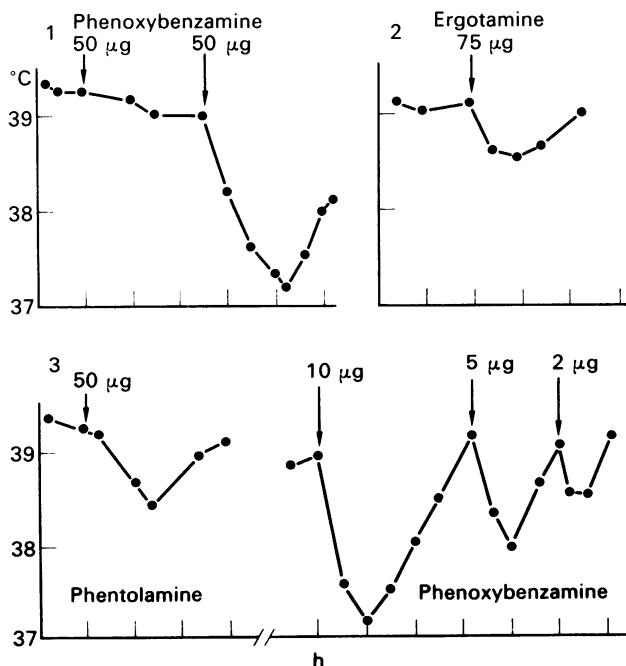


FIG. 1. Records of rectal temperature from three unanaesthetized rabbits. Rabbit 1: at first arrow, intravenous; at second arrow, intraventricular injection of phenoxybenzamine (50  $\mu$ g). Rabbit 2: at arrow, intraventricular injection of ergotamine (75  $\mu$ g). Rabbit 3: intraventricular injection at first arrow of phentolamine (50  $\mu$ g), and at second, third and fourth arrows, of phenoxybenzamine (10, 5 and 2  $\mu$ g). Between first and second arrow, 24 h interval.

rabbit 2 (record a). In rabbit 1, the first two reserpine injections greatly diminished the phenoxybenzamine response. After two more such injections the response was abolished, as shown in record b obtained one day after the last of these injections. After 5 days (record c) the hypothermic response began to return, after 9 days (record d) it had partly, and after 15 days (record e) fully recovered. In rabbit 2, two intraventricular injections of reserpine were sufficient to abolish the phenoxybenzamine response; it remained abolished for at least 4 days (records b and c) and had fully recovered after 7 days (record d).

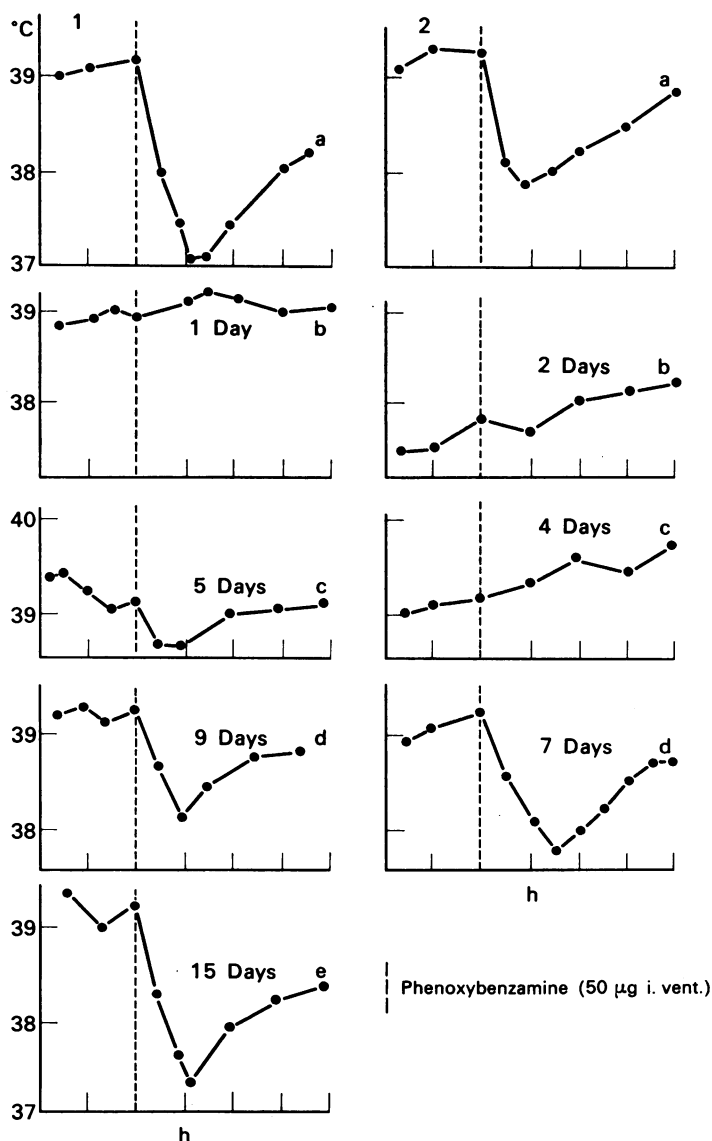


FIG. 2. Records of rectal temperature from two unanaesthetized rabbits. Between records a and b, intraventricular injections of reserpine phosphate (0.75 mg) at 24 h intervals (four injections in rabbit 1, two injections in rabbit 2). The days refer to days after last reserpine injection.

### Phentolamine

On intraventricular injection this blocking agent also lowered temperature, but not as much as phenoxybenzamine, and the onset of the fall was delayed. Temperature began to fall after a latency of 15–30 minutes. In rabbit 3 of Fig. 1, in which the hypothermic effect of phentolamine (50  $\mu$ g) was compared with that of phenoxybenzamine (10, 5 and 2  $\mu$ g) it was less than one-tenth as potent. In other rabbits the difference was not as great. The fall in temperature obtained with phentolamine (50  $\mu$ g) in Fig. 1 amounted to 0.6° C; even with 200  $\mu$ g the effect did not increase much and temperature rarely fell more than 1° C. The fall was associated with dilatation of the ear vessels and tachypnoea; the injections, unlike those of phenoxybenzamine, caused some restlessness.

### Ergotamine

Its effect on temperature when injected intraventricularly was similar to that of phentolamine. It was a little less potent. In rabbit 2 of Fig. 1, 75  $\mu$ g produced a fall of 0.55° C.

### Propranolol, pronethalol and Trasacor

Intraventricular injections of these three  $\beta$ -adrenoceptor blocking agents did not affect temperature, or produced a gradual fall or rise of 0.2–0.3° C. It is not certain if these small changes in temperature were responses to the drug injections as they were not obtained regularly in the same rabbit on repeated injections, and were

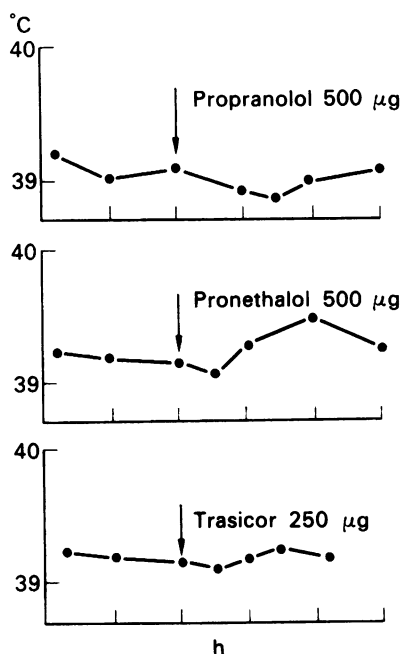


FIG. 3. Records of rectal temperature obtained on different days from an unanaesthetized rabbit. At the arrows, intraventricular injections of propranolol (500  $\mu$ g) (top record), pronethalol (500  $\mu$ g) (middle record) and Trasacor (250  $\mu$ g) (bottom record).

difficult to distinguish from the fluctuations in temperature that occurred spontaneously. Figure 3 shows the small changes after intraventricular injections of propranolol (500  $\mu\text{g}$ ), pronethalol (500  $\mu\text{g}$ ) and Trasicor (250  $\mu\text{g}$ ).

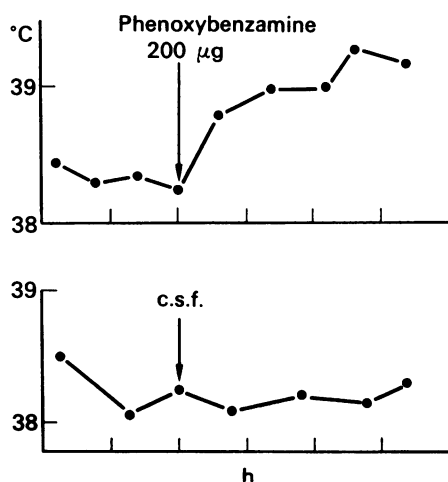


FIG. 4. Records of rectal temperature obtained on different days from an unanaesthetized cat. At the arrows, intraventricular injections of phenoxybenzamine (200  $\mu\text{g}$ ) (top record) and of artificial c.s.f. (0.2 ml) (bottom record).

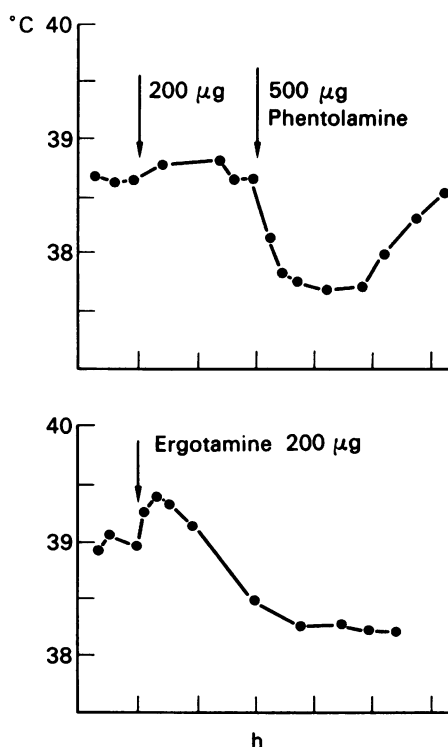


FIG. 5. Records of rectal temperature obtained from two unanaesthetized cats. At the arrows, intraventricular injections of phentolamine (200 and 500  $\mu\text{g}$ ) (top record) and of ergotamine (200  $\mu\text{g}$ ) (bottom record).

### *Cats*

#### *Phenoxybenzamine*

An intraventricular injection of 200  $\mu\text{g}$  caused a long lasting rise in temperature but not in all cats, and in those in which it was obtained it occurred only with the first, or the first two or three injections given at intervals of a few days. Figure 4 shows the rise produced by a first injection in a cat in which the second and third injection of phenoxybenzamine (200  $\mu\text{g}$ ) also produced hyperthermia. Injected intraperitoneally, this dose of phenoxybenzamine did not affect temperature. In one cat the intraventricular injection of 200  $\mu\text{g}$  produced a fall of  $0.5^{\circ}\text{C}$  lasting about 1 h, and this effect was again obtained when the injection was repeated 3 weeks later.

#### *Phentolamine*

Typical results obtained with intraventricular injections of 200 and 500  $\mu\text{g}$  are illustrated in Fig. 5. The injection of 200  $\mu\text{g}$  produced a small rise, usually of  $0.1\text{--}0.2^{\circ}\text{C}$  only, as illustrated in the figure, but sometimes as much as  $0.6^{\circ}\text{C}$ . The injection of 500  $\mu\text{g}$  however produced a fall. Temperature fell  $0.5\text{--}1^{\circ}\text{C}$  during the first hour and then remained low for another hour or two. During the fall, the cat was sedated and was lying on its side, the vessels of the pinna were dilated, there was midriasis, salivation and tachypnoea, but no panting. Tachypnoea subsided once temperature had reached its lowest level, and salivation ended when temperature began to recover. Neither the fall in temperature nor the other effects were obtained when phentolamine (500  $\mu\text{g}$ ) was injected intraperitoneally.

#### *Ergotamine*

In most cats, an intraventricular injection of 100 or 200  $\mu\text{g}$  produced a small gradual rise in temperature, but the same response was often obtained when these doses of ergotamine were injected intraperitoneally. In one cat the rise produced by the intraventricular injection of 200  $\mu\text{g}$  was followed by a long-lasting fall, and this happened again when the injection was repeated a week later. The result of the first injection is shown in the bottom record of Fig. 5. On intraperitoneal injection this dose of ergotamine produced only a weak hypothermic effect in this cat. Both with intraventricular and intraperitoneal injections of these doses of ergotamine, retching and vomiting often occurred a few minutes after the injection.

#### *Propranolol and Trasacor*

Intraventricular injections of propranolol (100–500  $\mu\text{g}$ ) did not affect temperature. Trasacor injected intraventricularly in these doses usually had no effect on temperature, but in a few cats temperature fell  $0.2\text{--}0.6^{\circ}\text{C}$  during the first 30 min after the injection and returned to the preinjection level during the next 30 minutes. Another effect obtained in some cats with Trasacor was retching and vomiting, which occurred a few minutes after the injection.

### *Rats*

An intraventricular injection of phenoxybenzamine (5 or 20  $\mu\text{g}$ ) resulted in a long lasting fall in rectal temperature, as illustrated in Fig. 6. With these injections,



temperature began to fall after a latency of several minutes, reached its lowest level in 1–1.5 h and then remained low for several hours. The magnitude of the fall varied more from animal to animal than from the amount of phenoxybenzamine (5–20  $\mu\text{g}$ ) injected. For instance, in the two experiments of Fig. 6, the hypothermia produced by 20  $\mu\text{g}$  in the one rat was smaller than that produced by 5  $\mu\text{g}$  in the other. However, full recovery usually took longer after the injection of the larger dose. The effect of an intraventricular injection of phenoxybenzamine (1  $\mu\text{g}$ ) was doubtful, since large fluctuations in temperature occurred spontaneously. The bottom record of Fig. 6 shows that an intraventricular injection of 10  $\mu\text{l}$  of artificial c.s.f. had no immediate effect on temperature, but about 70 min after the injection, temperature began to fall and fell more than half a degree. If an injection had been given at this time, the fall might have appeared to have been the result of the injection.

### Discussion

The aim of the experiments was to find out if, by the use of adrenoceptor blocking agents, evidence could be obtained for a continuous release of either adrenaline

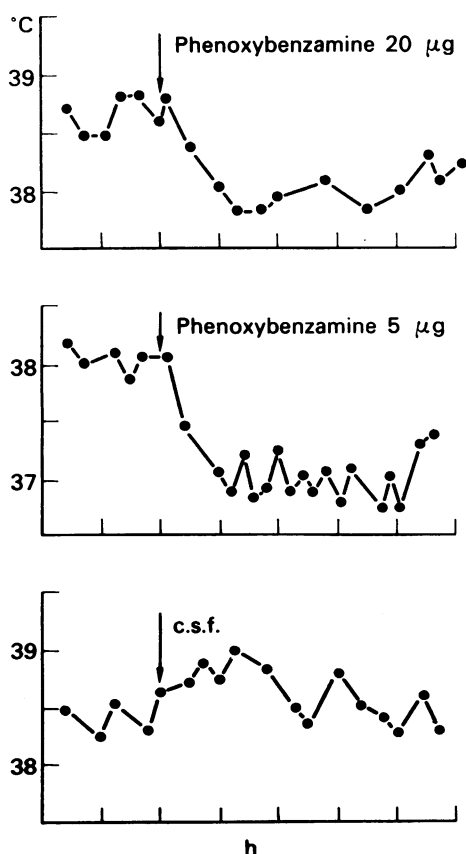


FIG. 6. Records of rectal temperature obtained from two unanaesthetized rats. At the arrows, intraventricular injections of phenoxybenzamine (20  $\mu\text{g}$ ) in the one rat (top record), of phenoxybenzamine (5  $\mu\text{g}$ ) (middle record) and of artificial c.s.f. (10  $\mu\text{l}$ ) (bottom record) in the other rat.

or noradrenaline from adrenergic neurones innervating the anterior hypothalamus and thereby exerting a 'tonic' influence on body temperature. Adrenaline is about 2-4 times as potent as noradrenaline in changing body temperature when acting on the anterior hypothalamus, at least in cats (Feldberg & Myers, 1964), but its concentration in the hypothalamus is only approximately 10% that of noradrenaline (Vogt, 1954). Therefore, its transmitter function in the hypothalamus for temperature regulation would appear to be less important than that of noradrenaline. Although adrenaline appears to act not only on  $\beta$ - but also on  $\alpha$ -adrenoceptors in the brain, the finding that the  $\beta$ -adrenoceptor blocking agents examined had scarcely any effect on temperature when they were injected into the cerebral ventricles is in accord with the view that adrenaline is not released in the hypothalamus in amounts sufficient to have a tonic influence on body temperature. However, some results obtained on intraventricular injection of  $\alpha$ -adrenoceptor blocking agents suggest such an action for noradrenaline. The strongest evidence in favour of this view was obtained in rabbits with phenoxybenzamine because its hypothermic action was lost after intraventricular injections of reserpine which deplete the adrenergic fibres in the hypothalamus of its noradrenaline stores (Cooper, *et al.*, 1967). The finding that after a few days the hypothermic action of phenoxybenzamine gradually returned is readily explained on the assumption that the stores became gradually replenished. If the hypothermia produced by intraventricular phenoxybenzamine is entirely the outcome of blockade of the  $\alpha$ -adrenoceptors, as suggested by the results obtained with reserpine, it would follow that in the rabbit a strong tonic influence is exerted on temperature by noradrenaline continuously released in the hypothalamus, since in some experiments temperature fell over 2° C after the injections of phenoxybenzamine (50 or 100  $\mu$ g). It would further follow that the blockade of the receptors is reversible and that the second irreversible stage of blockade is not attained with these doses injected intraventricularly. Otherwise, temperature would scarcely have returned after a few hours and fallen again with a renewed phenoxybenzamine injection.

The weak hypothermic effects produced in rabbits by intraventricular injections of the other two  $\alpha$ -adrenoceptor blocking agents, phentolamine and ergotamine, also suggest a tonic influence on temperature brought about by a continuous release of noradrenaline in the hypothalamus. Both phentolamine and ergotamine are less potent  $\alpha$ -adrenoceptor blocking agents than phenoxybenzamine, which could explain why they produced comparatively weaker hypothermic effects. On the other hand, the possibility has to be kept in mind that the strong hypothermic effect of intraventricular phenoxybenzamine, although abolished by reserpine, is not entirely the result of removal of the effect of continuously released noradrenaline but that phenoxybenzamine has an additional non-specific depressant effect on those cells in the hypothalamus which are activated by stimuli that raise temperature.

In cats in which intraventricular noradrenaline lowers temperature any removal of the effect of continuously released noradrenaline in the hypothalamus should result in a rise in temperature; phenoxybenzamine had this effect. However, the rise was not obtained regularly, even in the same cat with repeated injections. This would imply that a tonic influence of continuously released noradrenaline does not play the same role in temperature regulation as in rabbits and that its influence varies not only from cat to cat, but also under different conditions. The explanation for this difference between the two species may lie in the different temperature

effects produced by noradrenaline when acting as adrenergic mediators in the anterior hypothalamus, a tonic influence may mainly be the function of a monoamine that raises temperature. From the results obtained with phentolamine and ergotamine, no definite conclusions can be drawn about a tonic influence of continuously released noradrenaline on body temperature because the hyperthermic effects produced with smaller doses were extremely small and in the case of ergotamine, may not have resulted from an action on the hypothalamus since they were often obtained also when the same doses were injected intraperitoneally. The hypothermia that occurred when a larger dose of phentolamine was injected intraventricularly can certainly not be explained by removal of an effect of noradrenaline on the anterior hypothalamus; it may in fact have resulted not from the blocking effect on  $\alpha$ -adrenoceptors, but from an unspecific effect of the phentolamine.

It is possible, however, to explain the hypothermia obtained in rats with phenoxybenzamine as the result of removal of the effect of continuously released noradrenaline, although its main effect when acting on the anterior hypothalamus is to lower temperature. But noradrenaline has a hyperthermic effect as well and this effect is obtained particularly when noradrenaline is applied in near threshold doses (Feldberg & Lotti, 1967; Lomax *et al.*, 1969). We would therefore have to assume that it is mainly through this effect that it exerts its 'tonic' function.

The idea that noradrenaline, continuously released in the anterior hypothalamus, exerts a 'tonic' influence on body temperature is supported by results obtained with imipramine and desmethylimipramine, which inhibit the uptake of released noradrenaline by the presynaptic membrane. These drugs should therefore affect temperature in the opposite way from the  $\alpha$ -adrenoceptor blocking agents, and so they do. On injection into the cerebral ventricles, imipramine lowers temperature in cats, and desmethylimipramine raises it in rabbits, and, further, the effects are much diminished when synthesis of noradrenaline is inhibited by  $\alpha$ -methyl-*p*-tyrosine. These findings were described by Cranston, Hellon, Luff & Rawlins (1971) and communicated to the Physiological Society at the same Meeting as the findings with phenoxybenzamine obtained in rabbits and cats (Feldberg & Saxena, 1971). However, whereas the results obtained with the  $\alpha$ -adrenoceptor blocking agents suggest that a continuous release of noradrenaline plays a greater role for temperature regulation in rabbits than in cats, such a species difference was not suggested by the findings obtained with the inhibitors of noradrenaline uptake: they were apparently equally effective in both species. This difference illustrates the need for caution in postulating physiological functions merely from pharmacological effects.

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