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EFFECTS OF NORADRENALINE AND CARBACHOL ON TEMPERATURE REGULATION OF RATS

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1 Noradrenaline (0.2 to 20 μg) and carbachol (0.1 to 1 μg) injected into the preoptic/anterior hypothalamic area, evoked dose-dependent falls in core temperature at all sites tested, followed in most experiments by delayed increases that were not dose-related. Muscarine (0.1 to 10 μg) produced effects similar to those evoked by carbachol.

2 These falls in core temperature were associated with increases in tail temperature, locomotor activity and CO_2 elimination (a measure of metabolic rate).

3 The temperature responses to noradrenaline (10 μg) and to carbachol (1 μg) were antagonized by intrahypothalamic injections of phentolamine (10 μg) and atropine (1 μg), respectively.

4 Analysis of the temperature responses and their respective latencies indicates that carbachol-induced hypothermia was mediated by cholinoceptors in the anterior hypothalamus, whereas hypothermia after noradrenaline was mediated by adrenoceptors throughout the preoptic/anterior hypothalamic area.

5 Vasodilatation of the tail blood vessels contributed significantly to the hypothermia evoked by carbachol, and to that evoked by injections of noradrenaline into the anterior hypothalamus.

6 Hypothermia induced by noradrenaline injection into the preoptic area, was mediated by effector mechanisms additional to non-evaporative heat loss.

Introduction

Noradrenaline and acetylcholine within the preoptic and anterior hypothalamic areas play an important role in the temperature regulation of vertebrates. When injected into these regions, these amines produce marked changes in body temperature which are usually consistent in a given species. One exception is the rat, for which considerable conflict exists since different authors have reported both hypothermic (Avery, 1971; Kirkpatrick, Lomax & Jenden, 1967) and hyperthermic (Avery, 1971; Beckman, 1970) responses to noradrenaline and to acetylcholine (or carbachol).

The consistency seen in species other than rats demonstrates that even though a drug may have more than one action on temperature regulation (Bligh, Cottle & Maskrey, 1971), a single response (hypothermia or hyperthermia) is observed. The more complex responses of the rat could be explained by the small size of the rat brain permitting drugs to diffuse to contiguous sites all of which affect body temperature, or by differences in experimental techniques, for example, the site from which temperature is recorded (brain, liver and rectal temperatures can vary independently of each other; Birnie & Grayson, 1952) and whether the animal is restrained since restraint alone can elevate body temperature (Briese & DeQuijada, 1970; Poole & Stephenson, 1977a) and will even prevent drug-induced changes in behavioural thermoregulatory activity (Martin, Pryzbylik & Spector, 1977). Temperature responses to intraventricular amine injections are not considered because drugs so injected have variable access (dependent on injection volume) to other thermosensitive sites, for example, in the brain stem.

Temperature recordings should be continuous, since with intermittent measurements short lasting responses may have abated in the time between amine injection and the first measurement. Another factor is the size of the dose. Thus, Myers (1975) considers that large doses of cholinomimetics cause not only depolarization but depolarization blockade, and hence, aberrant results; responses to intrahypothalamic injection of noradrenaline at thermoneutrality range from hypothermia with small doses to hyperthermia with large doses (Veale & Whishaw, 1976) and *vice versa* (Rewerski & Kubikowski, 1969). The direction of the temperature response to noradrenaline may also be dependent on the precise injection site within the hypothalamus (Veale & Whishaw, 1976).

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In an attempt to reconcile these differences, noradrenaline and carbachol were injected into selected preoptic and anterior hypothalamic sites of unrestrained rats in a thermoneutral environment. Body temperature was recorded continuously from chronically implanted intrathoracic thermistors together with other relevant variables, e.g. tail temperature, locomotor activity and CO_2 elimination. A preliminary account of this work has appeared (Poole & Stephenson, 1977b).

Methods

Twenty-five male Wistar rats (275 to 325 g) were anaesthetized with halothane and a 22 gauge stainless steel guide cannula was stereotactically implanted into the left or right preoptic area or anterior hypothalamus at co-ordinates derived from the atlases of Fifková & Maršala (1967) and König & Klippel (1963). The co-ordinates were between 1.0 mm anterior and 1.5 mm posterior to bregma, 0.5 or 1.0 mm lateral to the midline and at a depth of 8.2 mm below the top of the skull. After further growth to 325 to 350 g (about 2 weeks) the rats were anaesthetized with halothane and thermistor probes implanted chronically into their thoracic cavities (Poole & Stephenson, 1977a). Before and after implantation, the rats were housed singly in plastic cages (335 mm × 210 mm × 170 mm) at 23 ± 1.5°C with water and food (Diet 41B, Dixons Foods, Ltd.) *ad libitum*, and subject to a 12 h light (06 h 00 min to 18 h 00 min)/dark (18 h 00 min to 06 h 00 min) cycle.

At least 2 weeks after implantation of the thermistor probes, rats were placed singly in a perspex environmental chamber (335 mm × 290 mm × 280 mm) at 23 ± 0.5°C (the mid-point of their thermoneutral range; Poole & Stephenson, 1977c) through which air flowed at 2 l/min. The chest probe and a second thermistor probe taped to the dorsal surface of the tail, 20 mm from its base, were connected to a Devices pen-recorder via a microcable (Radiospares, Ltd.), a mercury concentric swivel (Campden Instruments Ltd.) and bridge circuits (Allen & Lanworn, 1968). For central injections, a 27 gauge stainless steel inner cannula, connected with polyethylene tubing (Portex PP20, Portland Plastics Ltd.) to a 10 µl syringe, was inserted so that its tip was 0.2 mm below the end of the guide cannula. The inner cannula contained pyrogen-free sterile saline (0.9% w/v NaCl) for control injections or one of the following drugs in sterile saline: (−)-noradrenaline hydrochloride (0.2 to 20 mg/ml, Sigma), carbamylcholine (carbachol) chloride (0.1 to 2 mg/ml, BDH), (±)-muscarine chloride (0.1 to 10 mg/ml, Labkemi AB, Sweden), atropine sulphate (1 mg/ml, BDH), or (−)-noradrenaline hydrochloride (10 mg/ml) with a proprietary preparation of phentolamine (10 mg/ml, Rogitine, Ciba). The pH of all injected solutions was between 4 and 5. When core temperature and tail temperature had been monitored for 90 min during which time body temperatures had stabilized (Poole & Stephenson, 1977a), 0.5 or 1 µl of saline or one of the above drugs was injected (over 1 s) into the preoptic area or anterior hypothalamic area and the resulting temperature changes were recorded. In 4 experiments atropine (1 µg in 1 µl) was injected immediately before the rat was placed in the chamber and carbachol (1 µg in 1 µl) was injected into the same site, 90 min later. At least 1 week elapsed between experiments in the same rat.

In experiments in which CO_2 elimination and locomotor activity were recorded simultaneously, the rats were placed singly in a glass experimental chamber (120 mm diameter, 210 mm high) and the inner cannula inserted as previously described. The chamber was placed on an activity meter (Motron Products, Ltd., Sweden) in a room maintained at 23 ± 1.5°C and dry, CO_2-free air passed through it at 2 l/min. The air leaving the chamber was passed over calcium chloride and then to a CO_2 analyzer (Hartmann & Braun) whose output was displayed on a potentiometric recorder. When CO_2 elimination and locomotor activity had been monitored for at least 90 min, saline, noradrenaline (10 µg in 0.5 µl) or carbachol (1 µg in 0.5 µl) was injected as before and the resulting changes in activity and CO_2 elimination were measured. Again at least 1 week elapsed between experiments in the same rat.

Cannulae positions were subsequently confirmed histologically. The extent of drug diffusion was estimated from experiments in anaesthetized rats. Evans blue (0.2% in saline) was injected in a volume of 0.5 µl, into the preoptic area and anterior hypothalamus via acutely implanted guide cannulae. Rats were killed 15 min after injection, the brain was removed, rapidly frozen, and sectioned on a freezing microtome.

Results

Noradrenaline (0.2 to 20 µg in 1 µl) and carbachol (0.2 to 1 µg in 1 µl) injected into the anterior hypothalamus consistently evoked hypothermia and increased tail temperature, the latter indicating vasodilatation and hence increased non-evaporative heat loss. The fall in core temperature and increase in tail temperature and the maximum changes in these temperatures were dose-related, the larger doses producing correspondingly greater effects often with a shorter latency to onset (Table 1). Typical responses to the largest and smallest doses of each drug are illustrated in Figures 1 and 2. The hypothermia was accompanied by characteristic changes in behaviour.

Table 1 Effects of injections of noradrenaline, carbachol and saline (each 1 µl) into the posterior part of the anterior hypothalamus on core and tail temperatures

Drug	Dose (µg)	n	Core temperature at injection (°C)	Latency to onset of fall (min)	Maximum fall (°C)	Time of maximum fall (min)	Duration of hypothermia (min)	Range and means of rebound hyperthermia (°C)	Latency to increase in tail temperature (min)	Maximum increase in tail temperature (°C)	Duration of response (min)
NA	0.2	4	37.7 ± 0.3	1.1 ± 0.1	0.4 ± 0.1	6.4 ± 2.5	18.7 ± 1.6	0 – 0.7 (0.4 ± 0.4)	1.4 ± 0.1	1.5 ± 1.2	17.5 ± 1.7
NA	0.5	4	37.4 ± 0.7	1.0 ± 0.6	1.0 ± 0.5	7.1 ± 0.4	18.3 ± 4.4	0 – 0.4 (0.2 ± 0.2)			
NA	1.0	5	38.3 ± 0.7	1.5 ± 0.5	1.0 ± 0.3	6.9 ± 1.3	28.3 ± 16.2	0 – 0.8 (0.2 ± 0.4)	0.9 ± 0.1	3.2 ± 1.3	25.6 ± 5.3
NA	2.0	4	38.3 ± 0.6	0.8 ± 0.3	1.3 ± 0.4	8.8 ± 1.3	46.5 ± 21.6	0 – 0.8 (0.2 ± 0.4)			
NA	5.0	4	37.6 ± 0.2	0.8 ± 0.2	1.5 ± 0.8	20.3 ± 5.5	45.8 ± 7.2	0 – 1.1 (0.8 ± 0.5)			
NA	10.0	6	38.0 ± 0.6	0.8 ± 0.5	1.6 ± 0.4	14.0 ± 3.8	50.9 ± 10.5	0 – 1.0 (0.3 ± 0.4)	1.1 ± 0.3	2.9 ± 1.0	16.4 ± 5.0
NA	20.0	4	38.0 ± 0.5	0.8 ± 0.2	3.1 ± 0.3	29.1 ± 18.6	94.8 ± 13.9	0.2 – 0.6 (0.4 ± 0.2)			
CCh	0.1	4	38.1 ± 0.3	1.0 ± 0.5	1.4 ± 0.3	13.3 ± 1.3	33.8 ± 8.5	0 – 0.7 (0.5 ± 0.4)	2.5 ± 1.7	3.9 ± 1.5	30.3 ± 9.4
CCh	0.2	4	38.2 ± 0.5	1.4 ± 0.7	1.5 ± 1.0	14.9 ± 5.4	36.1 ± 20.4	0 – 0.7 (0.4 ± 0.4)			
CCh	1.0	4	37.6 ± 0.2	0.7 ± 0.4	2.4 ± 0.4	25.3 ± 4.7	80.5 ± 26.7	0 – 1.1 (0.4 ± 0.5)	0.9 ± 0.1	4.4 ± 1.0	31.7 ± 1.9
0.9% Saline		4	37.9 ± 0.3		0.1 ± 0.1			0 – 0.2 (0.2 ± 0.1)			

The values indicate means ± s.d. The mean changes in core temperature after saline are calculated from the maximum changes observed within 3 h after injection.

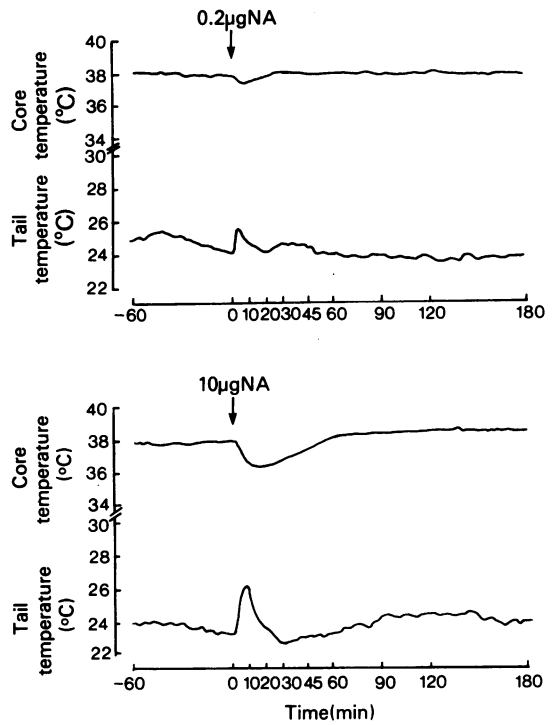

Figure 1 Typical effects of small (0.2 μg) and large (10 μg) doses of noradrenaline (each in 1 μl) injected into the posterior part of the anterior hypothalamus on core and tail temperatures.

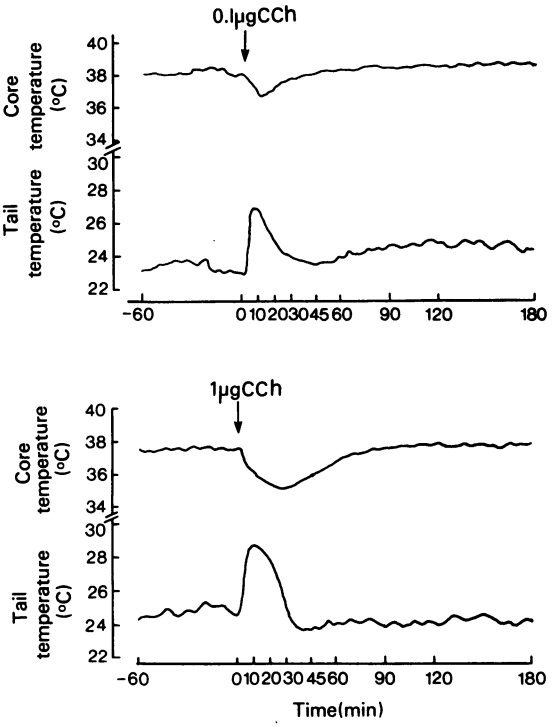

Figure 2 Typical changes in core and tail temperatures evoked by injection of carbachol (CCh, 0.1 and 1 μg in 1 μl) into the posterior part of the anterior hypothalamus.

As core temperature began to fall after noradrenaline or carbachol injection, the rats became very active, moving around the chamber and frequently rearing against the chamber walls. With carbachol, this activity began to decline within 5 to 10 min, the rats then often assuming a prone position. Noradrenaline produced an essentially similar behavioural response although the induced activity was less intense but of longer duration. Saliva-spreading (evaporative heat-loss) was not observed after injection of either drug. Recovery was followed in about 70% of the experiments by an increase in core temperature above normal. This increase started immediately after recovery from the hypothermia (15 to 90 min depending on dose), was not dose-dependent, and persisted for more than 3 h in some experiments. Intrahypothalamic injection of saline (1 μl) did not significantly affect body temperature (Table 1) or behaviour of 4 rats recorded for at least 3 h after injection; saline acidified to pH 3.5 with dilute HCl was also without effect.

To determine whether or not these amines were acting at the same or different sites within the preoptic/anterior hypothalamic area, approximately equipotent doses of noradrenaline (10 μg) and carbachol (1 μg) were injected in a volume of 0.5 μl into various loci within the preoptic anterior hypothalamic area; latencies to onset and magnitude of the changes in core and tail temperatures were measured (Figure 3). Injection of either drug into any of the selected sites caused a fall in core temperature and an increase in tail temperature. The response latencies for both drugs were shortened as the locus of injection was moved caudally from the anterior to the posterior margin of the preoptic/anterior hypothalamic area. As seen in Figure 3, the greatest differences in responses were observed between the preoptic area and anterior hypothalamus, this probably reflecting the distance between injection sites, i.e. 1.0 mm compared with the 0.6 mm separating the anterior and posterior margins of each area. Carbachol-induced changes in both core and tail temperatures were greater ($P < 0.001$) after injection into the anterior hypothalamus than after injection into the preoptic area, and the latencies to onset of both responses were shorter ($P < 0.001$) after intrahypothalamic injection. In contrast the falls in core temperature after noradrenaline were similar ($P > 0.05$) throughout the preoptic area and anterior hypothalamus although the latency to onset was shorter ($P < 0.01$) with injections into the anterior hypothalamus. However, much larger ($P < 0.001$) in-

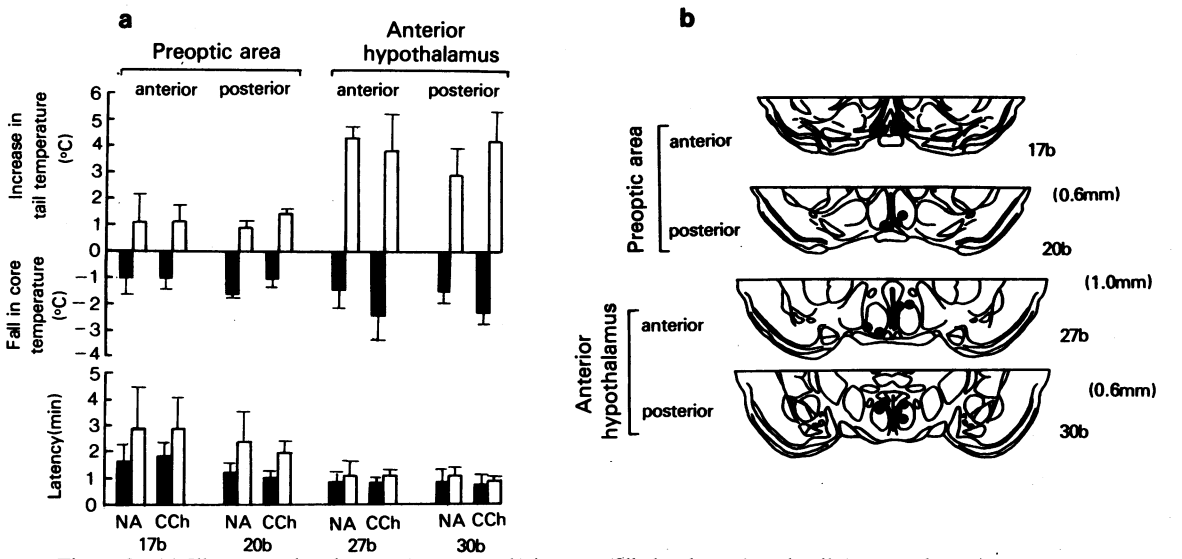

Figure 3 (a) Illustrates the changes (mean ±s.d.) in core (filled columns) and tail (open columns) temperatures and their latencies evoked by injection of noradrenaline (10 μg in 0.5 μl) and carbachol (1 μg in 0.5 μl) into 4 regions of the preoptic anterior hypothalamic areas of 19 rats. Each drug was injected once into the sites illustrated in (b); each injection site represents one rat. Sections 17b, 20b, 27b and 30b refer to the atlas of König & Klippel (1963) and the distances in mm refer to the distances between these sections.

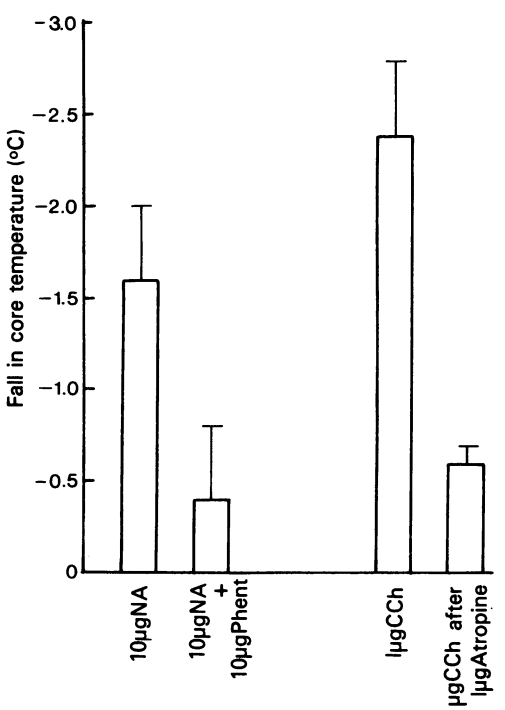

Figure 4 The effects of phentolamine (Phent) and atropine on the mean maximum falls in core temperature evoked by noradrenaline ($n = 5$) and carbachol ($n = 4$) respectively. Vertical bars indicate s.d.

creases in tail temperature, with shorter ($P < 0.005$) latencies to onset, were evoked by noradrenaline injections into the anterior hypothalamus.

Phentolamine (10 μg in 1 μl) injected into the anterior hypothalamus had no significant effect on core temperature and tail temperature ($P > 0.05$). When phentolamine (10 μg) and noradrenaline (10 μg) were injected together (in a volume of 1 μl) core temperature decreased by 0.4 ± 0.4°C (mean ± s.d.) although no increases in tail temperature were observed. This fall in core temperature was significantly smaller ($P < 0.005$) than the 1.6 ± 0.4°C fall evoked by injection of noradrenaline alone (1 μg in 1 μl) into the anterior hypothalamus (Figure 4). Atropine (1 μg in 1 μl) injected alone into the anterior hypothalamus increased core temperature by 0.6 ± 0.3°C ($P < 0.02$), between 90 min and 3 h after injection, but had no significant effect on tail temperature ($P > 0.05$). When atropine (1 μg in 1 μl) was injected immediately before a rat was placed in the experimental chamber, the subsequent injection of carbachol (1 μg in 1 μl) into the same site, 90 min later, lowered core temperature by 0.6 ± 0.1°C. This fall was significantly smaller ($P < 0.001$) than the fall of 2.4 ± 0.4°C obtained in rats which had not been pretreated with atropine (Figure 4). Pretreatment with atropine also abolished the increase in tail temperature evoked by carbachol. Injections of muscarine (0.1 to 10 μg in 1 μl) into the anterior hypothalamus evoked falls in core temperature and increased tail temperature: 0.1 μg decreased core temperature by 0.9 ± 0.2°C and in-

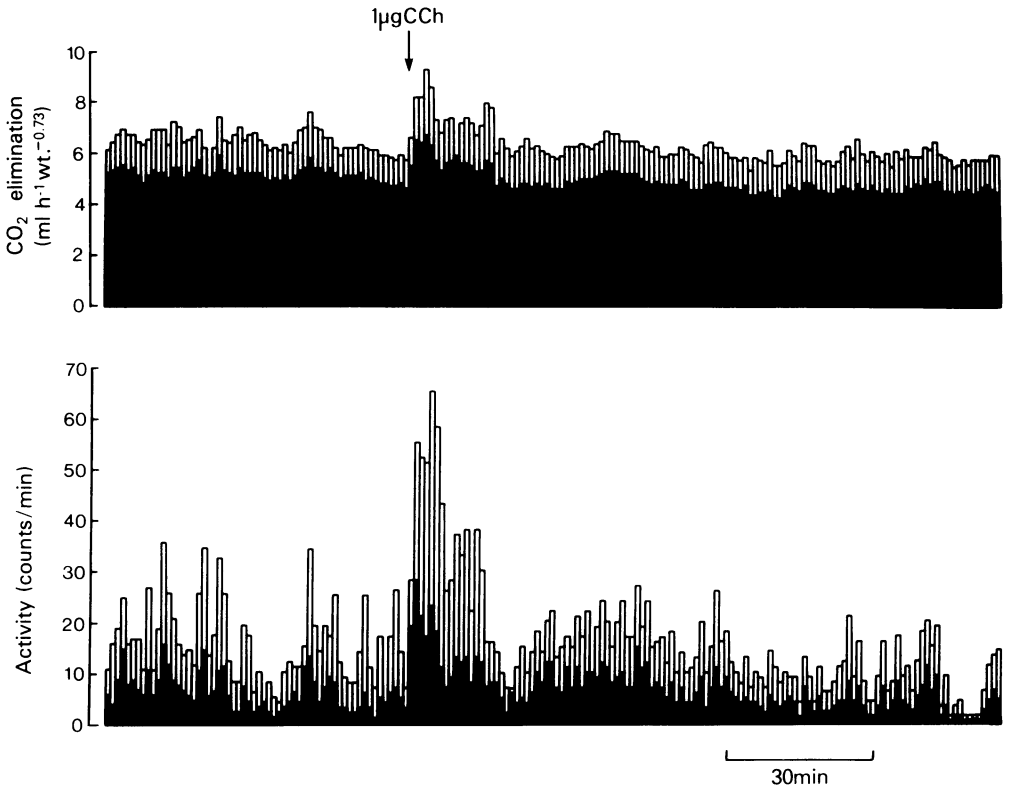

Figure 5 Mean changes in CO_2 elimination and locomotor activity caused by injection of carbachol (1 μg in 0.5 μl) into the preoptic anterior hypothalamic area of 7 rats. The columns indicate mean (filled) and s.d. (open) of the responses at 1 min intervals.

creased tail temperature by 1.3 ± 0.3°C, whereas 10 μg decreased core temperature by 2.2 ± 0.4°C and increased tail temperature by 2.6 ± 0.7°C. The delayed increases in core temperature, seen after noradrenaline and carbachol alone, were unaffected by phentolamine and atropine, and also occurred after injections of muscarine.

To determine whether or not changes in behaviour and metabolism contributed to the hypothermia, locomotor activity and CO_2 elimination were monitored after injections of noradrenaline (10 μg in 0.5 μl) and carbachol (1 μg in 0.5 μl) into the preoptic area (section 20b, Figure 3) and anterior hypothalamus (section 27b, Figure 3). The injection of carbachol (Figure 5) and noradrenaline into either site produced increases in locomotor activity and elevated CO_2 elimination: since the effects at both sites were similar the results from both sites for each drug have been pooled. The increase in locomotor activity was more pronounced after carbachol than after noradrenaline but of shorter duration (approx. 20 min and 40 min, respectively).

Injections of 0.5 μl of Evans' blue into the preoptic area and anterior hypothalamus produced stained spherical areas of no more than 1 mm diameter, 15 min later (Figure 6).

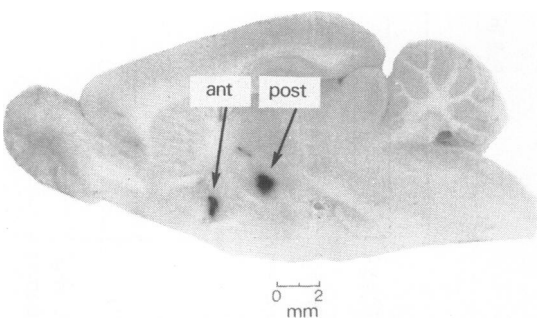

Figure 6 Photograph of an unstained, frozen sagittal brain section illustrating the extent of diffusion, 15 min after injection of Evans' blue (0.5 μl) into two sites about 2.5 mm apart. The A–P coordinates correspond approximately to those shown in Figure 3 by sections 17b (ant) and 30b (post) respectively.

The outline of the brain has been retouched.

Discussion

Both carbachol and noradrenaline evoked dose-dependent falls in core (thoracic) temperature at all sites tested within the preoptic/anterior hypothalamic area. The falls in core temperature were associated with increades in both tail temperature and locomotor activity. In about 70% of experiments falls in core temperature were followed, 15 to 90 min after injection, depending on the duration of the fall, by longer lasting increases in core temperature. In contrast, these delayed increases were not dose-related and could not have been due to prostaglandin release from tissue damaged by the injection (Feldberg, 1975) because core temperature was not elevated in the 3 h following saline injection (1 μl) into the hypothalamus. Since the increases were unaffected by phentolamine and atropine they were unlikely to be due to separate and more persistent effects of noradrenaline and carbachol on, for example the set-point (reference) temperature. A parsimonious and more satisfactory explanation is that they represent a rebound phenomenon which compensates for the earlier fall in temperature.

The carbachol responses are consistent with much of the existing literature on cholinomimetics. In partially restrained rats, intra-hypothalamic injection of acetylcholine lowered hypothalamic temperature and increased tail temperature, the response usually being followed by a rebound increase in hypothalamic temperature (Crawshaw, 1973). Increases in locomotor activity after acetylcholine were less evident than in the present study with carbachol, but in one instance quoted by Crawshaw (1973) such activity, itself reversed the fall in hypothalamic temperature. This reversal may have been dependent on the use, by Crawshaw (1973), of a restraint harness, which permitted some movement, or to hypothalamic temperature rising despite a fall in core temperature. Whichever explanation applies, it emphasizes the close relation between body temperature and motor activity which exists at thermoneutrality in rats (Poole & Stephenson, 1977c).

The above results contrast with the hyperthermia obtained in rats by Avery (1971) after intrahypothalamic injection of larger doses of carbachol (3 to 8 μg); the increases were not dose-related and were maximal 2 to 3.5 h after injection, thus coinciding with the occurrence of 'rebound hyperthermia' in the present study. Although Avery (1971) recorded rectal temperature intermittently, it is unlikely that the first determination (30 min after injection) was made at a time when a compensatory (rebound) increase was taking place (suggested by Crawshaw, 1973), since in the present study hypothermia after a smaller dose of carbachol (1 μg) was maximal at 25.3 ± 4.7 min. While handling, necessary for insertion of a rectal probe, would be expected to decrease the duration of a hypothermic response, this is unlikely to be the entire reason for the discrepancy because even in continuously restrained rats, marked falls in rectal temperature have been described by other authors after injection of cholinomimetics (Kirkpatrick *et al.*, 1967) or iontophoretic administration of acetylcholine (Kirkpatrick & Lomax, 1970) into the hypothalamus.

Atropine pretreatment reduced carbachol-induced hypothermia by 75% and abolished the carbachol-induced increase in tail temperature. Atropine alone evoked hyperthermia after intrahypothalamic application, confirming the results of Kirkpatrick & Lomax (1967). These data, taken together with the finding that intrahypothalamic injections of muscarine evoked similar temperature responses to carbachol, support the concept that hypothalamic muscarinic cholinoceptors are mediators of heat dissipating responses in the rat. These cholinoceptors are probably located in the anterior hypothalamus, since the same dose of carbachol (1 μg in 0.5 μl) injected into the preoptic area evoked smaller changes in core and tail temperatures than after injection into the anterior hypothalamus, the reduced responses starting after significantly longer latencies. Vasodilatation of the tail blood vessels (increasing heat loss), although contributing to carbachol-induced hypothermia, is precluded as the sole cause of the hypothermia since the tail temperature response started after a consistently, but not significantly longer latency than the core temperature response.

Noradrenaline (0.2 to 20 μg), in the present study, caused dose-related falls in core temperature and increases in tail temperature. Similar falls in rectal temperature were obtained by Lomax, Foster & Kirkpatrick (1969) after injection of noradrenaline (2.5 and 5 μg) into the rostral hypothalamus of restrained rats; smaller doses (0.5 μg) produced inconsistent responses which frequently included a prolonged rise in temperature, temporally related to the rebound hyperthermia seen in the present study. Hypothermia was also reported after injection of noradrenaline (5 μg) into the preoptic area but a large dose (25 μg) caused hyperthermia; hypothermia resulted when the injections (5 μg and 25 μg) were made into the lateral hypothalamus (Veale & Whishaw, 1976). In the present study, injection of noradrenaline into the preoptic area (10 μg) and anterior hypothalamus (0.2 to 20 μg) evoked only falls in core temperature, the magnitude of the evoked falls being similar from injections throughout the preoptic anterior hypothalamic area. The shorter latencies of both core and tail responses after the injection into the anterior hypothalamus suggests that this region mediated the hypothermia seen after injection of noradrenaline into the preoptic area. Mechanisms additional to non-evaporative heat loss probably contributed significantly to

the hypothermia observed after injection of noradrenaline into the preoptic area, because the hypothermia was not associated with marked increases in tail temperature. Since CO_2 elimination did not fall after injections of noradrenaline (or carbachol), it is unlikely that reduced metabolic rate contributed to the falls in core temperature. Intrahypothalamic application of phentolamine decreased noradrenaline-evoked hypothermia by 75% and abolished the increase in tail temperature, suggesting that α-adrenoceptors are mediators of hypothermia in the rat.

Hyperthermia has also been reported after injection of noradrenaline (10 μg in 1 μl) into the anterior hypothalamus of rats (Rewerski & Kubikowski, 1969). However, these rats were anaesthetized and the authors did not record rectal temperature until 1 h after injection. In the present study, this dose of noradrenaline (10 μg in 1 μl) caused a hypothermia persisting 50.9 ± 10.5 min which was usually followed by a delayed increase in core temperature. Therefore the hyperthermia observed by Rewerski & Kubikowski (1969) at 1 h after injection was probably a rebound hyperthermia.

Thus the above conclusion does not support that of Bruinvels (1975) and of Satinoff & Cantor (1975) that noradrenaline-induced hypothermia derives from an action at sites caudal to the anterior hypothalamus. These authors obtained hypothermia after intraventricular injection of noradrenaline and interpreted their findings on the assumption that noradrenaline acting on the preoptic/anterior hypothalamic area produced hyperthermia. Evidence for this assumption derived principally from the study of Beckman (1970) in which noradrenaline (0.15 μg or less) injected bilaterally into the preoptic/anterior hypothalamic area of rats produced small but dose-dependent increases in hypothalamic temperature. Since the doses used by Beckman (1970) were ineffective in the present study, small changes in hypothalamic temperature may be related to local drug-induced changes in hypothalamic blood flow and/or metabolic rate and therefore of no thermoregulatory significance. Alternatively, hypothalamic temperature may be more sensitive than body temperature to drug-induced thermoregulatory changes; with recordings of body temperature (e.g. thoracic or rectal) responses can be detected only when the effect is of sufficient magnitude to affect the temperature of the whole animal.

Apart from their role in temperature regulation, noradrenaline and acetylcholine within the anterior hypothalamus are involved in cardiovascular control. Their injection into this site alters heart rate and blood pressure (Brezenoff, 1972; Struyker-Boudier, Smeets, Brouwer & Van Rossum, 1974). These cardiovascular effects may contribute to, or oppose the induced hypothermia, but it is unlikely that interference from cardiovascular centres is the cause of the hyperthermia reported by some authors because hypothermic responses were also evoked by amine injections into the preoptic area, a site not mediating cardiovascular effects. Differences in experimental technique are the most likely cause of the conflict in the literature for, apart from the small increases in hypothalamic temperature seen by Beckman (1970), the authors who reported hyperthermia after noradrenaline and acetylcholine (or carbachol) recorded rectal temperature, which necessitated restraint. The importance of these differences in technique has been clearly demonstrated by Martin *et al.* (1977), who showed that restraint reversed temperature responses to morphine and heroin. In the present study, in which core temperature was recorded from unrestrained rats, noradrenaline and carbachol evoked dose-dependent falls in core temperature and increases in tail temperature at all sites tested within the preoptic/anterior hypothalamic area. Carbachol-induced hypothermia was mediated by cholinoceptors in the anterior hypothalamus whereas hypothermia after noradrenaline was mediated by adrenoceptors throughout the preoptic/anterior hypothalamic area. Although vasodilatation of the tail blood vessels (increasing non-evaporative heat loss) contributed significantly to carbachol-induced hypothermia and to hypothermia evoked by injections of noradrenaline into the anterior hypothalamus, noradrenaline-induced hypothermia evoked from the preoptic area was mediated by means in addition to non-evaporative heat loss.

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