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# Cardiovascular responses of rats to intrahypothalamic injection of carbachol and noradrenaline

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**1** Carbachol (0.1–2 μg) and noradrenaline (5–20 μg) injected into the anterior hypothalamus of unanaesthetized unrestrained rats evoked dose-dependent falls in heart rate and increases in arterial blood pressure.

**2** When the above amine injections were repeated in rats anaesthetized with chloral hydrate, sodium pentobarbitone or halothane the evoked bradycardias were usually smaller and the changes in arterial blood pressure more variable.

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

**4** The bradycardias evoked by carbachol (1 μg) and by noradrenaline (10 μg) were abolished by pretreatment with intra-arterial injection of methyl atropine (100 μg 100 $g^{-1}$).

**5** The hypertensive responses to carbachol (1 μg) and to noradrenaline (10 μg) were reduced by pretreatment with intra-arterial injection of thymoxamine (500 μg 100 $g^{-1}$).

## Introduction

Hilton and co-workers (Hilton & Spyer, 1971; Coote, Hilton & Zbrozyna, 1973) have suggested that cardiovascular integrative centres are longitudinally arranged within the CNS from the preoptic area in the forebrain, through the anterior and posterior hypothalamus, to the medulla oblongata in the hindbrain.

The preoptic area and hypothalamus (PO/AH) of the rat contain high concentrations of noradrenaline, acetylcholine and other amines (Vogt, 1959; Jacobowitz & Goldberg, 1977) and injection of these substances into or electrical stimulation of these areas evokes rapid and pronounced changes in blood pressure and heart rate. Both the presence or absence of anaesthetic and the type of anaesthetic used can influence the changes induced by hypothalamic injection. Noradrenaline lowered blood pressure and heart rate when injected into the PO/AH of rats anaesthetized with pentobarbitone (Struyker Boudier, Smeets, Brouwer & Van Rossum, 1974) but evoked a biphasic change in blood pressure (an increase followed by a fall) while still lowering heart rate in rats anaesthetized with chloral hydrate (Poole, 1980). Injections of noradrenaline into the third ventricle of unanaesthetized, restrained, water-loaded rats (Hoffman, 1979) and into the PO/AH of unanaesthetized unrestrained rats (Poole, 1980) evoked changes in blood pressure and heart rate similar to those evoked in rats anaesthetized with chloral hydrate.

The cholinoceptor agonist, carbachol, increased blood pressure but produced variable changes in heart rate when injected into the posterior hypothalamus of unanaesthetized unrestrained rats (Buccafusco & Brezenoff, 1979). In contrast, carbachol injection into the anterior hypothalamus of unanaesthetized unrestrained rats increased blood pressure and evoked substantial falls in heart rate (Poole, 1980).

Since the state of the animal, i.e. unanaesthetized or anaesthetized, the choice of anaesthetic agent, and the locus of injection within the hypothalamus appear to determine not only the magnitude of the induced cardiovascular responses but also their direction, it is not surprising that the mechanisms underlying the effects of intracranial administration of carbachol and noradrenaline are poorly understood. In an attempt to obtain further information about these mechanisms, noradrenaline and carbachol were injected into the anterior hypothalamus of unanaesthetized unrestrained rats and rats anaesthetized with pentobarbitone, chloral hydrate or

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halothane. Arterial blood pressure and heart rate were recorded continuously and the effects of intrahypothalamic and intra-arterial injections of appropriate antagonists on the amine-induced cardiovascular changes investigated.

## Methods

The rats used were male Wistars, received at 150–250 g, 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/dark cycle (lights on 06 h 00 min, off 18 h 00 min.

### *Materials*

Intra-arterial catheters were made from 100 mm lengths of polyethylene tubing (Portex 800/100/160, i.d. 0.5 mm, o.d. 1.0 mm, Portland Plastics Ltd) coated with dichloromethyl silane (DCMS: 2% in heptane, Aldrich Chemical Co. Ltd) and filled with heparin solution (1000 units/ml, Evans Medical Ltd) in pyrogen-free sterile saline (150 mM NaCl). Plugs for the catheters were 8 mm lengths of 22 gauge stainless steel wire.

### *Operative procedures*

Sixty rats (275–325 g) were anaesthetized with halothane and, under aseptic conditions, a 22 gauge stainless steel guide cannula with stylette was stereotactically implanted into the left or right anterior hypothalamus. The co-ordinates were 0.2 mm posterior to bregma, 0.5 mm lateral to the midline and at a depth of 8.5 mm below the surface of the skull. After further growth to 325–350 g (about 2 weeks) the rats were anaesthetized with halothane and, under aseptic conditions, a 30 mm incision was made along the midline of the throat and upper thorax. An intra-arterial catheter was inserted 25 mm into the right carotid artery so that its tip lay close to the junction of the carotid artery with the aorta; the catheter was secured with ligatures and the free end drawn subcutaneously to the skull, exteriorised immediately behind the existing implant and closed with a plug. The portion of the catheter immediately distal to the cap was attached with acrylic cement to the implant on the skull.

### *Experimental procedures*

*Unanaesthetized rats* Forty eight hours after implantation of intra-arterial catheters, rats were placed singly in a perspex experimental chamber (335 mm × 290 mm × 280 mm) at 23 ± 0.5°C through which air flowed at 2 litres $min^{-1}$. The intra-arterial catheter was connected via a length of polyethylene tubing (Portex 800/100/120, i.d. 0.38 mm, o.d. 1.09 mm) containing heparin saline to a three-way tap, one arm of which was connected to a 1 ml syringe for drug injection and another to a blood pressure transducer. Heart rate was measured from the blood pressure by a Devices Instantaneous Ratemeter and displayed with blood pressure on a Devices pen recorder. Intra-arterial infusions were made in a volume of 100 μl 100 $g^{-1}$ at a rate of 50 μl $min^{-1}$ immediately after a rat was placed in the chamber.

For intrahypothalamic injections a 27 gauge (390 μm o.d.) stainless steel injection cannula was inserted so that its tip protruded 0.2 mm below the tip of the guide cannula. Polyethylene tubing (Portex 800/100/100, i.d. 0.28 mm, o.d. 0.61 mm) connected the injection cannula to a 10 μl syringe. The injectate volume was 0.5 μl made over 1 s. Except for atropine, drugs were injected when a rat had been in the chamber for 45 min and the cannula was left in position after injection. Atropine was injected immediately before a rat was placed in the chamber and carbachol was injected into the same site, 45 min later. At least 48 h elapsed between experiments in the same animal.

*Anaesthetized rats* Experiments were performed as in unanaesthetized animals except that rats were anaesthetized with chloral hydrate (100 mg $ml^{-1}$, 0.4 ml 100$g^{-1}$, BDH), sodium pentobarbitone (60 mg $ml^{-1}$, 0.1 ml 100 $g^{-1}$ Sagatal, May & Baker Ltd) or halothane (2% v/v in oxygen at 2 litres $min^{-1}$, May & Baker Ltd) before being placed in the experimental chamber.

### *Drugs*

Intravenous injections: pyrogen-free sterile saline (150 mM NaCl), methyl atropine (atropine methyl nitrate, 2.73 mM base in saline, BDH) and thymoxamine (17.9 mM base in saline, W.R. Warner Ltd).

Intrahypothalamic injections: pyrogen-free sterile saline (150 mM NaCl, pH 5.0; osmolarity 0.31 osmol $l^{-1}$) or one of the following drugs in sterile saline (the concentrations are given in terms of the base): (−)-noradrenaline hydrochloride (59.1–236.4 mM, Sigma; pH 4.0–4.5; osmolarity 0.42–0.76 osmol $l^{-1}$); carbamylcholine (carbachol) chloride (1.36–27.18 mM BDH; pH 5.5–5.6; osmolarity 0.31–0.33 osmol $l^{-1}$); atropine sulphate (6.91 mM, BDH; pH 5.5, osmolarity 0.31 osmol $l^{-1}$; phentolamine mesylate (71.09 mM Ciba) and (−)-noradrenaline hydrochloride (118.2 mM) giving a pH of 4 and osmolarity 0.58 osmol $l^{-1}$.

Cannulae positions were subsequently confirmed

histologically and the data described below pertain to rats with intracerebral guide cannulae tips in the anterior hypothalamus, between sections 24b and 30b of the atlas of König & Klippel (1963).

Results are expressed as the mean ± 1 standard error of the mean (s.e.mean) of the number of determinations given in the text. Mean carotid arterial blood pressure (MAP) was obtained by adding 1/3 (pulse pressure) to diastolic blood pressure. Changes in blood pressure and heart rate of both unanaesthetized and anaesthetized rats after saline injections were typically ± 5 mmHg and ± 10 beats $min^{-1}$ respectively. Significance of the differences between results was determined using Students' *t* test.

## Results

### *Unanaesthetized rats*

Carbachol (0.1 to 2.0 μg, i.e. 0.5 μl of 1.36 to 27.18mM) and noradrenaline (5 to 20 μg, i.e. 0.5 μl of 59.1 to 236.4mM) injected into the anterior hypothalamus evoked dose-related increases in

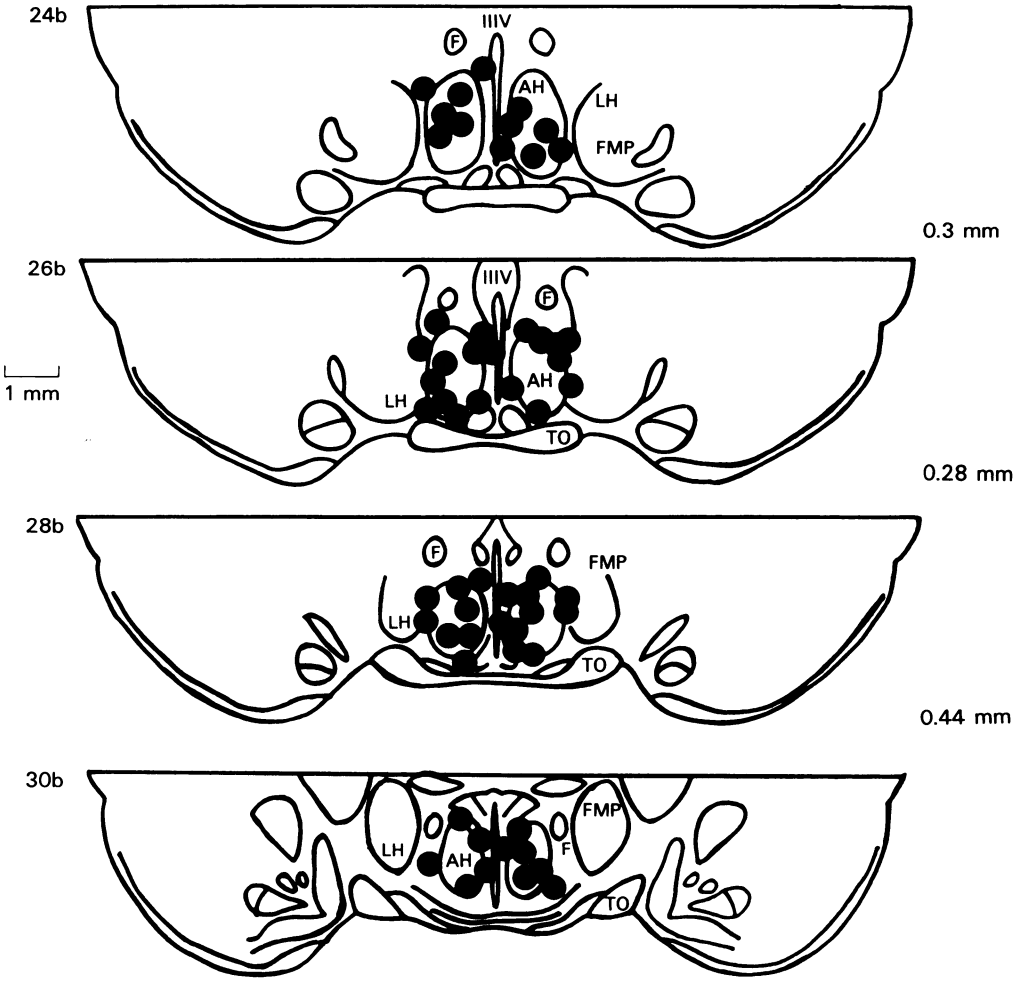


**Figure 1** The intrahypothalamic injection sites of the 60 rats injected. Each circle represents the injection site of one rat: the centres of the circles represent the centres of the lesions made by the injection cannulae. (The diameters of the circles do not indicate the size of the lesions made or the spread of injectate). Sections 24b to 30b refer to the atlas of König & Klippel (1963) and the distances in mm on the right of the figure are the distances between these sections. (IIIV = 3rd Ventricle, F = columna fornicis, AH = anterior hypothalamus, LH = lateral hypothalamus, FMP = fasciculus medialis prosencephali, CO = chiasma opticum, TO = tractus opticus).

blood pressure (both systolic and diastolic) and falls in heart rate (Table 1). Typical responses to submaximum doses of each drug are illustrated in Figure 2. Increased blood pressure frequently preceded decreased heart rate, the latencies to onset of the respective responses being in the ratio of $20 \pm 10$s to $42 \pm 18$s for carbachol (1μg) and $28 \pm 10$s to $45 \pm 21$s for noradrenaline (10μg). The responses were accompanied by forward locomotion and other behavioural changes that have been described previously (Poole & Stephenson, 1979).

Carbachol (1μg) increased MAP, initially $113 \pm 1$ mmHg ($n = 18$), by $39 \pm 3$ mmHg, within $17 \pm 3$ min; the duration of the hypertension was $118 \pm 17$ min. In 8 rats this long-lasting response was preceded by a transient hypertension, as in Figure 2a. Heart rate, initially $387 \pm 10$ beats min$^{-1}$, was rapidly decreased by $124 \pm 10$ beats min$^{-1}$ within $15 \pm 2$ min; the duration of the bradycardia was $61 \pm 9$ min.

**Table 1** Maximum changes in blood pressure (Δ MAP) and heart rate (Δ HR) evoked by intrahypothalamic injections of carbachol (CCh, 1μg), noradrenaline (NA, 10μg) and saline (each in 0.5 μl) in unanaesthetized rats.

| Drug | Dose μg | n | + Δ *MAP* (mmHg) | − Δ *HR* (beats min$^{-1}$) |
|---|---|---|---|---|
| CCh | 0.1 | 4 | 19± 5 | 70±11 |
| CCh | 0.5 | 4 | 29± 7 | 85± 5 |
| CCh | 1.0 | 18 | 39± 3 | 124±10 |
| CCh | 2.0 | 4 | 52± 9 | 130±21 |
| NA | 5.0 | 4 | 10± 6 | 78±13 |
| NA | 10.0 | 14 | 24± 4 | 95± 7 |
| NA | 20.0 | 8 | 29±10 | 137±24 |
| 0.9% Saline | | 4 | 5± 3 | 10± 4 |

The values indicate means ± s.e.mean. The mean changes in MAP and HR after saline were calculated from the maximum changes observed within 90 min of injection.

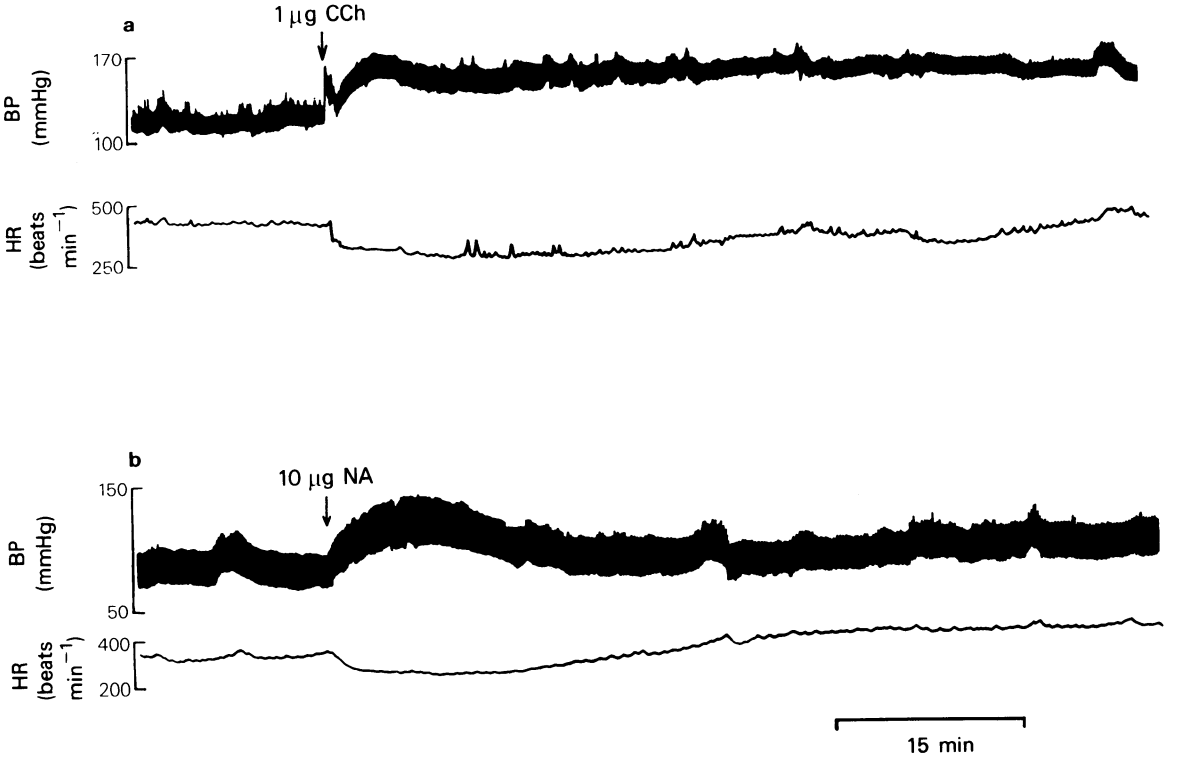


**Figure 2** The changes in carotid arterial blood pressure (BP) and heart rate (HR) of two unanaesthetized rats evoked by injections of carbachol (CCh, 1 μg) and noradrenaline (NA, 10 μg) into the anterior hypothalamus.

Noradrenaline (10 μg) also increased MAP, initially 109 ± 4 mmHg ($n = 14$), by 24 ± 4 mmHg within 4 ± 1 min; the duration of the hypertension was 12 ± 2 min. In 5 rats the hypertension was followed immediately by a fall in MAP of 15 ± 5 mmHg, 37 ± 5 min after injection, the duration of the hypotension was 84 ± 16 min. Heart rate, initially 404 ± 10 beats $min^{-1}$ fell by 95 ± 7 beats $min^{-1}$ within 7 ± 1 min; the duration of the bradycardia was 23 ± 3 min. In 9 rats the bradycardia was followed by an increase in heart rate which reached 44 ± 8 beats $min^{-1}$ above the pre-injection rate 43 ± 7 min after injection; the duration of the bradycardia was 83 ± 7 min.

*Antagonists* Intra-arterial (i.a.) infusions of saline (0.1 ml 100 $g^{-1}$), methyl atropine (100 μg 100 $g^{-1}$) and thymoxamine (500 μg 100 $g^{-1}$), had no effect on MAP. Saline had no effect on heart rate (384 ± 11 beats $min^{-1}$), but heart rate had increased to 439 ± 12 beats $min^{-1}$ ($P < 0.05$) 40 min after methyl atropine infusion, and to 419 ± 15 beats $min^{-1}$ ($P > 0.05$) 40 min after thymoxamine infusion.

Methyl atropine pretreatment (100 μg 100 $g^{-1}$, intra-arterially) abolished the bradycardia evoked by carbachol (1 μg) and by noradrenaline (10 μg) and slightly reduced carbachol-evoked hypertension, but enhanced noradrenaline-induced hypertension (Figures 3 and 4).

Thymoxamine pretreatment (500 μg 100 $g^{-1}$, intra-arterially) reduced by 75% the noradrenaline-(10 μg) evoked bradycardia of 95 ± 7 beats $min^{-1}$ to 23 ± 17 beats $min^{-1}$ ($P < 0.005$, Figure 3). Thymoxamine pretreatment also reduced carbachol-evoked bradycardia and hypertension, besides noradrenaline-induced hypertension.

Atropine (1 μg) injected alone into the anterior hypothalamus had no effect on MAP or heart rate. When atropine (1 μg) was injected into the hypothalamus immediately before a rat was placed in the chamber, the subsequent injection of carbachol (1 μg) into the same site 45 min later had no signific-

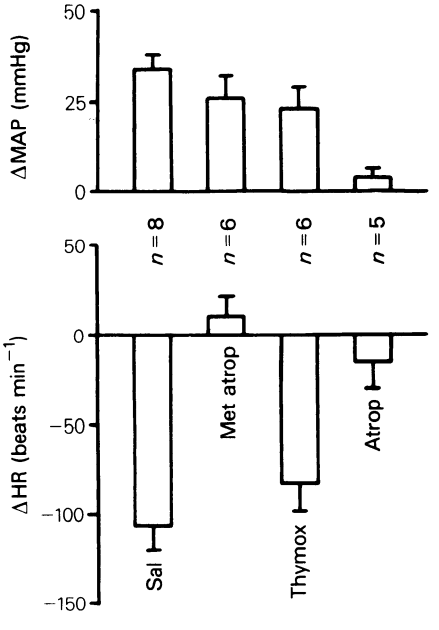


**Figure 3** The effects of pretreatment with saline (0.1 ml 100 $g^{-1}$), methyl atropine (100 μg $g^{-1}$) and thymoxamine (500 μg 100 g), administered intra-arterially, and atropine (1 μg), injected into the hypothalamus, on the maximum changes in MAP and heart rate (HR) evoked by intrahypothalamic injection of carbachol (CCh, 1 μg) in unanaesthetized rats. Vertical bars indicate s.e.mean.

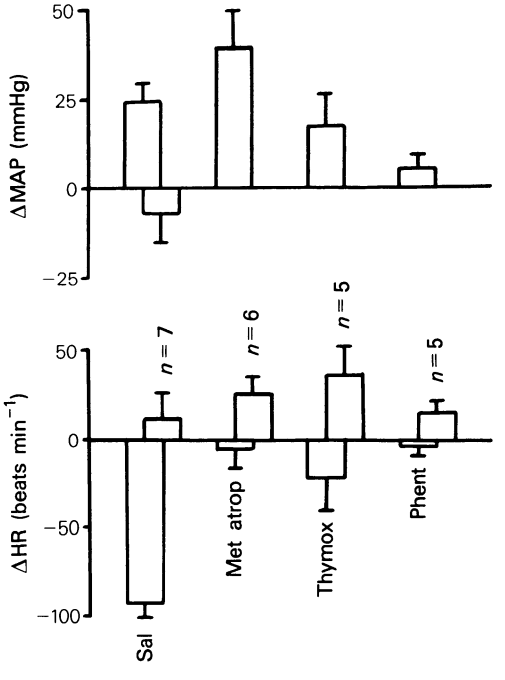


**Figure 4** The effects of pretreatment with saline (0.1 ml 100 $g^{-1}$), methyl atropine (100 μg 100 $g^{-1}$) and thymoxamine (500 μg 100 $g^{-1}$), administered intra-arterially, and phentolamine (10 μg), injected into the hypothalamus, on the maximum changes in MAP and heart rate (HR) evoked by intrahypothalamic injection of noradrenaline (10 μg) in unanaesthetized rats. Vertical bars indicate s.e.mean.

ant effect on either MAP or heart rate (Figure 3). Intrahypothalamic injection of phentolamine (10 μg) and noradrenaline (10 μg) together (in a volume of 0.5 μl) had no significant effect on either MAP or heart rate (Figure 4).

*Anaesthetized rats*

The maximum changes in MAP and heart rate evoked by intrahypothalamic injections of carbachol (1 μg, i.e. 0.5 μl of 13.59 mM) and noradrenaline (10 μg, i.e. 0.5 μl of 118.2 mM) in rats anaesthetized with chloral hydrate, sodium pentobarbitone or halothane are summarized in Table 2. The latencies to onset of the changes in blood pressure and heart rate were typically 30–40 s for both drugs.

*Carbachol* In 6 rats anaesthetized with chloral hydrate, carbachol (1 μg) lowered MAP, initially 71 ± 4 mmHg, by 28 ± 5 mmHg within 4 ± 1 min, and decreased heart rate by approximately 100 beats $min^{-1}$. In 4 rats the hypotension was followed by an increase in MAP of 18 ± 6 mmHg within 13 ± 8 min of injection even though the bradycardia persisted for about 40 min.

Under sodium pentobarbitone anaesthesia, carbachol (1 μg) evoked a biphasic response in MAP. There was an initial decrease of 14 ± 2 mmHg from 93 ± 11 mmHg ($n = 5$) within 4 min, followed by an increase of 18 ± 5 mmHg within 22 min of injection. The duration of this biphasic response was 33 ± 10 min. In 2 rats the hypotension was preceded by a short-lasting (3 min) increase in MAP of 7 mmHg which was followed immediately by the hypotension. In 1 rat there was a monophasic increase in MAP of 16 mmHg within 21 min which lasted for 65 min. Heart rate, initially 399 ± 31 beats $min^{-1}$ was decreased by 85 ± 9 beats $min^{-1}$ within 19 ± 3 min; the duration of the bradycardia was 51 ± 8 min.

In three halothane-anaesthetized rats, carbachol (1 μg) lowered MAP, initially 61–85 mmHg, by 14–17 mmHg within 4–7 min; the duration of the hypotension was 16–40 min. In 1 rat the fall was preceded by an increase in MAP of 9 mmHg within 1 min; the duration of the increase was 2 min and it was immediately followed by the hypotension. Heart rate, initially 303–390 beats $min^{-1}$ was decreased by 23–70 beats $min^{-1}$ within 4–10 min; the duration of the bradycardia was 32–55 min.

*Noradrenaline* Noradrenaline (10 μg) was injected into the anterior hypothalamus of 6 rats anaesthetized with chloral hydrate. In 4 rats MAP, initially 85 ± 5 mmHg, was reduced by 20 ± 2 mmHg within 11 ± 5 min; the duration of the hypotension was 39 ± 5 min. In 2 rats MAP, initially 66 mmHg was increased by 24–30 mmHg within 2 min; the duration of the hypertension was about 34 min. Heart rate, initially 415 ± 10 beats $min^{-1}$, was decreased by 133 ± 32 beats $min^{-1}$ within 13 ± 2 min; the duration of the bradycardia was 56 ± 11 min. In 2 rats the bradycardia was followed by a tachycardia of 10–20 beats $min^{-1}$, 60–90 min after injection.

Noradrenaline was injected into the anterior hypothalamus of 4 rats anaesthetized with sodium pentobarbitone. In 2 rats MAP, initially 66 mmHg was decreased by 9 mmHg within 8–12 min; the duration of the hypotension was about 30 min. In the other 2 rats MAP, initially 71–86 mmHg, was increased by 32–44 mmHg within 7 min; the duration of the hypertension was 21–26 min. Heart rate, initially 380 ± 28 beats $min^{-1}$ was reduced by 74 ± 7 beats $min^{-1}$ within 9 ± 2 min; the duration of the bradycardia was 48 ± 16 min. In 3 of the 4 rats the bradycardia was followed immediately by an increase in heart rate of 25–40 beats $min^{-1}$, 60–90 min after injection.

## Discussion

Carbachol and noradrenaline evoked dose-dependent increases in blood pressure and falls in

**Table 2** Maximum changes in blood pressure (△ MAP) and heart rate (△ HR) evoked by intrahypothalamic injections of carbacol (CCh, 1 μg) and noradrenaline (NA, 10 μg) in anaesthetized rats.

| | *Dose* | | n | − △ *MAP* | + △ *MAP* | − △ *HR* | + △ *HR* |
|---|---|---|---|---|---|---|---|
| *Anaesthetic* | Drug | μg | | (mmHg) | (mmHg) | (beats $min^{-1}$) | (beats $min^{-1}$) |
| Chloral hydrate | CCh | 1 | 6 | 28 ± 5 | 18 ± 6[4] | 100 ± 30 | — |
| Sodium pentobarbitone | CCh | 1 | 6 | 14 ± 2[5] | 18 ± 5 | 85 ± 9 | — |
| Halothane | CCh | 1 | 3 | 14 – 17[3] | 9[1] | 23 – 70[3] | — |
| Chloral hydrate | NA | 10 | 4 | 20 ± 2 | — | 133 ± 32 | 10 – 20[2] |
| | NA | 10 | 2 | — | 24 – 30[2] | NR | NR |
| Sodium pentobarbitone | NA | 10 | 2 | 9 | — | 70 – 95[2] | 40[1] |
| | NA | 10 | 2 | — | 32 – 44[2] | 60 – 70[2] | 25 – 40[2] |

The values indicate mean ± s.e.mean where $n > 3$ ([1] = 1 rat, [2] = 2 rats, [3] = 3 rats, [4] = 4 rats; [5] = 5 rats, NR = not recorded).

heart rate when injected into the anterior hypothalamus of unanaesthetized rats. The cardiovascular responses frequently preceded, and were therefore not secondary to, increased locomotor activity. However, bouts of locomotor activity before and after amine injection elevated blood pressure and heart rate, thus amine-induced increases in locomotor activity contributed to the maintenance of the hypertension and diminished the bradycardia. Reduced heart rate was not simply a reflex bradycardia to the pressor response since increased blood pressure did not always precede a fall in heart rate.

The hypertension evoked by carbachol injection into the anterior hypothalamus was similar to that obtained by Buccafusco & Brezenoff (1979) from similar doses of carbachol injected into the posterior hypothalamus. Carbachol-evoked changes in heart rate were more site-dependent: carbachol elicited consistent and substantial falls in heart rate from the anterior but not the posterior hypothalamus.

The carbachol-induced hypertension and bradycardia were mediated by central muscarinic receptors since they were abolished by previous anterior hypothalamic injection of atropine. Pretreatment with systemic injection of methyl atropine abolished the evoked bradycardia, indicating that the bradycardia was effected by an increase in cardiac vagal tone. Prior administration of the α-adrenoceptor antagonist, thymoxamine, reduced by 32% the hypertension evoked by carbachol, suggesting that the hypertensive response to carbachol was in part mediated by an increase in sympathetic drive to the peripheral vasculature. Increased cardiac output may have contributed to the hypertension since the remaining pressor response to intravenous injection of noradrenaline in the presence of phentolamine (46% of control) was shown to be due entirely to increased cardiac output (Imms, Neame & Powis, 1977). However, carbachol reduced heart rate by 18–33% (depending on dose) therefore stroke volume would have needed to increase by as much as one third to effect an increase in cardiac output.

The hypertensive response to noradrenaline injection into the anterior hypothalamus of conscious unrestrained rats was similar to that evoked by noradrenaline injection into the third ventricle of conscious but restrained water-loaded rats (Hoffman, 1979). The subsequent depressor effects of noradrenaline in about 30% of experiments also accords with the data of Hoffman (1979) although the delayed increases in heart rate which frequently occurred in the present study (60% of experiments) were not reported.

Phentolamine, applied to the anterior hypothalamus together with the noradrenaline, abolished noradrenaline-induced hypertension and bradycardia suggesting that these responses were mediated by central α-adrenoceptors. Pretreatment with systemic injection of methyl atropine also abolished noradrenaline-evoked bradycardia, indicating that this response was effected by increased cardiac vagal tone. It is unlikely that methyl atropine pretreatment potentiated (by 63%) noradrenaline-evoked hypertension by blockade of cholinergic buffering mechanisms since methyl atropine pretreatment reduced (by 24%) the hypertensive response to carbachol.

Prior administration of thymoxamine (given intra-arterially) reduced noradrenaline-evoked bradycardia by 75% and the hypertension by almost 30%. Since blockade of peripheral α-adrenoceptors would account for the reduced hypertensive response but not the reduced bradycardia (which was mediated by increased cardiac vagal tone) it is possible that thymoxamine antagonized α-adrenoceptors in the anterior hypothalamus. Since thymoxamine readily penetrates the CNS (Pruvot, Agneray & Héquet, 1969; Phillips, Richens & Shand, 1973), it was not possible to determine the contribution made by increased sympathetic drive to noradrenaline-induced hypertension.

In anaesthetized rats, carbachol-evoked bradycardia was generally smaller than that obtained in conscious animals particularly when halothane was the anaesthetic agent, whereas noradrenaline-evoked bradycardia was similar in conscious rats and in rats anaesthetized with chloral hydrate but smaller in animals under sodium pentobarbitone anaesthesia. However, changes in blood pressure following amine injections in anaesthetized animals were more variable. Irrespective of the anaesthetic agent, carbachol usually evoked a biphasic response in which an initial fall preceded the pressor response and noradrenaline evoked purely pressor or depressor responses. The opposite effects of noradrenaline were not due to injection at different sites since these were frequently indistinguishable from subsequent inspection of cannulae positions. It is possible that the depth of anaesthesia determined the direction of the response to noradrenaline, a possibility that is consistant with the finding that responses of cortical neurones to iontophoretic application of monoamines (but not acetylcholine) were modified by the depth of anaesthesia (Johnson, Roberts & Straughan, 1969).

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