thalamus (Horn & Snyder, 1972). Rat striatal synaptosomes were employed for [^{3}H]-DA studies. In all experiments the final concentration of monoamine in the incubating medium was 2.6×10^{-8} M. To investigate the effects of drug pretreatment on rat hypothalamic synaptosomal [^{3}H]-5-HT uptake, drugs were injected i.p. 1 h prior to sacrifice. Org 6582 and fluoxetine were equipotent in blocking [^{3}H]-5-HT uptake and both compounds were more potent than chlorimipramine. One and two days after pretreatment with Org 6582 (20 mg/kg, i.p.), [^{3}H]-5-HT uptake was inhibited 55% and 34% respectively. There was no inhibition of [^{3}H]-5-HT uptake one day after chlorimipramine (80 mg/kg, i.p.) pretreatment.

Pretreatment with Org 6582 (80 mg/kg, i.p.) had no effect on [^{3}H]-NA uptake whereas desipramine (40 g/kg, i.p.) produced a 61% inhibition after 1 hour. [^{3}H]-DA uptake into striatal homogenates was unaffected by Org 6582 (80 mg/kg, i.p.) pretreatment whilst 1 h pretreatment with benztropine (40 mg/kg, i.p.), nomifensine (30 mg/kg, i.p.) or mazindol (40 mg/kg, i.p.) inhibited uptake by 25%, 38% and 46% respectively.

In other experiments drugs were added to the incubation medium at the commencement of the 10 min preincubation period prior to addition of ^{3}H-monoamine. Results are expressed as IC_{50} values, which is defined as the molar concentration of drug causing a 50% inhibition of uptake. IC_{50} values for blockade of [^{3}H]-5-HT, [^{3}H]-NA and [^{3}H]-DA uptake by Org 6582 were 1.8×10^{-7} M, 2.9×10^{-6} M and 1.3×10^{-5}M respectively. The corresponding values for chlorimipramine were 7.9×10^{-9} M, 1.1×10^{-7} M and 2.2×10^{-6} M. Kinetic analysis of the inhibition of [^{3}H]-5-HT uptake by rat hypothalamic synaptosomes showed that Org 6582 was a competitive inhibitor of 5-HT uptake with a K_i value of 8.9×10^{-8} M.

These observations reveal that Org 6582 is a competitive inhibitor of 5-HT uptake and confirm those previously found *in vivo* which demonstrated that Org 6582 is a potent, long acting, selective inhibitor of 5-HT uptake.

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Effects of intrahypothalamic injections of noradrenaline and carbachol on core temperature of unrestrained rats

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Amines (e.g. noradrenaline and acetylcholine) acting on the preoptic/anterior hypothalamic area play an important role in thermoregulation. Thus in rats, their injection into this site produces marked changes in body temperature. However, whereas some authors report hypothermia after noradrenaline, acetylcholine and their congeners, others obtain hyperthermia (e.g. Avery, 1971; Beckman, 1970; Kirkpatrick, Lomax & Jenden, 1967). These opposite effects may in part be attributed to differences in injected volume, ambient temperature and the site from which temperature is recorded (e.g. brain, rectal and liver temperatures may vary independently of each other). Since restraint, necessary for rectal temperature measurements, alone elevates body temperature, the effects of intrahypothalamic injections of the above amines were investigated in unrestrained rats in which body temperature was continuously measured from a thermistor implanted into the thoracic cavity (Poole & Stephenson, 1977a); in some rats, electrodes for recording electromyographic activity were placed in the neck muscles and an arterial cannula, for monitoring blood pressure and heart rate, in a carotid artery. Experiments were performed at 23 ± 1°C, the mid-point of their thermoneutral range (Poole & Stephenson, 1977b).

(–)-Noradrenaline hydrochloride (0.2 to 20 μg base in 1 μl of pyrogen-free 0.9% w/v NaCl solution) lowered core temperature. Latency to onset (0.8 ± 0.2 to 1.1 ± 0.1 min, mean ± s.d.) and the maximum fall (0.4 ± 0.1 to 3.1 ± 0.3°C) were dose-related, the larger doses producing correspondingly greater effects of shorter latency. Recovery occurred 18.7 ± 1.6 to 94.8 ± 13.9 min later, depending on dose, and after doses of 10 μg or less, this was followed by a 'rebound' hyperthermia of between 0.2 and 0.8°C. After small doses of noradrenaline (0.5 μg or less), this 'rebound' hyperthermia was sometimes greater than

the hypothermia. Tail temperature – normally 1–2°C above ambient temperature – rose by 1.5 ± 1.2°C after noradrenaline (0.2 μg) and 2.9 ± 1.0°C after noradrenaline (10 μg), indicating marked vasodilatation and increased heat loss. Carbamylcholine hydrochloride (0.1 to 1.0 μg base in 1 μl of pyrogen-free 0.9% w/v NaCl solution) although more potent than noradrenaline produced essentially similar effects on temperature with respect to latency (0.7 ± 0.4 to 1 ± 0.5 min), fall (1.4 ± 0.3 to 2.4 ± 0.4°C) and duration (33.8 ± 8.5 to 80.5 ± 26.7 min).

The relation of the above changes in core temperature to effects on some behavioural, metabolic and cardiovascular activities will be discussed.

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Noradrenaline concentration in hypothalamic and brain stem nuclei of renovascular hypertensive rats

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Catecholamine-containing neurones in brain stem and hypothalamus, are involved in blood pressure regulation. Changes in catecholamine concentration or the activity of synthetic enzymes have been described recently in localised areas of brain stem in spontaneously hypertensive rats (Versteeg, Palkovits, van der Gugten, Wijnen, Smeets & de Jong, 1976) and deoxycorticosterone-saline hypertension (Saavedra, Grobecker & Axelrod, 1976). In the present study noradrenaline levels were examined during the development of renovascular hypertension in the rat, which was produced by applying a silver clip to one renal artery with contralateral nephrectomy (One kidney Goldblatt model). Results were compared to those obtained from sham operated litter mates sacrificed at the same time. Nuclei were isolated and removed by the micro-dissection technique of Palkovits (1973) and noradrenaline concentration estimated by the radioenzymatic method of Henry, Starman, Johnson & Williams (1973).

The mean arterial pressure (MAP) of the clipped animals 72 h after operation was 146.77 ± 2.6, compared with 119 ± 2.18 ($P < 0.01$) in the sham operated group. In all regions investigated, both in brain stem and hypothalamus, there was a reduction in noradrenaline concentration in the hypertensive animals, compared with the sham operated controls. The reduction was significant in the nucleus of the solitary tract ($P < 0.05$) and the lateral reticular nucleus ($P < 0.01$) of the brain stem, whose levels were reduced to 49.6 ± 12.7%, and 52.49 ± 6.59% respectively. In the hypothalamus, the fall in noradrenaline was significant in the anterior hypothalamic, the paraventricular and the posterior hypothalamic nuclei ($P < 0.05$). The noradrenaline concentration was reduced to 62.73 ± 10.07%, 58.11 ± 7.89% and 57.67 ± 5.49% respectively in these areas.

Seven days after operation, the MAP of the renal artery clipped rats was 162.25 ± 4.43, compared with 111.94 ± 4.54 in shams ($P < 0.01$). At this time the noradrenaline levels of all the regions investigated were not different from sham operated animals. Four weeks after operation, the MAP was 161.28 ± 6.49 in hypertensives, compared with 124.4 ± 1.78 in shams ($P < 0.01$). There was a significant change in noredrenaline concentration ($P < 0.05$) in only two regions: the parahypoglossal nucleus of the brain stem, where it was reduced to 61.93 ± 5.1% of shams, and in punches removed from the cerebellar cortex, where levels were raised to 167.08 ± 19.47%.

At present it is not clear if the early changes in monoamine concentration reported have any direct causal relationship to the rise in arterial pressure, or merely reflect secondary attempts of arterial baroreflex mechanisms to compensate for the hypertension. In addition, more dynamic measures of