

Acute effects of a monoamine oxidase inhibitor, tranylcypromine, on thermoregulation in the conscious rabbit

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Summary

1. The effect of a single injection of the monoamine oxidase inhibitor, tranylcypromine, administered intravenously (20 mg/kg) or into the lateral cerebral ventricle (5–10 mg), on hypothalamic and rectal temperature, has been investigated.
2. Intravenous tranylcypromine causes a significant rise in body temperature, which is due, at least in part, to cutaneous vasoconstriction; this vasoconstriction is augmented by sympathectomy. It is concluded that this vasoconstrictor effect is not mediated via the central nervous system.
3. Intraventricular tranylcypromine caused a transient but significant fall in core temperature. This is interpreted as being compatible with selective augmentation of hypothalamic levels of 5-hydroxytryptamine.

Introduction

It has been suggested (Feldberg & Myers, 1964a) that the hypothalamic control of body temperature depends on the relative concentrations or rates of release of the monoamines, noradrenaline (NA) and 5-hydroxytryptamine (5-HT). The evidence for this hypothesis is based primarily on the effect on body temperature of injections of these compounds into the lateral ventricle or hypothalamus of a variety of animals. The amounts of injected monoamines used in these studies are, in nearly all cases, very large compared with the concentrations of endogenous amines in the hypothalamus, the levels of which are less than 1 $\mu\text{g/g}$ (Amin, Crawford & Gaddum, 1954; Vogt, 1954; Pscheidt, Morpurgo & Himwich, 1964), and there is considerable species variation in the effects of different amines.

Another approach to this problem is the alteration in the absolute or relative concentrations of the naturally occurring amines in the anterior hypothalamus by enzyme inhibition.

Injection of 0.1–1.0 mg of tranylcypromine into the cerebral ventricles caused an increase in the rectal temperature of cats and dogs, but not of rabbits (Feldberg & Lotti, 1967a; Feldberg, Hellon & Lotti, 1967), and doses of 0.03–0.1 mg caused hypothermia in the rat (Feldberg & Lotti, 1967b). Intraperitoneal injection of tranylcypromine (10 mg/kg) caused a rise in temperature in the dog (Feldberg & Lotti, 1967a).

In cats anaesthetized with pentobarbitone, the effluent from the third ventricle perfused with artificial cerebrospinal fluid was found to contain small amounts of

5-HT (Feldberg & Myers, 1965 ; El Hawary, Feldberg & Lotti, 1967). When tranlylcypromine was added to the perfusion fluid, the output of 5-HT increased and was accompanied by transient shivering and a rise in rectal temperature (El Hawary *et al.*, 1967).

In cats and dogs, 5-HT injected into the hypothalamus raises body temperature (Feldberg & Myers, 1964a, b, 1965 ; Feldberg *et al.*, 1967) and in both species 5-HT, but not NA, is a substrate for brain monoamine oxidase (MAO) (Vogt, 1959 ; Spector, Shore & Brodie, 1960 ; Spector, 1963 ; Pscheidt *et al.*, 1964). Feldberg *et al.* (1967) have therefore suggested that monoamine oxidase inhibition in the hypothalamus by tranlylcypromine would lead to potentiation and prolongation of the action of released 5-HT. Feldberg & Lotti (1967a) reported that intraventricular injection of tranlylcypromine had no effect in the rabbit. This could be interpreted as signifying that the absolute concentrations of both 5-HT and NA were increased by monoamine oxidase inhibition, while their relative concentrations remained steady, with no change in resting central temperature.

In the present experiments, the acute effects of tranlylcypromine on resting temperature have been examined.

Methods

Eleven experiments were performed on eight conscious female chinchilla rabbits weighing 2.0–2.5 kg.

Hypothalamic and rectal temperatures were measured with thermistors, and continuously recorded on an ultraviolet recorder (S.E. 2005). At least one week before the experiment, a stereotactic head plate, of the type described by Monnier & Gangloff (1961), was affixed to the animal's skull under pentobarbitone anaesthesia. The hypothalamic thermistor, mounted on the end of a needle (O.D. 0.5 mm), was positioned, using this apparatus, in the anterior hypothalamus.

Each animal was given tranlylcypromine sulphate (Smith, Kline & French Laboratories Ltd.), dissolved in sterile saline (20 mg/ml), either by intravenous injection of 20 mg/kg or by intraventricular injection of 5–10 mg. The effect of the injection on resting temperature was observed for 50 min.

In two rabbits the sympathetic nerve supply to one ear was cut by the method of Feldberg (1926), in which the stellate and superior cervical ganglia were removed. These animals were allowed to recover for 3–4 days, and the absence of sympathetic innervation confirmed by the lack of a vasoconstrictor response on the operated side to the intravenous injection of 1 μ g bacterial pyrogen (E pyrogen, Organon Labs. Ltd.). At least 2 days later the tranlylcypromine experiment was then carried out in the manner described ; in both cases the drug was injected intravenously. Skin temperature on each ear was measured with two STC M53 (5,000 Ω at 20° C) disc thermistors, attached with adhesive plaster to a shaved area of the ear midway between the central ear artery and the marginal vein.

Results

Effects of intravenous tranlylcypromine on resting temperature

The effects of intravenous tranlylcypromine are shown in Fig. 1, which shows the mean hypothalamic and rectal temperature changes in this series. For each rabbit

the hypothalamic or rectal temperatures at the time of the tranylcypromine injection (t_0) is taken as zero. This value was subtracted from temperatures at 10 min intervals before and after the start of the infusion, to give the temperature change at each point in time. The vertical lines indicate one standard error above and below the mean. It is clear that the pre-injection temperatures are steady, about values which do not differ significantly from t_0 . After the tranylcypromine injection, however, there is a rapid rise of both rectal and hypothalamic temperatures, which go up by a mean of 0.33° and 0.36° respectively within the first 10 min after the injection. Thereafter the rectal temperature reached a peak at 45–50 min (0.58° C above the t_0 value) and the hypothalamic temperature rose by 0.67° C during the same period.

Effects of intraventricular tranylcypromine on resting temperature

Four injections of tranylcypromine (5 mg and 10 mg in rabbit T_5 in one experiment, and 7.5 mg and 10 mg in rabbit T_4 in another) all caused a fall in rectal and hypothalamic temperature after a latent period of 1–2 min. The fall in temperature

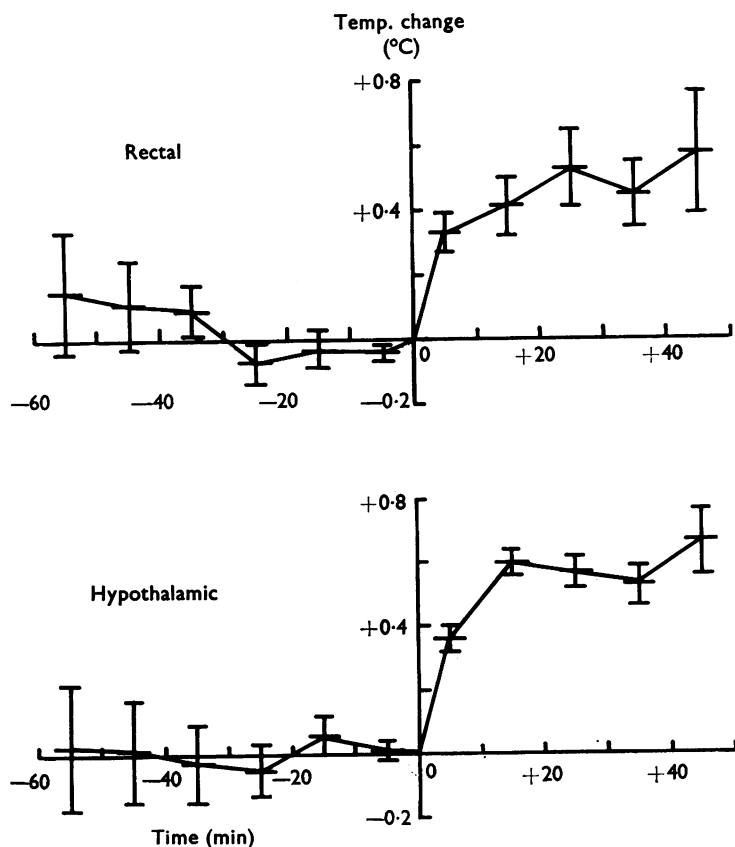


FIG. 1. Effect of intravenous tranylcypromine (20 mg/kg) on rectal and hypothalamic temperature. Ordinate: deviation from the temperature at $t=0$, in $^\circ$ C. Abscissa: time in minutes before and after the tranylcypromine injection. The means and standard errors are shown.

ranged from 0.3° to 0.6° C, and was maximal 10–15 min after injection. Temperatures returned towards their control values in 20–25 min (Fig. 2).

In all these experiments a control injection of 0.2–0.4 ml of normal saline was made, at least 10 min before the first injection of tranlycypromine. None of the saline injections caused any change in either rectal or hypothalamic temperatures, except for the very transient (less than 2 min) dip in the hypothalamic temperature record produced by the injection of the saline at room temperature. This short-lived drop in hypothalamic temperature was also seen in those experiments in which the tranlycypromine solution was injected.

Skin temperature responses to intravenous tranlycypromine

The result of one experiment of this type is shown in Fig. 3. This shows the temperature responses of both ears, one of which has been sympathectomized, to an intravenous injection of tranlycypromine 25 mg/kg at time 0. There is a rapid fall in ear temperature, which is greater on the sympathectomized than on the control ear, such that the temperature at 20 min is 6.25° C lower than t_0 on the sympathectomized ear, and 4.0° C lower than t_0 on the control ear. A similar result was obtained in another animal.

Discussion

Intravenous tranlycypromine

Intravenous tranlycypromine (20 mg/kg body weight) causes a rise in body temperature which appears to be due, at least in part, to cutaneous vasoconstriction. This vasoconstriction is augmented by sympathectomy. This implies that the effect is peripheral, and not central. It could be explained in one of two ways. First, it could represent a direct effect of tranlycypromine on the vessel wall. Tranlycypromine has a direct action on peripheral tissues such as the cat's nictitating membrane (Tsai & Fleming, 1965) or the fundus strip of the rat's stomach (El Hawary *et al.*, 1967). A second possibility is that the MAO inhibition may increase the catecholamine concentration in the blood, and that this is the cause of the cutaneous vasoconstriction; this is greater on the sympathectomized side because of the increased sensitivity of the denervated vessels to the effect of the catecholamines. Tranlycypromine has been shown to inhibit plasma MAO activity

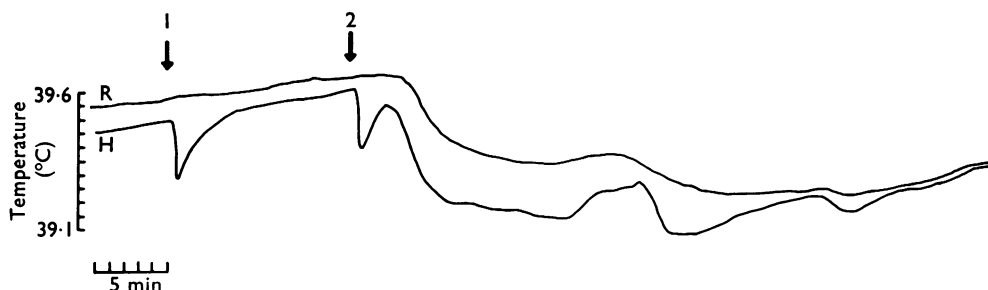


FIG. 2. Effect of intraventricular tranlycypromine on temperature. R, Rectal temperature; H, hypothalamic temperature. 1, Injection of 0.2 ml normal saline; 2, injection of 7.5 mg tranlycypromine (see text).

(Kobayashi, 1966) and because, in rabbits, oxidative deamination is the main catabolic pathway, at least in cardiac tissue and brain (Pletscher, Goschke, Gey & Tholen, 1961; Goldberg & Shideman, 1962; Spector, 1963), it is possible that tranlycypromine caused an increase in the circulating catecholamine concentration, although this was not measured. It is not possible, on the basis of these results, to decide which of these two possible mechanisms is operative.

Whether the cutaneous vasoconstriction was the sole cause of the rise in core temperature cannot be definitely established from these results. The time course of the changes in cutaneous flow and core temperatures in the present experiment are very similar, which would suggest that the ear skin vasoconstriction contributed at least in part to the hyperthermic response to intravenous tranlycypromine.

Shellenberger & Elder (1967) have reported experiments in which the intravenous injection of the MAO inhibitor pargyline produced an abrupt rise in temperature of about 1.0°C in 1–1.5 h in the conscious rabbit. This was associated with an increase in the brainstem levels of catecholamines of 40–50% and of 5-HT of 100%, both at 2 h. This was interpreted as supporting the hypothesis that the disproportionate increase in 5-HT in the brain stem was the cause of the temperature rise, and that these findings were consistent with the suggestion that temperature regulation results from a balance between the hyperthermic effects of 5-HT and the hypothermic effect of NA in the hypothalamus. This suggestion is incon-

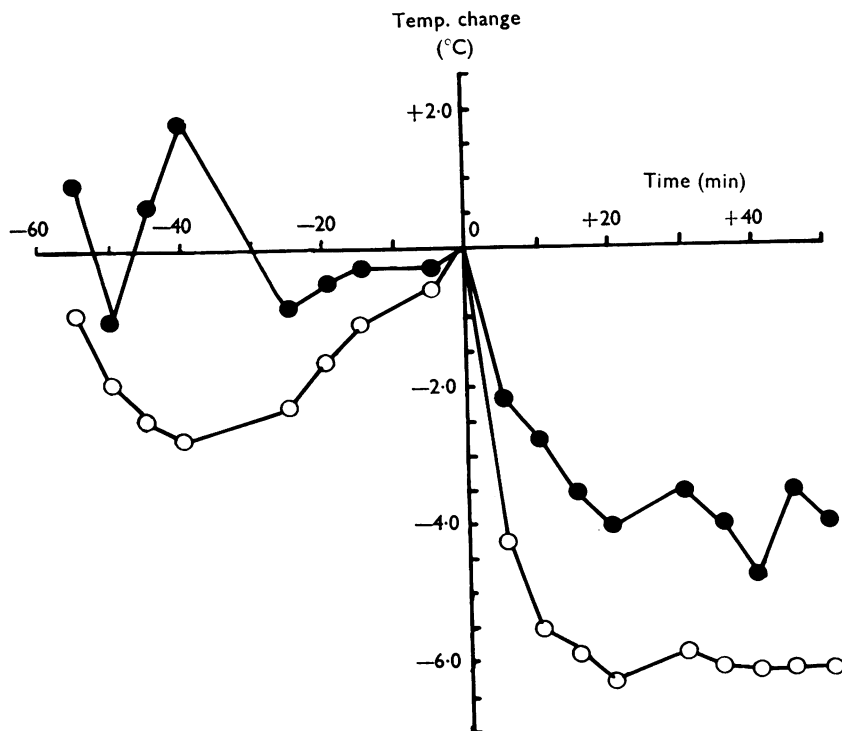


FIG. 3. Effect of the intravenous injection of tranlycypromine 20 mg/kg, at $t=0$, on skin temperature of the two ears, one of which was previously sympathectomized. ●—●, Control ear; ○—○, sympathectomized ear. Ordinate: Temperature change from the temperature at $t=0$, in $^{\circ}\text{C}$. Abscissa: time in minutes before and after the injection.

sistent with the findings of Cooper, Cranston & Honour (1965), who demonstrated a small hypothermic action of 5-HT when injected into the brain. Also, as has been suggested by the present study, the acute effects of an intravenous injection of a MAO inhibitor may not be mediated via a central mechanism at all, and the change in central monoamine concentration may be an incidental finding.

Feldberg & Lotti (1967a) found that the intraperitoneal injection of tranlycypromine (10 mg/kg) had no effect on rectal temperature in the rabbit. The difference between their findings and those reported here may reflect not only the difference in total dose used, but also the rate at which the drug is presented to peripheral sites of action, because this would be much more rapid after intravenous than after intraperitoneal injection.

Intraventricular tranlycypromine

Tranlycypromine injected into the lateral cerebral ventricle of the conscious rabbit causes a transient fall of temperature. This is the opposite effect to that produced by the drug when administered intravenously, and cannot therefore be explained on the basis of absorption of the tranlycypromine from the cerebrospinal fluid into the systemic circulation. The main action of the drug must therefore be on a central site. Intraventricular or intrahypothalamic 5-HT causes a similar transient fall in body temperature, so it is tempting to suggest that there is a rapid and selective augmentation of the hypothalamic 5-HT level by locally injected tranlycypromine, which causes the rectal temperature to fall. This is consistent with the report (Pscheidt *et al.*, 1964) that in a variety of animal species studied, including the rabbit, the increase in 5-HT in the brain produced by MAO inhibition tended to precede the increase in NA concentration.

There is a conflict with the results of Feldberg & Lotti (1967a), who found no change in rectal temperature after the intraventricular injection of 1 mg of tranlycypromine in the rabbit. The difference may be due to the fact that in the present experiments the dose of tranlycypromine was 5–10 times greater.

The present findings indicate that the amine oxidase inhibitor, tranlycypromine, can cause temperature changes in opposite directions in the rabbit, depending on the route of administration. The effects of intravenous injection are mediated, at least in part, by a peripheral action.

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(Received September 2, 1969)