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Effect of desipramine injected intracerebrally in normal or reserpinized rats

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Desipramine, 7·5–30 μg in 1 μl, injected under stereotaxic control into the brain of rats elicits a moderate hyperthermic response. This effect is more marked in animals made hypothermic by a previous treatment with reserpine. The response is not specific for any one of the six brain areas investigated (anterior part of the hypothalamus; nucleus rhomboideus thalami; third ventricle; posterior part of the hypothalamus; lateral part of the area amygdaloidea basalis; and lobus frontalis).

DESIPRAMINE given to animals made hypothermic by a previous administration of reserpine, induces a rapid and sustained increase of body temperature (Garattini & Jori, 1967). This effect requires the integrity of the central nervous system (Bernardi, Paglialunga & Jori, 1967). Since Bernardi, Jori & others (1966) showed that desipramine injected intracerebrally in reserpinized rats also elicits a hyperthermic reaction, the effect of desipramine injected by a stereotaxic technique into specific parts of the rat brain has been examined.

Experimental

Female Sprague Dawley rats of the average weight of 240 ± 10 g (brain weight 1·79 ± 1 g) were used. Under a light ether anaesthesia, microinjections of desipramine were made in different parts of the rat brain using a stereotaxic apparatus (C. H. Stoelting) with an adaptator to place a Hamilton 701 LT microsyringe with a cemented needle.

All operations were made at the same time in the morning. The average duration of an operation was 8 ± 1 min.

The microinjections were made into the nucleus rhomboideus thalami; anterior part of hypothalamus; posterior part of hypothalamus; third ventricle; lobus frontalis, and area amygdaloidea basalis pars lateralis.

The co-ordinates of these centres were calculated according to de Groot (1959) with the modification that the head of the rat was in the horizontal plane, and therefore the "O" point was in coincidence with the lambda point.

The volume of the microinjection was always 1 μl; pyrogen-free distilled water was used as a control. The pH of different concentrations of desipramine and water was the same (6·4 ± 0·05). After the operation, the animals were kept in individual Makrolon cages at 20° and a relative humidity of 60%. The body temperature was recorded with an automatic device (Jori & Paglialunga, 1966).

At the end of each experiment, the rats were decapitated and the brains were sectioned to check the site of the microinjection.

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Results

Table 1 summarizes the results obtained when desipramine was injected by stereotaxic technique into six different areas of the brains of normal rats. It is evident that a rise of body temperature, still present at 4–6 hr occurred after the injection of desipramine into the anterior part of the hypothalamus (AH), in the nucleus rhomboideus thalami (RH), in the third ventricle (V), and in the posterior part of the hypothalamus (PH).

TABLE 1. EFFECT OF DESIPRAMINE (DMI) ON BODY TEMPERATURE, AFTER MICRO-INJECTIONS IN DIFFERENT AREAS OF THE BRAIN OF NORMAL RATS

No. of rats	Area*	Treatment	Body temperature changes (°C ± s.e.) after hr			
			1	2	4	6
5	AH	Water	−0·1	−0·1 ± 0·1	−0·1 ± 0·1	−0·2
12	AH	DMI	+0·7	+0·8 ± 0·2	+1·0 ± 0·2	+0·8
5	RH	Water	−0·9	−0·4 ± 0·1	−0·6 ± 0·1	−0·6
5	RH	DMI	+0·3	+0·8 ± 0·1	+0·9 ± 0·1	+0·4
7	V	Water	−0·5	−0·2 ± 0·1	−0·2 ± 0·1	−0·3
4	V	DMI	+1·0	+1·3 ± 0·1	+1·3 ± 0·2	+0·8
4	PH	Water	−0·9	−0·4 ± 0·1	−0·5 ± 0·1	−0·4
5	PH	DMI	+0·3	+1·0 ± 0·2	+0·3 ± 0·1	0·0
4	LF	Water	−0·1	−0·1 ± 0·1	−0·1 ± 0·1	−0·1
5	LF	DMI	0·0	+0·2 ± 0·1	−0·2 ± 0·1	−0·2
4	ABL	Water	−0·6	−0·5 ± 0·1	−0·4 ± 0·1	−0·3
4	ABL	DMI	−0·2	−0·1 ± 0·1	+0·1 ± 0·1	0·0

See text.
DMI was given at the dose of 7·5 μg/brain in all the areas, except in V (30 μg/brain).

Desipramine (7·5 μg/brain) was without effect in the lobus frontalis (LF) and in the lateral part of the area amygdaloidea basalis (ABL).

Desipramine was also injected in three different doses in the anterior part of the hypothalamus (AH). Table 2 shows that there is no relation between the dose and the observed increase of body temperature.

TABLE 2. CHANGES IN BODY TEMPERATURE AFTER MICROINJECTIONS OF DESIPRAMINE (DMI) IN DIFFERENT DOSES IN THE ANTERIOR PART OF THE HYPOTHALAMUS OF RATS

No. of rats	Treatment	Dose μg/brain	Maximum increase in body temperature °C ± s.e. after microinjection	
			2 hr	4 hr
6	Water	—	no change	+0·2 ± 0·1
12	DMI	7·5	+0·8 ± 0·2	+1·0 ± 0·2
6	DMI	15·0	+1·1 ± 0·2	+1·2 ± 0·2
6	DMI	30·0	+1·1 ± 0·3	+1·1 ± 0·2

Other experiments were performed in rats reserpinized 16 hr before the injection of desipramine. Only rats showing a body temperature between 28° and 31° were used.

Fig. 1 summarizes the data obtained when desipramine (30 μg/brain) was injected into the six areas of the brains of reserpinized rats. In all cases desipramine elicited a rise of body temperature which was marked; controls injected with water showed a further hypothermic reaction. The

administration of desipramine at lower concentrations (7·5 μg/brain) appeared to be less effective in the three areas tested.

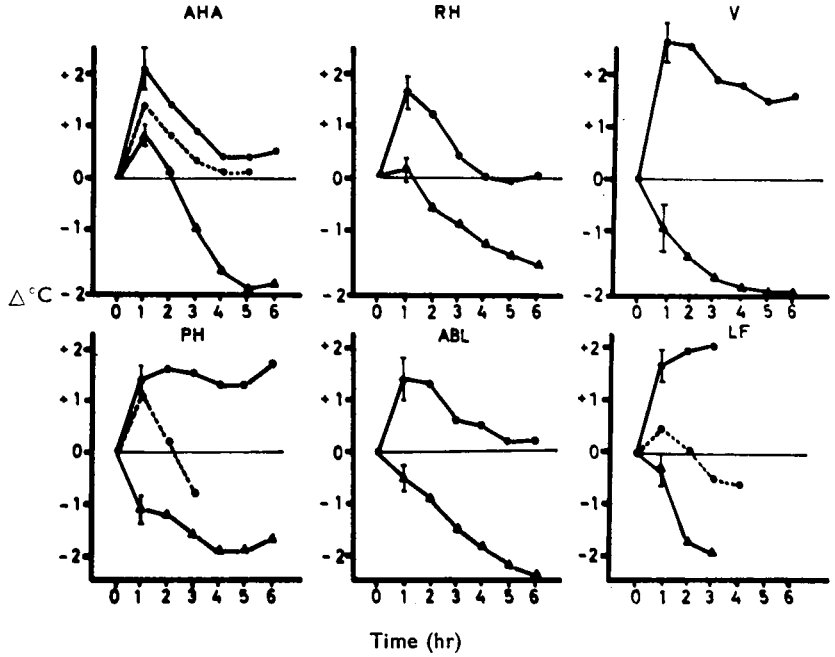

FIG. 1. Rats were injected with reserpine (5 mg/kg i.v.) 16 hr before the experiment and kept at a room temperature of 20°. Rats received a microinjection of distilled water (▲——▲) or desipramine 30 μg/brain (● —— ●) or 7·5 μg/brain (● - - - - ●). Each point represents the average of at least 5 animals. Vertical bars represent the standard errors. AHA (anterior part of hypothalamus); RH (nucleus rhomboideus thalami); V (third ventricle); PH (posterior part of hypothalamus); ABL (lateral part of area amygdaloidea basalis); LF (lobus frontalis).

To analyse the effect of desipramine it was also injected intravenously or into the nucleus rhomboideus thalami.

Table 3 shows that the effect of desipramine in reserpinized rats is more significant by intracerebral than by intravenous administration.

TABLE 3. EFFECT OF DESIPRAMINE (DMI) ON BODY TEMPERATURE OF RESERPINIZED RATS

No. of rats	Administration route	Treatment	Change of body temperature °C ± s.e.
10	Intravenously	Water	−0·23 ± 0·25
10	Intracerebrally (RH)	Water	−0·10 ± 0·19
10	Intravenously	DMI	+0·63 ± 0·15
10	Intracerebrally (RH)	DMI	+2·13 ± 0·34

Rats were injected with reserpine (5 mg/kg i.v.) 15 hr before the experiment and kept at room temperature of 20°. Body temperature was measured 1 hr after the treatment, at the time of the maximum increase observed. Desipramine (30 μg) and water were microinjected intracerebrally in the nucleus rhomboideus thalami (RH) and intravenously in the saphenous vein.

This factorial experiment was statistically analysed as 2 × 2 plan (treatment-route of administration). The interaction was significant ($P < 0·02$).

As the administration route does not modify the effect of the water injection it can be concluded that the effect of desipramine is significantly dependent on the route of administration.

Discussion

Desipramine induces a hyperthermic response when injected into the brain of normal rats by a stereotaxic technique. The effect is evident in the anterior and in the posterior part of the hypothalamus, in the thalamus (nucleus rhomboideus) and in the third ventricle, but not in the lobus frontalis or in the lateral part of the area amygdaloidea basalis. Desipramine injected intraperitoneally or intravenously is without effect on body temperature and only at high doses does it induce an hypothermic effect. When injected into the posterior part of the hypothalamus in a range of doses from 7·5 to 30 μg/brain, desipramine was hyperthermic without there being an evident relation between dose and effect.

The effect of desipramine was more marked in reserpinized animals. Better results were obtained when desipramine was injected into the posterior part of the hypothalamus and in the lobus frontalis.

Even in the thalamus nucleus rhomboideus, where the effect was less marked, the action of desipramine was significantly different from the effect elicited by the same dose of desipramine injected intravenously.

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