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Metabolic effects induced by the interaction of reserpine with desipramine

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The administration of desipramine to reserpinized rats induces an increase of body temperature without any change in blood glucose and liver or muscle glycogen. Instead there is an increase in the utilization of blood glucose after a glucose load and an increase of blood lactic acid. Plasma and brown adipose tissue free fatty acids are also increased. These findings are discussed in relation to the event linking the central stimulation induced by desipramine with the peripheral metabolic changes associated with the increase of body temperature.

THE interaction between imipramine-like drugs and reserpine (Garattini, 1958; Costa, Garattini & Valzelli, 1960; Sulser, Watts & Brodie, 1960) has been the subject of extensive investigations in an attempt to elucidate the mechanism of action of tricyclic antidepressant agents. In particular this laboratory has examined the increase in body temperature induced by desipramine and similar drugs in rats made hypothermic by previously administered reserpine (Garattini & Jori, 1967).

The increase in body temperature is probably of central origin because it can be reproduced by injecting desipramine into the brain (Bernardi, Jori & others, 1966) or even into selected thalamic and hypothalamic areas (Rewerski & Jori, 1968). This effect is abolished by pithing the animals and is decreased relative to the level of spinal transection (Bernardi, Paglialunga & Jori, 1968). The interaction between desipramine and reserpine is not due to inadequate reserpinization (Manara & Garattini, 1967) but is probably mediated by the adrenergic system (Sulser, Bickel & Brodie, 1964; Sulser & Sorowo, 1965). It is well known that tricyclic antidepressant agents inhibit the uptake of noradrenaline peripherally (Hertting, Axelrod & Whitby, 1961; Iversen, 1965; Callingham, 1967) and in the central nervous system (Glowinski & Axelrod, 1964).

Inhibition of noradrenaline uptake leads to an increased availability of the adrenergic mediator at the adrenergic sites (Sulser, Owens & Dingell, 1967), particularly in reserpinized animals where the stores of catecholamines are depleted, and may be responsible for the potentiation of catecholamines. Consistent with this hypothesis is the finding that the hyperthermic effect of desipramine in reserpinized animals is blocked by inhibitors of noradrenaline synthesis (Jori, Carrara & Garattini, 1966a) and by adrenergic blocking agents (Jori, Paglialunga & Garattini, 1966b).

The mechanisms which presumably link the effect of desipramine in the central nervous system to the peripheral metabolic events responsible for the increase in body temperature have now been investigated.

Experimental

MATERIALS AND METHODS

Female Sprague-Dawley rats, 150 $\pm$ 10 g, were injected intravenously with reserpine (5 mg/kg) 16 hr before the experiments. After which the

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animals were kept at 20° with a relative humidity of 56%. At the beginning of the experiments body temperatures were 28–30°. Blood samples for the glucose tolerance test were obtained from the ophthalmic plexus according to Riley (1960). The rate of glucose disappearance was calculated by the analytical method of Amatuzio, Stutzman & others (1953).

Glucose and lactic acid were measured by the enzymatic methods of Hugget & Nixon (1957) and Scholz, Schmitz & others (1959) respectively. Glycogen was measured by the method of Kemp & Kits von Heijningen (1954) and free fatty acids (FFA) in plasma and in brown adipose tissue were determined according to Dole (1956) with minor modifications.

Results

EFFECT OF DESIPRAMINE ON GLUCOSE AND GLYCOGEN CONCENTRATION

The blood glucose level of fasted reserpinized rats (5 mg/kg i.v.) was not significantly modified by desipramine (7·5 mg/kg i.p.) over 5 hr. However, after a glucose load, desipramine increased the rate of glucose removal from the blood stream, under the same experimental conditions. This is particularly significant considering that reserpine or desipramine, given alone, reduced the rate of glucose disappearance. The effect of desipramine in reserpinized rats was rapid, persisted for at least 2 hr and did not appear to depend upon the body temperature (Table 1). Chlorpromazine, reduced the glucose disappearance in normal and reserpinized rats (Table 1). Liver or muscle glycogen was not affected by desipramine.

TABLE 1. EFFECT OF DESIPRAMINE ON THE RATE OF BLOOD GLUCOSE DISAPPEARANCE IN NORMAL AND RESERPINIZED RATS

No. of rats	Treatment	Time between treatment and glucose administration (min)	Glucose utilization (rate of removal %/min ± s.e.)	Body temperature change °C ± s.e.
15	Saline	—	7·6 ± 0·4	—
15	Desipramine	15	3·8 ± 0·4*	—
5	Chlorpromazine	60	3·0 ± 0·6*	−1·0 ± 0·2
27	Reserpine + saline	—	4·3 ± 0·4	—
29	Reserpine + desipramine ..	15	7·5 ± 1**	+0·5 ± 0·06
5	Reserpine + desipramine ..	45	9·7 ± 2**	+2·2 ± 0·5**
5	Reserpine + desipramine ..	90	9·1 ± 1·5**	+4·5 ± 0·8**
5	Reserpine + desipramine ..	120	8·2 ± 0·8**	+6·2 ± 0·5**
5	Reserpine + chlorpromazine	60	3·9 ± 0·6	−0·2 ± 0·1

Desipramine (7·5 mg/kg i.p.), chlorpromazine (5 mg/kg i.p.) or saline were given 16 hr after reserpine (5 mg/kg i.v.). Glucose was injected i.v. at a dose of 1 g/kg.
Body temperature was measured before glucose load.
Rate of removal represents the rate of fall of glucose level per min as % of the increase above the fasting level.
$P < 0.01$ in respect to controls (*) or reserpinized rats (**).

EFFECT OF DESIPRAMINE ON THE LEVEL OF LACTIC ACID IN BLOOD

The effect of desipramine, and chlorpromazine, on blood lactic acid levels of normal and reserpinized rats treated with saline or glucose, is summarized in Table 2. Blood levels of lactic acid were much lower in reserpinized animals than in fasted control rats, but were increased in both

TABLE 2. EFFECT OF DESIPRAMINE ON BLOOD LACTIC ACID CONCENTRATION OF NORMAL AND RESERPINIZED RATS

No. of rats	Treatment	Time between treatment and saline or glucose (min)	Blood lactic acid mg % ± s.e.
11	Saline	—	20·7 ± 1·1
14	Desipramine + saline	15	10·2 ± 0·8*
5	Chlorpromazine + saline	15	12·2 ± 1·8*
19	Reserpine + saline		6·6 ± 0·4
15	Reserpine + desipramine + saline	15	10·8 ± 0·8*
5	Reserpine + chlorpromazine + saline	15	7·3 ± 0·5
7	Saline + glucose	15	25·8 ± 1·7
6	Desipramine + glucose	15	23·3 ± 3·8
13	Reserpine + glucose		8·7 ± 0·3
9	Reserpine + desipramine + glucose	15	14·9 ± 0·5**
10	Reserpine + desipramine + glucose	45	14·7 ± 1·2*
5	Reserpine + desipramine + glucose	90	14·1 ± 0·8**
10	Reserpine + desipramine + glucose	120	11·2 ± 0·4*

Reserpine (5 mg/kg i.v.) was given 16 hr before desipramine (7·5 mg/kg i.p.) or chlorpromazine (5 mg kg i.p.).
Glucose (1 g kg i.v.) was given 20 min before lactic acid determinations.
Experiments were made in 16 hr fasted rats, at 20°.
* $P < 0.05$; ** $P < 0.01$ relative to controls of each group.

groups after glucose administration. Desipramine enhanced the level of blood lactic acid in reserpinized rats treated with saline or glucose. In normal rats, desipramine decreased the blood lactic acid of saline-treated groups but had no effect on glucose-loaded groups. The effect of chlorpromazine was similar to desipramine in that it lowered blood lactic acid levels in normal rats but it was without effect in reserpinized animals.

EFFECT OF DESIPRAMINE ON FFA

Desipramine increased the level of plasma FFA by about 30% in reserpinized rats for at least 1 hr after its administration. Since the intrascapular brown adipose tissue is important for maintenance of body temperature (Donhoffer, Sardy & Szegvàri, 1964) the level of FFA in this tissue in reserpinized rats treated with desipramine or saline was investigated. It is evident from Table 3 that desipramine, although ineffective in normal rats

TABLE 3. EFFECT OF DESIPRAMINE ON THE BROWN ADIPOSE TISSUE FFA OF RESERPINIZED RATS

No. of rats	Treatment	Time between desipramine, chlorpromazine or saline and determination (min)	Brown adipose tissue FFA (μ-equiv./g) ± s.e.	Temperature difference °C ± s.e.	
				Subcutaneous	Rectal
9	Reserpine + saline	20	5 ± 0·4	—	—
8	Reserpine + saline	180	5·8 ± 0·4	−1·1 ± 0·2	−0·5 ± 0·2
9	Reserpine + desipramine	10	6·8 ± 0·7	+0·3 ± 0·1	−0·9 ± 0·1
9	Reserpine + desipramine	20	7·9 ± 0·5*	+0·7 ± 0·2	+1·1 ± 0·1
9	Reserpine + desipramine	40	7·7 ± 0·6*	+2·1 ± 0·5	+2·3 ± 0·5
9	Reserpine + desipramine	180	7·8 ± 0·8*	+4·3 ± 0·6	+4·7 ± 0·4
5	Reserpine + chlorpromazine	40	5·8 ± 0·25	+0·5 ± 0·4	+1·0 ± 0·4
5	Saline	40	9·2 ± 0·3	—	−0·3 ± 0·2
5	Desipramine	40	9·8 ± 0·6	—	−1·2 ± 0·2
5	Chlorpromazine	40	11·5 ± 0·7*	—	−2·4 ± 0·3

Subcutaneous temperature was measured over the intrascapular brown adipose tissue.
Reserpine (5 mg/kg i.v.) was given 16 hr before desipramine (7·5 mg/kg i.p.), chlorpromazine (5 mg/kg i.p or saline. Experiments were made at 20°C.
* $P < 0.01$ versus saline groups.

increased FFA in the brown adipose tissue or reserpinized animals. On the other hand, chlorpromazine increased the FFA in brown adipose tissue, in normal, but not in reserpinized rats.

Discussion

The results indicate that when desipramine is given to hypothermic reserpinized rats, metabolic changes occur that are associated with the increase in body temperature. Although no changes could be obtained in the level of blood glucose or of liver or muscle glycogen, it was observed that desipramine increased the utilization of glucose. Evidence for this effect was obtained by measuring the rate of removal of glucose in blood after a glucose load and by determining the levels of blood lactic acid. The increase of rate of glucose removal and the rise of blood lactic acid levels induced by desipramine in reserpinized animals are particularly significant considering that desipramine has opposite effects on the same parameters in normal rats. Chlorpromazine did not increase body temperature in reserpinized rats nor did it enhance glucose utilization or raise blood lactic acid levels. Desipramine also increased the level of FFA in plasma as well as in the intrascapular brown adipose tissue.

These biochemical manifestations of desipramine could be interpreted as causing an increase in energy metabolism with a resultant increase in body temperature thus allowing reserpinized animals to recover from the hypothermic condition.

Lipolysis in brown adipose tissue appears to be important in restoring body temperature after hibernation (Joel, 1965), and in normal rats for the maintenance of body temperature in emergency conditions (Donhoffer & others, 1964; Imai, Horwitz & Smith, 1968). The hydrolysis of triglycerides would serve the function of producing heat *in situ* (Joel, 1965) where are located large vessels important also for the brain circulation. It is difficult, however, to establish to what extent the observed biochemical changes precede or follow the increase of body temperature induced by desipramine in reserpinized animals. It is, however, significant that at 15–20 min after desipramine administration, the increases in glucose removal, blood lactic acid levels and plasma and brown adipose tissue FFA are accompanied by only a modest rise of blood temperature as measured in the subcutaneous tissue or in the rectal cavity.

Assuming that these biochemical changes are an important event in the interaction between desipramine and reserpine it remains to be established which hormonal or neurohormonal pattern links the central stimulation to the observed peripheral effects.

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