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Further effects of imipramine and its desmethyl derivative on the hypothermia induced by reserpine

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Imipramine and desipramine injected intracerebrally increase the temperature of fully reserpinised rats. Desipramine is more effective than imipramine in this. The effect of imipramine seems to be independent of the formation of desipramine in the brain. That imipramine, injected intraperitoneally, leads to an accumulation of brain desipramine has been confirmed.

IT is well known that imipramine-like antidepressant drugs prevent or counteract some of the biochemical, pharmacological and behavioural effects induced by reserpine or tetrabenazine. These include prolongation of barbiturate narcosis (Domenjoz & Theobald, 1959), bradycardia (Costa, Garattini & Valzelli, 1960), blepharospasm (Garattini, 1959; Costa & others, 1960; Sulser, Bickel & Brodie, 1961), gastric erosions (Garattini, Giachetti, Jori, Pieri & Valzelli, 1962; Metysova, Metys & Votava, 1964), and depletion of adrenal (Zbinden, 1962) but not brain catecholamines (Garattini & Valzelli, 1962; Pletscher & Gey, 1962; Sulser, Watts & Brodie, 1962). We have paid particular attention to the interaction between imipramine-like antidepressant drugs and reserpine, using as an end-point the change of body temperature. Thus it has been shown that imipramine potentiates the initial hyperthermia induced by reserpine (Jori, Paglialunga & Garattini, unpublished) and antagonizes the subsequent hypothermia (Garattini & others, 1962) at dose levels and times which do not modify the behavioural syndrome and the depletion of amines induced by reserpine (Garattini & others, 1962). However, the prolongation of the reserpine hyperthermia occurring in desipramine-treated rats was recently correlated with a decrease of the rate of noradrenaline release (Manara, Sestini, Algeri & Garattini, 1966). When imipramine-like drugs are given to fully reserpinised animals there is a reproducible and gradual increase of body temperature (Askew, 1963; Jori, Carrara, Paglialunga & Garattini, 1965; Morpurgo & Theobald, 1965). This effect could be considered specific because imipramine-like agents show, if anything, a small decrease of body temperature in normal animals and do not affect hypothermia induced by other agents such as chlorpromazine, meprobamate, α-methyldopa or 5-hydroxytryptamine (Garattini & others, 1962; Garattini & Valzelli, 1962).

A possible explanation may be found in the work of Axelrod and of Brodie and their colleagues (Axelrod, Whitby & Hertting, 1961; Brodie, Dick, Kielholz, Pöldinger & Theobald, 1961; Glowinski & Axelrod, 1964); and also of Iversen (1965). These authors have shown that imipramine-like drugs prevent the uptake of catecholamines, thereby enhancing their pharmacological effects (Sigg, 1959; Kaumann, Coussio & Izquierdo, 1962; Thoenen, Hürlimann & Haefely, 1964).

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We have also shown that imipramine-like drugs potentiate the hyperthermia induced by catecholamines either exogenously supplied by intravenous infusion (Jori, Paglialunga & Garattini, unpublished; Jori & Garattini, 1965) or endogenously released from storage sites by reserpine. Furthermore, unpublished results (P. Morselli) show that noradrenaline given intracerebrally acts like imipramine in increasing body temperature of fully reserpinised animals.

Gillette, Dingell, Sulser, Kuntzman & Brodie (1961) concluded that imipramine was not active by itself in stimulating tetrabenazine sedated animals, but that the effect was due to the formation of a metabolite, desipramine (DMI), which accumulates in the brain (Gillette & others, 1961; Dingell, Sulser & Gillette, 1964). Desipramine is more active than imipramine in some experimental conditions including the antagonism to reserpine-induced hypothermia (Garattini & others, 1962).

We now show that imipramine and more markedly desipramine counteract the hypothermic effect of reserpine, and that this effect is probably centrally mediated. Other data indicate that in this respect imipramine may act independently from desipramine, and therefore that formation of this metabolite is no prerequisite for this activity.

Experimental

MATERIALS AND METHODS

Female Sprague-Dawley rats, of mean weight 150 g, were kept in Makrolon cages at 22° and a relative humidity of 60%. Groups of at least 6 animals each were used.

Imipramine and desipramine were suspended as the hydrochloride in liquid paraffin and injected intracerebrally in a volume of 10 μl according to the technique described by Valzelli (1964). Reserpine (commercial ampoules) was given intraperitoneally at a dose of 2·5 or 5 mg/kg. Corresponding controls received only reserpine solvent and liquid paraffin respectively. Rectal temperature was measured with an electrical thermometer. Imipramine and desipramine in whole brain were determined according to the method of Dingell & others (1964).

Results

Fig. 1 illustrates the decrease of body temperature induced by reserpine as a function of time. When desipramine was given intracerebrally either together with or 4 or 16 hr after reserpine at a dose of 100 μg, there was an elevation of body temperature lasting for several hours, whereas no effect on the behavioural syndrome induced by reserpine was seen. The controls showed that an intracerebral injection of liquid paraffin does not affect the lowering of body temperature induced by reserpine. Furthermore, desipramine given intracerebrally to rats treated intraperitoneally with the reserpine solvent did not increase body temperature.

In Table 1 a comparison of the action of imipramine and desipramine on reserpine hypothermia is made. A clear effect is already present with

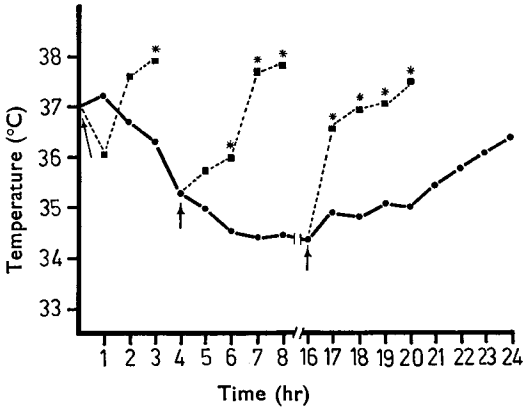

FIG. 1. Body temperature of rats treated with reserpine (2·5 mg/kg i.p. (—●—). At the arrows desipramine (100 μg) was injected intracerebrally (- - ■ - -). ($P<0{\cdot}01$ *).

25 μg of desipramine whereas it is necessary to give 100 μg of imipramine to obtain a well defined effect. Furthermore, with imipramine there was always an initial hypothermia, and antagonism toward reserpine hypothermia was only observed after a latent period of about 2–3 hr. Five hr after the administration of desipramine or imipramine their levels in brain were measured. The results are similar for the two drugs. On the average only about 10% of the quantity injected was recovered. There was no formation of desipramine in brain after administration of imipramine even at the largest dose. (In separate experiments not reported here in detail it was demonstrated that no desipramine could be detected 15, 30 or 60 min after imipramine was given intracerebrally to normal or reserpinised animals.)

Other experiments were made to verify if the concentrations of desipramine or imipramine detected in brain after intracerebral injection were similar to those found after an intraperitoneal administration of doses

TABLE 1. IMIPRAMINE AND DESIPRAMINE BRAIN CONCENTRATION AND EFFECT OF THESE DRUGS INJECTED INTRACEREBRALLY ON RESERPINE INDUCED HYPOTHERMIA IN GROUPS OF 4 RATS

Drug μg/rat		Difference in temperature (° C) between control and treated rats — Hr after treatment 1	2	3	4	5	Total increase °C	Brain conc. after 5 hr (μg)
Desipramine (intracerebrally)	15	0·1	0·6	0·9	0·4	0·8	2·8 ± 0·1	1·2 ± 0·1
	25	0·7	1·6	1·8	1·6	1·8	7·5 ± 0·4	3·9 ± 0·2
	50	1·0	1·9	2·3	1·9	2·3	9·5 ± 0·3	5·7 ± 0·5
	100	1·4	1·8	1·9	2·0	2·0	9·1 ± 0·4	8·5 ± 0·2
	150	1·2	1·3	2·7	2·2	2·6	10·0 ± 0·5	11·3 ± 1·5
Imipramine (intracerebrally)	15	0·2	0·8	0·4	0·5	0·3	2·2 ± 0·5	—
	25	−0·3	−0·1	0·2	0·9	0·6	1·3 ± 0·2	3·7 ± 0·6
	50	−0·6	−0·1	0·1	0·9	0·5	0·8 ± 0·1	8·4 ± 3·5
	100	−0·5	0·2	0·8	2·5	2·6	5·6 ± 0·3	7·2 ± 2·1
	150	−0·7	−0·2	0·3	3·0	3·4	5·8 ± 0·4	12·4 ± 1·7

All animals reserpinised (5 mg/kg i.p.) 16 hr before start of experiment.

known to antagonise reserpine hypothermia. The results, summarised in Table 2, show a good agreement with those in Table 1. Comparing the brain concentration of imipramine or desipramine in normal and reserpinised animals no striking differences were observed. When imipramine was injected intraperitoneally, desipramine accumulated in brain so that at the 5th hr there was at least twice as much desipramine as imipramine.

TABLE 2. THE EFFECTS OF IMIPRAMINE AND DESIPRAMINE ON RESERPINE-INDUCED HYPOTHERMIA WHEN INJECTED INTRAPERITONEALLY AND THEIR CONCENTRATIONS IN THE RAT BRAIN

No. rats	Treatment mg/kg i.p.	Reserpine 5 mg/kg (16 hr before)	Time between saline or drug and death (hr)	Body temp. (° C)	Brain conc. (μg)	
					Imipramine	Desipramine
5	Saline	+	1	28·9 ± 0·2	—	—
5		+	2	29·0 ± 0·1	—	—
5		+	5	29·8 ± 0·32	—	—
10	Imipramine 20	−	1	35·5 ± 0·35	14·7 ± 1·7	6·0 ± 0·6
5		−	2	35·4 ± 0·58	5·6 ± 1·3	6·4 ± 0·5
5		−	5	35·2 ± 3·4	4·0 ± 0·3	7·8 ± 1·2
5		+	1	32·5 ± 1·5	12·9 ± 1·3	3·5 ± 0·5
5		+	2	30·9 ± 1·4	9·6 ± 1·0	4·4 ± 0·9
5		+	5	36·4 ± 0·34	3·5 ± 0·68	8·0 ± 2·1
10	Desipramine 15	−	1	35·7 ± 0·35	—	14·2 ± 1·4
10		−	2	34·3 ± 0·59	—	14·0 ± 0·9
5		−	5	35·4 ± 0·14	—	8·9 ± 1·3
5		+	1	33·2 ± 1·30	—	7·8 ± 0·6
5		+	2	33·6 ± 1·32	—	9·9 ± 1·8
5		+	5	35·6 ± 0·71	—	8·2 ± 0·62

Discussion

An antagonism to the hypothermia induced by reserpine can be demonstrated when imipramine or desipramine is injected intracerebrally, suggesting that the drugs act centrally. This effect is not due to unspecific stimulation because the intracerebral injection of the solvent does not modify the hypothermia induced by reserpine. However, it must be stressed that with our experimental conditions imipramine or desipramine were effective only on body temperature without affecting the reserpine behavioural syndrome with the possible exception of a slight effect on blepharospasm.

When imipramine was given intraperitoneally there was an accumulation of desipramine in the brain. However the intracerebral administration of imipramine never gave concentrations of desipramine higher than 1 μg/brain (limit of sensitivity with the method used). These results are in agreement with previous data showing that liver, but not brain or other tissues, can demethylate imipramine (Dingell & others, 1964). Furthermore, the data obtained suggest that the effect on reserpine hypothermia exerted by imipramine does not seem to be mediated through the formation of desipramine. This direct action of imipramine has been reported for its anticonvulsant (Garattini & others, 1962) and the antioxytremorine (Lévy & Michel-Ber, 1965) effects.

It is possible that desipramine is formed from imipramine but rapidly metabolised or washed out from the brain, but this is unlikely because the half-life of desipramine in brain should be about 10 hr according to the data of Sulser, Bickel & Brodie (1964).

That a rather long latent period is necessary before the effect of imipramine on reserpine hypothermia is observed, suggests the possible formation of a metabolite.

Imipramine and desipramine are still effective in fully reserpinised animals when catecholamines are depleted, which does not detract from the hypothesis that they are acting by potentiating catecholamines. It has been shown that catecholamine synthesis is even increased after reserpine treatment (Brodie & Costa, 1962; Hillarp & Malmfors, 1964).

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