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Interaction between imipramine-like agents and catecholamine-induced hyperthermia

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Imipramine-like drugs potentiate the hyperthermic response obtained by infusion of noradrenaline, adrenaline and isoprenaline. In addition to this effect, desipramine increases the hyperthermic response induced by L-dopa (in monoamine oxidase blocked rats), reserpine (immediately after intravenous injection) and dexamphetamine. On the contrary, other types of hyperthermia, such as the one induced by phenethylamine in monoamine oxidase treated rats, and that by yeast, were not increased by desipramine. These results are discussed in relation to the mechanism of action of antidepressant drugs.

PREVIOUS work has shown that the hypothermia elicited by reserpine is prevented or counteracted by imipramine (Costa, Garattini & Valzelli, 1960), amitriptyline (Vernier, Hanson & Stone, 1962) and their nor-derivatives (Garattini, Giachetti, Jori, Pieri & Valzelli, 1962; Askew, 1963). The mechanism of such an antagonism is not well understood. It was also established that imipramine-like drugs do not change the level of brain 5-hydroxytryptamine (5-HT) and noradrenaline and do not affect

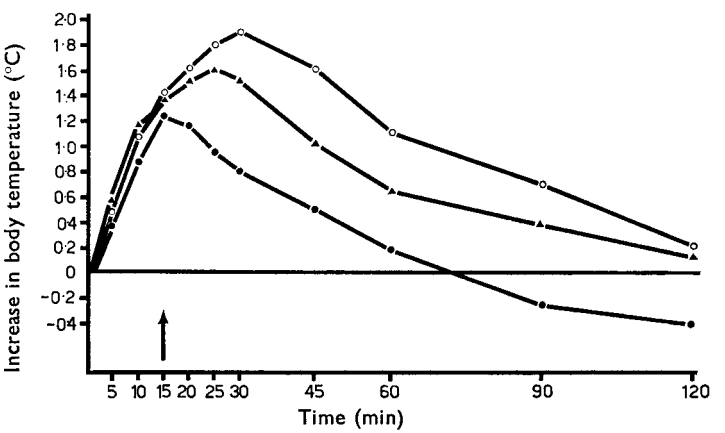

FIG. 1. Increase of body temperature in rats infused with noradrenaline (total dose 60 μg rat in 15 min) at a room temperature of 22°. The infusion was stopped at the arrow. Desipramine and imipramine, 15 mg/kg i.p. were given 1 hr before the infusion. —○— Desipramine + noradrenaline. —▲— Imipramine + noradrenaline. —●—Noradrenaline.

the depletion of these amines induced by a treatment with reserpine (Garattini & others, 1962) or reserpine congeners (Sulser, Watts & Brodie, 1962). Other investigations showed that imipramine and its analogues potentiate the pressor response (Sigg, 1959) and the contraction of the nictitating membrane (Sigg, 1959; Schaeppi, 1960) following the administration of noradrenaline, and the reduction of spleen volume (Thoenen, Huerlimann & Haefely, 1964) following adrenergic nerve stimulation.

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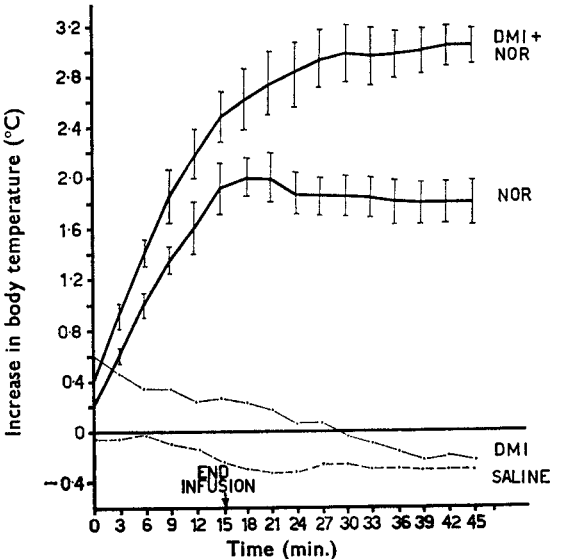

FIG. 2. Increase of body temperature in rats infused with noradrenaline NOR (total dose 60 μg/rat in 15 min) at a room temperature of 30°. The infusion was stopped at the arrow. Desipramine (DMI), 15 mg/kg i.p., was given 1 hr before the infusion.

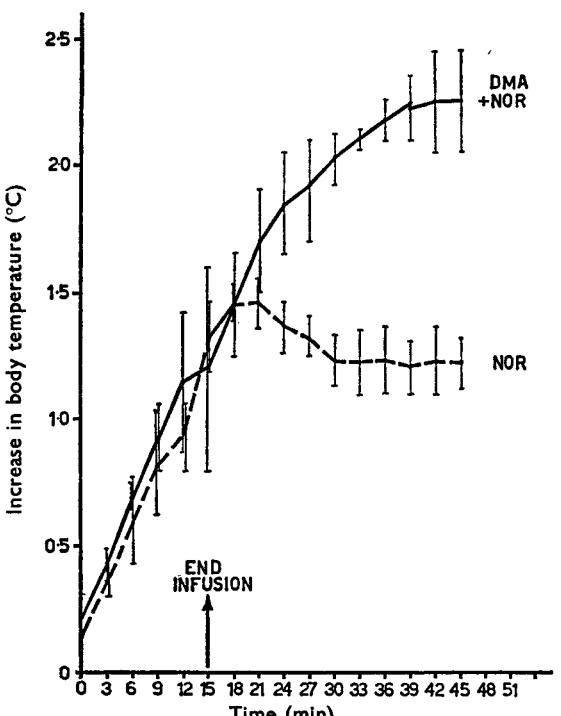

FIG. 3. Increase of body temperature in rats infused with noradrenaline (total dose 60 μg/rat in 15 min) at room temperature of 30°. The infusion was stopped at the arrow. Nortriptyline (DMA), 15 mg/kg i.p., was given 1 hr before the infusion.

Biochemical investigations have demonstrated that imipramine derivatives inhibit the uptake of labelled noradrenaline so that a larger concentration of the amine would probably be available at receptor sites (Hertting, Axelrod, Whitby & Patrick, 1961; Axelrod, Hertting & Potter, 1962; Titus & Spiegel, 1962). These data suggest that imipramine could antagonise the hypothermia induced by reserpine, through a potentiation of the activity of the endogenously formed catecholamines. The results reported in this paper are not in disagreement with this hypothesis.

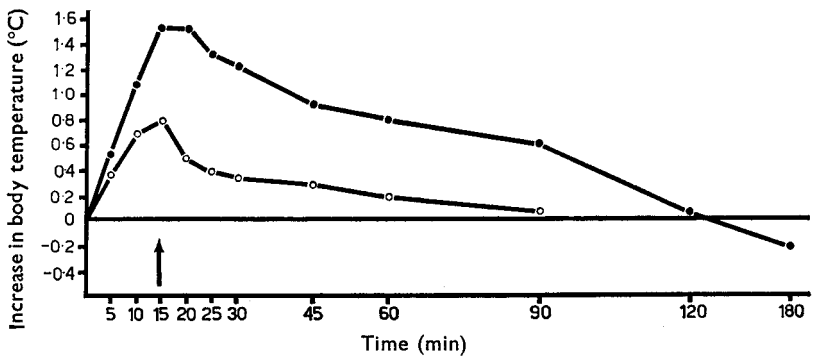

FIG. 4. Increase of body temperature in rats infused with adrenaline (total dose 6 μg/rat in 15 min) at a room temperature of 22°. The infusion was stopped at the arrow. Desipramine, 15 mg/kg i.p., was given 1 hr before the infusion. —●—Desipramine + adrenaline. —○—Adrenaline.

Experimental

MATERIALS AND METHODS

Sprague Dawley rats and Swiss mice were used. Animals were housed in Makrolon cages at a room temperature of 20° and at a relative humidity of 60%. The relatively low temperature was chosen to facilitate the onset of hypothermia in reserpinised animals. During the infusion of noradrenaline into the rat tail vein, with a Braun apparatus at a speed of 0·1 ml/min, the room temperature was elevated to 30° to obtain a significant hyperthermia although the same results were qualitatively obtained at a temperature of 22°. Body temperature was determined by inserting an electrical thermometer into the rectal cavity.

The drugs used and their sources were as follows: L-3,4-dihydroxyphenylalanine (dopa), phenethylamine, iproniazid phosphate (Hoffman-La Roche), dexamphetamine, noradrenaline bitartrate, adrenaline (Recordati), isoprenaline (Biosintex), pheniprazine (Lakeside), reserpine (Ciba), imipramine and desipramine (Geigy), and nortriptyline (Merck, Sharp and Dohme and Pharmacia).

Results

EFFECT ON HYPERTHERMIA INDUCED BY INFUSIONS OF NORADRENALINE

Noradrenaline infused in rats at a concentration of 4 μg/rat/min induced an elevation of body temperature which returned gradually to

normal on termination of the infusion. Animals pretreated with imipramine or desipramine showed a higher rise and, particularly, a more sustained increase of the body temperature (see Fig. 1). Similar results were obtained with desipramine and nortriptyline at a room temperature of 30° (Figs 2, 3).

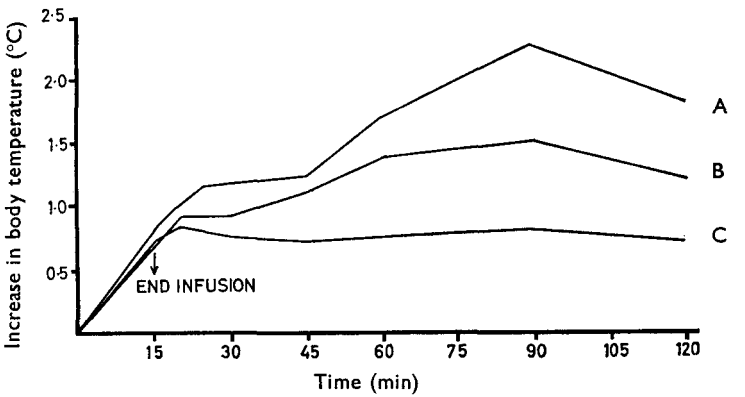

FIG. 5. Increase of body temperature in rats infused with isoprenaline (total dose 600 μg/rat in 15 min) at a room temperature of 22°. The infusion was stopped at the arrow. Desipramine and nortriptyline, 15 mg/kg i.p., were given 1 hr before the infusion. A, desipramine + isoprenaline. B, nortriptyline + isoprenaline. C, saline + isoprenaline.

EFFECT ON HYPERTHERMIA INDUCED BY ADRENALINE

An infusion with adrenaline (0·4 μg/rat/min) produced a hyperthermia which rapidly disappeared after the end of the infusion. Fig. 4 shows that desipramine potentiated and prolonged this effect of adrenaline.

EFFECT ON HYPERTHERMIA INDUCED BY ISOPRENALINE

Isoprenaline infused at the dose of 40 μg/rat/min induced an increase in body temperature lasting for about 2 hr after the end of the infusion. Desipramine and nortriptyline enhanced and prolonged this type of

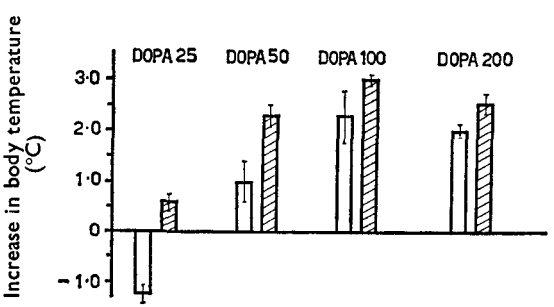

FIG. 6. Increase of body temperature in rats (with a blockade of monoamine oxidase: pheniprazine 10 mg/kg i.p. 16 hr before test) induced by various doses of dopa (25–200 mg/kg i.p.) with (hatched columns) or without (open columns) desipramine 1 hr before at a dose of 7·5 mg/kg. Increase in body temperature was recorded 30 min after administration of dopa.

hyperthermia (see Fig. 5). On the other hand, pretreatment with a monoamine oxidase inhibitor (pheniprazine) or with chlorpromazine (unpublished results from this laboratory) did not potentiate, but rather inhibited, the hyperthermia induced by isoprenaline.

Effect on hyperthermia induced by dopa

In animals with a blockade of monoamine oxidase, dopa induces a hyperthermia which is considered of central origin (Van der Wende & Spoerlein, 1962; Everett, Will & Evans, 1964). In our experiments pheniprazine (10 mg/kg i.p.) was given to mice 16 hr before the test was made. Desipramine was injected intraperitoneally 1 hr before dopa. Under these conditions, there was a clear enhancement of the increase in body temperature over that observed in animals treated only with the monoamine oxidase inhibitor followed by dopa.

The enhancement was evident with doses of dopa which did not induce hyperthermia (see Fig. 6). The effects of larger doses of dopa which in itself induced a hyperthermic action were only prolonged by a pretreatment with desipramine (see Fig. 7).

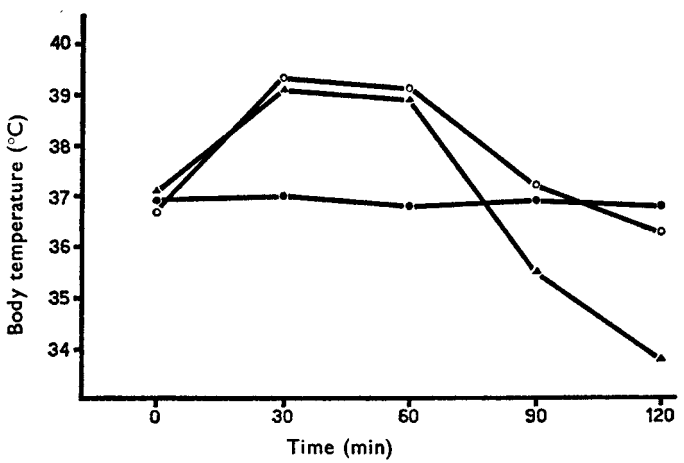

FIG. 7. Increase of body temperature in rats (with a blockade of monoamine oxidase: pheniprazine 10 mg/kg i.p. 16 hr before test) induced by dopa (200 mg/kg i.p.) with or without desipramine 1 hr before at a dose of 15 mg/kg. —●—Desipramine. —○—Desipramine + dopa. ▲ Dopa.

Effect in reserpinised animals

Desipramine raised the body temperature in hypothermic reserpinised mice. The effect of 7·5 mg/kg of desipramine was similar to that elicited by 500 mg/kg of dopa A combination of both drugs resulted in a more prolonged effect (see Fig. 8).

When rats were injected with reserpine it was possible to observe in the first 2 hr an increase in body temperature of about 1·5°, which was more evident and reproducible when the animals were restrained (unpublished results from this laboratory). Desipramine and nortriptyline given before reserpine enhance, and more frequently prolong, this hyperthermia (see Fig. 9).

EFFECT ON OTHER TYPES OF HYPERTHERMIA

To ascertain the significance of this interaction between imipramine-like drugs and catecholamines it was considered of interest to investigate the effect of desipramine on other types of drug-induced hyperthermia. Dexamphetamine showed a clear hyperthermic effect in rats and in mice.

Table 1 summarises data obtained in mice. Desipramine prevented the effect of low doses of dexamphetamine (5 mg/kg) but prolonged the hyperthermia induced by 15 mg/kg. In rats, an inhibition was always observed at the beginning (first hour) followed by a potentiation of the hyperthermic response (see Table 2). These data showed large variations

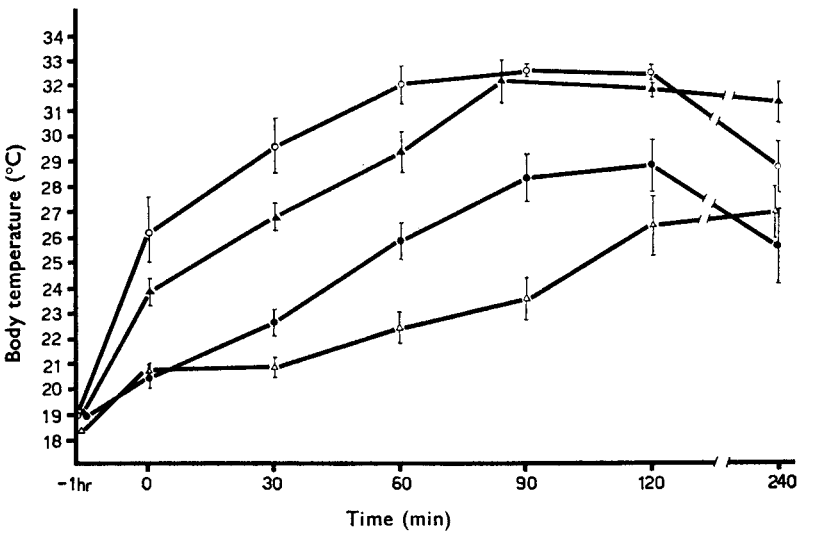

FIG. 8. Increase of body temperature in mice treated 16 hr before the test with reserpine (2·5 mg/kg i.p.) at a room temp. of 20° C. Dopa was given at a dose of 500 mg/kg i.p. and desipramine at a dose of 7·5 mg/kg i.p. —▲—Desipramine + dopa. —○—Desipramine. —▲—Control. —●—Dopa.

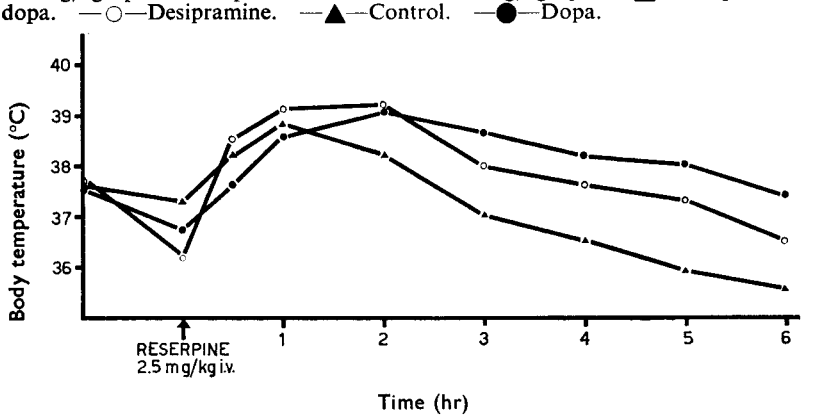

FIG. 9. Effect of desipramine and nortryptiline at a dose of 15 mg/kg i.p. on the hyperthermia induced in rats by an intravenous injection of reserpine (2·5 mg/kg i.v.) at a room temp. of 22° C. —●—Desipramine. —○—Nortryptiline. —▲—Control.

in the different experiments but the trend was similar. The hyperthermia induced by phenethylamine in iproniazid-treated rats was significantly reduced when desipramine was given. Finally the increase of body temperature following a subcutaneous injection of yeast was not affected by desipramine (see Table 3).

Table 4 presents a summary of the effects induced by desipramine on the various types of hyperthermia studied.

TABLE 1. EFFECT OF DESIPRAMINE ON THE HYPERTHERMIA INDUCED BY DEXAMPHETAMINE IN MICE

No. of mice	Treatment	mg/kg i.p.	Body temperature ° C after min				
			−60	0	30	60	90
20	Saline	—					
	Dexamphetamine	5	37·2	36·9	38·5	37·0	36·3
20	Desipramine	7·5					
	Dexamphetamine	5	37·0	35·6	35·5	35·4	35·6
20	Saline	—					
	Dexamphetamine	5	37·2	36·8	39·1	37·3	35·6
10	Nortriptyline	7·5					
	Dexamphetamine	5	37·3	36·8	38·8	36·3	35·7
10	Saline	—					
	Dexamphetamine	15	38·7	37·8	40·0	38·2	38·0
10	Desipramine	7·5					
	Dexamphetamine	15	38·4	37·1	39·5	39·0	39·2
10	Desipramine	7·5	38·4	36·8	36·4	35·9	35·7
5	Saline	—	38·7	37·9	37·8	—	37·4

Dexamphetamine was given at 0 and desipramine 60 min before infusion.
Animals were housed 5 per cage (10 × 20 × 15 cm).

TABLE 2. EFFECT OF DESIPRAMINE ON THE HYPERTHERMIA INDUCED BY DEXMPHETAMINE IN RATS

Treatment	mg/kg	Body temperature ° C after min								
		−60	0	30	60	90	120	240	300	360
Dexamphetamine	15	36·9 ±0·3	36·3 ±0·1	38·4 ±0·2	39·3 ±0·4	39·6 ±0·3	39·0 ±0·2	37·4 ±0·1	37 ±0·2	36·8 ±0·1
Desipramine + dexamphetamine	15	36·9 ±0·3	35·9 ±0·2	37 ±0·4	38 ±0·6	38·9 ±0·5	38·9 ±0·4	39·1 ±0·2	38·7 ±0·1	39·1 ±0·4
Desipramine + dexamphetamine	7·5	36·9 ±0·2	36·2 ±0·1	37·6 ±0·4	38·7 ±0·6	38·9 ±0·3	38·5 ±0·2	38·2 ±0·4	37·8 ±0·4	38·3 ±0·6
Dexamphetamine	15	36·9 ±0·2	37·5 ±0·1	39·4 ±0·2	39·6 ±0·2	38·7 ±0·2	38·7 ±0·2	37·1 ±0·1	37·2 ±0·1	37·5 ±0·1
Desipramine + dexamphetamine	15	36·9 ±0·2	36·7 ±0·2	37·3 ±0·3	38·3 ±0·4	38·5 ±0·4	38·4 ±0·2	38·2 ±0·5	38·4 ±0·5	38·4 ±0·5
Desipramine + dexamphetamine	7·5	37 ±0·1	37·2 ±0·2	38 ±0·4	38·8 ±0·2	39·3 ±0·3	39·1 ±0·3	38·1 ±0·6	38·1 ±0·5	38·2 ±0·6

Desipramine was given 60 min before dexamphetamine.

Discussion and conclusions

The results show that desipramine enhances the hyperthermic effect induced by a number of adrenergic agents. A significant potentiation and prolongation of the body temperature increase was detected when imipramine, or its congeners, was given before an infusion of noradrenaline, adrenaline and isoprenaline. These results are consistent with biochemical findings demonstrating that imipramine reduced the uptake of labelled noradrenaline (Hertting & others, 1961; Axelrod & others, 1962; Titus & Spiegel, 1962). However, with isoprenaline, it is not yet known if there is any uptake and binding.

The hyperthermia occurring shortly after the administration of reserpine seems to be related to a release of catecholamines because we have found it to be inhibited by adrenergic blocking agents (unpublished results). Imipramine and its congeners prolong this hyperthermia and this fact suggests that the previously reported inhibition of the hypothermia induced by reserpine (Garattini & others, 1962) may only be the result of the prolongation of the hyperthermic phase. The present experiments are not in disagreement with the hypothesis that imipramine enhances the effect of reserpine by potentiating endogenous catecholamines which may be released. Similarly the symptomatology described when desipramine is combined with a short-acting reserpine derivative (Ro 4.1284) may be due to a central potentiation of catecholamines in relation to the speed of

TABLE 3. EFFECT OF DESIPRAMINE ON THE HYPERTHERMIA INDUCED BY PHENETHYLAMINE AND YEAST IN RATS

Treatment	mg/kg	Body temperature ° C after, min						
		−60	0	30	60	90	120	150
Phenethylamine	5	37·1±0·3	37·1±0·3	39·3±0·7	39·3±0·9	39·3±0·9	38·7±0·4	37·9±0·3
Desipramine + phenethylamine	15 5	36·9±0·1	36·1±0·3	36·6±0·4	36·7±0·5	37·0±0·6	37·2±0·7	37·2±0·4
Desipramine + phenethylamine	7·5 5	36·8±0·2	36·4±0·1	38·3±0·2	38·6±0·2	38·8±0·2	—	38·5±0·3
		0	5 hr	6 hr	7 hr 30 min	8 hr 30 min		
Yeast	1,500	36·2±0·2	37·9±0·1	37·8±0·2	37·7±0·2	36·9±0·1		
Desipramine + yeast	15 1,500	35·8±0·3	37·5±0·1	36·5±0·2	36·8±0·2	36·7±0·2		

Desipramine was given 60 min before phenethylamine and 5 hr after yeast.
Rats received 200 mg/kg of iproniazid phosphate 16 hr before phenethylamine.

TABLE 4. EFFECT OF DESIPRAMINE ON VARIOUS TYPES OF HYPERTHERMIA

Agent	Types of effect observed
Noradrenaline	enhancement and prolongation
Adrenaline	" " "
Isoprenaline	" " "
Dopa*	" " "
Reserpine	" " "
Dexamphetamine	prolongation
Phenethylamine*	inhibition
Yeast	no effect

* In animals pretreated with a monoamine oxidase inhibitor.

their release (Sulser, Bickel & Brodie, 1964). This interpretation may also be a basis for reconciling the discrepancies observed in various laboratories about the degree of antagonism between desipramine and reserpine.

The potentiation of the dexamphetamine-induced hyperthermia is in agreement with many data already available concerning an increased effect of amphetamine in animals pretreated with imipramine-like drugs (Carlton, 1961; Stein, 1962; Theobald, Buch, Kunz, Morpurgo, Stenger & Wilhelms, 1964; Morpugo & Theobald, 1965). More difficult to interpret is the inhibition of the hyperthermia induced by phenethylamine in rats receiving desipramine. This result, and the fact that desipramine

does not interfere with the changes of body temperature induced by yeast, suggests that desipramine is not a general potentiator of hyperthermic responses (Loew, 1964).

The results described here permit us to broaden the pharmacological knowledge about imipramine and its congeners. The potentiation of catecholamine hyperthermia is specific for these antidepressant agents and it is not shared by a tranquilliser like chlorpromazine. While the hyperthermia induced by noradrenaline is potentiated by monoamine oxidase inhibitors (unpublished data from this laboratory) that induced by isoprenaline is not potentiated by pheniprazine. This suggests another test enabling antidepressant agents belonging to the monoamine oxidase inhibitors or to the imipramine class to be distinguished.

At present the potentiation of the catecholamine hyperthermic responses seems to be a characteristic feature of the imipramine-like drugs which should be added to the already known interactions with reserpine and amphetamine.

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