An interaction between the antidepressant drugs desipramine and modaline sulphate

SIR,—Modaline sulphate is a non-hydrazine monoamine oxidase inhibitor, also showing imipramine-like activity and clinical antidepressant effects (Feldman, 1963; Dunlop, De Felice & others, 1964).

This compound, however, requires an initial biotransformation by liver microsomal enzymes, to an active unknown intermediate, before the anti-monoamine oxidase-like (Dubnick, Morgan & Phillips, 1963; Horita, 1966) or the imipramine-like (Jori, Carrara & others, 1965) effects can be demonstrated. On the other hand, tricyclic antidepressant agents, such as imipramine and desipramine, are strong inhibitors of some liver microsomal enzymes important for drug metabolism.

This biochemical activity may be responsible for several interactions of imipramine-like agents with various central nervous system-active drugs. In fact, imipramine potentiates the barbiturate sleeping time by inhibiting the metabolic degradation of pentobarbitone (Kato, Chiesara & Vassanelli, 1963), it shows an anti-tremorine activity by preventing the biotransformation of tremorine to its active metabolite, oxotremorine (Sjöqvist & Gillette, 1965; Hammer & Sjöqvist, 1966) and it potentiates and prolongs the behavioural and hyperthermic effects of amphetamine (Valzelli, Consolo & Morpurgo, 1966) by reducing its hydroxylation to *p*-hydroxyamphetamine (Consolo, Dolfini & others 1967). It was, therefore, interesting to investigate the interaction of desipramine on the pharmacological effects of modaline sulphate.

Experiments *in vivo* and *in vitro* were made to evaluate the potency of the monoamine oxidase inhibition after modaline in rats pretreated with desipramine or SKF 525 A, another compound known to inhibit several liver microsomal enzymes (Brodie, Gillette & La Du, 1958).

Monoamine oxidase inhibition was measured *in vivo* by potentiation of tryptamine symptomatology according to Tedeschi, Tedeschi & Fellows (1959) and the results obtained are in Fig. 1. Fig. 1A represents the effect of desipramine at various dose levels. The activity of modaline is strongly reduced

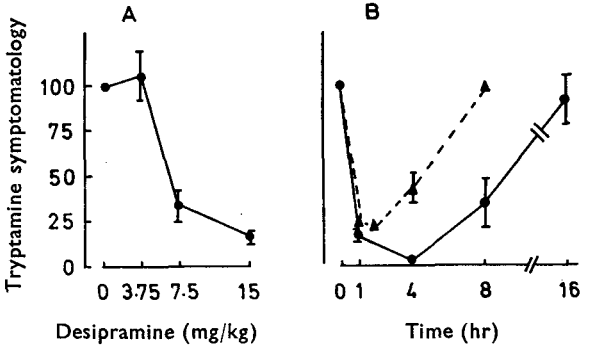

FIG. 1. The tryptamine symptomatology (hunching of the back, backward locomotion, Straub tail, salivation and clonic convulsions of the anterior paws) was scored according to an arbitrary scale. The maximum potentiation induced by modaline was calculated = 100. Vertical bars represent the standard error. A. Desipramine was given intraperitoneally 1 hr before modaline. Modaline (8 mg/kg, i.p.) was injected 30 min before tryptamine (7·5 mg/kg, i.v.). B. ●———● Desipramine (15 mg/kg, i.p.) or ▲ - - - ▲ SKF 525 A (50 mg/kg, oral) was given at various times before modaline and tryptamine.

TABLE 1. MONOAMINE OXIDASE ACTIVITY IN BRAIN HOMOGENATES OF RATS

No. of rats	Treatment	mg/kg	Kynuramine oxidized (μmoles/hr/mg protein) ± s.e.
10	Controls ..		0·033 ± 0·001
10	Desipramine ..	15	0·034 ± 0·001
10	SKF 525 A ..	50	0·034 ± 0·002
15	Modaline ..	8	0·005 ± 0·001*
10	Desipramine .. + modaline ..	15 8	0·012 ± 0·001†
6	SKF 525 A .. + modaline ..	50 8	0·014 ± 0·002†

Desipramine or SKF 525 A was given intraperitoneally and orally, respectively, 1 hr before modaline. Rats were killed 45 min after modaline. Brains were removed, frozen, homogenized and incubated with the substrate kynuramine according to the method of Weisbach & others (1960). Values are expressed as μmoles/hr/mg of protein.

* $P < 0.01$ relative to controls.

† $P < 0.01$ relative to the group receiving modaline only.

by 7·5 and 15 mg/kg of desipramine. The inhibition induced by 15 mg/kg of desipramine is long-lasting and it is still present after 8 hr (Fig. 1B). Desipramine alone did not modify at any dose the response to tryptamine. SKF 525 A is also active at 50 mg/kg, but when the time interval between the injection of SKF 525 A and modaline was more than 4 hr, the interaction disappeared.

The effect of desipramine was also present after repeated treatments (70% inhibition after 7 days of treatment), but it was reversible and completely disappeared 5 days after the last treatment.

The monoamine oxidase inhibition *in vitro* was measured by the Weissbach method (Weissbach, Smith & others, 1960) on brain homogenates, using kynuramine as oxidizable substrate. Table 1 shows that the monoamine oxidase activity of brain of rats treated *in vivo* with modaline is blocked, but it may be partially restored if desipramine or SKF 525 A are given previously. These agents, at the dose used, are unable to affect by themselves the monoamine oxidase activity in brain.

The *in vitro* data corroborate those obtained *in vivo* on the potentiation of tryptamine symptomatology, showing that the decreased activity of modaline sulphate in desipramine-pretreated rats may be dependent on a reduced inhibition of the monoamine oxidase enzymatic system. On the other hand, these data emphasize that a strong inhibition of monoamine oxidase is necessary to elicit potentiation of tryptamine symptomatology in rats, and that a partial recovery of the enzymatic activity is able to prevent it.

As modaline acts on monoamine oxidase by means of its metabolite (Dubnick & others, 1963; Horita, 1966) it can be tentatively concluded that desipramine reduces the activity of modaline by inhibiting its biotransformation at the level of the hepatic microsomes.

These experimental observations may assume some practical importance as desipramine and modaline belong to the same category of antidepressant drugs and might be associated in clinical treatment.

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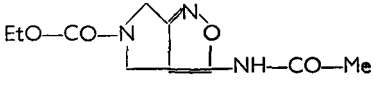
Effects of ethyl 3-acetamido-4*H*-pyrrolo[3, 4-c]-isoxazole-5(6*H*)carboxylate on tissue levels of catecholamines and 5-hydroxytryptamine in the rat

SIR,—Various agents have been found which cause a marked lowering of the tissue levels of catecholamines or 5-hydroxytryptamine (5-HT) or both. Some of these depletors, such as α-methyldopa, guanethidine or reserpine, are used in hypertension. The compound, ethyl 3-acetamido-4*H*-pyrrolo-[3,4-*c*]isoxazole-5(6*H*) carboxylate (I;CL-62375), has recently been found to cause hypotension in the rat. We now report that administration of this compound to the rat causes alterations in the tissue levels of catecholamines and 5-HT.



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Brain catecholamine levels (Lippmann & Wishnick, 1965), brain 5-HT (Bogdanski, Pletscher & others, 1956), heart noradrenaline (Anton & Sayre, 1962) and adrenal catecholamines (Lippmann & Wishnick, 1965), were measured in female rats, Sherman strain, of about 150 g.

CL-62375 was administered intraperitoneally in a single injection (0·5 ml 1% starch, M/15 potassium phosphate buffer, pH 7·0) at 100, 150, 250 or 400 mg/kg and the animals were decapitated 5 hr later. In the heart there was a decline in the noradrenaline level of 70, 42 and 35% at 250, 150 and 100 mg/kg, respectively. In the brain there was a lowering in the catecholamine content of 70% at 250 mg/kg and 40% at 150 mg/kg. The brain 5-HT showed a maximum decline of 30% at the 250 mg/kg level. The 400 mg/kg level was lethal. Thus, there was an appreciable effect on the catecholamine levels in the heart and brain