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Interactions between monoamine oxidase inhibitors and sympathomimetic amines in the rat isolated vas deferens

SIR,—It has been assumed (Iversen, 1967) that monoamine oxidase inhibitors do not potentiate the effects of catecholamines administered exogenously or released by nerve stimulation. However, it has been shown (Bhargava, Kar & Parmar, 1963) that amphetamine, pheniprazine and tranylcypromine potentiate the responses of hypogastric nerve-vas deferens preparation elicited by electrical stimulation, and that monoamine oxidase inhibitors produce a large potentiation of the pharmacological actions of tyramine (Griesemer, Barsky & others, 1953; Goldberg & Sjoerdsma, 1959; Spano, 1966). Tranylcypromine and pheniprazine potentiate also the effects of catecholamines on the heart of reserpinized cat but not in the normal cat (Lee, Shin & Shideman, 1961).

In view of these conflicting reports, we have thought it worth while to study the interactions between some monoamine oxidase inhibitors and sympathomimetic amines in the rat isolated vas deferens preparation, using the technique of Laporte, Jané & Valdecasas (1966), since this is one of the most suitable preparations to assess *in vitro* noradrenaline supersensitivity (Cuenca & Valdecasas, 1965; Ursillo & Jacobson, 1965; Benvenutti, Bonaccorsi & Garattini, 1967). The monoamine oxidase inhibitors assayed were: pheniprazine, a hydrazine derivative, and tranylcypromine, amphetamine and pargyline, all non-hydrazine derivatives. Sympathomimetic agents used were a direct-acting amine, noradrenaline, and an indirect-acting amine, tyramine.

Tranylcypromine and pheniprazine have no action on the rat isolated vas deferens in concentrations up to 1×10^{-6} g/ml. Stronger concentrations elicit small and irregular contractions, and an increase of the residual tonus. To see the same effects with amphetamine, higher concentrations must be used (1×10^{-4} g/ml).

After these apparently ineffective stimulations with tranylcypromine the sensitivity of the vas deferens to catecholamines increases markedly. This

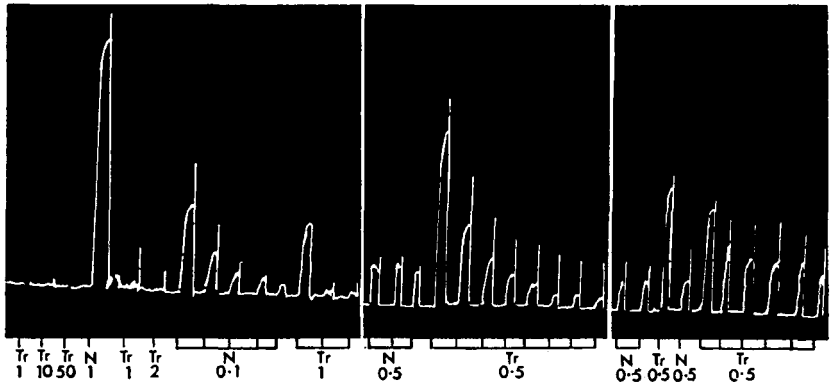

FIG. 1. The responses of isolated rat vas deferens to succesive doses of tranylcypromine (Tr) and noradrenaline (N), added to the bath at the points indicated. Drug concentrations μg/ml.

supersensitivity is highly transient and is observed in preparations from normal or reserpinized rats. But after stabilization of the responses of the preparation to catecholamines, the vas deferens becomes highly sensitive to tranylcypromine (Fig. 1): with concentrations of tranylcypromine completely ineffective before the stimulation with catecholamines, contractions of the same size and characteristics as the responses obtained with noradrenaline are elicited. This supersensitivity to tranylcypromine decreases but is long-lasting, and, when stabilization occurs, the sensitivity of the preparation to this monoamine oxidase inhibitor is markedly greater than before its previous stimulation with noradrenaline. These interactions are also seen in the reserpinized animal (1 mg/kg, 24 hr before). The same effects are seen with pheniprazine, but to a lesser extent. Supersensitivity of the vas deferens to amphetamine after its stimulation with noradrenaline also exists, but is quickly lost. In contrast, pargyline does not elicit any response of the vas deferens either before or after its stimulation with noradrenaline. However, the administration of repeated concentrations of pargyline potentiates about fivefold the effects of tyramine, while the responses to catecholamines are much less increased than is so with the other drugs tested. Potentiation of the effects of tyramine after tranylcypromine, amphetamine or pargyline is slight.

It has not been possible to reproduce these interactions between noradrenaline and tranylcypromine in other *in vitro* preparations of the same animal, like the isolated atria or the perfused renal artery (Garattini, Bonaccorsi & Laporte, unpublished). These results seem to confirm the uniqueness of the rat isolated vas deferens preparation for the study of adrenergic mechanisms, and to show that not all the monoamine inhibitors tested by us act in the same fashion on this preparation. It seems therefore that the direct or indirect effects elicited by these inhibitors on the rat vas deferens are not always a consequence of its biochemical action on the monoamine oxidase.

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