On the ability of desipramine to interfere with reserpine-induced noradrenaline release

SIR,—Desipramine has been shown to inhibit the depleting effect of reserpine on adrenal catecholamine content in the rat (Zbinden, 1962; Shore & Busfield, 1964). However, it fails to prevent the depletion induced by reserpine of noradrenaline stored in the mouse heart (Stone, Porter, Stavorski, Ludden & Totaro, 1964) and rat brain (Sulser, Watts & Brodie, 1962; Garattini, Giachetti Jori, Pieri & Valzelli, 1962), imipramine being slightly active at very high doses in the latter tissue (Pletscher & Gey, 1962).

In these earlier experiments the effects of the drugs were related to a single point in time so that no information on amine levels in terms of time response is available. Brodie and his colleagues have recently re-emphasised the importance of a dynamic approach to similar problems in their kinetic study of noradrenaline release by tyramine (Neff, Tozer, Hammer & Brodie, 1965).

Therefore experiments were designed to assay noradrenaline at various times after treatment with reserpine alone or in combination with desipramine.

Several hours after administration of reserpine, a fall in noradrenaline occurs which is quicker in normal than in desipramine-pretreated animals.

Female Sprague-Dawley rats, 160–200 g, after 14 hr fasting were injected in the tail vein with 2·5 mg/kg reserpine (Serpasil, Ciba). In pretreated animals desipramine dissolved in distilled water (15 mg/kg i.p.) was administered 1 hr before reserpine; all other animals received distilled water in place of desipramine.

Animals were decapitated at various times after the reserpine, organs removed, blotted on filter paper, wrapped in aluminium foil, collected in beakers embedded in broken ice-sodium chloride and preserved at $-20°$ until assayed. Individual animals were accurately timed in all the experiments.

Noradrenaline was estimated spectrofluorimetrically (Aminco Bowman) by a sensitive method employing alumina adsorption and production of fluorescent indole derivatives (Chang, 1964) with the following modifications: 2ml of 0·01N hydrochloric acid was shaken with 4 ml limpid butanol obtained after centrifugation of tissue butanol homogenate (adjust the pH for adsorption with 2 ml 2N sodium acetate); alumina was washed with 3 m 0·2N sodium acetate after discarding supernatant. The pH at the critical steps was as follows: alumina, supernatant pH 7, wash pH 7, eluate pH 4; oxidation, after ethylenediaminetetraacetic acid pH 5·2, final pH 5·4. The range of recovery was 60–70%. Samples containing 0·008 μg noradrenaline (equivalent to approximately 0·15 μg/g tissue, i.e., 15% of heart control values) give values 3 times greater than the blank.

TABLE 1. EFFECT OF DESIPRAMINE ON THE RELEASE OF HEART NORADRENALINE INDUCED BY RESERPINE IN RATS

	Noradrenaline μg/g rat heart $\pm$ s.d. after:			
	30 min	1 hr	3 hr	4 hr
Reserpine	0·48 $\pm$ 0·1 (4)	0·19 $\pm$ 0·09 (4)*	0·06 $\pm$ 0·02 (4)**	0·06 $\pm$ 0·02 (4)
Desipramine + reserpine	0·64 $\pm$ 0·1 (4)	0·35 $\pm$ 0·05 (3)	0·14 $\pm$ 0·01 (4)	0·08 $\pm$ 0·03 (4)

Animals were killed at various times after reserpine as specified; figures in parenthesis indicate the number of observations on which the mean is based. Similar experiments on a total of 42 hearts from treated rats yielded results in agreement with these above (i.e., six pairs of significantly different means).

* $P < 0.05$ (between means at equivalent time).

** $P < 0.01$ (between means at equivalent time).

Control animals heart noradrenaline 1 $\pm$ 0·1 μg/g.

In a typical experiment (Table 1) animals were treated on the same day: each time point was later analysed separately. Single organ specimens were individually assayed.

Our results are not in disagreement with the findings previously reported indicating that desipramine is ineffective in preventing depletion of noradrenaline from sympathetic nerve endings by large doses of reserpine. However, as Table 1 illustrates, although the catecholamine stores at 4 hr are lowered in both reserpine and desipramine pretreated reserpinised animals to almost undetectable amounts, the time required to reach the depletion is prolonged by desipramine pretreatment. When rats so "protected" are killed at the times shown after reserpine administration, the noradrenaline content of their hearts is significantly higher after the same interval than that of animals receiving reserpine alone.

A similar, although probably less pronounced, tendency of desipramine to modify time response patterns of noradrenaline release induced by reserpine has been observed in the brain. But the variability and lower amine levels make the experiments on the brain of questionable significance.

Other authors (Axelrod, Whitby & Hertting, 1961; Titus & Spiegel, 1962; Glowinski & Axelrod, 1964), have shown that imipramine and desipramine impair the uptake of noradrenaline by adrenergic nerve terminals. Since the uptake is an important mechanism for restoring most of the released neurohormone in the nerve endings, our data would appear to contrast with present views. However, it is possible that the inhibition of noradrenaline uptake by desipramine creates a relatively high concentration of the catecholamine which tends to slow down the reserpine-induced outflow of it. If this is true then a concentration of noradrenaline at the receptor sites higher than after reserpine alone might be expected after the combination of desipramine and reserpine.

An example of a pharmacological correlation of this biochemical interpretation is the study describing desipramine potentiation and prolongation of the initial hyperthermia elicited by reserpine in the same animal species, doses, and times (Jori & Garattini, 1965).

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