conclusion is supported by earlier work which suggested that the reserpine antagonism of the anticonvulsant effect of diphenylhydantoin (Chen, Ensor & Bohner, 1954) was competitive and not the result of brain amine depletion (Gray, Rauh & Shanahan, 1963).

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Rapid release of ^{3}H-metaraminol induced by combined treatment with protriptyline and reserpine

SIR,—Two different amine uptake and concentrating mechanisms of the adrenergic neurone have been demonstrated, namely, the amine transport mechanism of the cell membrane, "the cell membrane pump", and the uptake mechanism of the specific storage granules (Carlsson, Hillarp & Waldeck, 1962; Hamberger, Malmfors, Norberg & Sachs, 1964; Hillarp & Malmfors 1964; Malmfors, 1965; Carlsson & Waldeck, 1965a, b). Either of these mechanisms can be selectively blocked by drugs. Thus protriptyline and desipramine were found to block the former, reserpine and prenylamine the latter mechanism.

In the present investigation the effect of simultaneous blockade of the two mechanisms, or of either mechanism alone, was investigated, using ^{3}H-metaraminol as an indicator. Mice were given ^{3}H-metaraminol 0·02 mg/kg intravenously, followed after 15 min by protriptyline 10 mg/kg i.v., or reserpine 0·5 mg/kg i.v., or a mixture of both. The animals were killed 15 or 45 min after the administration of the inhibitors. Determination of ^{3}H-metaraminol in heart was performed as described earlier (Carlsson & Waldeck, 1965a). Given alone protriptyline or reserpine caused a moderate reduction of ^{3}H-metaraminol in the heart (Table 1). In combination, however, the two drugs caused a rapid and pronounced decrease of the amine. Within 15 min, 80% of the ^{3}H-metaraminol had disappeared, and 45 min after the drug mixture had been given only 5% was left. Preliminary experiments where reserpine was replaced by prenylamine gave essentially the same result.

Analogous results were obtained in experiments where the ^{3}H-metaraminol had been given 3 days before protriptyline and reserpine, alone or in combination.

TABLE 1. RELEASE OF ^{3}H-METARAMINOL BY PROTRIPTYLINE AND RESERPINE FROM THE HEARTS OF MICE

Treatment at zero time*	^{3}H-metaraminol in ng/g tissue	
	after 15 min	after 45 min
Control	52 52	43 45
Protriptyline ..	34 35	27 28
Reserpine	28 46	29 25
Protriptyline + reserpine	11 12	3 2

The values are single values, obtained from 6 pooled hearts.

* ^{3}H-metaraminol 0·02 mg/kg i.v. 15 min before zero time.

Inhibition of the two uptake mechanisms probably results in unmasking of physiological release mechanisms (Carlsson 1965). Blockade of the cell membrane pump will thus unmask amine release through this membrane. The comparably slow release induced by blockade of this mechanism alone probably indicates that the concentration of free amine in the neurone cytoplasm is low. Blockade of the uptake mechanism of the storage granules will unmask amine release from these granules into the cytoplasm. The most probable reason why blockade of this mechanism alone does not result in rapid loss of amine, is that the cell membrane pump is able to cope fairly successfully with the amine released into the cytoplasm.

Experiments are in progress to investigate the effect of the drug combination on labelled and endogenous noradrenaline.

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