Prior administration of SKF 525–A markedly inhibited the hyperchlorhydria produced by reserpine, indicating that hyperchlorhydria was probably due to a metabolite.

Efforts to isolate from the urine of animals treated with reserpine the metabolite responsible for potentiating the histamine response, have so far been unsuccessful.

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In vivo inhibition of ^{3}H-noradrenaline uptake by mouse brain slices *in vitro*

SIR,—Pretreatment of animals with reserpine decreases the capacity of tissues to accumulate tritiated noradrenaline *in vitro* (Dengler, Spiegel & Titus, 1961a; Ross & Renyi, 1966). Several other psychoactive compounds added to brain slices *in vitro* are known to inhibit the uptake of noradrenaline (Dengler, Spiegel & Titus, 1961b). However, pretreatment of mice with these compounds does not seem to decrease the noradrenaline uptake by subsequently prepared brain slices. In contrast to reserpine, most of these compounds seem to act reversibly and are probably loosely bound to the tissues. The tissue contents of these substances may therefore decrease during the *in vitro* incubation procedure by diffusion of the compounds into the incubation medium. We have tried to avoid this diffusion by using a briefer incubation period than was used in the aerlier experiments.

Mice were injected intraperitoneally with the compounds and they were killed at the time noted in Table 1. The incubation of the brain cortex slices with the tritiated noradrenaline and the extraction of the amine taken up was as previously described (Ross & Renyi, 1964), with the exception that the incubation time was only 5 min. Four animals were used for each compound. The content of the amine in the slices was expressed as nmol/g. The statistical significance was calculated according to the Student's *t*-test.

The results obtained are presented in Table 1. Compounds supposed to inhibit the noradrenaline uptake at the cell membrane level (Carlsson & Waldeck, 1965), namely, desipramine, imipramine or amitriptyline, were strong inhibitors of the uptake of tritiated noradrenaline under the conditions used. But cocaine, which when added *in vitro* is a powerful inhibitor of the noradrenaline uptake by brain slices, had only a slight effect when injected *in vivo*. This finding would seem to suggest that too small amounts of cocaine reach the mouse brain *in vivo*.

The large dose of chlorpromazine strongly inhibited the noradrenaline uptake, but the smaller dose had no effect although the animals were strongly tranquillised. This result may indicate that the phenothiazine class of tranquillisers

has the same inhibitory effect on the noradrenaline uptake as have the antidepressive agents mentioned above, but that this effect is pharmacologically masked by their more potent tranquillising action (cf. Bickel, Sulser & Brodie, 1963).

(±)-Amphetamine in a high dose which produced behavioural stimulation in mice also had a strong inhibitory action on the amine uptake in cortical slices. The lower, pharmacologically inactive dose, however, had no effect on the uptake. Whether there is any relation between the stimulatory action and the inhibition of uptake of amine by amphetamine remains to be elucidated.

The pretreatment of the mice with reserpine or tetrabenazine caused only a slight, insignificant decrease in the capacity of the tissue to accumulate noradrenaline under the brief incubation condition used in contrast to that found with longer incubations (Ross & Renyi, 1966). This result is in agreement with the view that reserpine blocks the granular storage mechanism for noradrenaline (Hillarp & Malmfors, 1963).

TABLE 1. EFFECT OF PRETREATMENT OF MICE WITH SOME PSYCHOACTIVE COMPOUNDS ON THE NORADRENALINE UPTAKE BY BRAIN CORTEX SLICES *IN VITRO*

Compound	Dose mg/kg i.p.	Time after injection hr	Noradrenaline uptake nmol/g ± s.e.
Control	—	—	0·117 ± 0·004 (n = 15)
Desipramine HCl	10	0·5	0·094 ± 0·007*
	10	1	0·086 ± 0·008†
	10	2	0·097 ± 0·004†
	10	4	0·110 ± 0·012
	2	1	0·097 ± 0·004†
Imipramine	20	1	0·091 ± 0·007‡
Amitriptyline	20	1	0·088 ± 0·003‡
Cocaine HCl	20	0·5	0·107 ± 0·002*
	20	1	0·123 ± 0·006
Chlorpromazine HCl	20	1	0·072 ± 0·007‡
	5	1	0·127 ± 0·002
(±)-Amphetamine sulphate	10	1	0·068 ± 0·009‡
	2·5	1	0·119 ± 0·003
Reserpine	5	18	0·104 ± 0·006
Tetrabenazine HCl	60	1	0·106 ± 0·005
Haloperidol	2·5	1	0·124 ± 0·003
Chlordiazepoxide	20	1	0·125 ± 0·004

* $0{\cdot}05 > P > 0{\cdot}01$ † $0{\cdot}01 > P > 0{\cdot}001$ ‡ $P < 0{\cdot}001$

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