on 43 cells (31 cells excited, 12 cells depressed by both drugs) on which responses of approximately identical sizes were established. Responses were regarded as approximately of equal magnitude if the ratio of the equilibrium changes in firing rate for the two responses (response to tyramine/response to noradrenaline) was 1.0 ± 0.2. The mean equipotent ejecting current ratio was 3.1 ± 0.3 (excitatory responses) and 2.8 ± 0.5 (depressant responses). For both excitatory and depressant responses noradrenaline had a greater apparent potency than tyramine (t test: $P<0.0005$ and $P<0.005$, respectively).

The effects of continuously applied desipramine (for methods see Bevan, Bradshaw & Szabadi, 1977) were studied on 28 cells excited by both noradrenaline and tyramine. Homocysteic acid was used as a control agonist. On 26 cells desipramine could discriminate between responses to tyramine and noradrenaline: the response to tyramine was antagonised, whereas the response to noradrenaline was either potentiated (6 cells) or unaffected (20 cells). Recovery of responses to tyramine usually was only partial and occurred after 1–2 hours. On two cells responses to both monoamines were antagonised. Responses to homocysteic acid were not affected.

The effect of desipramine was studied on six cells depressed by both monoamines: on 5 of these responses to tyramine were antagonised, whereas the response to noradrenaline was either potentiated (4 cells) or unaffected (1 cell). On one cell depressant responses to both monoamines were equally antagonised by desipramine.

Tyramine is an indirectly acting sympathomimetic amine: its pharmacological effects have been attributed to the action of noradrenaline released by tyramine from sympathetic terminals (Burn & Rand, 1958). It has been reported that desipramine blocks the uptake of tyramine into sympathetically innervated tissues, and thus prevents its pharmacological actions (Brodie, Costa, Gropetti & Matsumoto, 1968). Our results are consistent with the hypothesis that a similar interaction may occur on brain cells.

This work was supported by the North Western Regional Health Authority and the Mental Health Foundation.

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Potentiation of monoamine responses of denervated cells by a noradrenaline uptake inhibitor (viloxazine)

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Monoamines are inactivated by reuptake into presynaptic terminals (Ross & Renyi, 1967; Coyle & Snyder, 1969). It has been suggested that tricyclic anti-depressants potentiate responses to monoamines by a mechanism dissociated from their uptake blocking ability (Bradshaw, Roberts & Szabadi, 1974). It is of interest therefore to examine the ability of an uptake inhibitor to potentiate monoamine responses following degeneration of presynaptic terminals.

Male albino Wistar rats (200–350 g) were anaesthetized with halothane (0.6%) and prepared for the recording of the spontaneous activity of cortical cells using the techniques described by Bradshaw *et al.* (1974). Drugs were applied by microiontophoresis from the following solutions: noradrenaline bitartrate (0.2M, pH 3.5); 5-hydroxytryptamine bimalinate (0.2M, pH 3.5); viloxazine hydrochloride (Vivalan, ICI Ltd.) (0.2M, pH 6.0). Ten–14 days before each experiment a unilateral electrolytic lesion was placed in the median forebrain bundle at stereotaxic coordinates AP + 3.4; lat. 1.6; vert. − 2.8 (König & Klippel, 1963). Lesions of approximately 2 mm diameter were produced with a direct current of 2 mA passed for 20 s from a bipolar stainless steel electrode. Uptake of monoamines by neocortical synaptosomes was reduced to 21% by this lesion.

Excitatory and depressant responses to 5-HT and noradrenaline were recorded from neocortical cells on both lesioned and unlesioned sides. Changes in the proportions of these responses have been reported elsewhere (Jones & Roberts, 1977a). Excitatory responses occurred much less frequently than in unlesioned cortex. Only a single study of the effect of viloxazine on an excitatory response to noradrenaline was obtained. Viloxazine potentiated this response to

200% of control. The potentiating action of viloxazine on depressant responses can be summarized as follows: noradrenaline, unlesioned sides, 2 cells (average potentiation 169%); lesioned sides, 4 cells (209%); 5-HT, unlesioned sides, 2 cells (203%); lesioned sides, 7 cells (182%).

Viloxazine is not a tricyclic antidepressant but has been shown to act similarly to tricyclics in potentiating cortical cell responses to monoamines in unlesioned animals (Jones & Roberts, 1977b). There is evidence to suggest that viloxazine is an inhibitor of NA uptake into brain tissue. (Lippmann & Pugsley, 1976). It would therefore seem likely that potentiation of responses is due to uptake blockade. However, the potentiating effects of viloxazine appear to be unimpaired following lesions which should have caused degeneration of presynaptic terminals. The potentiation therefore may be dissociated from the blockade of reuptake. Bevan, Bradshaw & Szabadi (1975a,b) have reported other evidence for a similar conclusion with regard to tricyclics.

Viloxazine is much less effective in blocking the reuptake of 5-HT. Nevertheless it strongly potentiates responses to 5-HT in both lesioned and unlesioned hemispheres. This further suggests a dissociation between the potentiation of monoamine responses and the blockade of reuptake.

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Effects of mazindol on the *in vitro* uptake of monoamines by the rat brain

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Previous studies have revealed that the anorectic drug mazindol is an extremely potent inhibitor (being 4–5 times more potent than desipramine) of rat brain noradrenaline (NA) uptake *in vivo* as assessed by the effect of drug pretreatment on the ability of intracerebroventricularly injected 6-hydroxydopamine to lower brain NA levels (Sugrue, Shaw & Charlton, 1977). Using the same method mazindol, unlike tricyclic antidepressants, also blocked dopamine (DA) uptake. Pretreatment with mazindol had essentially no effect on the ability of *p*-chloroamphetamine to lower the concentration of 5-hydroxytryptamine (5-HT) in the rat brain. The interpretation of this finding is that mazindol is devoid of effect on 5-HT uptake *in vivo* (Sugrue *et al.*, 1977). The relative lack of effect of mazindol observed on 5-HT uptake *in vivo* contrasts with *in vitro* findings. For example, mazindol has been observed to block 5-HT uptake by rat striatal synaptosomes (Koe, 1976, Kruk & Zarrindast, 1976). The objective of this study was to investigate the effects of mazindol on the uptake of NA, DA and 5-HT by synaptosome rich homogenates obtained from selected regions of rat brain. Two experimental approaches were used. In the first, drugs were directly added to the incubation medium at the start of the preincubation period (*in vitro* experiments). In the second, rats were injected i.p. with the drug under study 1 h prior to death and synaptosomal [^{3}H]-monoamine uptake subsequently determined (*ex vivo* experiments).

Male Wistar rats weighing 180–220 g were used. The uptake of [^{3}H]-DA into synaptosome rich homogenates of corpus striatum and the uptake of [^{3}H]-NA and [^{3}H]-5-HT into synaptosome rich