Some interactions between fenfluramine and antidepressant drugs: effects on 5-hydroxyindole concentrations in rat brain

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Fenfluramine has been shown to produce a prolonged depletion of 5-hydroxytryptamine from rat brain (Costa, Groppetti & Revuelta, 1971) and norfenfluramine, which may be the biologically active metabolite of fenfluramine, increases the turnover rate of 5-hydroxytryptamine in the tel-diencephalon (Costa & Revuelta, 1972). It has been suggested that fenfluramine may have a reserpine-like effect on brain monoamines (Ziance & Rutledge, 1972). The ability to reverse the monoamine-depleting effects of reserpine is often taken as an index of potential clinical antidepressant activity, as there is evidence that decreased brain monoamine concentrations may be the biochemical bases of some types of depression (Coppen, 1967). It was therefore of interest to examine interactions between fenfluramine and antidepressants with respect to effects on 5-hydroxytryptamine metabolism.

Fenfluramine alone was found to reduce 5-hydroxytryptamine levels in whole rat brain (60 min after an intraperitoneal dose of 5 mg kg^{-1}) and also caused a slight reduction of 5-hydroxyindoleacetic acid concentrations. The same dose of fenfluramine antagonized the effects of imipramine (5 and 10 mg kg^{-1}), iproniazid (100 mg kg^{-1}) and amphetamine (5 mg kg^{-1}) on both 5-hydroxytryptamine and 5-hydroxyindoleacetic acid concentrations. Surprisingly, fenfluramine also antagonized the depleting effect of reserpine (5 mg kg^{-1}) and the 5-hydroxytryptamine-elevating effect of a combination of reserpine (5 mg kg^{-1}) and iproniazid (100 mg kg^{-1}). These results indicate that, far from having a reserpine-like effect on 5-hydroxytryptamine metabolism, fenfluramine may stabilize the intraneuronal storage granules (the "stable pool"). A stabilization of the storage granules might prevent the incorporation of newly-synthesized 5-hydroxytryptamine and also the re-uptake mechanism; such an effect could explain both the depletion of 5-hydroxytryptamine and the increase in its turnover rate described by other authors.

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Changes in the concentrations of 5-hydroxytryptamine and noradrenaline in six areas of rat brain during recovery from chronic methylamphetamine administration

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The effects of the acute administration of amphetamines on brain monoamine metabolism are well documented: noradrenaline concentrations are reduced, primarily by a displacement of the amine from its storage granules to the extraneuronal site, though it is also suggested that amphetamines may have *in vivo* monoamine oxidase inhibitory activity and may interfere with neuronal re-uptake mechanisms; small doses of amphetamine (1–3 mg kg^{-1}) increase 5-hydroxytryptamine concentrations, whilst higher doses produce depletion, presumably by an effect similar to that exerted on noradrenergic neurons.

Mature male Wistar rats were given methylamphetamine hydrochloride (200 mg $litre^{-1}$) in the drinking water for a period of 3 weeks. Water was then substituted for the drug solution and groups of 10 rats were killed 0, 12, 24, 36 and 48 h later. Pronounced behavioural depression, similar to that produced after the withdrawal of (+)-amphetamine (Tonge, 1974) was observed 24 h after the withdrawal of methylamphetamine: the rats huddled together in a corner of the cage and had the appearance of animals that had received reserpine. Behaviour was apparently normal 48 h after drug withdrawal. Brains were removed and kept in a semi-frozen condition during dissection into six areas: cortex, hippocampus, striatum, thalamus/hypothalamus, mid-brain and pons/medulla. Nora-