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-

drenaline and 5-hydroxytryptamine concentrations were determined by the methods of Welch & Welch (1969) and Curzon & Green (1970) respectively. When compared with litter-mate untreated rats, noradrenaline concentrations were found to have been reduced in all areas of the brain by chronic methylamphetamine administration; 5-hydroxytryptamine concentrations were also reduced in the striatum and mid-brain, but were unaltered in the thalamus/hypothalamus, the hippocampus and the pons/medulla, and were increased in the cortex. In all areas except the striatum, 5-hydroxytryptamine concentrations were lower 24 than 0 hours after withdrawal. Noradrenaline concentrations fell steadily for 36 h in the striatum, rose, for 48 h in the thalamus/hypothalamus and cortex, and showed an initial rise in the hippocampus, mid-brain and pons/medulla followed in the cases of the mid-brain and pons/medulla by falls to below 0 h levels 24 h after withdrawal.

These results suggest that chronic methylamphetamine ingestion may affect not only the release of monoamines, but also their synthesis and transport along neuron axons. They also suggest a biochemical basis for the marked "post-amphetamine depression" frequently reported in man.

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Biogenic amines and the anti-nociceptive activity of agents with a non-opiate structure

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The anti-nociceptive activity of morphine has been associated with several putative central neurotransmitters, including 5-hydroxytryptamine (5HT) and noradrenaline (NA). The interactions of these amines with morphine have been studied using intracerebroventricular (ICV) injections both in rats (Sparkes & Spencer, 1971) and mice (Calcutt & Spencer, 1971). A recent report from our laboratory (Sewell & Spencer, 1974) showed that in mice, ICV-administered 5-HT acutely potentiated not only morphine's anti-nociceptive activity, but also that of a range of narcotic agonist and partial agonist agents, whilst ICV-administered NA antagonized the effects of these agents. Each of the agents examined so far has been structurally related to the naturally-occurring opiates, and the purpose of this report is to describe the effects of these amines when given to animals receiving analgesics of clearly different chemical structure.

Male albino mice of the ICI strain, weighing 18–22 g, were used throughout, and nociceptive sensitivity was determined using the tail immersion technique. Four analgesics were examined: pethidine; AH 7921, 3,4-dichloro-*N*-(1-dimethylamino) cyclohexylmethyl benzamide, a recent analgesic shown to be active in the mouse, dog and monkey (Brittain, Kellett & others, 1973); profadol, *m*-(1-methyl-3-pyrrodinyl) phenol, which is active clinically (Beaver, Wallenstein & others, 1969); and (+)-amphetamine. All four possess activity in this test, but with different slopes to their dose-response lines, AH 7921 possessing the steepest and (±)-amphetamine the shallowest slopes. ICV-administered 5-HT (10 μg/animal) significantly prolonged the anti-nociceptive effect of pethidine (15 mg kg^{-1}), AH 7921 (2·5) and profadol (10). Further, as previously reported with the opiates, ICV NA (10 μg) significantly attenuated the activity of pethidine (50 mg kg^{-1}), AH 7921 (5) and profadol In contrast, ICV-administered 5HT (10 μg) significantly reduced the activity of (±)-amphetamine (5 mg kg^{-1}), whilst NA (10 μg) marginally potentiated the effects of (+)-amphetamine (7·5).

As well as pethidine, AH7921 and profadol have each previously been classified as narcotic analgesics. Consequently it appears that, irrespective of chemical structure, narcotic agonist and partial-agonist analgesics will be potentiated by ICV-administered 5HT and antagonized by NA, whilst agents with a different anti-nociceptive action will interact with