The results have shown that the imipramine-induced marked blockade of the neuronally evoked responses of the guinea-pig and rat bladders—the preparations known to be atropine resistant—could not be due to its atropine-like action. Imipramine exhibits local anaesthetic action (Sigg, 1959; Ritchie & Greengard, 1961) and procaine has been reported to block the neuronally evoked responses of the guinea-pig (Weetman, 1972) and the rat bladders (Huković & others, 1965; Dhattiwala, Jindal & Kelkar, 1970). It therefore seems reasonable to attribute the powerful blocking effect of imipramine to its procaine-like action at the nerve terminals and the adjacent effector cell membrane; only the latter recovers fully on repeated washes as shown by full recovery of acetylcholine responses and only partial recovery of the neuronal responses. To what extent the local anaesthetic action of imipramine might be involved in human nerve-bladder transmission is a problem worth investigating.

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The effect of methysergide on 5-hydroxytryptamine turnover in whole brain

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Considerable evidence has been accumulated to support the concept that methysergide bimaleate acts by blocking 5-hydroxytryptamine (5-HT) receptors (Nerebski, Romanowski & Kadjiela, 1962; Dewhurst & Marley, 1965; Koella, 1966; Banna & Anderson, 1968; Clineschmidt & Anderson, 1970; Marin, 1970). We have undertaken to determine the effect of methysergide on concentrations of 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) in whole brain and to consider the results in terms of the hypothesis that 5-HT receptor blockade causes increased 5-HT turnover. To examine the effect of simultaneous dopaminergic blockage relevant to the action of methiothepin, experiments were also performed in which haloperidol was given simultaneously with methysergide.

White male guinea-pigs (225–250 g) were given different dosages of methysergide (UML-491, Sandoz, Inc.) and haloperidol (Haldol, McNeil Labs., Inc.) subcutaneously. Animals were housed under conditions of standard laboratory lighting and had free access to food and water. Upon completion of desired treatment intervals animals were decapitated, brains rapidly removed and plunged into liquid nitrogen. 5-HT and 5-HIAA were determined spectrophotofluorometrically by the method of Curzon & Green (1970).

† Correspondence.

Table 1 shows the effect of various drug regimes on whole brain 5-HT and 5-HIAA concentrations (expressed as a percentage of controls). Methysergide (3 mg kg^{-1}) significantly decreased the 5-HT content of whole brain at 15 min ($P < 0.05$). At 60 to 120 min, there was no significant alteration in whole brain 5-HT with methysergide (3 and 10 mg kg^{-1}). Haloperidol 0·5 mg kg^{-1}, failed to alter 5-HT concentrations at 120 min while 10 mg kg^{-1} caused a significant increase in whole brain 5-HT at 120 min ($P < 0.01$). The simultaneous administration of methysergide and haloperidol at two different dosages had no effect on whole brain 5-HT at 120 min. Various drug regimes were ineffective in altering whole brain 5-HIAA concentrations (all > 0.2).

The failure of methysergide to alter 5-HIAA concentrations in the present study suggests that it does not change 5-HT turnover in whole brain. Andén, Corrodi & others (1968) also noticed no increase in 5-HT synthesis after methysergide (0·2 mg kg^{-1}, i.p.) in conjunction with a 5-HT synthesis inhibitor. These findings raise questions concerning the site(s) of action of methysergide and the generality of synaptic regulatory mechanisms drawn from the study of other neurotransmitter systems.

The increase in homovanillic acid (HVA) concentrations following receptor blockade is probably a consequence of increased dopamine turnover (Andén,

Table 1. *Effect of various drug regimes on whole brain 5-HT and 5-HIAA content.* Values given as percentages of normal. Control animals were given a saline pretreatment and were routinely included in every assay. Significance was evaluated by Student's *t*-test (2-sided). The number of samples in each measurement is indicated in parentheses. Respective control groups consisted of at least six animals and had an absolute average of 5-HT 297 ± 27 ng g^{-1} and 5-HIAA 62 ± 10 ng g^{-1}. None of the values of 5-HIAA achieved statistical significance (all $P > 0.1$).

Drug	Dose mg kg^{-1}	Post-injection time interval (min)† 15		120	
		5-HT	5-HIAA	5-HT	5-HIAA
Methysergide	3	89±6(7)*	97±22(7)	98±10(8)	102±21(8)
Methysergide	10			109±11(6)	95±19(60)
Haloperidol	0·5			98±13(6)	93±24(6)
Haloperidol	10			122±12(6)**	111±23(6)
Methysergide + haloperidol	3 0·5			109±9(6)	110±24(6)
Methysergide + haloperidol	10 10			96±9(6)	89±18(6)

* $P < 0.05$. ** $P < 0.01$.
† 60 and 90 min. 5-HT content after methysergide (3 mg kg^{-1}) 96 ± 10(8) 95 ± 11(7).
60 and 90 min. 5-HIAA content after methysergide (3 mg kg^{-1}) 94 ± 19(8) 91 ± 15(8).

Dahlstrom & others, 1966; Nyback & Sedvall, 1968) presumably due to a negative feedback neuronal loop. Conversely, stimulation of postsynaptic receptors by the direct agonist apomorphine decreased dopamine turnover, possibly operating to spare dopamine through the same feedback loop (Andén, Rubenson & others, 1967). Similarly, methiothepin, a compound with anti-5-HT as well as antidopamine and anti-noradrenaline properties, increased 5-HT turnover as evidenced by increased 5-HIAA concentrations with 5-HT concentrations unchanged (Monachon, Burkard & others, 1972; Fuller & Perry, 1974). It is tempting to attribute this increase to neuronal feedback analogous to the dopaminergic situation described above.

The failure of methysergide to alter 5-HT turnover in the present study suggests either that methysergide does not act as a central 5-HT receptor blocker, or that some other mechanism must be responsible for the methiothepin-induced increase in 5-HT turnover. The central anti-5-HT actions of methysergide have been shown in many systems. The limited data do not suggest that methiothepin is a more widespread 5-HT antagonist than methysergide, and it is difficult to reconcile the profound effect of the former on whole brain 5-HT turnover with our results.

An alternate hypothesis that methiothepin elevates 5-HIAA through some other mechanism such as a combination of its several antimonoamine properties is more probable. Previous work has shown that the noradrenergic system has an inhibitory effect on 5-HT neurons. The methiothepin-induced elevation of 5-HIAA is prevented by simultaneous treatment with clonidine, a noradrenergic agonist (Lloyd & Bartholini, 1974) while interference with noradrenergic turnover by 6-hydroxydopamine (Blondaux, Juge & others, 1973) or inhibition of dopamine β-hydroxylase (Johnson, Kim & Boukma, 1972) enhances 5-HT turnover. The antidopamine activity of methiothepin has not been studied with regard to 5-HT turnover although some data are available for other neuroleptics. In the present study haloperidol (0·5 mg kg^{-1}) failed to alter 5-HT concentrations at 120 min. At 10 mg kg^{-1} it caused a significant increase in brain 5-HT ($P < 0.01$), and this increase was abolished by simultaneous treatment with methysergide 10 mg kg^{-1}. Haloperidol in doses up to 10 mg kg^{-1} failed to alter 5-HIAA concentrations at 2 h with or without simultaneous methysergide (10 mg kg^{-1}) administration. This finding suggests two possible explanations: *i*) the methiothepin-induced increase in 5-HIAA is not related to simultaneous blockade of 5-HT and dopamine and (*ii*) methysergide does not act purely as a 5-HT receptor blocker.

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