mechanism, be increasing the excitability of spinal motoneurones (Barasi & Roberts, 1974b). Several publications, however, have indicated an opposite action of 5-HT (Clineschmidt & Anderson, 1970; Engberg, Flatman & Kadzielawa, 1974) although other reports seem to indicate an increased excitability of motoneurones following administration of monoamines and other drugs (Banna & Anderson, 1968; Marley & Vane, 1967; Sinclair & Sastry, 1974).

In recent studies with the halothane anaesthetized rat conditioning stimulation of nucleus raphes medianus increased lumbar flexor motoneurone field potentials on 22 occasions and had no effect on 10. The extensor field potentials were increased on 16 occasions and unaffected on 4. Iontophoretically applied 5-HT increased flexor potentials on 38 occasions and had no effect on 13. Similarly extensor fields were increased on 32 occasions and unaffected on 8.

To assist with the interpretation of changes in the field potential amplitude, glycine, glutamate and potassium were applied by iontophoresis into the ventral horn. Glycine reduced the amplitude of the field potential on 12 occasions, having no effect on 3. Glutamate increased the potential amplitude on 10 occasions, had no effect on 12 occasions but also reduced the field potential on 8 occasions. Potassium increased the field on 10 occasions in 24 studies but never reduced the amplitude. These observations are compatible with the suggestion that an increased field potential amplitude may be an index of increased motoneurone excitability.

A further test of this postulate involved stimulating the ventral root or muscle nerve (with lumbar dorsal roots sectioned) with 3 to 6 stimuli at 80-200 Hz. The field potential progressively declines in amplitude during the train, presumably due to the failure of propagation of the antidromic spike from axon to soma in a progressively larger proportion of the population of activated motoneurones (Eccles, 1950). 5-HT, glutamate and potassium all tended to prevent this progressive decrease in amplitude. This provides further support for the postulate that motoneurone excitability is increased by these drugs.

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The selective inhibition of 5-hydroxytryptamine re-uptake by Org 6582

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Re-uptake by the membrane pump is considered to be the major means by which monoamines are inactivated at the neural synapse. Numerous studies have shown that tertiary tricyclics, such as chlorimipramine, preferentially inhibit the membrane amine pump of central 5-hydroxytryptaminergic (5-HT) neurones whereas secondary tricyclics, such as desipramine, preferentially block the membrane amine pump of central noradrenergic (NA) neurones (Bopp & Biel, 1974). Several recent reports have emphasized the desirability of compounds exerting a specificity of effect on monoamine re-uptake (Iversen, 1974; van Praag, 1974). The studies to be reported reveal Org 6582 (*dl*-8-chloro-11-anti-amino-benzo-(b)-bicyclo [3.3.1] nona-3,6a (10a) diene hydrochloride) to be a selective inhibitor of 5-HT re-uptake.

In vivo blockade of 5-HT re-uptake was studied

by investigating the effect of drug pretreatment on the ability of *p*-chloroamphetamine to lower rat brain 5-HT levels. Intraperitoneally administered Org 6582 was approximately twice as potent as fluoxetine, five times more potent than chlorimipramine and 14 times more potent that desipramine in blocking the ability of *p*-chloroamphetamine to lower brain 5-HT content. Org 6582, whilst having no effect on amine steady-state levels, decreased rat brain 5-HT turnover. Rat brain 5-hydroxyindole acetic acid (5-HIAA) levels were also decreased by Org 6582. The reduction in both 5-HT turnover and 5-HIAA levels is in all probability due to re-uptake blockade.

Peripheral *in vivo* blockade of NA re-uptake was determined by measuring the effect of drug pretreatment on the ability of (−)-metaraminol to lower rat heart NA levels. The i.p. ID_{50} values for desipramine and chlorimipramine were 5.5 mg/kg and 29.6 mg/kg respectively. Org 6582 (60 mg/kg i.p.) did not antagonize the (−)-metaraminol-induced fall in rat heart NA content. Central catecholaminergic re-uptake was studied by investigating the effect of i.p. drug pretreatment on the ability of intraventricularly administered 6-hydroxydopamine (100 μg) to lower rat brain NA and dopamine (DA) levels. The 6-hydroxydopamine-induced fall in rat brain DA content was unaltered by the prior injection of either Org 6582 (60 mg/kg), chlorimipramine (60 mg/kg) or desipramine (30 mg/kg). Pretreatment with either chlorimipramine (60 mg/kg) or desipramine (30 mg/kg), but not with Org 6582 (60 mg/kg), blocked the reduction in brain NA content elicited by 6-hydroxydopamine. Org 6582 had no effect either on steady-state levels or on the turnover of NA and DA in the rat brain.

The results of this study reveal Org 6582 to be a potent selective inhibitor of 5-HT re-uptake.

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Effect of LSD on rat brain 5-hydroxytryptamine metabolism at elevated environmental temperature

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Rat brain tryptophan and 5-hydroxyindoleacetic acid (5-HIAA) concentrations (Tagliamonte, Tagliamonte, Perez-Cruet, Stern & Gessa, 1971) and the firing of 5-hydroxytryptamine (5-HT) containing neurones (Weiss & Aghajanian, 1971) are increased at elevated temperature. The latter two changes appear related, as both are blocked by D-lysergic acid diethylamide (LSD) (Weiss & Aghajanian, 1971). Their relationship to the tryptophan increase is unclear as although this can increase brain 5-HT turnover (Tagliamonte *et al.*, 1971; Knott & Curzon, 1972) additional 5-HT formed is not necessarily released to the synapse. Therefore, we have studied the effects of a 40° C environment on tryptophan disposition and on brain 5-HT metabolism and their modification by LSD.

Male Sprague-Dawley rats (180-200 g) were caged in eight groups of three in a chamber at 25° ± 2° C. Four groups were transferred to a chamber at 40° ± 3° C for 60 min and then killed. LSD tartrate (500 μg/kg i.p.) was given to two of the test groups (40° C) immediately before transfer, and to two control (25° C) groups. Plasma tyrosine, total and free tryptophan and brain tyrosine, tryptophan, 5-HT and 5-HIAA were determined (Curzon, Joseph & Knott, 1972; Knott & Curzon, 1972).

Exposure to 40° C increased plasma total and free tryptophan but not percentage free tryptophan. Brain tryptophan increased markedly, 5-HIAA moderately and 5-HT was not significantly altered (Table 1). Plasma and brain tyrosine were significantly increased (75 and 95% respectively). LSD had no significant effect on either brain or plasma tryptophan, but significantly decreased 5-HIAA (Table 1). The fall was greater at 40° C so that the drug treated rats at both temperatures had similar values.

In another experiment, the rats were given L-tryptophan (50 mg/kg i.p.) 15 min after transfer to the 40° C chamber and then killed 45 min later.