Uptake of [^{3}H]5-hydroxytryptamine and [^{3}H]noradrenaline by slices of rat brain incubated in plasma from patients treated with chlorimipramine, imipramine or amitriptyline

Great interest has been focused in recent years on the purported role of monoamines in the depressive syndrome (for review see McClure, 1971). Monoamine systems in the brains of various species have been mapped out (Fuxe, 1965; Ungerstedt, 1971) and noradrenaline nerve terminals have been demonstrated in human cerebral cortex (Nyström, Olsson & Ungerstedt, 1972). Tricyclic antidepressants have been shown to be effective in about 60% of depressions treated (Bennet, 1967). These drugs affect the monoamine neuron by inhibiting the uptake of the released transmitters noradrenaline and/or 5-hydroxytryptamine (5-HT) through the membrane pump of the nerve terminals. Various tricyclic antidepressants have different profiles of potency in inhibiting the uptake into noradrenaline and 5-HT nerve terminals, each drug having its own pattern (Carlsson, Corrodi & others, 1969; Shaskan & Snyder, 1970; Lidbrink, Jonsson & Fuxe, 1971; Ross, Renyi & Ögren, 1972). We have previously studied the active uptake of [^{3}H]noradrenaline (^{3}H-NA) and [^{3}H]5-hydroxytryptamine (^{3}H-5-HT) into their respective nerve terminals by using slices of rat cerebral cortex incubated in human plasma which was drawn from patients before and during treatment with antidepressant drugs (Hamberger & Tuck, 1973).

In the present study, plasma from patients taking chlorimipramine, imipramine or amitriptyline was incubated according to this method in order to elucidate the effect of clinical doses on noradrenaline and 5-HT neurons.

Female Sprague-Dawley rats were killed, immediately decapitated and their brains removed. Thereafter, small cortical slices (about 0·05 mm thick, 3 mm in diameter and weighing approximately 5 mg) were dissected out as previously described (Hamberger & Tuck, 1973). The slices were then incubated at 37° in heparinized patient plasma which had been centrifuged at 10 000 *g* for 30 min and then stored frozen for 1–2 months. All patients were hospitalized and were deemed to be depressed and in need of tricyclic antidepressants by independent psychiatrists. Some patients were given chlorimipramine intramuscularly twice daily in a dose of 25–50 mg, others were given either imipramine or amitriptyline (the choice was made arbitrarily at a dosage of 3 × 50 mg by mouth three times daily, except three patients who received 25 mg three times daily). The results are expressed as per cent of uptake of added ^{3}H-NA or ^{3}H-5-HT by slices incubated in each patient's drug free plasma taken before therapy was initiated (Hamberger & Tuck, 1973).

From Table 1 it is seen that only chlorimipramine produced a pronounced blockade of the neuronal uptake of ^{3}H-5-HT. Imipramine and amitriptyline produced little or no blockade of the 5-HT uptake. In all three groups a blockade of the ^{3}H-NA uptake was obtained. This was most marked in the imipramine group and least in the chlorimipramine group.

The values of the 5-HT and noradrenaline membrane pump blockade ought not to be compared, as they are derived from experiments in two different model systems using different isotope concentrations and are expressed as per cent of their own controls rather than in absolute figures (*cf.* Hamberger & Tuck, 1973).

Our results are in good agreement with those obtained in model experiments where amitriptyline and imipramine were less potent on the 5-HT membrane pump than chlorimipramine (Carlsson & others, 1969; Hamberger & Tuck, 1973). Of the drugs tested here only chlorimipramine produced a blockade of the 5-HT membrane pump.

Table 1. *Uptake of [^{3}H]noradrenaline and [^{3}H]5-hydroxytryptamine by rat cerebral slices incubated in plasma from patients treated with tricyclic antidepressants.*

Drug	Number of patients*	Uptake of ^{3}H-5-HT as % of control**	Uptake of ^{3}H-NA as % of control ***
Chlorimipramine (25–50 mg i.m. twice daily)	9	72 ± 5	43 ± 3
Imipramine orally (25–50 mg thrice daily)	10	97 ± 6	33 ± 3
Amitriptyline orally (25–50 mg thrice daily)	10	93 ± 5	39 ± 3

* The same patient's plasma was in separate experiments incubated both with ^{3}H-NA and ^{3}H-5-HT.

** The slices were first incubated in the patient's plasma for 15 min before addition of ^{3}H-5-HT to a final concentration of 2×10^{-9}M. After incubation for 15 min, the slices were quickly rinsed in drug-free Krebs Ringer bicarbonate buffer for a few seconds and the radioactivity was determined. The values are calculated as % of the ^{3}H-5-HT uptake in plasma, drawn before treatment. The values are expressed as the mean ± s.e.

*** The procedure was as for ^{3}H-5-HT except that final concentration of ^{3}H-NA was 2×10^{-8}M.

The mean uptake of ^{3}H-5-HT by the 5-HT membrane pump obtained after chlorimipramine (72%) would roughly correspond to a plasma concentration of 10^{-7} M. Imipramine and amitriptyline, in clinical dosage predominantly inhibited the noradrenaline membrane pump. However, these compounds were administered by different routes. The oral administration permits metabolism via the liver, and thus perhaps a more pronounced effect of metabolites, whereas the intramuscular injection initially by-passes the liver. It has been suggested that endogenous depression is a biochemically heterogeneous syndrome and that dysfunction of either the noradrenaline or 5-HT transmitter systems may be involved (see Sjöqvist, 1971). The present results demonstrate an inhibitory effect of chlorimipramine in clinical use on 5-HT neurons.

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REFERENCES

BENNET, I. F. (1967). In *Antidepressant Drugs*, p. 375. Editors: Garattini, S. & Dukes, M. N. G. Amsterdam: Excerpta Medica.
CARLSSON, A., CORRODI, H., FUXE, K. & HÖKFELT, T. (1969). *Eur. J. Pharmac.*, **5**, 357–366.
FUXE, K. (1965). *Z. Sellforsch.*, **55**, 573–596.
HAMBERGER, B. & TUCK, J. R. (1973). *Eur. J. clin. Pharmac.*, **6**, 229–235.
LIDBRINK, P., JONSSON, G. & FUXE, K. (1971). *Neuropharmac.*, **10**, 521–536.
MCCLURE, D. J. (1971). *Can. Psychiat. Ass. J.*, **16**, 247–252.
NYSTRÖM, B., OLSON, L. & UNGERSTEDT, U. (1972). *Science*, **176**, 924.
ROSS, S. B., RENYI, A. L. & ÖGREN, S.-O. (1972). *Eur. J. Pharmac.*, **17**, 107–112.
SHASKAN, E. G. & SNYDER, S. H. (1970). *J. Pharmac. exp. Ther.*, **175**, 404–418.
SJÖQVIST, F. (1971). *Int. Pharmacopsychiat.*, **120**, 147–169.
UNGERSTEDT, U. (1971). *Acta physiol. scand.*, Suppl. **367**, 1–48.