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Plasma protein binding of tricyclic antidepressive drugs

It has been shown (Yates, Todrick & Tait, 1964) that tricyclic antidepressive drugs inhibit the uptake of 5-hydroxytryptamine (5-HT) by human blood platelets. We have examined the effects of imipramine, chlorimipramine, desipramine and trimipramine on this system both in plasma and in protein-free physiological medium (Cooley & Cohen, 1967). The concentrations of the more potent inhibitors used are similar to those found in the plasma of patients on therapeutic dosage.

The results in Fig. 1 show that the platelets in the protein-free medium are more sensitive to the inhibiting action of the drugs than those in plasma. Statistical analysis shows that the slope of the two inhibition (%) : concentration curves for each drug are not significantly different; this permits calculation of the potency ratios between the two media (Finney, 1964). It also suggests that the drug-induced inhibition of uptake of 5-HT by platelets in plasma and buffer is due to the same phenomenon. Furthermore, if the drug-induced inhibition of uptake by the platelets is reduced in the presence of plasma because of pharmacological inactivation of the drugs by protein binding, it allows an assessment of the "percentage free drug" to be calculated. (An alternative explanation, that the treatment which the platelets had received has in some way damaged them and increased their sensitivity, is not supported by evidence since the endogenous platelet 5-HT concentrations and uninhibited uptake remain substantially unaltered on transfer from plasma to buffer.) The "percentage free drug" and the values for the inhibitory potencies in each medium are given in Table 1; also included are figures from a previous investigation (Todrick & Tait, 1969). The inhibitory potencies are expressed as the negative logarithms of the concentration of the drug which causes 50% inhibition of 5-HT uptake (pI50). Our results for "percentage free drug" are within the fairly wide range of results reported by other workers using ultrafiltration and dialysis techniques [Borgå, Azarnoff & Sjöqvist, 1968; Bickel & Weder, 1968; Crammer (personal communication) finds approximately 20% free imipramine]. This suggests that these drugs are inactive when bound to plasma protein but proof of this point awaits definitive physico-chemical studies.

Table 1. *Calculated "percentage free drug" values and inhibitory potencies in plasma or buffer for four tricyclic antidipressive drugs*

Drug	Percentage free drug (with 95% fiducial limits)		pI50 Buffer medium	pI50 Plasma (75%)	pI50 Plasma (75%) (Todrick & Tait, 1969)
Imipramine	23·8	(18·5–30·4)	6·56	5·94	5·71
Desipramine	27·0	(23·5–30·8)	5·63	5·05	5·02
Chlorimipramine	8·4	(7·4–9·6)	7·74	6·68	6·50
Trimipramine	15·7	(12·8–18·8)	4·88	4·06	3·92

The composition of the buffer medium (Cooley & Cohen, 1967) was (mmol litre^{-1}): Na^+ 142, K^+ 5, Mg^{++} 0·29, phosphate 45, pH 7·6, glucose 5·5.

Blood was taken from a large group of healthy volunteers.

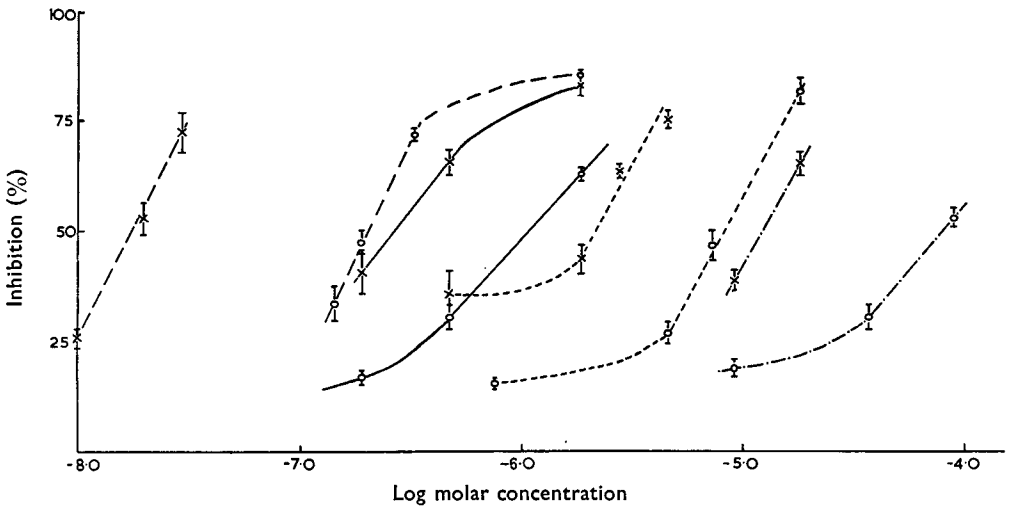

FIG. 1. Inhibition of 5-HT uptake by platelets. Incubation of platelets was with 5-HT 1 μg/ml at 37° in 75% plasma (○), in phosphate buffer (×). Drugs tested were imipramine ——, desipramine - - -, chlorimipramine — — —, trimipramine - · - ·.

In this group of drugs, there is a 400-fold range in inhibitory potency in respect of 5-HT uptake but only a three-fold range in our assessed "percentage of free drug" (8·4—27%). Such potency differences cannot therefore be adequately explained in terms of differing percentages of free drug (an idea advanced by Borgå & others (1968) as a possible explanation of species differences in sensitivity to drugs of this class). Furthermore, the most potent drug is apparently the most strongly bound to proteins and the least potent drug is the next most strongly bound.

It must be concluded that the differences in potency in this group of drugs depends more on their individual molecular structure than on their degree of binding to circulating proteins. The potency ranking reported here is identical with that found by Carlsson, Corrodi & others (1969) in studies on rat brain hydroxytryptaminergic neurons.

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