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Relation between the Effects of Antidepressant Drugs on the Uptake of Monoamines and on the Spontaneous Activity of Central Neurons (1)

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Tricyclic antidepressants are characterized by their inhibitory effect on the reuptake of noradrenaline (NA) and of 5-hydroxytryptamine (5-HT) by nerve endings. Secondary aminated derivatives (desipramine, nortriptyline) are more potent inhibitors of NA uptake than their tertiary aminated analogues (imipramine, chlorimipramine and amitriptyline) which are more potent blockers of 5-HT uptake (Carlsson *et al.*, 1969*a*, *b*; Ross and Renyi 1975).

Electrophysiological studies have demonstrated that these drugs decrease the frequency of discharge of the noradrenergic neurons of the locus coeruleus (L.C.) (Nybäck *et al.*, 1975) and of the serotonergic neurons of the dorsal raphe (D.R.) (Sheard *et al.*, 1972). In a previous work, these drugs were perfused intravenously in order to determine the total dose necessary to reduce the frequency of discharge to 50 % of the control rate (ID_{50}) and to perform a quantitative comparison of various antidepressant drugs (Scuvée-Moreau and Dresse, 1979). A complementary study was initiated to investigate the inhibition of the reuptake of NA and of 5-HT corresponding to the perfusion of these tricyclic antidepressants at the doses which reduce to 50 % the frequency of discharge of L.C. and D.R. neurons. The inhibition of the uptake of ^{14}C-NA and ^{3}H-5-HT was measured simultaneously on cerebral cortex slices.

The preliminary results, obtained with the dibenzazepine derivatives desipramine, imipramine and chlorimipramine, are represented in Table I. These drugs, perfused at the doses which reduce to 50 % the activity of L.C. neurons, cause a similar inhibition of about 40–50 % of the reuptake of NA. In the same way, perfusion of these drugs at the doses which decrease to 50 % the activity of D.R. neurons induces a similar inhibition of about 20 % of the reuptake of 5-HT.

In the case of desipramine the dose perfused of 12 mg kg^{-1} was not sufficient to decrease the activity of D.R. neurons and the inhibition of the uptake of 5-HT was not significant.

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It can be concluded that the perfusion of these drugs at the doses which reduce to 50 % the activity of L.C. and D.R. neurons causes a more pronounced corresponding inhibition of the reuptake of NA than of the reuptake of 5-HT. Other experiments will be necessary to complete these results and to elucidate their meaning. One possibility is that the serotonergic neurons of the dorsal raphe are more sensitive to an accumulation of the transmitter than the noradrenergic neurons of the locus coeruleus.

TABLE I

Percentage of inhibition of the uptake of ^{14}C-NA and ^{3}H-5-HT in cortex slices induced by three tricyclic antidepressants, perfused at the doses (ID_{50}) necessary to produce a 50 % decrease in the frequency of discharge of locus coeruleus (L.C.) and dorsal raphe (D.R.) neurons

Drug	ID_{50} (mg kg^{-1})		% Inhibition of Uptake		n
	L.C.	D.R.	^{14}C-NA	^{3}H-5-HT	
Desipramine	0.3		40 ± 4	N.S.	8
		>12	81	N.S.	1
Imipramine	1.4	1.4	53 ± 5	23 ± 6	3
Chlorimipramine	3		43 ± 2	51 ± 2	6
		0.35	N.S.	19 ± 3	6

n = number of experiments; N.S. = not significant.

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