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

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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, nortriptiline) 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., 1969a, 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.) (Nyberg 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 (Scuvèe-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 $^{3}$H-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.

References


(1) Communication at the meeting of the Belgian Physiological and Pharmacological Society, Namur, November 17, 1979.
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

<table>
<thead>
<tr>
<th>Drug</th>
<th>ID$_{50}$ (mg kg$^{-1}$)</th>
<th>% Inhibition of Uptake</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>L.C.</td>
<td>D.R.</td>
</tr>
<tr>
<td>Desipramine</td>
<td>0.3</td>
<td>&gt;12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Chlorimipramine</td>
<td>3</td>
<td>0.35</td>
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n = number of experiments; N.S. = not significant.

**References**


Dopamine (DA) was infused into the 3rd ventricle of 2 goats. The 3rd ventricle of hydrated goats was infused into the supraoptic nucleus (SNO) flow (Gueguen et al., 1983). Experiments reported here were performed into the 3rd ventricle using osmotic pumps and salt excretion.

Under general anesthesia, a catheter was placed into the anterior chamber of both eyes and connected to a cannula via this cannula either 50 or 100 μl/min. Most of the 50 μl/min water per kg body weight was given by the catheter. The urinary osmolality was measured with the above system. Sodium and potassium were measured with the above system. Plasma flow (RPF) was measured with the above system.

Infusion of DA (0.1 mg/kg) into the 3rd ventricle of both goats induced a reduction in urinary Na+ and Cl− concentrations (exposure to Na+ and K+) and the Na+ and K+ content of the herbivore gland. Infusion of NE (Vandepitte et al., 1982) into the 3rd ventricle of both goats induced a decrease in urinary Na+ and K+ concentrations (exposure to Na+ and K+) and the Na+ and K+ content of the herbivore gland. Infusion of NE (Vandepitte et al., 1982) into the 3rd ventricle of both goats induced a decrease in urinary Na+ and K+ concentrations (exposure to Na+ and K+) and the Na+ and K+ content of the herbivore gland.