COMPARISON OF AFFINITY FOR MODEL MEMBRANES AND RELATIVE HYDROPHOBICITY OF CHEMICALLY DIFFERENT ANTIDEPRESSANTS

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The writers previously reported close correlation between the ability of antidepressants belonging to different chemical groups to change the surface charge density of the lipid phase of biological membranes and the effect of these compounds on reassimilation of neurotransmitters by synaptosomes [1]. It was therefore interesting to study whether interaction between antidepressants and model phospholipid membranes is the simple passage of these compounds from water into an organic solvent (if liposomes can be regarded as such), and also to compare the relative hydrophobicity of the substances and their neurochemical characteristics.

EXPERIMENTAL METHOD

Interaction of antidepressants with a bicyclic (befuraline), tricyclic (imipramine, desmethylimipramine, chlorimipramine), and tetracyclic (pyrazidole) structure with liposomes was studied as described previously [1]. The effect of the drugs in concentrations of 50 and 500 μM on neurotransmitter accumulation was studied on the coarse synaptosomal fraction of rat brain by a radioisotope method [2]. The relative hydrophobicity of the compounds was estimated from their partition coefficients in a two-phase water—organic system of N-octanol and water. The test preparation was dissolved in 1 ml of distilled water, 1 ml octanol was added, and the system was vigorously mixed on a laboratory mixer for 2 min. The resulting emulsion was centrifuged at 4000g for 20 min, after which serial dilutions were prepared from each phase and the volume of the samples was made up to 3 ml. Absorption spectra of the antidepressants were photographed on the Perkin-Elmer 402 spectrophotometer (USA). Quantitative determination of the drugs in the samples was carried out on an SF-16 spectrophotometer at wavelengths corresponding to the absorption maxima of the compounds. The data were processed and correlation analysis carried out on a TI-51-III electronic calculator (Italy). The crystalline preparation of pyrazidole was generously provided by Academician of the Academy of Medical Sciences of the USSR M. D. Mashkovskii.

EXPERIMENTAL RESULTS

Nowadays to estimate the relative hydrophobicity of compounds the method of investigating their distribution in two-phase water—organic systems is widely used [6-8]. A system of N-octanol and water is most commonly adopted [3-5], and it was chosen in this case to assess the relative hydrophobicity of chemically different antidepressants.

Values of the partition coefficient (K_p) of the preparations in this system and their natural logarithms are given in Table 1.

The results indicate that the most hydrophobic of the compounds tested is the bicyclic antidepressant befuraline. Demethylation of the nitrogen atom in the side chain (in the case of desmethylimipramine) was not reflected in the relative hydrophobicity of the compound, whereas substitution of a halogen in the tricyclic system (chlorimipramine) increased the hydrophobicity of the preparation. The tetracycline antidepressant pyrazidole had less affinity for octanol than befuraline and chlorimipramine, but it was more hydrophobic than imipramine and desmethylimipramine. On the whole imipramine, desmethylimipramine, and pyrazidole have stronger affinity for water ($K_p < 1$) whereas befuraline and chlorimipramine have stronger affinity for octanol ($K_p > 1$).

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TABLE 1. Characteristics of Distribution of Antidepressants in n-Octanol—Water System (M ± m)

Compound	K_p	ln K_p
Imipramine	0,163±0,023	—1,814±0,127
Desmethylimipramine	0,168±0,024	—1,784±0,125
Chlorimipramine	1,45±0,11	0,372±0,03
Befuraline	3,79±0,3	1,332±0,09
Pyrazidole	0,69±0,06	—0,371±0,03

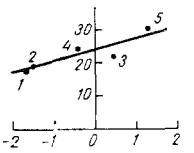

Fig. 1. Correlation between relative hydrophobicity of chemically different antidepressants and their effect on serotonin reassimilation by synaptosomes. 1) Imipramine, 2) desmethylimipramine, 3) chlorimipramine, 4) befuraline, 5) pyrazidole. Concentration 500 μM. Abscissa, ln K_p; ordinate, serotonin uptake (in %).

Comparison of the data with those for interaction between antidepressants and model phospholipid membranes revealed close correlation between the binding constants of the antidepressants with model membranes and their partition coefficients in an n-octanol—water system ($r = 0.8$). Meanwhile correlation was absent between the relative hydrophobicity of the antidepressants, the relative number of binding centers and the total affinity of the compounds for model phospholipid membranes, and also with the effect of the compounds on the surface charge density of the lipid phase of biological membranes. Interaction of the antidepressants with model phospholipid membranes thus differs in the case of the compounds tested from simple passage of the compounds from water into an organic solvent, although the binding constants are determined by the relative hydrophobicity of the substances.

Assessment of relations between the neurochemical and physicochemical characteristics of these antidepressants revealed close correlation between the relative hydrophobicity of the compounds and their effect, in a concentration of 500 μM, on reassimilation of serotonin by synaptosomes ($r = 0.9$). However, there was no correlation between the relative hydrophobicity of these substances and their neurochemical effects in a concentration of 50 μM, or with their effect on reassimilation of noradrenalin and dopamine by synaptosomes (in a concentration of 500 μM).

The results confirm the previous hypothesis that accumulation of cations by antidepressants in the lipid bilayer of presynaptic membranes and changes in surface charge density of the membranes connected with this process may be the cause of the disturbance of functional activity of the neurotransmitter transport system through the presynaptic membranes; interaction of antidepressants with the lipid bilayer of the membranes, moreover, differs from the simple passage of the substance from water into an organic solvent.

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