PHARMACOLOGY

THE SIGNIFICANCE OF SULFHYDRYL GROUPS IN THE ACTION OF DERIVATIVES OF QUATERNARY AMMONIUM BASES (RE: THE ACTION MECHANISM OF THE GANGLIOBLOCKING DRUGS)

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Substances blocking the synaptic transmission of impulses in the autonomic ganglia have become widely used of recent years since the most different branches of practical medicine have found them of value. However, the all-purpose use of these drugs is hampered because of the insufficient information available on the nature of the processes which occur when synaptic transmission is blocked.

It has now been recognized that acetylcholine plays a leading role in stimulation transmission through the autonomic ganglia, and this has made it possible to divide all ganglioblocking substances into two groups: depolarizing substances (which act like excess concentrations of acetylcholine) and competitive substances (which prevent the action of acetylcholine on the ganglionic cholinergic structures) [17]. Because of their chemical proximity to acetylcholine, one group of ganglioblocking agents — derivatives of quaternary ammonium bases — are regarded by a majority of authors [1, 10, 18 et al.] as possessing the competitive type of action. There has been experimental verification of this proposal, and we ourselves recently obtained results corroborating the fact that the action mechanism of this group of gangliolitics is competitive [12].

Although there has been some progress in research investigating the intimate action mechanism of ganglioblocking agents, the literature still contains hardly any information concerning the biochemical structures which participate in the processes effecting the conduction of impulses through the ganglia. The works of M. L. Belen’kii [3, 4 et al.] have demonstrated the role played by disturbances in the carbohydrate metabolism and by the associated accumulations of high-energy phosphorus compounds in the action of substances influencing the cholinergic structures of the carotid sinus. N. B. Vysotskaya [5] succeeded recently in showing that ganglionic blockade by means of the depolarizing type of substance, particularly nicotine, is attended by changes in the content of high-energy phosphorus compounds, while the content of ATP in the ganglionic tissue is not materially affected by substances with the competitive type of action.

The question of the possible participation of ganglioblocking substances as in the metabolic processes, and particularly in the protein metabolism, is of special interest. In their many works, Kh. S. Koshtoyants and his co-workers [6, 7, 10, 11, 13 et al.] have assembled a considerable number of factors, which suggest that cholinergic stimulation, as well as the action of artificially introduced acetylcholine, is a process immediately connected with nerve cell metabolism and which occurs with the active participation of acetylcholine in the biochemical transformations of the innervated tissues. In these investigations, Kh. S. Koshtoyants lays particular emphasis on the role of the sulfhydryl groups as the most reactive and labile of the groups contained in the protein molecule.

Considering the role of sulfhydryl groups in the action mechanism of acetylcholine and taking into account the competitive effects caused by gangliolitics which are derivatives of quaternary ammonium groups, we decided to demonstrate the effect of the latter under conditions in which the content of sulfhydryl groups was changed.
The experiments were performed on isolated biological subjects (isolated heart of a frog, rectus abdominis muscle of a frog) and on intact animals (cats and white mice). Cysteine was used to provide surplus sulfhydryl groups; urea was also used, as in the opinion of many authors, it possesses the ability to break up the protein molecule and liberate the reactive sulfhydryl groups [2, 8, 14 et al.]. We used a thiol poison, cadmium chloride, to bind the tissue sulfhydryl groups. The ganglioblocking substances used were different salts of hexamethylene-1, 6-bis-trimethylammonium: the iodide (Hexonium), the pyridine-3-carbonate (Hexonate), and the benzoate. All the substances were dissolved in a Ringer's solution for use in the experiments on the isolated organs, while aqueous solutions were used in the experiments on the animals. A total of 45 experiments were performed on a frog's heart isolated according to Straub; 20 experiments were performed with the frog's rectus abdominis muscle, and 12 acute experiments were performed on cats. We used 50 mice in the experiments determining the toxicity of the gangliolytics.