ON THE CHARACTERISTICS OF THE CENTRAL ACTION OF GANGLIONIC BLOCKING AGENTS

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The biochemically-reactive structures of the central nervous system have the property of reacting to substances with both nicotinic and muscarinic action [2, 3, 5, 6, 8]. Thus, the presence of the corresponding n- and m- cholinergic structures can be considered in the central nervous system (according to the classification proposed by S. V. Anichkov [1]). Valuable materials for the study of this problem can be obtained by investigating the action of pharmacological agents from the group of parasympatholytics, which block the specific reactions that arise when the two above types of biochemically active structures participate.

In studying the group of parasympatholytic substances – derivatives of quarternary ammonia compounds, we obtained data which indicated the presence of n-cholinergic structures in the central nervous system [12]. It was shown that tetraethylammonia (TEA), the derivatives pentamethylene-bis-and hexamethylene-bis (trimethylammonia) have the property of blocking the typical reaction of frogs to nicotine, the central nature of which was proved by a number of works [4, 9, 11, et al.,].

In the present communication,data are presented which touch on the further study of the central parasympatholytic action of a number of ganglionic blocking agents – quarternary ammonia derivatives.

EXPERIMENTAL METHODS

The experiments were carried out on white mice weighing from 15 to 23 g. Nicotinic (0.6-0.8 mg nicotine base intraperitoneally) and arecoline (0.4-0.6 mg of arecoline hydrobromide subcutaneously) spasms were caused in mice and the effect of the following ganglionic blocking agents were tested on them: 1) the iodine salt of hexamethylene-bis(trimethylammonium) (synonym: hexamethonium), 2) the iodine salt of hexamethylene-bis (triethylammonium), 3) the dipyridine-β-carboxylic salt of hexamethylene-bis (trimethylammonium), 4) the iodine salt of tetraethylammonium (synonym: tetamon-I), 5) the pyridine-β-carboxylic salt of tetraethylammonium 6) the bromide salt of pentamethylene-bis (quinolinedimethylammonium).* Endurable dosages were prepared of each of these preparations corresponding to their biological activity, determined by establishing the minimum lethal dose (DL_{50}).

EXPERIMENTAL RESULTS

Hexamethylene-bis(trimethylammonium) in doses of 0.5 - 1 mg and hexamethylene-bis(triethylammonium) in doses of 0.4-0.7 mg proved to be ineffective: they did not block spasms and did not inhibit mortality after administration of an absolute lethal dose of nicotine (0.8 mg). Out of 16 mice which had been administered this

* The tetamon-I and pentamethylene-bis (quinolinedimethylammonium)-dibromide were synthesized by I. B. Simon at the Ukrainian Institute of Experimental Endocrinology, the rest of the preparations by A. I. Lopushansky at the Chernovitsy Medical Institute.

dose of nicotine, 14 died after the injection of hexamethonium; preliminary administration of hexamethonium caused the death of 13 mice out of 14. In the same way, 12 mice which received hexamethylene-bis (triethylammonium) died of spasms either before or after injection of a lethal dose of nicotine. The salt of hexamethylene-bis(trimethylammonium) and nicotinic acid, named hexonat by us, proved considerably more effective.

The preliminary administration of hexonat (0.4-3 mg intraperitoneally) to 24 mice ensured "protection" against a lethal dose of nicotine and eliminated nicotinic spasms completely or partially in the majority of cases. Of 14 mice which received 1 mg of hexonat, 4 animals died following the subsequent administration of an absolute lethal dose of nicotine; consequently, the percentage of mortality decreased 3 times in comparison with control experiments. Similar data were obtained with the subsequent administration of hexonat to 16 mice which had received a lethal dose of nicotine: only 4 mice died.

The antispasmodic action of the iodine salt of TEA and its homolog, the salt of tetraethylammonium and nicotinic acid and named tetronat by us, was studied on 30 animals. The iodine salt of TEA did not affect the nature or outcome of the nicotine reaction substantially. In contrast, to this, tetronat proved to be sufficiently effective, especially when administered subsequently (at the height of the spasms). Out of 18 mice which received an absolute lethal dose of nicotine and tetronat, 12 survived, and spasms were almost completely absent among them; only a slight tremor of the body and tail, greater mobility were noted. For control, experiments were set up to study the nicotinolytic effect of nicotinic acid and its sodium salt. All 12 mice which received a lethal dose of nicotine died, in spite of the administration of nicotinic acid (in a dose of 1-5 mg) or of its sodium salt (in a dose of 0.8-5 mg).

Nicotinolytic Action of Ganglionic Blocking Agents on White Mice Administered a Lethal Dose of Nicotine

Ganglionic blocking agent	Dose (in mg)	Experimental results
Hexamethylene-bis(trimethylammonium)	0.5	4/4
	0.6	5/6
	0.8	8/10
	1.0	10/10
Hexamethylene-bis(triethylammonium)	0.4	4/4
	0.5	4/4
	0.7	4/4
Hexonat	0.4	2/5
	0.5	1/6
	0.6	1/5
	0.75	0/4
	1.0	4/14
	1.4	1/3
	3.0	1/3
Tetraethylammonium	1.0	4/4
	2.0	4/4
	3.0	4/4
Tetronat	0.5	2/2
	0.7	1/4
	0.75	1/4
	1.0	1/3
	2.0	0/2
	3.0	1/3
Pentamethylene-bis(quinolinedimethylammonium)	0.1	2/2
	0.15	2/2
	0.2	3/3

Note. In the column "Experimental results" the numerator is the number of dead mice, the denominator is the total number of mice tested for the given dose of the substance.

The quinoline derivative of pentamethonium did not affect the nature and outcome of nicotinic poisoning substantially; all the mice died which received the preparation both before and after the administration of a lethal dose of nicotine. The action of the most effective of the substances investigated—hexonat—was studied on arecoline spasms in 11 mice. The administration of hexonat against a background of arecoline in quantities which block the nicotine reaction, was not accompanied by changes in the tremor typical of arecoline; preliminary administration of hexonat was equally ineffective.

The study of the antispasmodic action of atropine on nicotinic and arecoline spasms of mice was undertaken as a control. Atropine in a wide range of doses (0.4-1 mg) did not eliminate the spasms and did not decrease the percentage of mortality of administration of a lethal dose of nicotine. Arecoline spasms were easily blocked by atropine, which corresponded to data in the literature [3, 10]. The data regarding the nicotinolytic action of the studied substances are summarized in the table.

The investigations which were carried out allowed the establishment of the fact that, of the studied group of quarternary ammonium compounds, two substances, derivatives of hexamethylene-bis (trimethylammonium) and tetraethylammonium, with nicotinic acid have a pronounced nicotinolytic effect.

The nicotinolytic action of these two compounds can be explained from the point of view of competition with acetylcholine, which is evident for parasympatholytic substances in the central nervous system as well [7], as a result of which, blocking of the n-cholinergic structures of the brain is observed. The following facts indicate that these competing reactions take place in the central nervous system. Supplementary experiments were set up by us to study the blocking action of the two narcotic substances—chloral hydrate and barbamyl — on the nicotinic spasms of mice. It was found that the narcotic with primarily cortical action—chloral hydrate — had not substantial effect, while the narcotic with primarily brain stem action (barbamyl) weakened or eliminated the spasms in a number of experiments, decreasing the percentage of mortality at the same time after the administration of a lethal dose of nicotine. Combining the data we obtained with the similar experiments of N. V. Golyakhovskaya on arecoline, we reached the conclusion that the spastic action of nicotine depends primarily on stimulation of the subcortical areas.

Since the m-cholinolytic—atropine—did not eliminate the spastic action of nicotine while blocking the arecoline tremor, and since, on the other hand, the n-cholinolytic ganglionic blocking agents—hexonat and tetronat— had a nicotinolytic effect, while not affecting the cortical, arecoline spasms, according to N. V. Golyakhovsky , we reached the conclusion that, first, the initial pharmacological reactions to the nicotinolytic action of the studied substances are localized chiefly in the subcortical areas and, second, the primarily n-cholinergic structures of the brain are blocked. The difference we found between the action of the nicotinic acid salts of quarternary ammonium derivatives and their iodides indicates that the nature of the anion substantially affects the pharmacological properties of the salt.

SUMMARY

The central cholinolytic action of parasympatholytic preparations — derivates of quaternary ammonium bases — were studied on their action on convulsions elicited in mice by nicotine or arecoline.

It was found that derivates of hexamethylene-bis(trimethylammonium) and tetraethylammonium with nicotinic acid had a most pronounced nicotinolytic effect causing no arecoline convulsions.

Our experiments confirm that n-cholinoreactive structures of the subcortical area are blocked when parasympatholytics of this group are used.

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