DIFFERENCES IN THE PERMEABILITY OF THE BLOOD-BRAIN BARRIER TO CHOLINOLYTIC SUBSTANCES

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Investigations by several authors [1, 3] have shown that quaternary cholinolytics pass much less freely through the blood-brain barrier (BBB) than the tertiary compounds. Investigations of the permeability of the BBB of cats to cholinolytics revealed a difference not only between tertiary and quaternary compounds, but also between individual tertiary compounds [2].

In the present investigation the permeability of the BBB of mice was investigated to two tertiary (atropine and benactyzine) and one quaternary (lachesine) cholinolytics, and the physicochemical properties of these substances were studied.

EXPERIMENTAL METHOD

Experiments were carried out on 360 male albino mice weighing 20-21 g. The cholinolytics were dissolved in 0.9% sodium chloride solution, and injected intravenously in a dose of 0.05 ml/10 g body weight or into the lateral ventricle in a dose of 0.01 ml [6]. Correct placing of the solution of cholinolytic in the lateral ventricle was verified in each case by injection of 1% methylene blue solution through the needle in situ and by subsequent histological examination of the brain.

The degree of penetration of the cholinolytics through the BBB was judged from the size of the dose preventing arecoline tremor in mice (ED_{50}). Arecoline, in a dose of 0.25 mg/kg, was injected subcutaneously 10 min after the injection of the cholinolytic.

The percentage ionization of the cholinolytic drugs was calculated at pH 7.3 and 8.0. The constant of basicity (PK_a) was measured by the semineutralization method using the Czech AK-2 potentiometer with a glass electrode, and with the cholinolytic in a concentration of 0.001 M/liter. The coefficient of distribution was determined at 20° in hexane-phosphate buffer, pH 7.4. Solubility in water was determined at 20° in bidistilled water.

RESULTS

The results of experiments on the prevention of arecoline tremor by cholinolytic drugs injected in different ways are given in Table 1. The material was analyzed statistically by the method of Miller and Tainter [8].

It is clear from Table 1 that the cholinolytics, when injected into the lateral ventricle, prevented the arecoline tremor in mice in approximately equal doses (the differences were not statistically significant). Following intravenous injection of these drugs, a statistically significant difference was observed between them with respect to prevention of arecoline tremor. For instance, the dose of atropine required to prevent the tremor was twice the dose of benactyzine. Whereas lachesine did not prevent arecoline tremor in mice, higher doses of this drug caused death of the animals. So far as their peripheral cholinolytic action was concerned, in the case of benactyzine this was less marked than for atropine and lachesine. Thus, for the prevention of arecoline salivation, the dose of benacty-

TABLE 1. Doses of Cholinolytic (in mg/kg) Preventing Arecoline Tremor and Salivation, Depending on Method of Injection (ED_{50})

Cholinolytic	Arecoline tremor		Salivation
	intracerebral injection	intravenous injection	intravenous injection
Atropine	0,014±0,002	1,76±0,24	0,20±0,014
Benactyzine	0,013±0,0025	0,81±0,16	2,8±0,27
Lachesine	0,011±0,0019	—	0,18±0,018

Note. Arecoline Tremor not prevented.

TABLE 2. Physicochemical Properties of Cholinolytic Drugs

Cholinolytic	Molecular weight	Percentage ionization	PK_a	Coeffi. of distribu.	Solubility in water, %
Atropine	325,844	99,7	9,85	0,01	80,1
Benactyzine	363,88	96,0	8,68	5,78	7,1
Lachesine	363,89	99,9	10,37	0,01	37,06

zine required was ten times higher than the doses of atropine and lachesine. The difference between the doses of atropine and lachesine was not statistically significant.

Hence, the results of the investigations on mice were in full agreement with the findings obtained by the authors in experiments on cats [2], and they demonstrate that differences in the permeability of the BBB are found not only between tertiary and quaternary cholinolytics, but also between individual members of the group of tertiary compounds (the permeability to benactyzine was higher than that to atropine).

In the opinion of a number of authors [4, 5, 7, 9], the penetration of drugs into the central nervous system depends on their degree of ionization, their solubility in lipids, and their molecular weight. The permeability of the BBB is higher to compounds of low molecular weight, readily soluble in lipids, and nonionized. To shed light on the role of these factors in the permeability of the BBB to cholinolytics, certain of their physicochemical properties are shown in Table 2.

It is clear from Table 2 that the molecular weight, the percentage ionization, and the solubility in water had no significant effect on the permeability of the BBB to these cholinolytics. The molecular weight of benactyzine and lachesine are practically identical, but benactyzine penetrated much faster than lachesine through the BBB. The molecular weight of atropine is smaller than that of benactyzine, but atropine passed less readily through the BBB than benactyzine. At pH 7.3 and 8.0, atropine and lachesine are practically completely ionized compounds, but in relation to their passage through the BBB, they differed considerably (atropine penetrated much faster into the central nervous system than lachesine).

It is probable that the value of PK_a and of the coefficient of distribution are of definite importance to the passage of these cholinolytics through the BBB, although no complete parallel was observed between these factors and the degree of penetration of atropine and lachesine through BBB. Compounds with a low PK_a and a high coefficient of distribution passed relatively readily through the BBB (benactyzine). Conversely, substances with a high PK_a and a low coefficient of distribution penetrated only slowly into the central nervous system (lachesine).

The penetration of substances through the BBB is a complex physiological process. Their passage through this barrier probably depends also on other physicochemical properties (chemical structure, active groups, their spatial disposition, the distance between the active centers of the molecule, and so on).

The study of the effect of these factors on the penetration of substances through the BBB is important for the planned synthesis of central cholinolytics and other pharmacological compounds.

SUMMARY

The object of study was the physicochemical properties and the penetration through the BBB (hematoencephalic barrier) in albino mice of atropine, amysil, and lachesine which were injected intravenously and into the lateral ventricle of the brain. The degree of penetration of these substances through the brain barrier was determined by the size of the dose (ED_{50}) preventing arecoline tremor in mice.

Comparison of the degree of penetration of cholinolytics through the BBB with their physicochemical properties showed that the molecular weight, percentage of ionization, and solubility of cholinolytics in water did not have a substantial effect on their penetration through the BBB. The PK_a and distribution coefficient were of certain significance for atropine, amysil, and lachesine penetration. As regards penetration through the BBB a difference was established not only between the tertiary and quaternary cholinolytics but also between tertiary compounds (amysil showed better penetration into the brain than atropine).

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of the first issue of this year.
