PHARMACOLOGY

THE EFFECT OF LARGE DOSES OF PENICILLIN AND STREPTOMYCIN ON THE AMMONIA CONTENT OF BRAIN

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Experimental investigations and clinical observations show that the brain is sensitive to penicillin and streptomycin. The effect of these antibiotics on cerebral tissue leads at times to serious sequelae.

Definite connection between the functional state of the brain in animals and the formation of ammonia in the brain has been shown in a number of studies by G. E. Vladimirov [1], E. A. Vladimirova [2-6] and others. The amount of ammonia in the brain increases when the animals are excited by chemotherapeutic substances or by unconditioned and conditioned reflexes; in the presence of inhibitory states the cerebral ammonia content declines.

With this in mind a study was made of the effect of large doses of penicillin and streptomycin on the ammonia content of the cerebral tissue.

EXPERIMENTAL METHOD

White male rats weighing from 160-200 g were given subcutaneous injections of solutions of highly purified penicillin and streptomycin salts – sodium salt of crystalline benzylpenicillin with activity of 1650 active units/mg and crystalline streptomycin sulfate with activity of 770 active units/mg.

Control animals were given physiologic solution. After 40-60 minutes the animals were frozen in liquid oxygen in toto in a chamber described by E. A. Vladimirova [3]. Following freezing the ammonia content of the cerebral hemispheres was determined using the method of vacuum distillation with steam in a Parnas apparatus with subsequent addition of Nessler's reagent to the distillates and colorimetric examination. In addition to determination of ammonia the concentration of the antibiotic in the brain was estimated biologically in the majority of animals.

EXPERIMENTAL RESULTS

The results of determinations of ammonia in the brain of the animals are presented in Table 1.

The data shown in Table 1 show that penicillin in doses of up to 500,000 active units, streptomycin sulfate in doses of up to 100,000 active units and the calcium chloride complex of streptomycin in doses up to 200,000 units exerted no effect on the ammonia content of rat brain. With very large doses of penicillin (1 million active units per rat) there is an approximately $1\frac{1}{2}$-fold increase in the ammonia content.

Penicillin concentration in cerebral tissue following administration of 100,000 active units of the antibiotic amounted to only 2-4 active units per 1 g tissue. The concentration was 10-15 active units per 1 g tissue following administration of 400,000-500,000 active units of penicillin. When 1-1.5 million active units of penicillin

TABLE 1

Ammonia Content of White Rat Brain 40-60 Minutes after Subcutaneous Administration of Various Doses of Penicillin and Streptomycin.

Norm	Penicillin		Streptomycin		
NH_3, in mg%	Dose of antibiotic, in thousands of active units	NH_3, in mg%	Streptomycin preparation	Dose, in thousands of active units	NH_3, in mg%
0.35	100	0.48	Streptomycin sulfate	50	0.45
0.36	200	0.42	ditto	65	0.37
0.43	200	0.47	» »	100	0.38
0.48	300	0.41	» »	100	0.40
0.51	400	0.44	» »	100	0.41
0.51	500	0.39	» »	100	0.47
0.52	500	0.46	» »	100	0.55
0.54	500	0.57	» »	100	0.57
0.59	—	—	» »	—	—
mean 0.48	—	mean 0.46		—	mean 0.45
—	1 000	0.57	Calcium chloride complex of streptomycin	100	0.41
—	1 000	0.59	ditto	100	0.44
—	1 500	0.64	» »	100	0.56
—	2 000	0.89	» »	200	0.53
—	2 500	0.87	» »	200	0.53
		mean 0.71		—	mean 0.49

were injected the concentration of the latter was 25-35 active units, and when 2-2.5 million active units were given the concentration was 30-45 active units per 1 g tissue. If it is taken into account that part of the penicillin determined in the brain was in the blood it can be taken that penetration of penicillin into cerebral tissue is slight. It is evident that when massive doses of penicillin (over 1 million active units) are given to animals those relatively small amounts of the antibiotic which penetrate into cerebral tissue are able to evoke a state of excitation and lead to an increase in the ammonia content.

The following fact deserves attention. If rats are given the potassium and not the sodium salt of penicillin an increase in ammonia content ($1\frac{1}{2}$-2-fold) is already noted when the administered dose amounts to 500,000 and 1 million active units. Experiments with subcutaneous injection of potassium chloride demonstrated that high concentrations of potassium ions themselves led to increased ammonia content.

Another antibiotic, streptomycin, penetrated into cerebral tissue to a greater extent. Thus, following administration of 100,000 active units of streptomycin sulfate the concentration of the antibiotic in the brain one hour later fluctuated from 62 to 288 active units per 1 g tissue. The behavior of the animals which received penicillin and calcium chloride complex of streptomycin did not differ from the behavior of the control animals.

Administration of large doses of streptomycin sulfate (100,000-150,000 active units) produced after 30-40 minutes a state of profound inhibition in some rats. The animals became immobile and ceased to react not only to the stimuli but even to touch. The ammonia content of the brain was determined in several of these animals after freezing. The results of these experiments, shown in Table 2, indicate an appreciable decrease in the ammonia content of the brain.

TABLE 2

Ammonia Content of White Rat Brain after Subcutaneous Injection of Large Doses of Streptomycin Which Produced a State of Inhibition in the Animals.

Dose of streptomycin sulfate, in thousands of active units	NH_3, in mg%
100	0.22
100	0.27
150	0.20
150	0.25
150	0.28
	Mean 24.4

The streptomycin content of the brain in these animals varied from 384 to 600 active units per 1 g tissue. Hence in these experiments relatively high concentrations of streptomycin in the brain led to a state of inhibition which was rapidly reflected in lowering of the ammonia content.

The results obtained show that penicillin and streptomycin can cause changes in the ammonia content of the brain only when their concentration in cerebral tissue reaches relatively high levels; the character of such change is different for penicillin and streptomycin: the former can increase the ammonia content of the brain, which indicates that this antibiotic may be regarded as a central nervous system stimulant whereas streptomycin, which can lower the ammonia content of the brain, produces inhibition of the central nervous system.

It would seem unlikely that the intramuscular injection of the usual therapeutic doses of penicillin and streptomycin would cause disturbances of the functional state of the nervous system and changes in ammonia content of the brain in man, since streptomycin and especially penicillin penetrate into the cerebral tissue slowly. However, in the presence of impairment of the blood-brain barrier and in intrathecal injection of the antibiotics conditions may arise in which the antibiotic concentration in the brain may be high enough to cause disturbances of the functional state of the nervous system and changes in the ammonia content.*

SUMMARY

Experiments on rats demonstrate that large doses of penicillin and streptomycin may cause changes in the content of ammonia in the brain (penicillin increases and streptomycin decreases the content). These changes are considered to be due to the effect of these antibiotics on the central nervous system (a stimulating effect of penicillin and a depressing one of streptomycin).

LITERATURE CITED

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** In Russian.