THE EFFECT OF GLUTAMINE AND γ-AMINOBUTYRIC ACID ON THE EXCITATION PROCESSES IN THE CENTRAL SYNAPSES

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In previous investigations, we have reported the inhibitory effect of glutamic acid, glutamine, asparagin, glycine and alanine on the contractile activity of skeletal muscles induced by proserine [neostigmine] and guanidine. In experiments on white mice, glutamic acid showed an anticonvulsive effect under conditions of proserine poisoning [1, 2]. We then decided to study the effect of glutamine on proserine convulsions in white mice.

Some of the literature data concerning glutamine's effect on the central nervous system are contradictory. According to the experiments of Tower and Elliott performed on brain tissue sections, the ability of brain tissue to bind acetylcholine is disturbed in epilepsy, hypoxia and in poisoning by the convulsant poison methionine-sulfoximine; this disturbance is eliminated by glutamine and asparagin, but not by glutamic acid [12]. In experiments on mice and rats poisoned with convulsant poisons (methionine-sulfoximine and Metrazol) and also on rats with electrically induced convulsions, glutamine and asparagin showed an unreliable prophylactic effect [10].

EXPERIMENTAL METHODS AND RESULTS

Experiments were performed on 100 male white mice weighing 16-22 g each. The experimental substances were administered subcutaneously: glutamine (300 μ g per 1 g weight) to 50 mice 10 minutes before the injection of proserine (0.3 μ g per 1 g weight); proserine alone (0.3 μ g per 1 g weight) was administered to 50 control animals. For purposes of comparison, we treated the effect of glutamine on convulsions induced in mice by Cardiazol. The experiments of this series were performed on 100 animals in the same age group: 50 mice were injected with glutamine in the same dose used in the experiments with proserine 10 minutes before the injection of Cardiazol (80 μ g per 1 g weight); the control mice received Cardiazol only (80 μ g per 1 g weight).

In the experiments with proserine, preliminary administration of glutamine reduced the number of animals in which convulsions developed from 72 to 46%, the number of animals that died from 32 to 26%. In the experiments with Cardiazol, this dose of glutamine showed no anticonvulsive effect, but did reduce the number of deaths (from 30 to 15%). The inhibitory effect of glutamine was not apparent in the case of the proserine-induced convulsions. We obtained analogous results with glutamic acid in the earlier investigation [2].

Fig. 1 shows the results of the experiments with proserine and Cardiazol. The number of mice which developed convulsions and the number which died are expressed in percent with the error indicated. The anticonvulsive effect of glutamine is statistically significant ($t = 2.7$) in proserine poisoning, but absent in Cardiazol poisoning.

The next series of experiments tested the effect of γ-aminobutyric acid on proserine intoxication in white mice; this acid is generally acknowledged to be a metabolite which materially affects the activity of brain tissue. The majority of researchers believe γ-aminobutyric acid to have an inhibitory effect on synaptic excitation [5, 7 et al.]. Since the metabolism of γ-aminobutyric acid, which is realized through the tricarboxylic acid cycle, is closely linked with the metabolism of glutamic acid (γ-aminobutyric acid forms from glutamic acid under the influence of the specific carboxylase; this reaction is reversible), one would expect the two acids to have similar effects on proserine intoxication. The effect of γ-aminobutyric acid on the course and issue of proserine intoxication was compared with its effect on the course and issue of Cardiazol and strychnine poisoning.

The experiments were performed on 200 male white mice weighing 16-20 g each. Proserine (0.3 μg per 1g weight), strychnine nitrate (0.7 μg per 1 g weight) and Cardiazol (80 μg per 1 g weight) were injected subcuta-

neously; γ-aminobutyric acid was subcutaneously injected 10 minutes before the above substances in a dose of 100-200 μg per 1 g animal weight (before strychnine and proserine poisoning only) and into the lateral ventricles of the brain in a dose of 40-60 μg.

The subcutaneously administered γ-aminobutyric acid did not affect the course and issue of poisoning induced by proserine or strychnine; inadequate permeation of the substance through the blood-brain barrier could explain this [8 et al.]. In subsequent experiments, therefore, γ-aminobutyric acid was injected into the lateral ventricles of the brain. With this mode of administration, the motor activity of the animals increased in a number of cases; sometimes convulsions developed followed by brief respiratory depression and decreased motor activity. The experimental substances were not administered until these symptoms had disappeared.

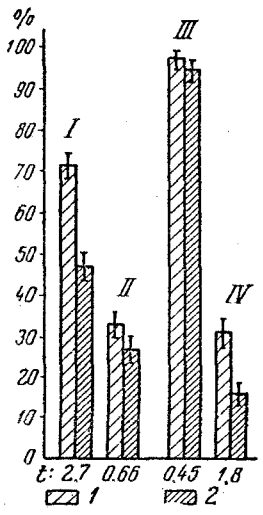

Fig. 1. Effect of glutamine on course and issue of proserine (I and II) and Cardiazol (III and IV) poisoning: 1) percent of animals in which convulsions developed and percent of animals which died in control experiments; 2) percent of animals in which convulsions developed and percent which died after preliminary glutamine administration; t—significance criterion.

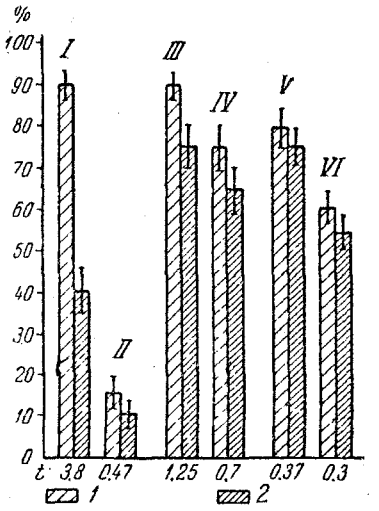

Fig. 2. Effect of γ-aminobutyric acid on course and issue of Cardiazol (I and II), proserine (III and IV) and strychnine (V and VI) poisoning: 1) percent of animals in which convulsions developed and percent which died in control experiments; 2) percent of animals in which convulsions developed and percent which died after preliminary glutamine* administration; t— significance criterion.

Contrary to our expectations, γ-aminobutyric acid did not exert a clear anticonvulsive effect with proserine poisoning in the experiments with intracranial administration either (90% of the control animals had convulsions, as against 75% of the experimental animals). Nor was this effect observed in the experiments with strychnine (80% of the animals had convulsions in the control, 75% in the experiment). In the experiments with Cardiazol, however, the same dose of γ-aminobutyric acid reduced the number of animals in which convulsions developed considerably (from 90 to 40%).

Fig. 2 gives the results of the experiments with Cardiazol, proserine and strychnine. The number of animals in which convulsions developed and the number that died are expressed in percent, error indicated.

Therefore, γ-aminobutyric acid was only observed to have a statistically significant anticonvulsive effect in the case of Cardiazol poisoning (t = 3.8). The results of the experiments with Cardiazol are in accord with the literature data [4, 11 et al]. No statistically significant effect of γ-aminobutyric acid on the course and issue of poisoning caused by either proserine (t = 1.2 and 0.7) or strychnine (t = 0.37 and 0.3) was observed. The results of the experiments with strychnine agree with the data of Elliott, Hobbiger et al. [3], but contradict McLennan's data [6].

* As in original, although γ-aminobutyric acid would seem to be indicated here [Publisher's note].

The experimental material obtained indicates that glutamine, like glutamic acid [2], has a definite anticonvulsive effect on convulsions induced by proserine, which are evidently cholinergic in nature. In accord with the data of Tower and Elliott which we cited earlier [12], we propose that this effect of glutamine is due to its effect on the acetylcholine bond.

γ-Aminobutyric acid was found to be effective with convulsions induced by Cardiazol, which, according to the literature data, are chiefly non-cholinergic in origin [9]. Because γ-aminobutyric acid affects Cardiazol-induced but not strychnine-induced convulsions, one must propose that γ-aminobutyric acid acts primarily on the excitation synapses and does not affect the inhibitory synapses of Renshaw's cells.

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