POTENTIATION OF THE CONVULSANT ACTION OF STRYCHNINE BY INTRAVENTRICULAR INJECTION OF KYNURENINES INTO THE FROG BRAIN

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It has recently been shown that the main metabolites of intermediate metabolism of the amino acid tryptophan, namely kynurenines, can increase the excitability of the CNS and participate in the production of convulsions. An excitatory action of kynurenines has been demonstrated in insects, and an excitatory and convulsant action in amphibians [4] and mammals [1, 2].

This investigation is a continuation of others conducted previously. Its aim was to study the effect on the convulsant action of strychnine of six kynurenines: L-kynurenine (K), and quinolinic (QA), nicotinic (NA), anthranilic (AA), picolinic (PA), and xanthurenic (XA) acids.

EXPERIMENTAL METHOD

Experiments were carried out on grass frogs *(Rana temporaria)*, chiefly males, weighing 16-50 g (altogether 460 frogs), in the fall and winter.

The frogs were fixed by pins through their limbs to a board; the lower jaw and tongue also were fixed. Solutions of the kynurenines were injected from a syringe at a depth of 3 mm, strictly in the center of a line joining the lateral contours of the suprascapulae, corresponding to projection of the floor of the 4th ventricle. Control examinations of the frog brain revealed a mean accuracy of 75% for injections of methylene blue.

To begin with the kynurenines for study were injected intraventricularly in a volume of 0.01 ml. Aqueous 0.2% solutions of kynurenines were diluted with 0.5% methylene blue solution in the ratio of 1:1 to verify the accuracy of injection. In the control group, which accompanied each experiment, 0.25% methylene blue solution was injected into the cerebral ventricles, also in a volume of 0.01 ml. The mean pH of all 0.2% aqueous solutions of kynurenines was 5.0-6.0.

A solution of strychnine nitrate, in a subthreshold dose not inducing convulsions was injected into the submandibular pouch 5 min after the intraventricular injection (for each batch of frogs the subthreshold convulsant dose of strychnine was determined separately, and it varied from 0.5 to 1.25 mg/kg).

The optimal dose for kynurenines, which potentiated the appearance of strychnine convulsions, was determined in test experiments (10 μg).

Effects of the kynurenines alone, injected into the cerebral ventricles in a dose of 50-100 μg without strychnine, also were investigated. The pH of 2% aqueous solution of the kynurenines was 4.0-5.0.

All frogs were distributed by weight, into groups of six animals. Each frog was placed separately in a glass jar and numbered. All the effects observed were recorded visually over a period of 40 min after injection of strychnine. The experimental results were assessed by the chi-square criterion.

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TABLE 1. Potentiation of Convulsant Action of Strychnine by Injection of Kynurenines (10 μg) into Cerebral Ventricles of Frogs

Substance injection	Number of frogs				
	total	with motor excitation	%	with convulsions	%
Methylene blue in H_2O (1:1)	101	0	0	5	5
Kynurenines:					
Quinolinic acid	84	44 ‡	52	45 ‡	54
L-kynurenines	54	11 †	20	31 ‡	57
Nicotinic acid	17	7 ‡	41	12 ‡	70
Picolinic acid	12	5 †	41,6	5 †	41,6
Xanthurenic acid	12	4	33,3	2	16,6
Anthranilic acid	12	0	0	0	0

*$P<0,05$. [Not denoted in Russian original – Publisher].
† $P<0,02$.
‡ $P<0,01$.

EXPERIMENTAL RESULTS

Kynurenines injected in the cerebral ventricles caused convulsions in frogs receiving a subthreshold dose of strychnine (Table 1).

This action was most clearly manifested in the case of QA, K, and NA; it was weaker in the case of PA and absent altogether in XA and AA.

It was shown previously that AA has neither excitatory nor convulsant action in experiments on frogs [4], mice [1], and rats [2]. The optimal dose of kynurenines potentiating the convulsant action of strychnine was 10 μg. It caused no visible changes. In smaller doses (1-5 μg) the action of kynurenines on convulsions evoked by injection of strychnine was not significant.

Nearly all convulsions began with a preliminary stage of excitation, which was not found in the control, in which the animals also were given strychnine subcutaneously.

Intraventricular injection of kynurenines alone in a dose of 100 μg gave rise to convulsions in 25% of animals in the experiments with DA, and to motor excitation in all animals in experiments with K and QA; AA did not affect the behavior of frogs; NA in those doses gave the opposite effect, namely a sharp increase in muscle tone. Doses of all kynurenines below 100 μg had no effect.

The kynurenines tested (except XA and AA), when injected into the cerebral ventricles thus significantly potentiated the convulsant action of strychnine.

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