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ROLE OF KYNURENIN AND ITS DERIVATIVES IN CARDIAC ARRHYTHMIAS

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KEY WORDS: kynurenin; kynurenin derivatives; cardiac rhythm.

Kynurenin is a natural derivative of the essential amino acid, tryptophan, and increased accumulation of kynurenin in the body, or its increased excretion, is regarded as a sensitive indicator of deficiency of pyrixodal-5-phosphate, i.e., the active form of vitamin B_6 [2, 3, 6]. No information could be found in the literature on the effect of kynurenin and its derivatives on the genesis of cardiac pathology. In patients with attacks of angina at rest, not responding to nitrites, kynurenin accumulation in the blood serum after administration of L-tryptophan is considerably increased [4]. Correction of intermediate tryptophan metabolism and normalization of kynurenin accumulation in the blood serum are accompanied by improvement of the patient's condition, or even by recovery [5].

The aim of this investigation was to study the effects of kynurenin and its derivatives on activity of the isolated frog heart.

EXPERIMENTAL METHOD

Experiments were carried out on 50 hearts isolated from winter frogs by Straub's method [1]. Activity of the isolated heart was maintained by Ringer's solution for cold-blooded animals, containing (in 1 liter): 6.5 NaCl, 0.3 g KCl, 0.002 g $CaCl_2$, and 0.2 g $NaHCO_3$. For the experiments various quantities of L-kynurenin sulfate (from Serva, West Germany), 3-hydroxy-DL-kynurenin (from Koch-Light, England), and kynurenic and xanthurenic (from Dr. T. Schuchardt, Munich, West Germany), 3-hydroxyanthranilic (Serva), and quinolinic acids (the last of these was synthesized in the Department of Organic Chemistry, J. Pelse Riga Polytechnical Institute, under the direction of Professor O. Ya. Neiland), were added to this solution. Cardiac contractions were recorded on a clockwork kymograph and an eight-channel polygraph (Nihon Kohden, Japan). Parallel with mechanical contractions, the electrical potentials of the heart were recorded on the polygraph; one electrode was located on the atrium, the other in the nutrient solution. The results were subjected to statistical analysis. Standard deviations of arithmetic mean values were calculated the t test carried out. The significance of results corresponding to the t test was calculated by the method in [8]. Differences were considered significant if their probability was over 95% ($P < 0.05$).

EXPERIMENTAL RESULTS

Under the influence of kynurenin the heart rate was slowed, but the slowing was significant only with L-kynurenin in a concentration of 10^{-4} M, when the heart rate (HR) reached 15.4 ± 0.9 beats/min, i.e., 29% less than initially. A further increase in the kynurenin concentration resulted in complete AV heart block (Fig. 1). Like kynurenin itself, 3-hydroxy-DL-kynurenin (Fig. 2) caused marked bradycardia which lasted 1-3 min. HR at this time was 10-40% below the initial value. The force of the cardiac contractions was unchanged. After addition of xanthurenic acid to the nutrient fluid in concentrations of 10^{-6} to 10^{-3} M, either transient bradycardia (for 15-60 sec) appeared, or prolonged bradycardia developed, with the heart rate falling by 10-30% below the initial level.

During short periods of bradycardia HR fell by 50% below the initial level. Bradycardia induced by xanthurenic acid was accompanied by weakening of the cardiac contractions by 5-10%.

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TABLE 1. Effect of Various Concentrations of L-Kynurenin on HR (± standard deviation) of the Isolated Frog Heart (n = 15)

Kynurenin concentration, M	HR, beats/min	P
Before addition of kynurenin	21,4±1,8	—
10^{-6}	17,8±0,9	>0,1
10^{-5}	17,9±1,3	>0,1
10^{-4}	15,4±0,9	<0,02

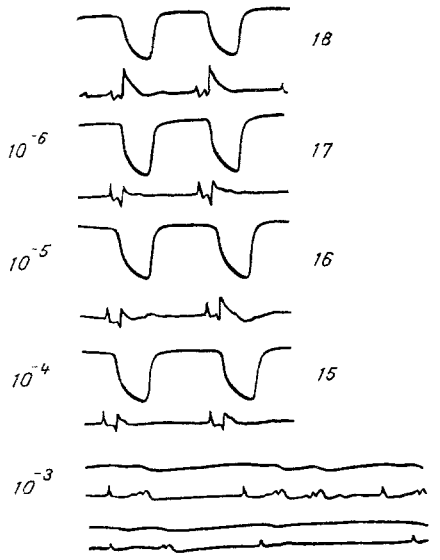

Fig. 1

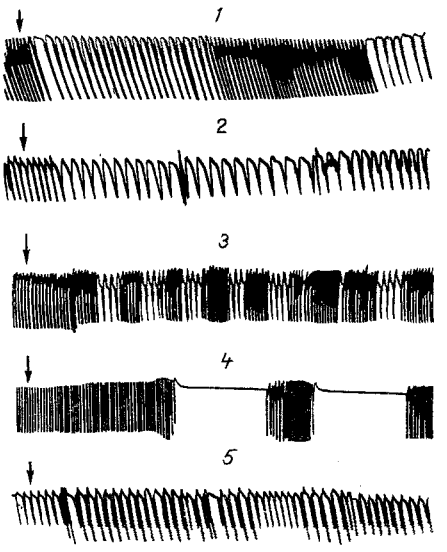

Fig. 2

Fig. 1. Effect of various concentrations (in M) of L-kynurenin (numbers on the left) on HR (numbers on the right) of a frog. AV) Atrioventricular conduction. Here and in Fig. 3, recording on a polygraph.

Fig. 2. Effect of kynurenin and its derivatives on activity of the isolated frog heart. Arrow indicates beginning of action of: 1) L-kynurenin; 2) 3-hydroxy-DL-kynurenin; 3, 4) xanthurenic acid; 5) 3-hydroxyanthranilic acid. Recording on clockwork kymograph.

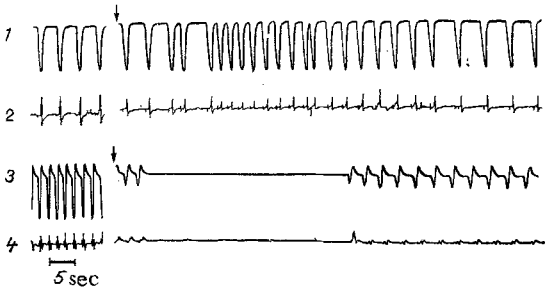

Fig. 3. Effect of quinolinic acid in concentrations of 10^{-6} M (1, 2) and 10^{-3} M (3, 4) on contractions of isolated frog heart.

In some cases, with xanthurenic acid in concentrations of 10^{-4} and 10^{-3} M, complete arrest of the isolated frog's heart was observed in diastole for 1 min, after which cardiac activity was fully restored. Kynurenic acid in concnetrations of 10^{-6} and 10^{-3} M caused no appreciable changes in activity of the isolated frog's heart. Different disturbances of the cardiac rhythm were produced by 3-hydroxyanthranilic acid: in a concentration of 10^{-5} M single extrasystoles appeared, but grouped extrasystoles with a concentration of $5 \cdot 10^{-5}$ M. The force of

the cardiac contractions was reduced in all experiments with 3-hydroxyanthranilic acid, i.e., a negative inotropic effect was seen on the isolated frog's heart. Under the influence of quinolinic acid, cardiac arrhythmias appeared with concentrations as low as 10^{-6} M, in the form of single extrasystoles and episodes of tachycardia (Fig. 3). The force of the cardiac contractions was virtually unchanged, but during paroxyms the voltage of the ECG of the isolated frog's heart decreased significantly. With quinolinic acid in a concentration of 10^{-3} M bradycardia developed, and against its background cardiac arrest in diastole for 53 sec was observed in some cases, after which the cardiac activity was restored but the bradycardia was more marked than before transient cardiac arrest. The results of this investigation also were confirmed by those of clinical investigations: a raised serum kynurenin level was observed during atrial fibrillation of bradycardic type, sinus node weakness, sinus bradycardia, and chronic AV block [7]. A new pathogenetic pathway of onset of cardiac arrhythmias has thus been discovered.

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NEW ASPECTS OF THE NEUROPHYSIOLOGICAL MECHANISM OF ACTION OF NOOTROPIC DRUGS

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KEY WORDS: spectral analysis of the EEG; nootropic drugs; spatial synchronization; learning; free behavior.

Much experimental material has now been collected on nootropic drugs as agents improving mental working capacity and leaning and memory processes, and suggestions regarding their biochemical mechanism of action have been put forward [8, 12, 13]. Meanwhile the neurophysiological mechanisms of action of nootropic drugs have received little study.

During visual and frequency analysis of the EEG of animals and man, as a rule no action of nootropic drugs can be detected [5, 12]. Spectral analysis of the human EEG reveals definite, but often opposite, changes in the power spectra of the EEG due to these drugs and, in particular, reduction of slow frequencies with an increase of power in the α-band and some increase in β-activity. However, these effects have been observed mainly in complex forms of pathology (aging, ischemia, cerebrovascular disturbances) and during long-term administration of the drugs [7, 9, 10, 14].

The clearest electrophysiological manifestation of the action of nootropic drugs is observed with the use of transcallosal evoked potentials [1, 11, 12]. However, the strengthening of transcallosal responses under the influence of drugs, observed in these investigations, cannot entirely explain the mechanism of their nootropic effect.

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