STUDY OF THE MECHANISM OF ACTION OF ETHIMIZOLE ON ENERGY METABOLISM IN THE MYOCARDIUM AFTER NEUROGENIC INJURY

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KEY WORDS: neurogenic injury to the myocardium; calcium; energy metabolism; adenyl cyclase.

Numerous investigations have demonstrated the stimulating action of ethimizole on energy metabolism in the tissues of damaged organs of animals exposed to extremal influences [1]. There is evidence that ethimizole activates the brain cyclic AMP system through stimulation of adenyl cyclase [2].

The object of the present investigation was to study the role of intracellular calcium, the presence of which is essential for the working of many enzymes and for the regulation of muscle contraction, and also of adenyl cyclase in the action of ethimizole on energy metabolism of the neurogenically injured myocardium.

EXPERIMENTAL METHOD

Dystrophic injuries were induced in the myocardium of male rats weighing 180-200 g by the method described in [1]. Ethimizole (10 mg/kg) was injected intraperitoneally 30 min before the beginning of electrical stimulation.

The state of the energy metabolism was characterized by investigation of the creatine phosphate level in the heart muscle [4].

The intracellular calcium concentration was determined with an AAC-1 atomic absorption spectrophotometer (East Germany) at a wavelength of 4227 Å. For this purpose myocardial tissue was dried at 80°C to constant weight and incinerated in concentrated nitric acid on a sand bath at 210°C for 6 h. The mineral residue was transferred to test tubes and made up to 5 ml with bidistilled water. Nitric acid without tissue was used as the control. The calcium concentration was expressed in micromoles/g tissue.

Adenyl cyclase activity was determined by a radioactive method based on measurements of the velocity of conversion of ^{14}C-ATP into ^{14}C-cyclic AMP [5]. The ^{14}C-cyclic AMP was separated from the other nucleotides by high-voltage paper electrophoresis [6]. The location of the cyclic AMP after electrophoresis was determined with the aid of UV-luminescence. Radioactivity of ^{14}C was measured on a Nuclear Chicago scintillation counter. Adenyl cyclase activity was expressed as the number of counts per minute per milligram protein. Protein was determined by Lowry's method.

EXPERIMENTAL RESULTS

In experimental dystrophy there was a significant decrease in the concentration of both creatine phosphate (from 0.98 ± 0.06 to 0.36 ± 0.04 μmole/g) and of calcium (from 8.2 ± 0.8 to 6.4 ± 0.6 μmoles/g). Preliminary injection of ethimizole prevented the fall in the calcium and creatine phosphate concentrations in the myocardium (9.1 ± 0.8 and 0.85 ± 0.05 μmoles/g respectively).

To study the mechanism of action of ethimizole on energy metabolism and on changes in the Ca^{++} concentration a series of experiments was carried out to study the effect of ethimizole on adenyl cyclase activity. The investigations showed that adenyl cyclase activity in animals receiving ethimizole was increased threefold compared with that in the control animals (from 160 ± 30 to 510 ± 90 cpm/g).

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It can be concluded from these results that the action of ethimizole on energy metabolism in the myocardium is effected through adenyl cyclase, with subsequent activation of the slow ionic channels by cyclic AMP-dependent protein kinases [7]. As the result of activation of these channels more extracellular calcium enters the cells during the plateau of the action potential and is retained in the intracellular depots. Meanwhile, there is some evidence [3] that activity of the slow channels is determined to a greater degree by the state of the intracellular energy metabolism and it depends on activity of creatine phosphokinase, located in the plasma membrane. Normalization of calcium metabolism under the influence of ethimizole after neurogenic injury to the myocardium correlates with restoration of the creatine phosphate level, reflecting the close interaction between energy formation processes and activity of the calcium pump in the mechanism of the effect of ethimizole on metabolism of the neurogenically injured heart.

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EFFECT OF ARMIN ON SYNAPTIC TRANSMISSION IN THE FROG NERVE – MUSCLE PREPARATION

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KEY WORDS: armin; synaptic transmission; nerve–muscle preparation.

Many anticholinesterase drugs are considered to have a nonspecific action which complicates purely anticholinesterase effects [3]. Data in the literature on the presynaptic action of anticholinesterase drugs are few in number and contradictory in nature [4, 5]. The mechanisms of the blocking action of the organophosphorus cholinesterase inhibitor armin* on neuromuscular transmission during low-frequency stimulation have not yet been explained.

The object of the present investigation was to study the effects of armin on the various components of the frog neuromotor synapse.

EXPERIMENTAL METHOD

Experiments were carried out on nerve–muscle preparations of the frog pectoralis muscle placed in a transparent plastic chamber with a capacity of 1.5 ml, through which the test solutions flowed. The nerve was stimulated in the solution surrounding the muscle by square pulses 0.1 msec in duration, applied through a "suction" electrode. The frequency of stimulation was 1 Hz and its strength 2-3 thresholds.

The resting membrane potential (MP) of the muscle fibers and spontaneous miniature and evoked end-plate potentials (MEPP and EPP respectively) were recorded intracellularly by the standard microelectrode

*Ethyl-p-nitrophenyl ester of ethylphosphinic acid.

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