ANTIARRHYTHMIC ACTION OF MONOETHANOLAMINE ON MYOCARDIAL EXPLANTS OF CHICK EMBRYOS IN TISSUE CULTURE

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Experiments on myocardial explants of chick embryos in tissue culture reveal the antiarrhythmic properties of monoethanolamine (ethanolamine). Experimental arrhythmia was produced by injection of strophanthin and aconitine. Both the therapeutic and the prophylactic action of ethanolamine was more marked than that of quinidine. Ethanolamine restored regular contractions of the explants when stopped by cadmium chloride. The mechanism of action of ethanolamine is discussed in connection with its ability to liberate sulfhydryl groups.

Monoethanolamine (ethanolamine) increases the number of total and freely reacting sulfhydryl groups of the contractile proteins of muscles [1], and this evidently causes restoration of the contractions of the isolated frog's heart when stopped by cadmium chloride [2].

Changes in the reactivity of the sulfhydryl groups of myocin can give rise to definite changes in bioelectrical potentials on account of changes in the membrane gradients for different ions [4].

With this fact in mind, it could be supposed that ethanolamine, which modifies the selective permeability of the myocardial cell membranes, could affect the processes of excitation and conduction of impulses determining the regular contractions of the heart. The investigation described below was carried out to test this hypothesis.

EXPERIMENTAL METHOD

The antiarrhythmic activity of ethanolamine was studied in tissue cultures of the myocardium of 6-10-day chick embryos. Arrhythmia could not be evoked in explants obtained at earlier times. The technique of making the explants and the original method developed for objective photoelectric recording of the contractions of the monolayer of myocardial cells were described recently [3]. After the background of rhythmic contractions had been recorded, experimental arrhythmia was produced with strophanthin K in a concentration of $5 \cdot 10^{-6}$– $1 \cdot 10^{-6}$ g/ml, or aconitine ($1 \cdot 10^{-13}$ g/ml). To change the solutions, 0.1 ml of semisynthetic nutrient medium (85% Eagle's medium and 15% horse serum) was withdrawn through the upper hole in the specially designed transparent plastic chambers, and the same volume of the test substance was added. The antiarrhythmic activity of monoethanolamine was compared with the activity of quinidine. Concentrations with prophylactic and therapeutic action were determined.

To confirm the specific action of ethanolamine on the SH-groups of tissue enzymes, its effect on the arrest of contractions of the myocardial explants produced by administration of toxic concentrations of cadmium chloride ($1 \cdot 10^{-4}$ g/ml) was studied.

Experiments were carried out on 112 myocardial explants from chick embryos.

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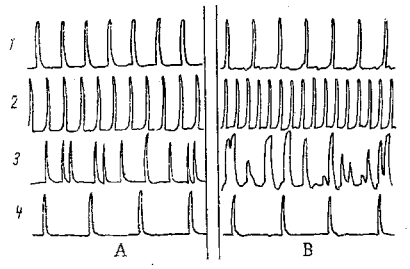

Fig. 1

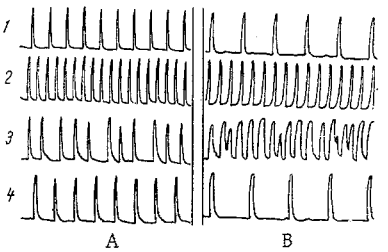

Fig. 2

Fig. 1. Antiarrhythmic effect of ethanolamine. Photoelectric recording of contractions of myocardial explants of chick embryo. A) Normal contractions (1), contractions 3 min (2) and 5 min (3) after administration of aconitine in concentration of $1 \cdot 10^{-13}$ g/ml and after addition of ethanolamine in a concentration of $7 \cdot 10^{-4}$ g/ml (4); B) normal rhythm (1), rhythm 4 min (2), and 8 min (3) after addition of strophanthin K in concentration of $1 \cdot 10^{-5}$ g/ml and after addition of ethanolamine in concentration of $5 \cdot 10^{-4}$ g/ml (4).

Fig. 2. Antiarrhythmic effect of quinidine. Photoelectric recording of contractions of myocardial explants of chick embryo. A) Normal contraction (1), contractions 3 min (2), and 5 min (3) after addition of aconitine and after addition of quinidine in concentration of $1 \cdot 10^{-6}$ g/ml (4); B) normal rhythm (1), rhythm 4 min (2), and 7 min (3) after addition of strophanthin in concentration of $5 \cdot 10^{-6}$, and after addition of quinidine in concentration of $2 \cdot 10^{-5}$ g/ml (4).

EXPERIMENTAL RESULTS

Ethanolamine, in concentrations of $5 \cdot 10^{-5}$–$5 \cdot 10^{-4}$ g/ml, had a definite antiarrhythmic action on aconitine arrhythmia. In a concentration of $7 \cdot 10^{-4}$ g/ml it had a therapeutic action on established arrhythmia, which disappeared after 1 min (Fig. 1A) and did not recur before the end of the experiment.

On the same model of arrhythmia, quinidine in a concentration of $1 \cdot 10^{-9}$–$5 \cdot 10^{-7}$ g/ml had no antiarrhythmic action, although it slightly reduced the rate of the arrhythmic contractions of the explant. In a concentration of $1 \cdot 10^{-6}$ g/ml, quinidine had an inconstant or transient antiarrhythmic effect, and a definite antiarrhythmic action was found only if quinidine was given in a concentration of $1 \cdot 10^{-5}$– $1 \cdot 10^{-4}$ g/ml. However, quinidine had a therapeutic effect only (Fig. 2A) and did not prevent the onset of arrhythmia. By contrast with ethanolamine, its antiarrhythmic action was short in duration, on the average 7-8 min. After disappearance of the arrhythmia, the frequency of the contractions of the explants was reduced considerably by the action of quinidine (by 85.5% of its initial level). Sometimes total arrest of the contractions took place.

Ethanolamine had a prophylactic antiarrhythmic action on the strophanthin model in a concentration of $1 \cdot 10^{-4}$ g/ml, and a therapeutic action in a concentration of $5 \cdot 10^{-5}$– $3 \cdot 10^{-4}$ g/ml (Fig. 1B). The antiarrhythmic action of ethanolamine was prolonged.

The prophylactic action of quinidine on strophanthin arrhythmia was not clearly defined, and its therapeutic action did not begin to appear until the concentration was $3 \cdot 10^{-6}$–$1 \cdot 10^{-5}$ g/ml (Fig. 2B). Just as in the experiments on aconitine arrhythmia, the antiarrhythmic action of quinidine was short in duration (3-5 min).

A definite difference between the character of the arrhythmias produced by aconitine and strophanthin was observed. Addition of aconitine to the medium with contracting explants initially caused an increase in frequency without any change in amplitude (phase 1). Later (phase 2) a typical disturbance of the rhythm developed, with an increase and decrease in the intervals between contractions (Figs. 1A, 2A). The character of development of strophanthin arrhythmia in phase 2 was somewhat different: 5-8 min after the increase in frequency of contractions with no change in amplitude, changes occurred in both the amplitude and the frequency of the contractions (Figs. 1B, 2B).

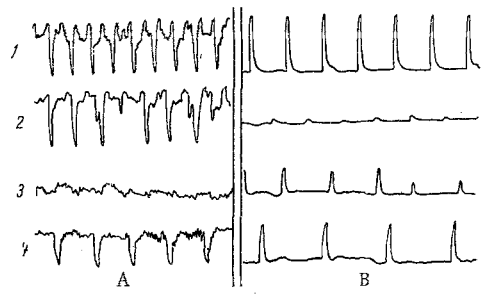

Fig. 3. Effect of ethanolamine and cysteine on myocardial explant whose rhythmic contractions are suppressed by cadmium chloride in concentration of $1 \cdot 10^{-4}$ g/ml. Photoelectric recording: A) normal contractions (1) contractions immediately (2), and 3 min (3) after addition of cadmium chloride and 1 min after addition of ethanolamine (4); B) normal contractions (1), contractions immediately after addition of cadmium chloride in concentration of $1 \cdot 10^{-4}$ g/ml (2), 1 min (3), and 5 min (4) after addition of cysteine.

The mechanism of the antiarrhythmic action of ethanolamine in strophanthin arrhythmia was evidently due to liberation of the sulfhydryl groups of the membrane adenosine triphosphatase, which are inhibited by high concentrations of cardiac glycosides. At the same time, the almost identical character of the activity of monoethanolamine indicates that the mechanism of the arrhythmic action of aconitine is also due to inhibition of sulfhydryl groups.

Selective inhibition of protein SH-groups by cadmium chloride did not produce any typical disturbance of the rhythm of contractions of the explants. Only in a concentration of $1 \cdot 10^{-4}$ g/ml did cadmium chloride sharply reduce the amplitude of the contractions or abolish them completely. The addition of ethanolamine in a concentration of $5 \cdot 10^{-5}$ g/ml restored rhythmic activity of the explants with some slowing of the rhythm and decrease in amplitude (Fig. 3A). A restorative action similar in character to that of ethanolamine was exhibited by cysteine in a concentration of $1 \cdot 10^{-3}$ g/ml (Fig. 3B). Despite the fact that cysteine is a donor of sulfhydryl groups, a higher concentration of cysteine than of ethanolamine was required in order to restore rhythmic contractions of the explants.

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