EFFECT OF NONACHLAZINE ON THE FREQUENCY AND AMPLITUDE OF CONTRACTIONS OF THE ISOLATED ATRIUM

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The effect of the new antianginal drug nonachlazine on the frequency and amplitude of contractions of the isolated atrium of guinea pigs and albino rats was studied. In experiments on the isolated atrium nonachlazine as a rule depresses these parameters. This effect of the drug on the isolated atrium is evidently due to the direct effect of nonachlazine on the myocardium and on the conducting system of the heart. No species differences were found in the character of the action of nonachlazine.

KEY WORDS: *nonachlazine; chronotropic effect; inotropic effect.*

The writers showed previously [1, 2] that the new antianginal drug nonachlazine, in experiments on the isolated auricle of the rabbit's heart in concentrations of $8 \cdot 10^{-7}$ - $8 \cdot 10^{-6}$ M lengthens the effective refractory period of the atrium through its negative chronotropic effect. In later investigations aimed at studying the mechanism of the coronary dilating action of nonachlazine and conducted on the whole animal (cats and rats) it was shown that nonachlazine has a biphasic action on cardiac activity: A short phase of weakening of cardiac activity (3-5 min) is followed by a considerable increase in the cardiac output and the contractile function of the myocardium (25-35 min). Special experiments showed that the second phase of the action of nonachlazine is connected with its ability to stimulate β-adrenergic structures in the myocardium, leading to the development of a positive inotropic effect [1, 2].

Since no such action was observed when the effect of nonachlazine was studied on the duration of the refractory period of the rabbit atrium, it was decided to make a systematic study of the effect of nonachlazine on the frequency and amplitude of contractions of the isolated atrium in animals of different species.

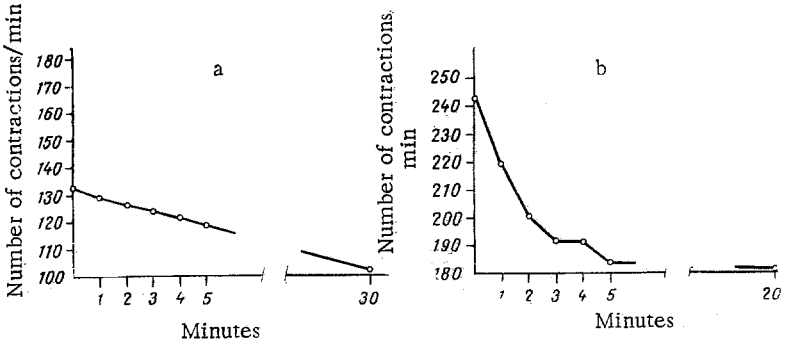

Fig. 1. Decrease in number of contractions of isolated atrium of albino rats (a) and guinea pigs (b) under the influence of nonachlazine ($8 \cdot 10^{-6}$ M).

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EXPERIMENTAL METHOD

The effect of nonachlazine on the frequency (chronotropic effects) and amplitude of the cardiac contractions (indirectly reflecting the inotropic effect) was studied on isolated atria of guinea pigs and albino rats, kept in oxygenated Ringer–Locke solution at 29-31°C. The cardiac contractions were recorded by means of a strain gauge and bridge circuit, connected through a preamplifier to a type EKPSCh-3 electrocardiograph.

To analyze the mechanism of action of nonachlazine, the chronotropic and inotropic effects were studied under the influence of the drug itself and the change in those effects was determined after preliminary action upon the adrenergic and cholinergic innervation of the heart. The following drugs were used: the β-adrenostimulator isoproterenol, the β-adrenoblocker propranolol, the cholinomimetic acetylcholine (AC), and the cholinolytic atropine. All drugs were added to the vessel containing the nutrient solution in the following concentrations (in M): nonachlazine $8 \cdot 10^{-9}$-$8 \cdot 10^{-6}$; isoproterenol $1.8 \cdot 10^{-8}$-$3.7 \cdot 10^{-8}$; propranolol $1.6 \cdot 10^{-7}$-$1.6 \cdot 10^{-6}$; AC $1.2 \cdot 10^{-6}$-$6 \cdot 10^{-6}$; atropine $2.8 \cdot 10^{-6}$-$2.8 \cdot 10^{-5}$. Observations on the action of the drugs continued for 30 min. Altogether there were 98 experiments.

EXPERIMENTAL RESULTS

The experiments showed that nonachlazine, in low concentrations ($8 \cdot 10^{-9}$-$8 \cdot 10^{-7}$ M) had no significant effect on the frequency and strength of the cardiac contractions. Starting with concentrations of $4 \cdot 10^{-6}$-$8 \cdot 10^{-6}$ M, as a rule a decrease in the amplitude and frequency of the contractions of the isolated atrium was observed. It is important to note that this effect was clearly defined in two thirds of the experiments. During the first 5 min, however, the drug had a distinct negative chronotropic action (the number of atrial contractions was reduced by 19%), and at the same time the amplitude of the contractions was reduced (by 10%). With an increase in the duration of action of the drug these negative effects increased; by the 20th minute the number of contractions was reduced by 26% and their amplitude by 24%; by the 30th minute the decrease was 39 and 24%, respectively. In one third of the experiments, during the first minutes after administration of nonachlazine in the same concentration, a brief (not more than 5 min) increase was observed in both the frequency (by 9%) and the amplitude (by 26%) of the cardiac contractions. By the 15th-20th minute of action of the drug in these experiments, a decrease in the frequency and amplitude of contractions of the isolated atrium by 25 and 24%, respectively, also was observed.

Nonachlazine potentiates the positive inotropic and chronotropic action of isoproterenol and produces a small increase in the amplitude and frequency of the cardiac contractions. After preliminary administration of propranolol, the usual action of nonachlazine is observed, i.e., propranolol has virtually no effect on the action of nonachlazine. The brief and ill-defined phase of potentiation produced by nonachlazine in one third of the experiments could not be controlled by the preliminary administration of propranolol, because of the inconstancy of its appearance. Nonachlazine reduced the inhibitory action of AC on the amplitude of the cardiac contractions to some extent. The effects of nonachlazine were not blocked by atropine.

No species differences were found in the character of the action of nonachlazine. The reactions described were observed equally in the atria of guinea pigs and of albino rats (Fig. 1).

The inhibitory effect of nonachlazine on the myocardium was thus predominant in experiments on the isolated atria of guinea pigs and albino rats. Considering that the drug lengthens the refractory period of the isolated atrium, it must be assumed that the negative phase of the action of nonachlazine is due both to its direct effect on the myocardium and its effect on the conducting system of the heart. If the results of the experiments on the isolated atrium are compared with those obtained in experiments on the intact animal, the first (inhibitory) phase of action of nonachlazine on the whole animal can also be explained by the direct effect of the drug on the myocardium and on the specific tissue of the heart. However, in the intact animal this effect is soon marked by the phase of strengthening of cardiac activity. In experiments on the isolated atrium, in which the number of β-adrenergic receptors is evidently small, as a rule the phase of potentiation is absent.

LITERATURE CITED

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