

EFFECT OF SULFHYDRYL GROUPS ON AUTOMATIC ACTIVITY OF THE CARDIAC PACEMAKERS

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Experiments on isolated rabbit hearts and also on hearts with a complete atrioventricular block were carried out to study the effect of an excess or deficiency of sulfhydryl groups on automatic activity of the cardiac pacemakers. Unithiol and cysteine in concentrations of $1 \cdot 10^{-6}$ – $1 \cdot 10^{-4}$ g/ml were used as donors of sulfhydryl groups and a deficiency of these groups was produced by addition of alloxan in concentrations of $1 \cdot 10^{-5}$ – $5 \cdot 10^{-5}$ g/ml. Changes in the concentration of sulfhydryl groups were found to have no marked action on automatic activity of the sinoatrial node. An excess of sulfhydryl groups led to poststimulation depression of automatic activity of potential pacemakers of the ventricles and could lead to the development of Luciani's periods. Conversely, with a deficiency of sulfhydryl groups, automatic activity of the ventricular pacemakers increased sharply, atrioventricular conduction was disturbed, and poststimulation depression of automatic activity was considerably reduced. Disturbances of cardiac activity evoked by a deficiency of sulfhydryl groups were completely abolished by unithiol or cysteine.

KEY WORDS: sulfhydryl groups; cardiac pacemakers; automatic activity; poststimulation depression of automatic activity; atrioventricular block.

Data in the literature on the effect of changes in the content of tissue sulfhydryl groups on cardiac activity are contradictory. Most investigations have dealt with the action of acetylcholine on the heart during a deficiency of SH groups. Several workers have shown that blocking sulfhydryl groups by salts of the heavy metals, forming mercaptide bonds, abolishes the response of the heart to vagus nerve stimulation and to injection of acetylcholine [2, 7], and also depresses ATPase activity in the myocardium [10, 11, 12]. According to observations by other workers, oxidizers of SH groups (alloxan, dihydroascorbic acid, etc.) potentiate cholinergic influences on the heart [3, 4] and do not lower ATPase activity. Substances acting as donors of sulfhydryl groups are used in clinical medicine in cases of poisoning by salts of heavy metals and overdosage of cardiac glycosides [5, 6].

The effect of changes in the concentration of sulfhydryl groups on automatic activity of the cardiac pacemakers has not been studied. The object of this investigation was to study the effect of a deficiency or excess of sulfhydryl groups on automatic activity of the sinoatrial node and the potential ventricular pacemakers of the heart.

EXPERIMENTAL METHOD

Experiments were carried out on isolated hearts of 24 rabbits. Tyrode's solution of the following composition (in mmoles/liter) was used for perfusion by Langendorff's method: NaCl 137, KCl 2.7, CaCl_2 1.8, MgCl_2 1.0, NaHCO_3 12.0, NaH_2PO_4 0.4, and glucose 5.5. The temperature of the solution was $36.5 \pm 0.3^\circ\text{C}$ and its pH 7.3–7.4.

Cysteine and unithiol in concentrations of $1 \cdot 10^{-6}$ – $1 \cdot 10^{-4}$ g/ml were used as donors of sulfhydryl groups [4]. A deficiency of SH groups was created by means of alloxan, which does not form mercaptide bonds [3].

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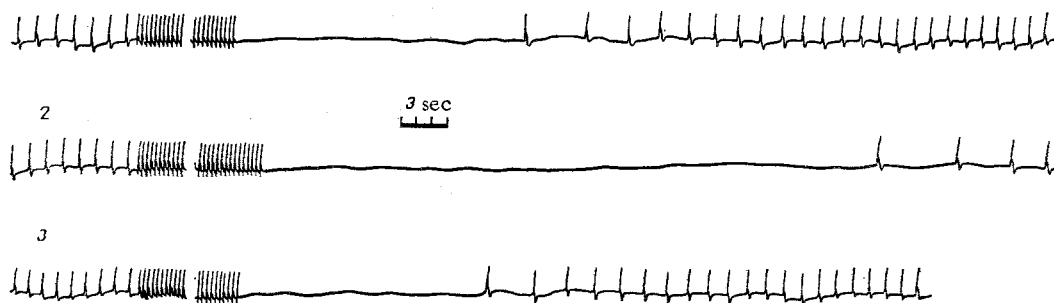


Fig. 1. Effect of excess of sulfhydryl groups on duration of preautomatic pause: 1) initial duration of preautomatic pause after cessation of fast electrical stimulation of ventricles of isolated rabbit's heart for 3 min under conditions of total atrioventricular block; 2) twofold increase in preautomatic pause after action of unithiol for 15 min in concentration of $5 \cdot 10^{-5}$ g/ml; 3) preautomatic pause during perfusion of heart with ordinary Tyrode's solution. Record of electrical activity of rabbit ventricles.

Alloxan was given in concentrations of $1 \cdot 10^{-5}$ – $5 \cdot 10^{-5}$ g/ml, sufficient to oxidize up to 20% of the total content of SH groups in the tissues or up to 50% of the SH groups of nonprotein thiol compounds [4].

The action of these substances was studied on the intact isolated heart and on a heart with complete atrioventricular block. The block was produced by applying a soft clamp to the upper parts of the bundle of His. After abolition of the flow of impulses from the sinoatrial node, automatic activity arises in potential cardiac pacemakers, so that the effect of a deficiency and excess of SH groups on the activity of the ventricular pacemakers was estimated from the frequency of spontaneous excitation and the duration of the preautomatic pause arising after cessation of fast electrical stimulation of the ventricles. Stimulation by square pulses of above-threshold strength, with a duration of 3 msec and a frequency 2.5–3 times higher than the spontaneous frequency of excitation, was carried out for 3 min.

Electrical activity of the atria and ventricles of the heart was recorded. The experimental results were subjected to statistical analysis by Student's method.

EXPERIMENTAL RESULTS AND DISCUSSION

In the experiments of series I on 12 isolated rabbits' hearts the effect of unithiol and cysteine as donors of sulfhydryl groups was studied on automatic activity of the sinoatrial node and of the potential ventricular cardiac pacemakers. During the action of these compounds in concentrations of $1 \cdot 10^{-6}$ – $1 \cdot 10^{-4}$ g/ml no significant changes took place in automatic activity of the sinoatrial pacemaker, which continued to generate impulses at a mean frequency of 172 ± 6.8 per minute. Under these circumstances no disturbances of intracardiac conduction were observed.

Under conditions of complete atrioventricular block unithiol (or cysteine) in the same concentration also had no significant effect on the frequency of idioventricular excitation, which averaged 58 ± 4.6 per minute, during perfusion of the heart for 10–20 min. Meanwhile these substances considerably facilitated poststimulation depression of automatic activity of the potential ventricular pacemakers. For instance, on the cessation of fast electrical stimulation of the ventricles of a heart with complete atrioventricular block the preautomatic pause was 16 ± 2.1 sec. Cysteine in concentrations of $1 \cdot 10^{-5}$ – $5 \cdot 10^{-5}$ g/ml increased the duration of the preautomatic pause after perfusion for 10–15 min to 43 ± 3.2 sec ($P < 0.01$), and unithiol in the same concentration increased it to 30.4 ± 2.9 sec ($P < 0.02$). After perfusion of the heart for 12–15 min with ordinary Tyrode's solution the duration of the preautomatic pause returned again to its initial value (Fig. 1).

During the action of unithiol or cysteine under conditions of complete atrioventricular block Luciani's periods, i.e., periodic depression of automatic activity of the idioventricular pacemaker, developed in 30% of the experiments. This phenomenon, evidence of the development of functional "weakness" of the potential pacemaker, was abolished by perfusion of the heart with ordinary Tyrode's solution.

In the experiments of series II on 12 isolated rabbits' ventricles the effect of a deficiency of sulfhydryl groups caused by alloxan on automatic activity of the cardiac pacemakers was investigated. During the action of alloxan in concentrations of $1 \cdot 10^{-5}$ – $5 \cdot 10^{-5}$ g/ml on the intact hearts, a transient increase in the frequency of cardiac contractions occurred within the first few minutes, the pacemaker migrated into the atria, atrial and

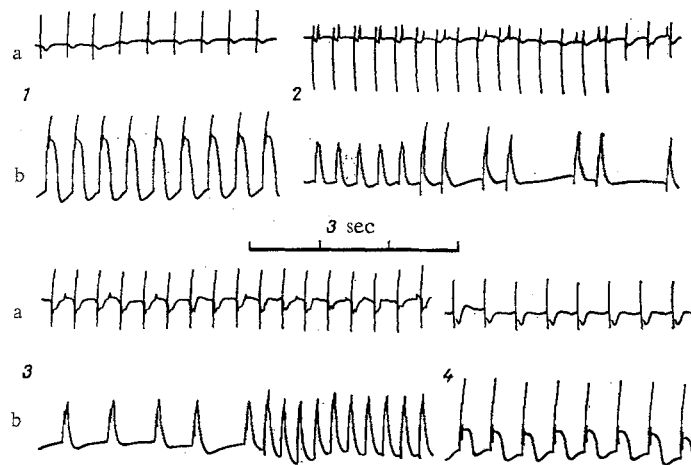


Fig. 2. Effect of deficiency of sulfhydryl groups on isolated rabbit's heart: 1) initial sinus rhythm; 2) development of complete atrioventricular block after action of alloxan for 2 min in concentration of $5 \cdot 10^{-5}$ g/ml; 3) development of burst of ventricular tachysystole after action of alloxan for 10 min; 4) restoration of regular sinus rhythm and of atrioventricular conduction after action of cysteine for 15 min in concentration of $5 \cdot 10^{-5}$ g/ml. Record of electrical activity of atria (a) and ventricles (b) of isolated rabbit heart.

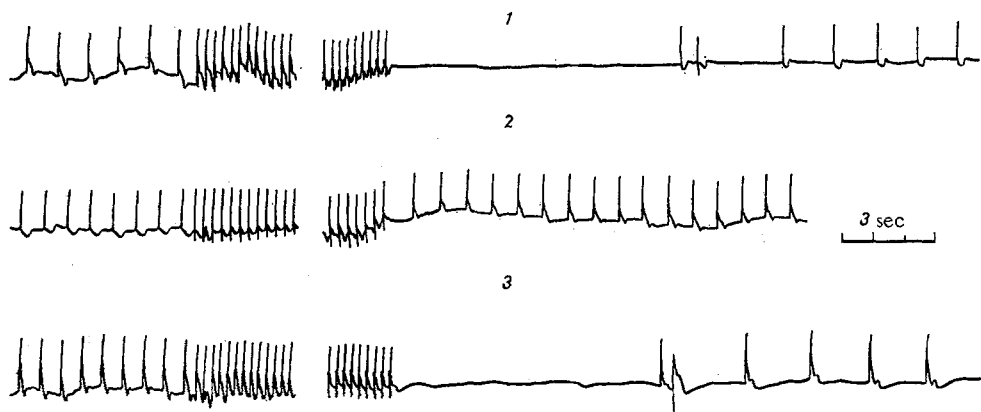


Fig. 3. Effect of deficiency of sulfhydryl groups on duration of preautomatic pause: 1) initial duration of preautomatic pause after cessation of fast electrical stimulation of ventricles of isolated rabbit heart for 3 min under conditions of complete atrioventricular block; 2) disappearance of preautomatic pause after exposure for 10 min to alloxan in concentration of $5 \cdot 10^{-5}$ g/ml; 3) preautomatic pause after exposure for 15 min to cysteine in concentration of $5 \cdot 10^{-5}$ g/ml. Recording of electrical activity of rabbit ventricles.

ventricular extrasystoles appeared, and intracardiac conduction was disturbed up to the degree of complete atrioventricular block. Against this background grouped ventricular extrasystoles and bursts of ventricular tachysystole frequently appeared (Fig. 2).

Under conditions of complete atrioventricular block alloxan, in the same concentrations, led to a marked and persistent increase in the frequency of idioventricular excitation from 62 ± 4.6 to 87 ± 5.7 per minute ($P < 0.02$). In 50% of experiments polytopic ventricular extrasystoles and bursts of paroxysmal ventricular tachysystole were observed. The preautomatic pause arising after the removal of stimulation was sharply reduced by alloxan or disappeared completely (on average from 23 ± 2.7 to 3 ± 0.4 sec; $P < 0.01$) (Fig. 3).

The action of alloxan was lasting and did not disappear after perfusion of the heart with ordinary Tyrode's solution for 30-40 min. The addition of unithiole or cysteine to the perfusion solution in a concentration of $5 \cdot 10^{-5}$ g/ml completely abolished all the effects of alloxan: After perfusion for 10-15 min the atrial and ventricular rhythm and the duration of poststimulation asystole returned to their initial values (Figs. 2 and 3).

The results of these experiments show that an excess or deficiency of sulfhydryl groups had no marked effect on automatic activity of the sinoatrial node. Meanwhile a change in the concentration of SH groups had a marked effect on automatic activity of the more distal pacemakers and on intracardiac conduction. In the presence of an excess of sulfhydryl groups automatic activity of the potential pacemakers of the heart was depressed, as shown by an increase in the duration of the preautomatic pause after the removal of rapid electrical stimulation and the appearance of Luciani's periods [1, 8]. Conversely, in a deficiency of SH groups automatic activity of the potential pacemakers of the heart was sharply increased and disturbances of atrioventricular conduction appeared. As a result atrial and ventricular extrasystoles and bursts of paroxysmal ventricular tachysystole developed and the poststimulation asystole diminished or disappeared. These results agree with the view that substances blocking sulfhydryl groups have a digitalis-like action [6, 9]. Disturbances of automatic activity of potential cardiac pacemakers and also the complete atrioventricular block arising under these circumstances were reversible in character for they were abolished by the addition of unithiol or cysteine, donors of sulfhydryl groups, to the perfusion solution.

Extrasystoles of varied origin, disturbances of intracardiac conduction, and bursts of ventricular tachysystole are complications of several heart diseases. The results of this investigation show that an excess of sulfhydryl groups, while having virtually no effect on automatic activity of the sinoatrial node, has a marked inhibitory action on the activity of heterotopic foci of excitation. This suggests that preparations containing sulfhydryl groups may be used for the treatment of these disturbances of cardiac activity.

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