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# GLUTAMIC ACID INCREASES THE MAXIMAL INTENSITY OF MYOCARDIAL CONTRACTILE FUNCTION

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KEY WORDS: papillary muscle; contractile function; glutamic acid

The chronoinotropic relationship for the myocardium of most mammals is characterized by an increase in the force or amplitude of contraction up to a certain optimal frequency, and if this frequency is exceeded, the amplitude of contraction decreases and alternation develops [3, 12]. Besides contraction, relaxation also is disturbed [3, 7].

The aim of this investigation was to compare depression of contraction and relaxation of the myocardium at a high frequency when energy formation is deficient; for this purpose isolated papillary muscles of varied thickness were used, for we know that the thickness of the muscles, because of an increase in oxygen diffusion, is a factor limiting maximal contractile function [1, 8, 10]. An attempt also was made to influence these processes with glutamic acid (GA), which has the property of improving the state of the myocardium when affected by hypoxia or hypoperfusion [4, 6].

## EXPERIMENTAL METHOD

Experiments were carried out on isolated papillary muscles from the guinea pig right ventricle. The muscles were contracted by electrical stimulation in Krebs' solution, saturated with 95% $O_2$ + 5% $CO_2$, pH 7.3-7.4 at 29°C. The contraction signal obtained from a photoelectric transducer and its first derivative were recorded on a "Gould Brush 2200" two-channel recorder. The thickness of the muscles was determined from the area of cross-section, using data for weight and length of the muscle. The maximal rate of contraction and relaxation was expressed as a ratio of muscle length in the usual way. Details of the technique were described previously [2]. In each experiment the frequency of contractions was increased stepwise from 0.5 to 3.5 Hz at steps of 0.5 Hz, and was maintained for 1 min at each frequency. GA (3.5 mM) was added to the perfusion fluid after the first series of increased frequency, and the second series was performed 30 min later in the presence of GA. The results were subjected to statistical analysis by Student's test and expressed in the form M ± m.

## EXPERIMENTAL RESULTS

The positive inotropic effect of an increase in frequency was sufficiently well marked in all experiments irrespective of the thickness of the muscles. Nevertheless, with an increase in thickness, not only the amplitude of contraction, but also the optimal frequency decreased (Fig. 1). For very thick muscles, in most experiments it was 2 Hz, compared with

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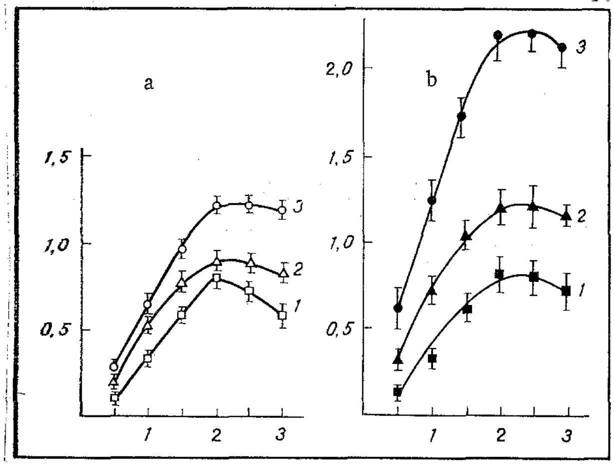
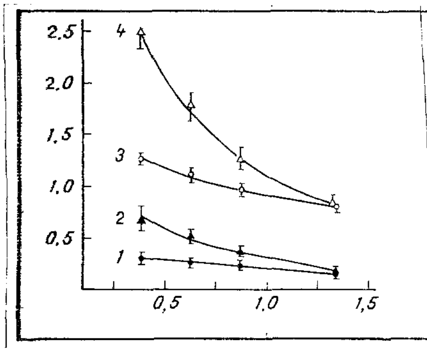



Fig. 1. Dependence of maximal rate of contraction (a) and maximal rate of relaxation (b) of guinea pig papillary muscles on frequency of contractions. Abscissa, frequency of contractions (in Hz); ordinate, units of muscle length per second. 1-3) Thickness of muscle 1.34 ± 0.11 $mm^2$ (n = 7), 0.70 ± 0.02 $mm^2$ (n = 28), and 0.38 ± 0.02 $mm^2$ (n = 12) respectively.



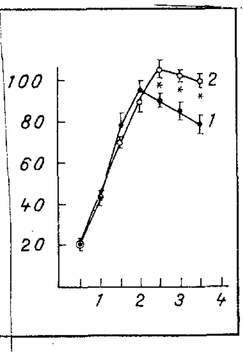




Fig. 2 Fig. 3

Fig. 2. Maximal rate of contraction (1, 3) and maximal rate of relaxation (2, 4) in muscles of different thickness. Abscissa, thickness of muscle (in $mm^2$), ordinate, units of length of muscle/sec. Frequency of contractions 0.5 Hz (1, 2) and 2 Hz (3, 4).

Fig. 3. Dependence (in %) of maximal rate of contraction on frequency of stimulation before (1) and after (2) addition of GA (3.5 mM). Abscissa, frequency of contractions (in Hz). Maximal value in each experiment before addition of GA taken as 100%. Asterisk indicates statistically significant differences.

3 Hz for thin muscles. Comparison of the rate of contraction showed that the optimal frequency was 0.5 Hz greater. The difference in the rate of contraction of the thin and thick muscles in absolute values was about equal within the range 1-2 Hz, and it increased at a higher frequency, whereas in the experiments on thick muscles appreciable depression of the amplitude and rate of contraction was observed.

At a low frequency of contractions (0.5 Hz) the maximal rate of relaxation of the thinnest muscles was twice as high as their maximal rate of contraction. With an increase in thickness of the muscles the difference between these parameters decreased, and there was no difference at all in the thickest muscles (Fig. 2). The situation was the same for a frequency of 2 Hz, at which in most experiments on thick muscles the maximal contraction velocity was observed. Thus irrespective of the frequency of contraction, an increase in thickness of the muscles correlates with predominant depression of the rate of relaxation.

The cause of this phenomenon was evidently connected with the triad of hypoxia, acidosis, and elevation of the extracellular $K^+$ level, characteristic of the pathogenesis of ischemia, and arising in the central zones of thick muscles [5, 8, 11]. In response to the isolated action of hypoxia or acidosis on the papillary muscles, the $Ca^{++}$ concentration acting in the myoplasm is unchanged [5], and the reduction in the force of contraction arising under these circumstances is linked with lowering of the sensitivity of the myofibrils to $Ca^{++}$ under the influence of acidosis. Moderate accumulation of extracellular $K^+$, through changes in the resting and action potentials, must be combined with reduced entry of $Na^+$ and $Ca^{++}$ ions into the cell. Since the rate of relaxation falls more rapidly than the rate of contraction in response to the isolated action of a reduced $Ca^{++}$ concentration, acidosis, and metabolic blockade, and also of hypoxia or of $Ca^{++}$-antagonists [2, 9, 13], it will be evident that during their combined action, the greater depression of relaxation than of contraction ought evidently to be even more marked.

In a separate series of experiments on nine muscles, whose average thickness was 0.81 ± 0.7 $mm^2$, the effect of GA (3.5 mM) was studied. Analysis of the results showed that its effect was stronger in experiments on thick muscles, characterized by a peak of the velocity or amplitude of contraction at a lower frequency, namely 1.5-2 Hz. In five such experiments the presence of GA in the perfusion fluid did not alter the parameters of contractile function over the frequency range from 0.5 to 2 Hz, but significantly increased them at a higher frequency of contractions, when under control conditions they were reduced (Fig. 3). A stronger effect, although in the same direction, was observed in four experiments, when the peak of contraction velocity was observed at 2.5-3 Hz. It was only at a frequency of 3.5 Hz that the presence of GA in the perfusion fluid was associated in all experiments with an increase of 10% in the amplitude of contraction, of 12% in the rate of contraction, and of 22% in the rate of relaxation.

The effect of GA is evidently associated with its ability to maintain a higher ATP level under hypoxic or ischemic conditions [4, 6]. These results suggest that the effect of GA on contraction and relaxation of the myocardium at a high frequency is due, at least in part, to an increase in the potential power of energy formation in the myocardial cells. The results of the present investigation may be interesting from the standpoint of the practical use of GA to increase the functional power of the myocardium in patients with ischemic heart disease during high-frequency electrical stimulation or during physical exercise.

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