There is evidence that dehydration and accompanying changes in tissue metabolism determine the resistance of the body to the action of unfavorable factors [7]. The participation of the cholinergic system of the perifornical region of the hypothalamus in maintaining resistance of cardiovascular functions in stress may be to some degree linked with its regulatory effect on water and electrolyte metabolism.

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EFFECT OF COOLING ON MECHANISMS OF MYOCARDIAL CONTRACTILITY AUTOREGULATION IN WARM-BLOODED ANIMALS

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KEY WORDS: cat's heart; autoregulation of contractility; cooling.

Starling's mechanism (dependence of the force of contraction of heart muscle on its length) and the chrono-inotropic mechanism (dependence of force on the frequency of contractions) are the fundamental myogenic mechanisms of autoregulation of myocardial contractility. However, no unequivocal answer has yet been given to the question of the effect of a factor such as cooling on these mechanisms. Some workers, for instance, have concluded that functioning both of Starling's mechanism and of the chrono-inotropic mechanism is improved with a fall of myocardial temperature [1, 6-8]. Other experimental studies, however, contradict this conclusion [9-11].

In the investigation described below the effect of temperature was studied on the efficiency of stretching and on the increase in heart rate connected with regulation of myocardial contractility in warm-blooded animals.

EXPERIMENTAL METHOD

Experiments were carried out on papillary muscles 4-8 mm long and not more than 1 mm in diameter, from the right ventricle of a cat's heart. The preparation was placed in a constant temperature chamber where one end was fixed to the stretching device, the other end to a 6MKh1S mechanotron force transducer [2]. The preparation was immersed in modified Krebs–Henseleit solution (in mM): NaCl 118.0, KCl 2.7, $CaCl_2$ 2.5, KH_2PO_4 1.0, $MgSO_4$ 1.2, $NaHCO_3$ 12.0, glucose 5.6. The solution was saturated with a gas mixture of 95% O_2 and 5% CO_2; the pH of the solution was 7.3-7.4. The muscle was stimulated by above-threshold square

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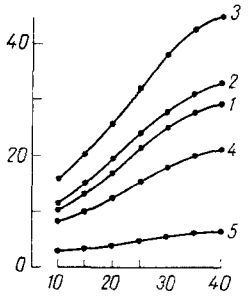

Fig. 1

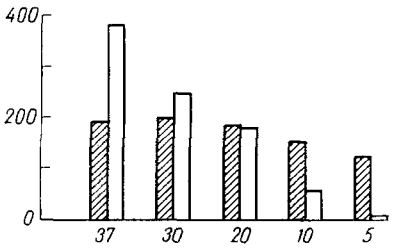

Fig. 2

Fig. 1. Effect of cooling on dependence of source of contractions of isolated myocardium on its length. Abscissa, degree of stretching (in % of initial length); ordinate, force of contractions (in $mN \cdot mm^{-2}$). 1-5) 37, 30, 20, 10, and 5°C respectively.

Fig. 2. Effect of cooling the myocardium on effectiveness of Starling mechanism and chrono-inotropic mechanism. Abscissa, temperature (in °C); ordinate, relative changes in force of contractions (in %). Shaded columns — changes in force of contractions during stretching of myocardium; unshaded columns — changes in force of contractions during increase in frequency of stimulation.

pulses from an ÉSU-1 electrical stimulator; the pulse duration was increased from 5 to 20 msec as the temperature fell. The temperature in the chamber was altered from 37 to 5°C. The force of contractions of the preparation under isometric conditions was recorded on an N-338 automatic writer after amplification of the signal from the force transducer.

There were two series of experiments. In series I dependence of the force of contractions on the degree of stretching, expressed as a percentage of the initial length of the muscle, was studied in 30 preparations at temperatures of 37, 30, 20, 10, and 5°C with an accuracy of 0.2%. To assess the effect of temperature on chrono-inotropic relations in the myocardium [6], stimulation was applied at optimal frequency for the given temperature.

In series II dependence of the force of established contractions on the frequency of stimulation was studied in 26 papillary muscles at the same temperature as in series I, but with stretching by 40%. The frequency of stimulation under constant temperature conditions was changed from values at which the previous contraction did not effect the parameters of the next contraction (single contractions) to values at which the force of contractions began to decline after reaching their maximum, corresponding to the optimal frequency of stimulation.

EXPERIMENTAL RESULTS

In the experiments of series I the optimal frequency of contractions at 37, 30, 20, 10, and 5°C was 2.42 ± 0.06, 1.42 ± 0.06, 0.42 ± 0.02, 0.13 ± 0.01, and 0.06 ± 0.004 Hz respectively. As the temperature fell from 37°C the force of contractions of the cat myocardium after initial stretching by 10% first increased from 10.1 ± 1.7 to 15.9 ± 2.2 $mN \cdot mm^{-2}$ at 20°C ($P < 0.01$) and then fell to 2.7 ± 0.3 $mN \cdot mm^{-2}$ at 5°C ($P < 0.01$), reflecting the direct effect of cooling on force. In turn, stretching of the myocardium led (Fig. 1) to an increase in the force of contractions at whatever temperature it was investigated (in all cases $P < 0.01$). Analysis of the effect of cold on the Starling mechanism by estimating the absolute increase in force at different temperatures, defined as the difference between the values of force at the initial and final degrees of stretching, showed that the absolute increase in the force of contractions during stretching of the muscles from 10 to 30% increased as the myocardial temperature fell from 37 to 20°C from 19.1 ± 3.3 to 28.8 ± 3.8 $mN \cdot mm^{-2}$ respectively, but rose during further cooling to 3.4 ± 0.5 $mN \cdot mm^{-2}$ at 5°C.

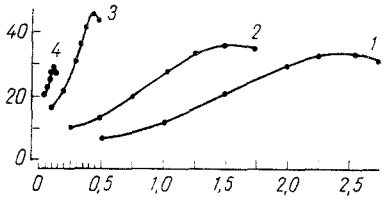

Fig. 3. Effect of cooling on dependence of force of contractions of isolated myocardium on frequency of its stimulation. Abscissa, frequency of stimulation (in Hz). Remainder of legend as to Fig. 1.

Under the influence of cooling the force of single contractions corresponding to the original frequency of stimulation for the given temperature, also changed: it increased from 7.0 ± 1.2 $mN \cdot mm^{-2}$ at 37°C to 20.5 ± 4.1 $mN \cdot mm^{-2}$ at 10°C ($P < 0.01$), after which it fell to 7.6 ± 2.2 $mN \cdot mm^{-2}$ at 5°C ($P < 0.01$ relative to the value of 10°C). An increase in the frequency of stimulation of the cat's myocardium during constant stretching led (Fig. 3) to an increase in the force of the established contractions at temperatures from 37 to 10°C (in all cases $P < 0.01$), but on cooling the myocardium to 5°C the chrono-inotropic effect was absent. The maximal absolute increase in force evoked by an increase in frequency to its optimal value for the given temperature rose with a fall of temperature from 26.8 ± 4.4 $mN \cdot mm^{-2}$ at 37°C to 29.4 ± 3.6 $mN \cdot mm^{-2}$ at 20°C ($P < 0.05$), but it then fell almost to zero at 5°C.

Calculations of the relative changes in the force of contractions within the ranges of frequency of stimulation studied showed that the maximal relative increase of force decreased regularly during cooling of the myocardium from 37°C (Fig. 2, unshaded columns). For instance, at 37, 30, 20, and 10°C the corresponding values of this parameter were 383 ± 78, 251 ± 52, 179 ± 39, and 43 ± 15% (in all cases $P < 0.01$ relative to the initial value at 37°C).

When the results are assessed it will be noted that they agree well with data in the literature indicating that the absolute increase in the force of contractions due to an increase in length or the frequency of stimulation of the isolated myocardium rises under the influence of a fall of temperature up to certain limits [1, 6-8]. On the basis of these data the authors cited concluded that the efficiency of the Starling mechanism and the chrono-inotropic mechanism in regulation of myocardial contractility increases during cooling. However, this approach, in our view, does not lead to a correct interpretation of the effect of cold on these mechanisms of autoregulation of contractility. It will be clear from Figs. 1 and 3 that the original force of myocardial contractions, corresponding to the initial degree of stretching and the initial frequency of stimulation, differed at different temperatures; consequently, comparison of the absolute increase in the length–force or frequency–force relationships does not make sense, because there is no common reference point and the direct action of cooling on the value of the force is disregarded.

To separate the effect of stretching or of increased frequency from the effect of temperature, the relative changes in the force of contractions of the myocardium must evidently be analyzed at one particular temperature. In that case, comparison of results obtained at different temperatures will show that the values of the relative increase in the force of contractions for the same degree of stretching do not differ significantly from each other for the cat myocardium within the temperature range from 37 to 20°C (Fig. 2). The small decrease observed in the relative increase of force at 10 and 5°C is evidently not the result of the action of cold on the Starling mechanism, but rather the result of a sudden deterioration in the general functional state of the myocardium of warm-blooded animals connected with qualitative changes at temperatures below 20°C [2, 4], preventing the Starling mechanism from being fully exerted under these conditions. This last effect is also confirmed by the fact that the relative increase in the force of contractions during stretching of the myocardium of warm-blooded animals is independent of temperature during cooling down to 0°C [3]. Meanwhile, the maximal relative increase in the force of contractions of the cat myocardium during an increase in the frequency of stimulation decreases successively as its temperature falls,

starting from 37°C (Fig. 2). Assessment of the relative changes in the force of contractions of the heart muscle of a warm-blooded animal (cat) during stretching or during an increase in the frequency of its stimulation thus convincingly proves that functioning of the Starling mechanism is independent of temperature and that the chrono-inotropic mechanism is inhibited by cold.

Considering that differences in the temperature sensitivity of biological phenomena to some extent reflect dissimilarity between the processes determining these phenomena [5], it can be concluded that the results of the present investigation also indicate differences in the nature of the processes lying at the basis of these two mechanisms of autoregulation of contractility. This confirms existing views that the predominant factor in the realization of the Starling mechanism is a physical process of change in the spatial mutual arrangement of the actin and myosin filaments, which is independent of temperature, whereas the predominant factor in the realization of the chrono-inotropic mechanism is chemical reactions in the process of electromechanical coupling, which are inhibited by cold.

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NONQUANTUM ACETYLCHOLINE RELEASE IN A NERVE-MUSCLE PREPARATION OF DYSTROPHIC 129/Rej MOUSE DIAPHRAGM

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KEY WORDS: congenital muscular dystrophy; nonquantum acetylcholine release; skeletal muscle.

A line of mice (129/Rej) is known which has a recessive genetic defect, manifested in the homozygous state as a lesion of the skeletal muscle, comparable in its features with the changes in human skeletal muscle in congenital muscular dystrophy, described as Duchenne's syndrome [5]. Some muscle fibers of these homozygous dystrophic mice are characterized in particular by extrasynaptic sensitivity to acetylcholine (ACh), resistance of their action potentials to tetrodotoxin, and lower values of resting membrane potential (RMP) than muscle fibers of phenotypically normal individuals [5, 7]. Such changes in the properties of the muscle membrane are known to be characteristic of denervated muscle fibers [1]. In this connection it has been suggested that the existing genetic defect is expressed ultimately as a disturbance of neurotrophic control of the muscle fibers [1, 5].

However, the affected muscle fibers of dystrophic mice are not excluded from motor activity and are indistinguishable from intact muscle fibers in the character of both quantum-

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