FREQUENCY-FORCE RELATIONSHIP IN THE HYPERTHYROID RAT MYOCARDIUM

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Hyperthyroidism reduces the sensitivity of the rat atrium to the negative inotropic action of an increase in heart rate [3]. This fact is not in agreement with data showing that the papillary muscles of the hyperthyroid cat can no longer respond by an increase in the force of contraction to an increase in the frequency of stimulation [2, 15]. It can be tentatively suggested that this contradiction can be explained by differences in the experimental conditions [7] and in the species and ages of the experimental animals [8], and also by the development of hypoxia in the hypertrophied myocardium, masking the action of hyperthyroidism on its contractility [2, 9, 11, 15].

The aim of this investigation was to repeat the study of the effect of hyperthyroidism on the frequency-force of contraction relationship for the fine papillary muscles of the rat, whose diameter (0.48-0.59 mm) ensures that their tissue receives an adequate oxygen supply [9].

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar albino rats weighing 135-256 g. Hyperthyroidism was induced by intraperitoneal injection of L-thyroxine ("Reanal," Hungary) in a dose of 100 μg/100 g body weight daily for one week. Administration of the hormone in accordance with this schedule led to hypertrophy of the heart and to an increase in the serum L-thyroxine concentration [1]. The papillary muscles were excised from the right ventricle, kept in O_2-saturated modified Tyrode solution ($CaCl_2$ 0.6 mM, NaCl 115 mM, KCl 6 mM, $MgCl_2$ 1.2 mM, glucose 11 mM, mannitol 1.1 mM, Tris-HCl 20 mM, pH 7.4, at 22°C). The contractile parameters of the papillary muscles were recorded under isometric conditions [1] with extracellular [Ca^{++}] of 1.8 mM, and the temperature of the incubation medium 30.0 ± 0.3°C. Dependence of the contractile parameters on frequency was determined as the frequency of contractions was gradually increased from 0.2 to 1.5 Hz. For each working cycle of the muscles

Table 1. Effect of Hyperthyroidism on Contractile Parameters of Rat Heart Muscle (M ± m)

Parameter	Euthyroid myocardium (n = 13)	Hyperthyroid myocardium (n = 11)	p
Force of contraction, mN/mm^2	40,5±3,5	30,0±2,9	<0,01
Maximal rate of contraction, mN/mm^2/sec	491,5±51,5	559,0±70,0	N. S.
Maximal rate of relaxation, mN/mm^2/sec	434,2±37,3	469,0±58,0	N. S.
TRMC, msec	145,8±5,8	100,0±4,9	<0,01

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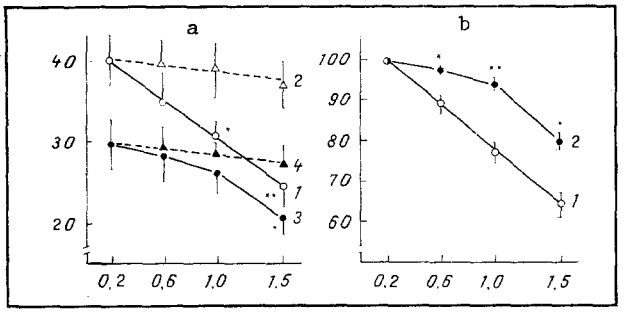

Fig. 1. Effect of increase in frequency of contraction on force of contraction on absolute (a) and relative (b) scales. a: 1) euthyroid myocardium (n = 13); 2) control level of force of contraction of euthyroid myocardium at 0.2 Hz; 3) hyperthyroid myocardium (n = 11); 4) control level for hyperthyroid myocardium at 0.2 Hz. Abscissa, frequency of contraction, Hz; ordinate, force of contraction, mN/mm^2). *p < 0.05, **p < 0.01 compared with control levels at 0.2 Hz. b: 1) euthyroid myocardium (n = 13); 2) hyperthyroid myocardium (n = 11). Abscissa, frequency of contraction, Hz; ordinate, force of contraction, percent of corresponding control level at 0.2 Hz. *p < 0.05, **p < 0.01 for comparison of hyperthyroid with euthyroid myocardium.

at a definite frequency of stimulation there was a corresponding period during which they worked at the control frequency of contraction, namely 0.2 Hz. Steady-state levels of the contractile parameters at increased frequencies of contractions of the muscles were estimated relative to their levels during the preceding working cycle at 0.2 Hz. The area of cross section of the papillary muscles was calculated by the method in [13]. Statistical analysis was carried out by Student's t test.

EXPERIMENTAL RESULTS

It will be clear from Table 1 that hyperthyroidism led to reduction of the force of contraction of the heart muscle by 25% compared with the euthyroid myocardium, as demonstrated previously [1, 3, 4]. There was a parallel reduction of the time taken to reach the maximal amplitude of contraction (TRMC), but the velocities of contraction and relaxation were unchanged. The developed force of myocardial contraction under isometric conditions is considered to be proportional to the product of intensity and duration (TRMC) of contraction [13]. Under these circumstances hyperthyroidism did not affect the elastic properties of the myocardium [2, 4, 10]. It can therefore be tentatively suggested that it was reduction of TRMC which led to a decrease in the force of contraction of the hyperthyroid myocardium in these experiments. The second cause of reduction of the force of contraction of the hyperthyroid heart muscle may have been a decrease in the apparent sensitivity of the heart muscle to extracellular calcium [1].

It will be clear from Fig. 1 that the force of contraction of the euthyroid and hyperthyroid muscles at a frequency of contraction of 0.2 Hz decreased equally in both groups in the course of the experiment. This indicates an equal degree of development of fatigue of the euthyroid and hyperthyroid papillary muscles throughout the course of the experiment. In both groups of myocardial muscles a decrease in the force of contraction was observed in response to an increase in the frequency of stimulation. Under these circumstances, however, two main differences were discovered between the euthyroid and hyperthyroid myocardium. First, with an increase in the frequency of contraction the force of contraction of the euthyroid papillary muscles began to decrease at low frequencies of contraction than in hyperthyroid muscles. Second, with an increase in the frequency of stimulation the force of contraction of the euthyroid heart muscles decreased much more than in hyperthyroid muscles. The results thus confirm qualitatively results [3] showing for the first time that not only the atrium, but also the ventricular myocardium of hyperthyroid rats have lower

sensitivity to the negative inotropic action of an increase in the frequency of contraction than the euthyroid muscle. It is interesting to note that this action of hyperthyroidism resembles the effect of an increased extracellular Ca^{++} concentration on the frequency dependence of the atria [16] and ventricular myocardium [8] of rats. The authors cited consider that the negative frequency dependence of the force of contraction of the papillary muscles of normal rats is due to shortening of the time required for complete accumulation of Ca^{++} in the sarcoplasmic reticulum. The force of contraction of the hyperthyroid myocardium is determined, just as in the normal heart, by the level and rate of change of the intracellular Ca^{++} concentration $[Ca^{++}]_i$ during systole [4, 5]. Potentiation of the force of myocardial contraction which we observed under the influence of hyperthyroidism, at raised frequencies of contraction, is due to stabilization of $[Ca^{++}]_i$, this may be brought about, on the one hand, by an increase in the slow Ca^{++}-current [12] and, on the other hand, by an increase in the rate of redistribution of Ca^{++} between the cytoplasm and myofibrils [6, 14]. The mechanisms described above, while responsible for the relatively low developed force of contraction, may possibly play an important role in adaptation of the heart muscle to the chronotropic action of hyperthyroidism.

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