epileptization for a comparatively long period of time. Consequently, inactivation of the Ca-pump of the membranes of nerve terminals may be a factor in the development and maintenance of pathological hyperactivity of neurons. Possible inhibition of transport Ca-ATPase activity in membranes of the endoplasmic reticulum, which were present in small numbers in our preparation, during the development of EA may also promote prolonged accumulation of Ca^{++} in the synaptoplasm, with all the consequences which that entails.

The study of regulation of systems for Ca^{++} inflow and outflow in neurons and nerve endings during the appearance and disappearance of EA is thus of great importance. The next step must now be to study the effect of known anticonvulsants on function of the electrically excitable Ca-channel. It can also be postulated that specific inhibitors of the Ca-channel may be potential anticonvulsants.

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EFFECT OF ADAPTATION TO PHYSICAL EXERCISE ON REACTIVITY OF THE ISOLATED RAT ATRIUM TO NORADRENALIN

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KEY WORDS: adaptation; physical exercise; adrenoreceptors; chronotropic and inotropic effects.

Adrenoreceptor reactivity of the heart during adaptation to physical exercise has been studied in numerous investigations [1, 5, 8, 10, 13-15], most of them devoted to β-adrenoreceptors. Some workers [1, 5, 8, 13] found that the number and activity of β-adrenoreceptors decrease as a result of adaptation to physical exercise, whereas others found no change [10, 15] or an increase [14]. These contradictions are evidently due to differences in the conditions of adaptation, and also to the fact that in some experiments adrenoreceptor reactivity was assessed in relation to the chronotropic effect of agonists, and in others, to the inotropic effect. The effect of adaptation to physical exercise on α-adrenoreceptor reactivity has not been seriously studied.

The aim of this investigation was to compare the effect of adaptation to physical exercise on the inotropic and chronotropic effects of α- and β-adrenoreceptor agonists.

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TABLE 1. Effect of Adaptation to Physical Exercise on Chronotropic and Inotropic Responses of the Isolated Rat Atrium to Noradrenalin

Parameter	Control (n = 8)	Adaptation (n = 8)	Difference from control	
			%	p
Initial frequency of contractions (FC), min^{-1}	227±8	199±4	−12	<0,01
Effect of noradrenalin (ΔFC)				
$4 \cdot 10^{-7}$ M	+14±3 (6±2 %)	+11±3 (6±2 %)	−23	>0,05 (>0,5)
$6 \cdot 10^{-7}$ M	+38±4 (16±3 %)	+29±3 (15±3 %)	−24	>0,05 >0,5
Initial developed tension (T), mg	640±40	660±60	+3	>0,5
Effect of noradrenalin (ΔT)				
$4 \cdot 10^{-7}$ M	+144±22 (20±2 %)	+222±24 (33±3 %)	+54	<0,05 (<0,01)
$6 \cdot 10^{-7}$ M	+178±22 (34±4 %)	+318±40 (55±6 %)	+79	<0,01 (<0,02)
Initial ICF (FC × T), $mg \cdot min^{-1} \cdot 10^{-2}$	150±9	128±10	−18	>0,05
Effect of noradrenalin (ΔICF)				
$4 \cdot 10^{-7}$ M	+40±4 (26±2 %)	+53±4 (41±5 %)	+33	<0,05 (<0,01)
$6 \cdot 10^{-7}$ M	+73±7 (53±8 %)	+95±9 (76±8 %)	+30	>0,05 (<0,05)

TABLE 2. Effect of Adaptation to Physical Exercise on Inotropic Response of the Isolated Rat Atrium to Phenylephrine

Parameter	Control (n = 7)	Adaptation (n = 7)	Difference from control	
			%	p
Initial developed tension (T), mg	576±39	584±42	+1,4	>0,5
ΔT under the influence of phenylephrine ($4 \cdot 10^{-6}$ M)				
Preceded by propranolol ($4 \cdot 10^{-6}$ M)	+188±30 (35±5 %)	+302±38 (59±8 %)	+60,6	(<0,05) <0,05
Preceded by propranolol and phentolamine (10^{-6} M)	+28±12 (6±2 %)	+36±12 (8±1 %)	+12,8	>0,5 (>0,5)

EXPERIMENTAL METHOD

Male Wistar rats weighing initially 120 g were adapted to physical exercise by swimming in warm water (32°C) for 8 weeks. The rats swam for 1 h 5 times a week: without a load on the 1st and 2nd weeks, with a load of 2.5% of body weight on the 3rd and 4th weeks, and with a load of 5% of body weight on the 5th to the 8th weeks. Animals of the same age served as the control. At the end of the periods of adaptation the animals were decapitated, and the right atrium was removed and placed in a constant-temperature bath (34°C) containing oxygenated Krebs–Henseleit solution (pH 7.4). The base of the atrium was securely fixed, and the apex of the auricle was attached to an F-50 myograph of the "Physiograph MP-4B" ink-writing instrument (Narco Biosystems, USA). Atrial function of adapted and control animals was recorded in parallel experiments. After transfer into the incubation medium the atria contracted spontaneously for 30-40 min, after which they were gradually stretched by means of a weight to the length at which they developed maximal systolic tension. The weight and initial length of preparations of the right atrium of adapted and control animals did not differ significantly. The following physiological parameters were determined: the spontaneous frequency of contractions (per minute), the developed systolic tension (in mg), and the intensity of contractile function (ICF), equal to the product of the frequency of contractions and the developed tension. After the initial values of the parameters had been recorded, the response of the preparations to two doses ($4 \cdot 10^{-7}$ and $6 \cdot 10^{-7}$ M) of noradrenalin, used as the β-adrenoreceptor agonist, was recorded. Next, in the presence of the β-blocker, propranolol ($4 \cdot 10^{-6}$ M) the action of the α_1-adrenoreceptor agonist phenylephrine ($4 \cdot 10^{-6}$ M) was tested twice (before and after addition of the α-adrenoblocker phentolamine in a dose of $2 \cdot 10^{-6}$ M). These concentrations of the adrenoreceptor agonists were chosen on the basis of the results of preliminary experiments as those giving rise to moderate effects, and which would enable the inotropic and chronotropic components of the response to be compared sufficiently clearly.

EXPERIMENTAL RESULTS

Data on the effect of noradrenalin on the frequency of contractions, developed tension, and ICF of the isolated atrium of the control and adapted animals are given in Table 1. It will be clear from Table 1 that the spontaneous frequency of atrial contractions in animals adapted to physical exercise was considerably lower than in the controls ($p < 0.01$). Consequently bradycardia, characteristic of the trained animal, was preserved also in the isolated atrium, i.e., in the absence of the spectrum of extracardial regulatory influences. It was shown previously, in experiments on the whole animal, that bradycardia induced by training is connected with depression of sympathetic influences [3, 4]. This view is not contradicted by the results of the present investigation. We know that release of minimal quantities (resting release) of noradrenalin, as well as its synthesis, uptake, and enzymic inactivation, take place in isolated preparations of the heart also [9]. The acting concentration of transmitter in the synaptic space, due to these processes, and its interaction with the adrenoreceptor evidently largely determine the spontaneous firing rate of the sinus node under conditions of the isolated atrium. In fact, activation of the β-adrenoreceptors of the preparation of propranolol, obtained in the present experiments, caused a significant decrease in the frequency of its contractions. This decrease, moreover, just as in the whole animal [4], was significantly greater in the control than in the adapted animals ($p < 0.05$), but the frequency of contractions of the preparations after β-blockade was largely equalized (151 ± 12/min in the control and 141 ± 7/min in the adapted animals; $p > 0.05$). It has been shown [11] that sympathectomy, performed before isolation of the heart, has a similar effect. According to the authors cited, the hearts of rats adapted to running, isolated and perfused by Langendorff's method, also contracted at a slower rate than in the control, but preliminary injection of 6-hydroxydopamine into the animals abolished this difference. Consequently, there are grounds for considering that the acting concentration of noradrenalin in the atrium of adapted animals in the present experiments was evidently lower than in the control, and this was responsible for the relatively slower frequency of contractions of the isolated preparations before β-adrenoreceptor blockade.

After the addition of exogenous noradrenalin the chronotropic effect was essentially proportional to the initial frequency of contraction and, if expressed as a percentage, it did not differ in the different groups. If, however, the absolute values of the chronotropic response were estimated, a tendency for it to weaken was observed in the adapted animals. Meanwhile the inotropic effect of noradrenalin, unlike the chronotropic effect, on atrial preparations from adapted animals was significantly higher (by 54-79%) than in the control ($p < 0.05$-0.01). The increase in ICF in the former also was 30-33% greater ($p < 0.05$), due to an increase entirely in the inotropic component of the response.

Consequently, the inotropic and chronotropic effects of noradrenalin, realized through β-adrenoreceptors [12], do not follow a parallel course as a result of adaptation of the animal to physical exercise, possibly due to a redistribution of these receptors in atrial structures which perform different functions.

The inotropic orientation of the atrial preparations from adapted animals to the action of catecholamines was manifested as an increase of activity also of α-adrenoreceptors, which mediate mainly the inotropic effect of agonists and do not participate in realization of the chronotropic effect [6, 12]. In the present experiments the α-adrenoreceptor agonist phenylephrine, against the background of β-blockade, likewise had no significant effect on the frequency of contraction of the preparations in either group, whereas its positive inotropic effect, as will be clear from Table 2, was of considerable magnitude. This effect was 60.6% higher in atrial preparations from adapted animals than in the control ($p < 0.05$). After α-adrenoreceptor blockade by phentolamine the action of phenylephrine was weakened by 7-8 times, and the intergroup difference no longer appeared. Consequently the effect of phenylephrine in the absence of phentolamine and its significant increase as a result of adaptation of the animals to physical exercise, are in fact due to activation of α-adrenoreceptors.

During adaptation to physical exercise, the inotropic component of the adrenergic response of the atrium thus increases significantly, whereas the chronotropic component, on the contrary, has a tendency to decrease. This is in good agreement with data obtained on the whole animal. It has been shown that during physical exertion (and consequently, during sympathetic activation) the heart of trained people and animals also is characterized by predominance of the inotropic component of the response, as is shown by an increase in cardiac output due to a greater increase in stroke volume, accompanied by a smaller increase

in the frequency of contractions [2, 7]. Incidentally, the mechanisms responsible for this most economical method of urgent adaptation of the heart to an increased load [2] are formed, at least partly, in the heart muscle itself due to changes in its α- and β-adrenoreceptors.

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CHANGES IN ACTIVITY AND REGULATORY PROPERTIES OF Na,K-ATP-ASE FROM THE MYOCARDIAL SARCOLEMMA DURING TOTAL GRADED ISCHEMIA

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In myocardial ischemia Na^+ accumulates in the cardiomyocytes, which lose K^+ [8]. A probable cause of this phenomenon is disturbance of the function of the Na-pump of the sarcolemma, which actively secretes Na^+ from the cell in exchange for K^+. For instance, it has been shown [4, 12, 15] that Na,K-ATPase activity of membranes isolated from ischemic zones of the myocardium is lower than in the control. However, there are as yet insufficient data to explain the mechanism of ischemic damage to the enzyme. In particular, hardly anything is known of the dynamics of changes in Na,K-ATPase activity and its ability to induce regulatory responses during the development of pathology. Accordingly the aim of this investigation was to study changes in myocardial ATPase activity in rats and guinea pigs and its response to the cardiac glycoside digoxin (DG) and the colinergic agent carbachol (CC) during total graded ischemia.

EXPERIMENTAL METHOD

Albino rats and guinea pigs weighing 150-200 g were decapitated. Graded total ischemia of the myocardium was induced by incubating the hearts in an environment of air at 37°C [9]. The structural and functional changes taking place in the myocardium under these conditions have been shown to be similar to the disturbances observed in models of ischemia created by

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