by a reduction in the number of red cells in the blood flowing along the microcirculatory bed of the organ. However, a reduction in the number of red cells in the blood flowing along the microvessels under these conditions may, at the same time, perhaps improve its rheologic properties, increase its flowability and thus play a compensatory role in ischemia [4].

Consequently, important hematologic parameters such as the red cell concentration in the blood and the hematocrit reading may vary considerably in the vascular system depending both on the place from which the blood samples are taken and the local blood flow rate.

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ROLE OF CALMODULIN IN MYOCARDIAL CONTRACTILITY

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Calmodulin is an activator of many enzymes, including those of the Ca^{2+}-pumps of the sarcolemma [5] and sarcoplasmic reticulum [6] – systems responsible for regulating the intracellular Ca^{2+} concentration. Drugs of the phenothiazine series, which can inactivate calmodulin, are often used in investigations of calmodulin-dependent processes. In the study of cardiac contractility, only one or two preparations with closely similar affinity for calmodulin are usually used [2, 4, 10]. Recently published research has shown that drugs of the phenothiazine series can not only bind with calmodulin and, correspondingly, inactive Ca^{2+}-calmodulin-dependent enzyme systems, but can also interact independently of calmodulin with Ca^{2+}-binding proteins [1, 8], and α-adrenoreceptors [9], and they may also have a membrane-stabilizing action [7]. In our opinion, in order to interpret more correctly the causes of the changes in contractility parameters when phenothiazones are used, the effect of several drugs of this group, with different affinity for calmodulin, ought to be compared.

The aim of this invetigation was to compare the action of compounds of the phenothiazine series, namely trifluoperazine (TF), frenolon (PR), majeptil (MJ), and chlorpromazine (CP), on contractility of the rat papillary muscle.

EXPERIMENTAL METHODS

Experiments were carried out on papillary muscles isolated from the left ventricle of male Wistar rats, contracting under isometric conditions at 31°C. To reduce the effect of the phenothiazine on α-adrenoreceptors, prazosin (10^{-7} M) was added to the perfusion solution 20 min before they were injected. There were five series of experiments: series I was the control (seven experiments); in series II, III, IV, and V the following substances were added respectively to the perfusion solution; TF (eight experiments), FR (seven experiments), MJ (seven experiments), and CP (six experiments). The Ca^{2+} concentration in the perfusion solution was increased from 2 to 4 mM (the Ca^{2+} test) 20 min after addition of the test preparation (10^{-5} M in all cases), but the frequency of stimulation before and during the Ca^{2+} test was temporarily increased from 0.5 to 2 Hz. The force of contraction and its first

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TABLE 1. Changes in Parameters of Contractility of Rat Papillary Muscle (in %) against the Background of a Raised Ca^{2+} Concentration under the Influence of Phenothiazines Differing in Their Affinity for Calmodulin

Parameter	Control	Drug				r
		CP	MJ	FR	TF	
$I/K_{0,5}$, mM^{-1}	0	0,059	0,083	0,167	0,25	—
T_{max}	29,4±5,9	49,5±9,0	24,4±4,7	38,5±8,9	37,3±6,0	0,18
ITI	−3,3±2,7	−3,1±3,4	−7,8±9,2	−14,2±11,0	−2,9±2,5	0,23
RI	2,4±4,6	−2,5±3,9	−7,8±1,2	−8,2±5,6	−13,0±6,0	0,92*

Legend. $I/K_{0.5}$) A parameter characterizing the degree of affinity of drugs of the phenothiazine series for calmodulin and used to calculate the coefficient correlation. *) Significant correlation ($P < 0.05$).

derivative were recorded. The maximal developed tension (T_{max}), the relaxation index (RI), as the ratio of the minimal value of the first derivative to T_{max}, and the index of tension increase (ITI), by analogy with RI as the ratio of the maximal value of the first derivative to T_{max}, were calculated. The value of the parameters during stimulation with a frequency of 2 Hz, against the background of the Ca^{2+} test, both in the control (C) and in each series of experiments, was expressed as a percentage of values obtained immediately before the test.

EXPERIMENTAL RESULTS

It was shown previously, by the method of displacement of the fluorescent probe 3,3'-dipropylthiocarbocyanine iodide from its complex with calmodulin by various drugs that, according to affinity for calmodulin, characterized by the constant of half-maximal displacement of the probe from calmodulin ($K_{0.5}$), the drugs used can be arranged in the following diminishing order: TF > FR > MJ > CP [1].

The present experiment showed that when drugs of the phenothiazine series were added to the perfusion solution no significant change took place in the calculated values of the parameters. With an increase in the Ca^{2+} concentration from 2 to 4 mM a significant increase in T_{max} was observed both in the control and in the experiments with phenothiazine. Depending on the degree of increase of this parameter the phenothiazines could be arranged in the following diminishing order: CP > FR > TF > C > MJ.

The coefficient of correlation (r) between the two series was 0.18 (Table 1).

ITI, which reflects the increase in Ca^{2+} concentration in the myoplasm during contraction, and RI, characterizing removal of Ca^{2+} from the cardiomyocyte, were reduced under the influence of the drugs tested. Depending on the degree of lowering of ITI the drugs were arranged in the following order: FR > TF > MJ > CP > C.

The coefficient of correlation of this series with the values of $K_{0.5}$ was 0.23 (Table 1). The order of the drugs relative to the degree of lowering of RI corresponded to the affinity of the phenothiazine for calmodulin: TF > FR > MJ > CP > C.

Correlation between the change in RI under the influence of the drugs and the affinity of these drugs for calmodulin was significant ($r = 0.92$, $P < 0.05$; Table 1).

Preparations of the phenothiazine series (TF, FR, and CP) thus potentiate the inotropic effect of an increase in the Ca^{2+} concentration in the perfusion fluid. The fact that a change in only one parameter (RI) correlates significantly with the degree of affinity of the drugs tested for calmodulin may be evidence of the important role of calmodulin in the regulation of those processes that are responsible for removal of Ca^{2+} from the myoplasm.

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