ROLE OF THE Ca^{2+}-BLOCKING EFFECT OF ALCOHOL IN THE GENESIS OF ISCHEMIC MYOCARDIAL DAMAGE

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The participation of Ca^{2+} ions in many biochemical processes of the cell and also in the regulation of various physiological functions of the body at a higher structural level has been known for a long time. However, the recently developed idea of Ca^{2+}-messenger system [12], integrating the previous concept into a qualitatively new entity, has stimulated research in this region. Substances modifying to some degree or other the action of Ca^{2+}, which include Ca^{2+}-blockers, have aroused consistent interest. The study of the Ca^{2+}-blocking effect of natural biotics, one of which is alcohol, is all the more important [11, 15]. The connection between acute and chronic alcohol poisoning and ischemic heart damage, including myocardial infarction (MI), has been demonstrated [2, 10]. Meanwhile, for most investigators, the role of Ca^{2+} ions in irreversible damage to the cardiomyocytes (CMC) is not in question [7, 9]. This provides the basis for the use of various Ca^{2+}-blockers as cardioprotectors [13], for they can evidently delay death and reduce the degree of the destructive changes in CMC. As yet information on ethanol-induced changes in Ca^{2+} in the myocardium is fragmentary and contradictory, and contamination of the effects of alcohol and ischemia in the genesis of disturbances of Ca^{2+} exchange between plasma and CMC has virtually not been studied, nor indeed has its effect on function of the damaged myocardium.

The aim of this investigation was to study the Ca^{2+}-blocking effect of ethanol on the distribution of Ca^{2+} between the blood plasma and CMC in the acute period of experimental myocardial infarction (EMI), and its electrocardiographic parameters in this period.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 180-220 g. Ethanol was injected intraperitoneally in a dose of LD_{25} 1 h before the operation to produce EMI, which consisted of ligating the left descending coronary artery (by Selye's method). Animals with EMI not receiving ethanol and intact rats (IR) served as the control. Samples of blood plasma and myocardial tissue were taken 1, 3, 6, 12, 24, and 48 h and 3 days after production of EMI, corresponding to the acute period. The plasma Ca^{2+} concentration was determined by an atom-absorption method on a "Hitachi-180-80" spectrophotometer (Japan). Fresh myocardial tissue was first dried for 48-72 h at 105°C an minced to a powder-like state. A dry weighed sample was dissolved in a mixture of 1N HCl and 0.75 N HNO_3 (1:3) with heating to boiling (in a proportion of 8-10 ml to 70 mg tissue), the sample was evaporated down to 3-5 ml, and after cooling, its volume was made up to 25 ml with bidistilled water, pure with respect to Ca^{2+}. The subsequent course of the determination was similar to that with samples of blood plasma. The ECG was recorded on a "Kardioluxe-300" electrocardiograph (Yugoslavia) at the same times, in six standard leads.

EXPERIMENTAL RESULTS

As Table 1 shows, hypercalcemia, which was higher in rats subjected to EMI and acute ethanol poisoning (ALC + EMI) after 1 h, became equal after 3 h, decreased until 6 h, and then increased until 12 and 24 h. The values in this group fell to those

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TABLE 1. Dynamics of Plasma Ca^{2+} Concentration in Rats of Experimental Groups

Stage of experiment	ALC+EMI, g/liter	EMI, g/liter
1 h	0,108±0,001*[1,2] (9)	0,087±0,003** (10)
3 h	0,120±0,005** (10)	0,114±0,03** (10)
6 h	0,097±0,005** (8)	0,120±0,01** (10)
12 h	0,130±0,004*[1,2] (10)	0,080±0,0008** (8)
24 h	0,130±0,004*[1,2] (10)	0,111±0,005** (8)
48 h	0,080±0,005*[1] (8)	0,107±0,002** (8)
3 days	0,110±0,006** (8)	0,115±0,002** (8)
	0,075±0,0006 (10)	

Legend. Here and in Table 2: number of experiments given in parentheses; $*p < 0.05$ compared with EMI, $**p < 0.05$ compared with IR.

TABLE 2. Heart Rate (HR) of Rats of Experimental Groups

Stage of experiment	ALC + EMI	EMI
1h	272±16*[1,2] (9)	329±11** (10)
3h	305±18*[1,2] (10)	357±10 (10)
6h	362±25 (8)	361±8 (10)
12 h	384±20 (10)	400±19 (8)
24 h	478±24*[1,2] (10)	400±20 (8)
48 h	435±19** (8)	422±17** (8)
3 days	420±13** (8)	395±17 (8)
	IR 371±12 (10)	

of IR after 48 h. Data on the Ca^{2+} concentration in the myocardium of rats with ALC + EMI, with EMI alone, and IR, are given in Table 2. The increase in this parameter was more marked in rats with EMI after 1, 3, and 6 h, and in rats with ALC + EMI after 12 h, and did not differ at the other times of the experiment.

The distribution of Ca^{2+} between plasma and myocardium was determined as the ratio of these values (Ca^{2+}_{pl}:Ca^{2+}_{my}), and we defined this as the coefficient of distribution. It will be clear from Fig. 1 that the time course of this coefficient differed in direction in rats with ALC + EMI and rats with EMI alone: in the first case, it changed from higher to lower values, in the 2nd case from lower to higher.

HR in rats with ALC + EMI was lower than in rats with EMI after 1 and 3 h, but it rose toward the end of the first day. In rats of this group, atrioventricular block and cardiac arrest were recorded in the initial period of the experiments. It is also important to note that the postoperative mortality was higher for rats with ALC + EMI during the first 3 h and after the first 24 h until the end of the acute period (45-50% and 55%, respectively). The corresponding figures for rats with EMI were 35% and 44%.

The hypercalcemia observed in both groups is a universal compensatory mechanism in response to ischemia, aimed at satisfying the increased myocardial Ca^{2+} demand. From our point of view the plasma parameters, like the Ca^{2+} level in the myocardium, are not sufficiently objective parameters of true fluctuations of Ca^{2+} during ischemia, and henceforward we shall use for this purpose the coefficient of distribution Ca^{2+}_{pl}:Ca^{2+}_{my}. Under these circumstances, it is possible to explain the contradiction between our results and data in the literature, in which hypocalcemia was found during MI [1]. Reduction of the Ca^{2+}_{pl}:Ca^{2+}_{my} coefficient in rats with EMI indicates that the plasma component of this ratio was in fact reduced, whereas the Ca^{2+} load on the myocardium was increased. The principal role in this process is ascribed to a change in activity of the Na^+/Ca^{2+}-pump in ischemia [4]. Nevertheless, overloading of CMC with Ca^{2+}, which was necessary to maintain contractility of the ischemic myocardium, may at the same time be interpreted as a factor of CMC destruction [7, 9]. Some workers [14] have shown that an increase in the cytosol Ca^{2+} level in CMC during ischemia does not lead to their death, which instead is associated with primary damage to the cell membrane, which activates Ca^{2+}-dependent proteases and closes this unique "vicious circle" in destruction of the cytoskeleton and death of the cell. Taking this report into consideration, we put forward the following interpretation of our own results: the Ca^{2+}-blocking effect of ethanol, most marked during the first few hours, reduces the Ca^{2+} load on the myocardium of rats with EMI. This leads to a decrease in myocardial contractility and, correspondingly, lowering of

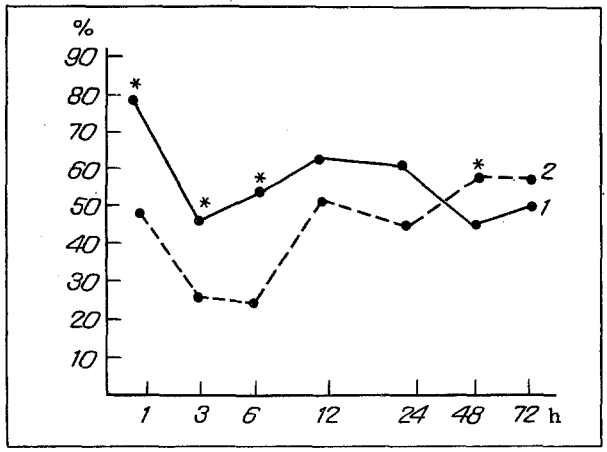

Fig. 1. Time course of ratio of Ca^{2+}_{pl}:Ca^{2+}_{my} in rats of experimental groups (1 — ALC + EMI, 2 — EMI). Value of parameter for intact rats taken as 100%. *$p < 0.05$.

HR. Considering that alcohol has a marked membranolytic action [5], it can be tentatively suggested that, despite the lower degree of Ca^{2+}-overloading, death of CMC in rats with ALC + EMI takes place on an increased scale, which leads not only to insufficiency of the control function, but also to disturbance of the coupling between excitability and contractility of the CMC. On the ECG this is reflected as atrioventricular blockade of varied degrees, or even cardioplegia. Toward the end of the acute period of EMI, in rats not receiving alcohol the value of the coefficient Ca^{2+}_{pl}:Ca^{2+}_{my} gradually increases, reflecting a tendency toward normalization of the plasma-tissue gradient. Meanwhile, this parameter in rats receiving alcohol fell in value, indicating delayed or retarded overloading of CMC with Ca^{2+} on account of the initial Ca^{2+}-blocking effect of ethanol.

A phenomenon of this kind can be explained both by diminution of this block in the course of alcohol elimination and by potentiated depression of Ca^{2+}-transport by ischemia and alcohol, which has been described for each of these factors separately [6, 8].

Thus, the Ca^{2+}-blocking effect of ethanol in the acute period of EMI behaves as a factor aggravating ischemic damage to CMC and destabilizing processes of excitability and contractility of the myocardium, which may lead to lethal complications of EMI in these experiments. The results suggest that alcohol disturbs adaptation of the myocardium to acute ischemia, largely due to the Ca^{2+}-blocking effect of ethanol in the initial periods of ischemia and to delayed Ca^{2+} overloading toward the end of the acute period.

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