SYMPATHETIC MECHANISM REGULATING CARDIAC FUNCTION DURING TRANSIENT CORONARY INSUFFICIENCY OF VARIED DURATION

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Previous investigations have shown that the development of acute transient coronary insufficiency (ATCI) in rats is characterized by stages in changes affecting contractile function and the cardiac rhythm: An initial hyperkinetic cardiac response during the first 10-15 min of myocardial ischemia (MI) is followed by a hypokinetic phase [2, 4, 6]. This rule concerning stages in the changes of cardiac activity in ATCI suggest that it depends on extracardial regulatory influences.

Considering that the sympathetic regulatory mechanism is one of the leading modulators of cardiac function (especially under extremal conditions), the investigation described below was undertaken with the aim of studying the state of the pre- and postsynaptic components of the adrenergic system of the heart in ATCI of varied duration.

EXPERIMENTAL METHOD

Experiments were carried out on 102 noninbred male albino rats weighing 200 ± 10 g. ACTI was produced by the method described previously [2] under urethane anesthesia (1200 mg/kg). The duration of the period of MI was 10, 40, and 120 min, and of the reperfusion period (RP) 40 min. The concentration of noradrenalin (NA) and dihydroxyphenylalanine (dopa) in the ischemic and peri-ischemic zones (together) of the myocardium of the left ventricle was determined [7]. The adrenergic properties of the heart were assessed by the dynamics of the chronotropic reaction,the change in pressure in the left ventricle, and an integrative index of cardiac activity [12] in response to injection of a standard dose of NA (0.5 μg/kg) into the right ventricle at intervals of 10 min. The reactions were recorded 20 sec after injection of the neurotransmitter (the mean time of development of the maximal cardiac response) and after 180 sec (the mean time for extinction of the reaction). The animals as a whole were divided into two groups: experimental (ATCI production) and control (mock operation). The results were subjected to statistical analysis by a parametric method.

EXPERIMENTAL RESULTS

In the course of ATCI stages in changes in the concentration of sympathetic mediator in the myocardium were observed (Fig. 1A, B, C – I), which coincided in time with the changes in contractile function of the heart described previously [3, 6]. During the period of MI there was a considerable increase in the NA concentration in the myocardium during the first 10-15 min, which was followed by a progressive decline in its level below the background value. The change in NA concentration under these circumstances reflected the level of its neuronal synthesis, as shown by the dynamics of the myocardial concentration of dopa, a product which limits the reaction of NA biosynthesis [9, 13]. During the period of resumption of the coronary blood flow, changes in the NA concentration differed depending on the duration of preceding MI. For instance, toward the 40th minute of RP it fell close to the background level after 10 min of ischemia, it was 56.9% lower than the background level after 40 min of MI, and 58% lower after 120 min. The dopa concentration remained above the background level during RP after 10 min of MI and fell progressively after 40 and 120 min.

The data indicate activation of the presynaptic neuroeffector component of the sympathetic mechanism regulating cardiac function in the initial stage of MI, and under ATCI conditions if the period of ischemia lasts 10 min. This process is probably based on intensification of neurotransmitter synthesis. ATCI with longer periods of MI (40 and 120 min) was characterized by depression of activity of extracardial sympathetic influences on the heart not only during the period of reduction of the coronary blood flow, but also, and this is important, during its resumption. This coincided with depression of neurotransmitter biosynthesis, despite restoration of the coronary perfusion. One possible cause of this effect may be alteration of the enzymes of NA synthesis and of the membrane apparatus of sympathetic nerve endings by products of free-radical lipid peroxidation (LPO), the intensity of which, as the writers showed previously [5, 6], is increased during the period of MI and, in particular, during subsequent RP. An argument in support of the pathogenetic role of LPO in ATCI

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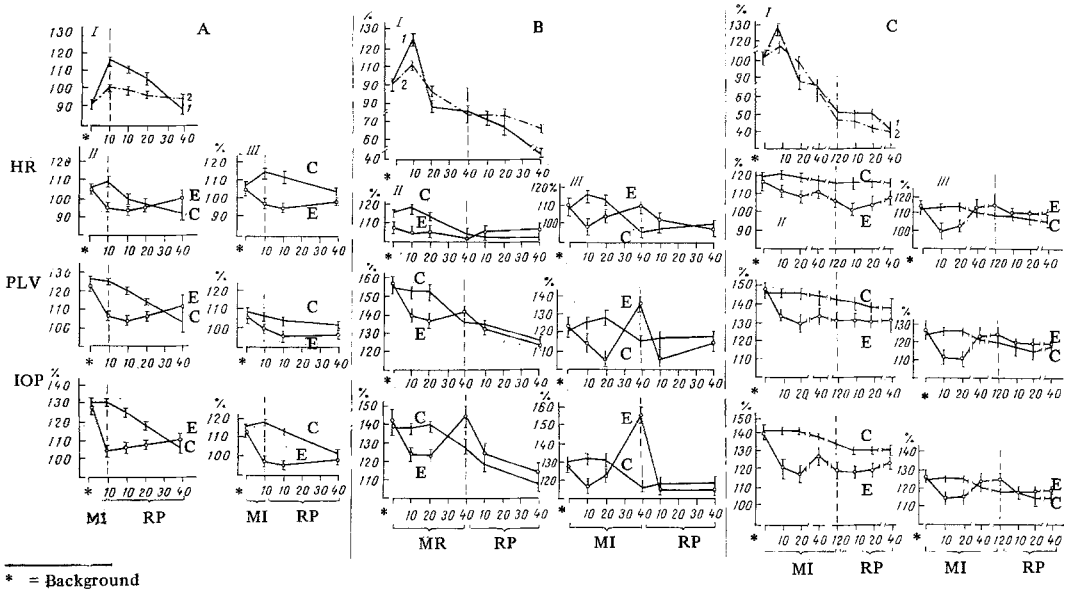

Fig. 1. Dynamics of NA and dopa concentrations in myocardium (I) and reaction of heart to standard dose of exogenous NA (II, III) in ATCI of varied duration. A) ATCI with period of MI lasting 10 min, B) 40 min, C) 120 min. Abscissa, duration of periods of MI and RP (in min); ordinate: I) concentration of NA (1) and dopa (2) in myocardium (in % of background); II) reactions of heart recorded 30 sec; III) 180 sec after injection of NA (in % of initial value). HR) Heart rate, beats/min; PLV) real pressure in left ventricle; IOP) Opie's index. E) Experiment, C) control. Vertical broken line indicates end of period of MI. At each point n = 8 (M $\pm$ m).

is the fact that oxygen-dependent dopa biosynthesis was depressed [11] despite the high pO_2 in the previously ischemized zone of the heart on resumption of the coronary blood flow [5].

In the course of ATCI the state of the postsynaptic component of the sympathetic neuroeffector mechanism regulating cardiac function also changed significantly (Fig. 1A, B, C – II, III). During the first 10 min of MI a rapid fall in the response of the heart to NA was observed in the experimental animals, which lasted for 20 min. In the control animals, the adrenergic properties of the myocardium remained close to their background level during the same time interval. Lowering of adrenergic reactivity of the heart during the first 10-20 min of MI was evidently due to increased liberation of endogenous NA into the synaptic space during this period. The increase in the quantity of sympathetic neurotransmitter in the synapse (and also, perhaps, in the cardiomyocytes by an $Uptake_2$ mechanism, according to [10]) has a suppressive action on the sympathetic receptor apparatus of the myocardial cells. This action may be due, in particular, to a decrease in the number of specific receptors, for the NA concentration in the heart is inversely proportional to the number of β-adrenoreceptors in it [14]. Later, with a 20 min period of MI, the cardiac reactions of the experimental animals recorded 20 sec after a standard dose of neurotransmitter were similar to those in the control. The same picture also was observed 180 sec after injection of NA. An important fact was noted under these circumstances – prolongation of the reaction of the heart (especially the change of pressure in the left ventricle) to the neurotransmitter in the case of MI lasting more than 30-40 min. During the RP period the responses of the heart to NA in the experimental animals either approximated in magnitude and duration to those in the control (after MI for 10 and 40 min), or they were weaker but more prolonged (after MI for 120 min). The latter, like prolongation of adrenergic reactions in late stages of MI, can be interpreted, on the one hand, as the result of injury to the enzyme monoamine oxidase [1] and the membrane apparatus of the cardiomyocytes by LPO products, and on the other hand as an adaptive reaction aimed at prolonging the adrenomimetic effect of the neurotransmitter when it is in short supply.

Analysis of the course of changes in the adrenergic properties of the heart revealed an important fact: shortening (by 33-50% compared with the background) of the period required for maximal response of the heart to injection of a standard dose of NA to develop, which was observed during the first 10-15 min of MI – in the period accompanied by disturbance of the cardiac rhythm in 99% of rats [4]. In the group of animals in which paroxysmal tachycardia and ventricular fibrillation were recorded, this period of time was almost two-thirds less than in the group of rats with milder arrhythmias in the form of extrasystoles, tachycardia, or bradyarrhythmia. The latter is evidence that the functional state of the adrenoreceptors of the cardiomyocytes during MI has a considerable effect on the possibility and character of disturbance of the cardiac rhythm.

The results of this investigation thus showed regular stages in the course of changes in functions of the sympathetic mechanism regulating cardiac activity during ATCI, coinciding in time with the dynamics of changes in contractile function and rhythm of the heart. This indicates, first, that the latter depend on extracardial regulatory influences and, second, that the sympathetic nervous system plays an essential role in the formation of adaptive reactions of the heart during ATCI. Under these circumstances the functional effect of sympathetic neuroeffector influences on the myocardium in ATCI is largely determined on the one hand by the intensity of neurotransmitter biosynthesis at the level of the presynaptic component of the sympathetic regulatory mechanism and, on the other hand, by the functional state of its postsynaptic component (the adrenergic receptors of the cardiomyocytes). The results help to some extent to explain the disturbance of cardiac activity during ATCI and, as a result of this, they help with the elucidation of the principles of its pathogenetic treatment. The results of the present investigation suggest the need for correction (!) of sympathetic neuroeffector influences on the heart in ATCI, especially if associated with a long period of MI. An argument in support of this conclusion is the writer's previous observations [6, 8] of a marked increase in resistance of the heart to ATCI during correction of extracardial sympathetic influences by means of myophedrine and visken (pindolol), drugs which prevent the cardiotoxic action of a high concentration of endogenous catecholamines and which also give rise to a "mild" sympathomimetic effect of their own.

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