Preclinical Study of the Effect of Cardiotropic Agents on Isolated Heart

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Direct effects of cardiotropic preparations on the hearts isolated from Wistar rats were examined. Deenergization of cardiomyocytes was modeled under conditions of hypoxic perfusion. Recovery of cardiac function during reperfusion was assessed by changes in the heart rate and contraction amplitude.

Key Words: *isolated heart; Wistar rat; perfusion; hypoxic deenergization; heart rate; heart contraction amplitude*

Specific activity of cardiotropic preparations can be assessed in experiments with direct application of these agents to isolated heart. An adequate criterion of activity of such preparations can be the degree of compensation of the disturbances in contractile function of the target organ induced by hypoxic deenergization [2,3]. To this end, the heart rate and contraction amplitude of the reperfused heart were calculated from measurements of the left ventricular pressure [1]. Digitized cardiogram was processed off-line using standard software.

MATERIALS AND METHODS

Experiments were carried out on the hearts isolated from Wistar male rats weighing 300-350 g. The animals were maintained under standard vivarium conditions at 20±2°C on PK-121-2 standard combined fodder (Informkorm) and water *ad libitum*. The rats were decapitated after overnight fast. The heart was isolated and fixed via the aorta to a cannula. Langendorff perfusion was performed at 38°C with Tyrode's solution containing (in mM): 137.0 NaCl, 5.0 KCl, 2.5 $CaCl_2$, 1.05 $MgCl_2 \times 6H_2O$, 7.7 $NaHCO_3$, 1.3 $NaH_2PO_4 \times 2H_2O$, 11.0 glucose, pH 7.4. For normoxia, Tyrode solution was oxygenated with 95% O_2 and 5% CO_2.

Continuous-flow normoxic perfusion was performed under a pressure of 80 cm H_2O. The level of Tyrode solution was maintained using a peristaltic pump, which fed the saline to the reservoir. During the first 5-6 min of the experiment, normoxic perfusion was performed to stabilize the work of the isolated heart. Hypoxic perfusion conditions were created in one channel of the two-channel perfusator [2]. The infuser supplied the dosed amount of preparation to aorta region.

The following procedures were performed successively: stabilization of the heart for approximately 6 min; normoxic perfusion (10 min); glucose-free hypoxic perfusion (10 min); and normoxic reperfusion with tested agent (10 min). The work of the heart was stabilized at the start of the experiments. The method described can be used to test any cardiotropic drug.

RESULTS

Preliminary glucose-free hypoxic perfusion partially deenergized cardiomyocytes. At the final stage of normoxic reperfusion with diluted Tyrode solution (1.5 mM glucose), the degree of restoration of the contractile function of the heart was assessed in the presence or absence of the test preparation. It is estab-

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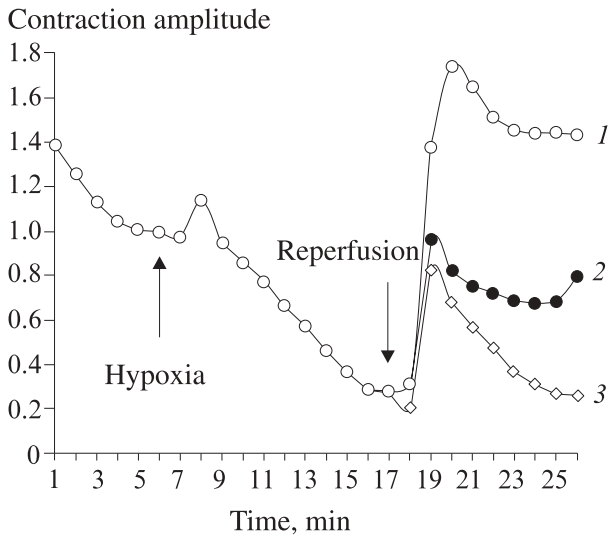

Fig. 1. Effect of glucose-free hypoxia and normoxic reperfusion with standard Tyrode solution+glucose (*1*), lean Tyrode solution+glucose (*2*) and lean Tyrode solution+preparation (*3*) on contraction amplitude of isolated rat heart. Here and in Fig. 2: the arrows mark onset of hypoxia and reperfusion.

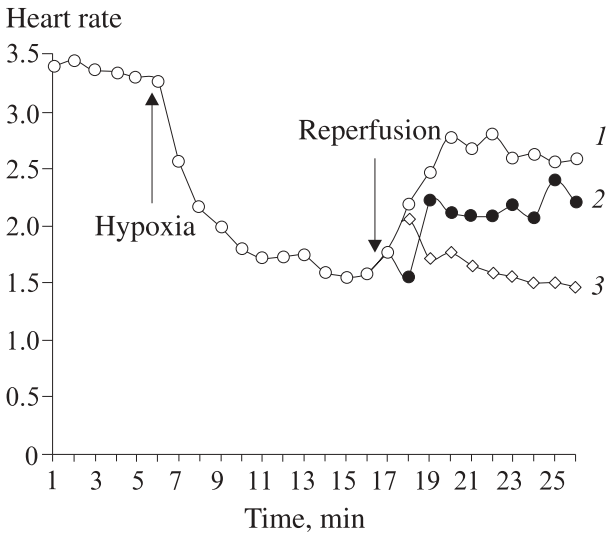

Fig. 2. Effect of glucose-free hypoxia and normoxic reperfusion with standard Tyrode solution+glucose (*1*), diluted Tyrode solution+glucose (*2*) and lean Tyrode solution+preparation (*3*) on the heart rate of isolated rat heart.

lished that contractile function restored better, when glucose concentration was higher (Fig. 1, Fig. 2). This is a well-known phenomenon, which needs no detailed discussion. During normoxic reperfusion, the tested preparation inhibited restoration of cardiac activity after hypoxia (Fig. 1, Fig. 2). Thus, the examined composite preparation has no cardiac stimulation potency, and it is characterized by specific toxicity.

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