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PROBLEM OF HEART SALVATION DURING REPERFUSION. OPIOID RECEPTOR AGONISTS AS A POSSIBLE SOLUTION

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Ischaemia/reperfusion cardiac injury contributes to morbidity and mortality during percutaneous coronary intervention, heart surgery and transplantation. Even when the recanalization of an infarct-related coronary artery is carried out successfully, there is still a risk of death due to reperfusion injury. Numerous pharmacological interventions have been found in experiments on animals. However, the translation of these interventions to clinical practice has been disappointing. None of the drug treatment has been able to improve in-hospital mortality of patients with acute myocardial infarction. The search for pharmacological agents able to salvage myocardium during reperfusion continues. Opioid receptor (OR) agonists represent one of the promising group of drugs for treatment of patients with myocardial infarction. It has been found that μ-, δ- and κ-OR agonists are able to attenuate heart injury when administered before or at the beginning of reperfusion. However, what kind of OR receptors need to be activated in order to protect the heart during reperfusion and the precise mechanism of this effect have yet to be elucidated.

Key words: ischemia/reperfusion injury, heart, myocardial infarction, cardioprotection, opioid receptor agonists.

The attempts to salvage myocardium during reperfusion using pharmacological interventions

It is commonly accepted that the only effective treatment of myocardial infarction is recanalization of the infarct-related coronary artery. This can be achieved by thrombolysis, percutaneous coronary intervention (PCI), or coronary artery bypass grafting [1-3]. Unfortunately, there is always a risk of death for patients with myocardial infarction, even when the recanalization of the coronary artery is carried out fast and successfully [4]. Therefore, there is a pressing need for creation of new generation drugs able to prevent reperfusion heart injury.

Nowadays, no drug is available, which would be able to attenuate effectively the area of necrosis and mortality in patients with acute myocardial infarction. Different pharmaceutical companies and scientific laboratories carry out the search for this kind of medicine. However, until now, no breakthrough has been achieved in this area.

A number of drugs have been clinically tested for reperfusion injury. For example, it has been proposed that the calcium sensitizer levosimendan has a potential to reduce infarct size. The randomized double-blind clinical study showed improvement of hemodynamic function in patients with ST-elevation myocardial infarction (STEMI) treated by PCI. However, no infarct-limiting effect of levosimendan was found [5]. Inhibitors of Na+/H+ exchanger that showed cardioprotective properties in animal models [6] failed to protect heart in clinical settings [7] and even demonstrated increased mortality [8]. The gold standard MPTP inhibitor cyclosporine A, which showed infarct-limiting effect in laboratory experiments [9-11], did not reduce the risk of the composite outcome of death from any cause, worsening of heart failure during the initial hospitalization/rehospitalization, or causing adverse left ventricular remodelling in patients with STEMI [12]. The P2Y12 receptor inhibitor clopidogrel appeared to reduce infarct size in patients with acute myocardial ischemia [13, 14], but had no effect on mortality in patients with this kind of pathology [15]. A statin atorvastatin neither improved left ventricular function, nor reduced infarct size in STEMI patients [16-18]. Intravenous adenosine infusion has been found to reduce infarct size and attenuate the No Reflow phenomenon in STEMI patients [19-22]. However, as Cohen M.V. and Downey J.M. [23] have pointed out, the ability of adenosine administered at or shortly before reperfusion to provide cardioprotection against infarction is indeed quite controversial. The authors noted that cardioprotective effect of the intravenous infusion of adenosine occurred when it was used as a form of preconditioning, prior to ischemia,

whilst given at reperfusion, adenosine simply did not protect the heart. The infarct-limiting effect of a piperazine derivative trimetazidine is also debatable [24, 25]. In general, the drugs mentioned above showed cardioprotective effects in experiments on animal models or in patients when administered prior to recanalization of the infarct-related coronary artery, but were ineffective in clinical settings when introduced during reperfusion. Furthermore, none of these medicines could improve in-hospital mortality of patients with STEMI.

Clinical relevance of the use of a cardioprotective agent prior to ischemia is restricted to cardiac surgery, when ischemia is caused by aortic cross-clamping. However, in most cases, it is impossible to predict an incident of acute myocardial ischemia and carry out the treatment prior to the ischemic event. A possibility to attenuate specifically the reperfusion heart injury had been unclear until the discovery of the phenomenon of ischemic postconditioning in 2003 [26]. The authors demonstrated that a few brief (30 sec each) episodes of ischemia and reperfusion produced at the commencement of reperfusion following prolonged ischemia halved infarct size. Based on these data, many scientist are trying to find the way to salvage the myocardium during reperfusion by treating the heart not before ischemia, but just before or during reperfusion. In this context, opioid receptor (OR) agonists represent a promising group of drugs.

Opioid receptors as novel targets for prevention of reperfusion heart injury

It has been shown [27-29] that OR agonists reduce infarct size when administered before the onset of reperfusion. Thus in 2004, Gross E.R. et al. [29] found that intravenous infusion of a preferential μ-OR morphine or δ-OR agonist BW373U86 (1mg/kg) 5 min prior to reperfusion in rats promotes decrease in infarct size-to-area at risk ratio (IS/AAR). These results are consistent with a recent study indicating that the selective μ-OR agonist endomorphine-1 (50 μg/kg) reduced infarct size when injected intravenously 5 min before reperfusion [30]. Infarct-limiting effect of morphine during reperfusion has also been confirmed by Gong et al. [27]. Intravenous injection of the selective κ1-OR agonist U-50,488 (0.1 mg/kg) 5 min before reperfusion reduced IS/AAR [28]. This effect was abolished by the inhibition of κ1-OR with nor-binaltorphimine.

The precise mechanism of the cardioprotective effect of the OR agonists during reperfusion has yet to be discovered. However, it has been established that ORs represent Gi/o-coupled receptors that inhibit adenylyl cyclase and activate phospholipase C, which in turn, synthesizes diacylglycerols stimulating protein kinase C (PKC) [31]. This was confirmed by the work of Peart J.N. & Gross G.J. They showed in the experiments on isolated perfused murine heart that pertussis toxin, which rybosylates the αi subunit of the Gi/o protein, eliminated the cardioprotective effect of morphine [32]. Currently it is suggested that Gi/o proteins serve as an intermediary link between ORs and the protein kinases that perform the protective signaling [33]. The following kinases may be involved in the cardioprotective mechanism of the ORs/ Gi/o activation: PKC [32, 33]; PI3 kinase, Akt, and MAPK – the RISK pathway [34, 35]; GSK-3β and JAK2 [36]. The endothelial nitric oxide synthase (eNOS) has been implicated in the preconditioning-induced triggering of Gi/o coupled receptors/PKC pathway [37] and could be involved in the protective effect of ORs [38]. Redox signaling has also been found to participate in the effects of ORs [39]. The studies have also indicated that these effects of OR agonists result in inhibition of mitochondrial permeability transition pore opening [33], which are critical in reperfusion-induced heart injury [40].

Taken together, it is of paramount importance to find a pharmacological intervention able to salvage myocardium during reperfusion and OR agonist represent a perspective group of drugs in this respect. Further studies are needed in order to establish what kind of ORs need to be activated to achieve the optimal heart salvation during reperfusion and the mechanism involved.

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