Cardioprotective effects in the ischemic myocardium induced by preconditioning of the distant organ: the role of peroxisome proliferator-activated nuclear receptors (PPARs) as a potential mechanism of protection

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Introduction and Objectives: Cardiovascular diseases are one of the leading causes of mortality in modern society. They are predicted to rise over the coming decades, due to aging population, longer survival of patients after acute myocardial infarction (AMI), and incidence of civilization diseases. Despite the progress in pharmacological therapy, interventional cardiology (PPCI) and surgery, there is a substantial unmet need for novel approaches that could specifically address repair and regeneration of damaged and/or lost myocardium during ischemia/reperfusion (IR). The concept of heart’s own protection is based on the principle that short-term cardiac adaptation to moderate stress increases heart resistance to subsequent sustained stress – phenomenon of preconditioning (PC). Ischemic PC (IPC) (brief episodes of IR prior to long-lasting ischemia) has been observed in all animal species including humans (8). It is manifested by a delay of necrotic and apoptotic processes in cardiomyocytes, reduction of lethal arrhythmias and by an improved post-IR functional recovery (1). However, in clinical conditions, application of IPC is limited by technical requirements (chest opening), relatively short duration of protection, and presence of comorbidities. On the other hand, so called „remote” IPC (RIPC) of the distant organ (7), in particular, its noninvasive modality (3), is more attractive from the clinical point of view, and is already being used in STEMI (MI with ST-segment elevation) patients prior to PPCI (9). Pathophysiological mechanisms of RIPC are not yet completely clear, however, it has been proposed that cardioprotective signal is transferred from the distant organ to a target one via neural and humoral pathways, and via systemic response of the organism (1). Figure 1 schematically represents triggering of RIPC by different stimuli, its timing and mediating mechanisms. One of potential players involved in the mechanisms of RIPC are peroxisome proliferator-activated nuclear receptors (PPAR) (4). PPAR activation is responsible not only for genomic effects associated with myocardial lipid metabolism and energy production (2) but also for pleiotropic (other than primary) lipid-independent properties of PPAR agonists that are similar to the effects of IPC (5). These effects are linked with the activation of cell survival cascades, antioxidative, antiapoptotic and antiinflammatory actions (6). Our study was, therefore, focused on the effects of RIPC on cardiac response to IR injury (namely, its impact on the size of myocardial infarction, contractile dysfunction, ventricular arrhythmias) and on the exploration of selected molecular mechanism of cardioprotection, in particular, PPAR-α activation.

Methods: RIPC was applied on the right hind limb of the anesthetized adult male Wistar rats by means of three cycles of 5-min pressure cuff inflation (200 mmHg) to stop blood flow in the femoral artery, intercepted with 5-min cuff deflation (Figure 2). To explore the role PPAR-α, an antagonist of

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Figure 1 Schematic presentation of remote preconditioning in distant organs/tissues, their stimuli and pathways of protective signal transduction to the target organs
PPAR-α MK886 (MK) was administered (3 mg/kg i.p.) prior to induction of RIPC. After completion of RIPC protocol, the hearts were rapidly excised and exposed to 30-min global ischemia and 120-min reperfusion in the Langendorff-perfusion setting. The size of infarction (IS) was detected by staining of the heart tissue slices with triphenyltetrazolium chloride (TTC). IS was normalized to the area at risk (AR) size (IS/AR). Postischemic restoration of heart function (recovery of LV developed pressure, LVDP) was expressed in % of the preischemic values. IS/AR, LVDP recovery and occurrence of ventricular arrhythmias served as the markers of IR injury in nonpreconditioned and preconditioned hearts.

Results: RIPC significantly reduced the size of myocardial infarction in the setting of acute IR \textit{ex vivo}, attenuated the severity of reperfusion-induced ventricular tachyarrhythmias and improved postischemic recovery of LVDP (Table 1). This is in accordance with the studies demonstrating the IPC-like effects of pretreatment of rats with hypolipidemic drugs, agonists of PPAR-α (5). Administration of PPAR-α antagonist MKK-886 reversed all cardioprotective effects that points out to an important role of this PPAR isoform in another form of endogenous cardioprotection as was shown previously (6).

Conclusions: These results confirmed the efficiency of limb RIPC in myocardial protection against acute ischemia. Blunting of cardioprotective effects by PPAR-α antagonist indicates that PPAR-α activation may play an important role as a potential mechanism mediating the transfer of RIPC-induced protective signaling to the heart. This noninvasive, easily applied, low-cost intervention appears as an attractive option of adjunct therapy in STEMI patients undergoing PPCI for acute MI, and PPAR-α agonists may additionally confer further benefits.

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References


