Opioid-Induced Cardioprotection against Ischemia-Reperfusion Injury: The Challenge in Diabetes

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Abstract

Ischemic heart disease is the leading cause of morbidity and mortality in diabetes. Patients with diabetes are particularly at risk of perioperative myocardial infarction, and are less resistant to myocardial ischemia-reperfusion injury (IRI), but the underlying mechanisms are very unclear. Opioid conditioning has been well demonstrated to be protective against myocardial IRI like ischemic conditioning, but this effect is compromised in diabetic condition, and little is known about the role of opioid-induced cardioprotection during diabetes. This brief review is to provide a summary of our present understanding of the effects of diabetes on opioids induced protection against myocardial IRI and the challenges of limiting IRI by opioids in the diabetic heart.

Keywords: Opioid; Ischemia-reperfusion injury; Ischemic conditioning; Diabetes

Introduction

Cardiovascular disease, especially ischemic heart disease (IHD), is a major complication in patients with diabetes and remains the leading cause of death globally [1-3]. The standard clinical therapy for ischemic heart disease is timely re-establishment of blood supply (i.e., reperfusion) in order to rescue the ischemic tissue. Paradoxically, however, restoration of blood flow may cause additional cell death in cardiomyocytes rather than initiate salvage the ischemic tissue, a phenomenon termed "ischemia-reperfusion injury (IRI)"[4-6]. In 1986, Murry et al. firstly observed that myocardial IRI could be reduced by ischemic preconditioning, which was achieved by brief episodes of ischemia and reperfusion, given before prolonged ischemia [7]. However, its clinical application has been limited because of the unpredictable occurrence of ischemia in patients. In 2003, Zhao et al. applied transient brief interruptions of reperfusion to ischemic episodes and resulted in reduced myocardial injury, termed “ischemic postconditioning” [8]. Subsequent studies expanded this beneficial myocardial conditioning to remote conditioning and pharmacological conditioning [9,10]. It is of note that myocardial conditioning such as preconditioning mediated cardioprotection could be blocked by opioid receptor antagonists [11] and mimicked by opioid receptor agonists, indicating the involvement of activation of opioid receptor signaling pathways in myocardial IRI protection . Fortunately, this opioid-induced cardioprotection is abolished or compromised under pathological conditions such as diabetes [12,13]. This review intends to help understand the role of opioid-induced cardioprotection against IRI and the challenges of limiting myocardial IRI in the diabetic hearts.

Subtypes of Opioid Receptors

An “opioid” is any narcotic not only derived from opium, suggesting endogenous substances such as enkephalins or endorphins that can effect on the brain to decrease the sensation of pain are also classified as opioids. Endogenous and exogenous opioid agonists exert their pharmacological and physiological effects through binding to specific opioid receptors. Opioid receptors (ORs) are classified into four major types, including the mu (µ), delta (δ), kappa (κ) and OR-like subtype1 receptor (ORL-1). The structures and functions of these four opioid receptor subtypes are well described by other reviews [14-16]. ORs are G-protein-coupled receptors [17]. After opioid agonist activates the ORs, G-protein signaling leads to a series of changes in intracellular signaling transduction, and subsequently affects cell function. The effects of µ, δ, and κ-receptor could be well inhibited by the non-selective opioid antagonist naltroxone [14], a drug widely used in clinic. ORs are mainly expressed in the brain and spinal cord [14]. Interestingly, studies also found that δ and κ but not µ receptor and ORL-1 are expressed in cardiac tissues [14,18,19]. This suggests that δ and κ-receptor may play an important role in mediating opioid-induced cardioprotection. Furthermore, cardiac issues are capable of synthesizing, storing, and releasing of opioid receptor peptides [20], such as endorphin, dynorphin, and encephalin, which have high affinity for µ-, κ- and δ-opioid receptors, respectively, indicating that these endogenous opioid peptides may contribute to ischemic tolerance in heart.

Role of opioid receptor in opioid-induced cardioprotection

It is not surprising, given the presence of δ and κ-OR expressed in the heart, that both the selective agonist of δ and δ-OR can reduce myocardial infract size in many species [21,22]. The roles of δ-OR in ischemic preconditioning are well documented by the review by Dragasis S et al. [14]. Several studies also found that cardioprotection mediated by postconditioning involved the activation of δ-OR [23,24]...
The challenge of opioid-induced cardioprotection in diabetes

Although the evidences of ORs (δ and κ-OR) and opioid-induced cardioprotection are clearly described above in non-diabetic condition, the effects of opioids induced cardioprotection under diabetic condition are compromised. It was reported that remifentanil effectively reduced myocardial infarction in normal rats, no matter it was used as preconditioning or as postconditioning stimuli or used as continuous infusion during ischemia and reperfusion [30]. However, in diabetic condition, the cardiac protection of remifentanil preconditioning against IRI was mitigated, which might be associated with reduced recovery of the activities of proteins involved in anti-apoptotic pathways including ERK1/2 [13]. Sufentanil is widely used in clinical anaesthesia because of its protective effects against myocardial IRI, but it was ineffective in preventing against IRI in diabetic rats, which is associated with the activation of GSK-3β [12]. Further, the selective κ-OR agonist significantly reduced the myocardial infarct size and increased the expression of stress-inducible heat-shock protein 70 in normal rats, but its effects were abolished in streptozotocin-induced diabetic rats which might be restored by insulin replacement [31]. However, the underlying mechanisms in which diabetes abolish opioid-induced cardioprotection are not certain.

Molecular perspectives of opioid-induced cardioprotection in diabetes

Cardioprotection by opioid conditioning and ischemic conditioning (in particular, preconditioning) appear to share common elements in cellular mechanisms [11]. Cardioprotection by preconditioning is mostly initiated through stimulation of G-protein coupled receptors by ligands, including bradykinin, opioids, acetylcholine and tumor necrosis factor (TNF)-alpha [32,33]. Then ligand-receptor binding activates multiple signaling cascades, especially protein kinase C (in particular, PKCε), reperfusion injury salvage kinase (RISK), including PI3 kinase/Akt, extracellular signal regulated kinase (ERK), p70S6 kinase and glycogen synthase kinase 3β (GSK-3β), or survival activating factor enhancement (SAFE) pathways, including janus activated kinase (JAK) and signal transducer and activator of transcription (STAT) [34-36]. Moreover, it is well demonstrated opioid-induced cardioprotection in normal rodents involves several similar signaling, such as protein kinase C (PKC) [37], GSK-3β [38], ERK [39], JAK/STAT [40], and so on. However, diabetes has been shown to be associated with impaired PI3 kinase/Akt signaling (components of both insulin signaling and the RISK pathway), essentially all kinases proposed to contribute to the infarct-sparing effect of ischemic conditioning. For example, impaired phosphorylation of PKC, PI3 kinase/Akt, ERK, STAT3, and GSK-3β have been demonstrated in diabetic hearts as reviewed by Wider J and Przyklenk K [2]. These are potential mechanisms that rendered the diabetic hearts are more susceptible to IRI and less sensitive to opioid conditioning (Figure 1). Consequently, further research should be directed at elucidating the role of OR-induced cardioprotection in diabetic condition and developing rational drug to reduce myocardial IRI and restore opioids induced cardioprotection in diabetes. A most recent study [41] showed that selective activation of κ-opioid receptor reduced hyperglycemia in streptozotocin-induced diabetic mice that might be relevant to increased adiponectin, a molecule with anti-ischemic and anti-diabetic property whose secretion is reduced in diabetes, which shed light on exploring the mechanism and effectiveness of opioid cardioprotection in diabetes.

Figure 1: Schematic of proposed mechanism of opioid conditioning or ischemic conditioning induced cardioprotection. Opioids conditioning or ischemic conditioning protects the heart against ischemia-reperfusion injury, which initiates through stimulation of G-protein coupled receptors by ligands, then activates multiple signaling cascades, especially protein kinase C (PKC), survivor activating factor enhancement (SAFE) and reperfusion injury salvage kinase (RISK) pathways, and ultimately attenuates ischemia-reperfusion injury, but these effects are abolished or compromised under diabetic condition.

Conclusion

Opioid conditioning mimics ischemic conditioning induced protection against myocardial IRI in normal condition. This effect is produced by the activation of ORs, especially δ-OR and κ-OR. However, the opioid-induced cardioprotection is abolished or compromised in diabetic conditions. Gaining more insight into the mechanism(s) by which diabetes affects opioid-induced cardioprotection may assist in developing new therapeutic strategies to improve cardiac function and to restore effectiveness of opioids conditioning in cardiac operations in the setting of diabetes, including patients with genetic predisposition to type 2 diabetes [42], whose glucose levels might only be slightly increase but yet may
accelerate the development of atherosclerosis and increase the risk of coronary heart disease.

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