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Opioids Modulate the Mitochondrial Membrane Permeability Transition Pore to Improve Myocardial Ischemia-Reperfusion Injury Research Progress

Jiashuo Li, Shu Song, Yibo Wang, Tianxiang Chen, Lili Gu, Mengyuan Tao, Shuhui Sun, Jinkun Xi, Wenji Liang, Xiaohan Yu, Zhumei Sun*

School of Clinical Medicine, North China University of Science and Technology, Tangshan, Hebei, 063000, China
**Corresponding author*

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Abstract: With the gradual improvement of cardiac surgery technology, the promotion and application of coronary artery thrombolysis, percutaneous coronary intraluminal plasty, cardiac surgery extracorporeal circulation and other technologies, myocardial ischemia and reperfusion injury, have attracted more and more attention from researchers. Myocardium ischemia-reperfusion injury (MIRI) is a more serious myocardial injury caused by reperfusion of ischemic myocardium, and there is often no effective treatment in the clinic, so how to avoid or alleviate MIRI has become a research hotspot. Studies have shown that mitochondria play a crucial role in myocardial protection, with mitochondrial permeability transition pores (mPTP) playing an essential role in MIRI. mPTP regulates mitochondrial membrane permeability to maintain mitochondrial stability, and opening mPTP will further worsen MIRI. Opioids such as Morphine, Fentanyl, Remifentanil, etc., are often used as analgesics in the clinic, but at present, they have been increasingly used in patients with MIRI injury. Opioids play a significant role in regulating mPTP opening, etc., and can regulate mPTP opening in various ways to inhibit MIRI effectively. This paper reviews the molecular mechanism and research progress of the occurrence and development of MIRI in recent years from many aspects further discusses the molecular mechanism and pathway of opioid regulation and intends to provide new ideas and theoretical basis for the prevention and treatment of MIRI.

1. Introduction

According to the data from the Chinese Cardiovascular Health and Disease Report 2020: With the development of social and economic development and changes in national lifestyle, the impact of cardiovascular disease risk factors on residents' health has become more and more significant, and the incidence of cardiovascular disease continues to increase. Presently, cardiovascular disease deaths account for the first cause of death among urban and rural residents in China, 46.66% in rural areas and 43.81% in cities [1]. Myocardial infarction causes the most common ischemia-

reperfusion injury in clinical practice, but there is often no effective prevention and treatment. Reperfusion is a standard treatment for ischemic heart disease, and myocardial ischemia-reperfusion can significantly reduce infarct size and improve cardiac function, but it can also trigger more severe myocardial injury. MIRI often occurs during reperfusion therapy for ischemic heart disease and is a common and urgent pathophysiological phenomenon in clinical practice. When ischemia occurs in myocardial tissue, restoration of blood flow is the most critical rescue measure, yet this process causes pathological manifestations such as oxidative stress damage, apoptosis and abnormal immune response [2]. Therefore, it is essential to elucidate the mechanism of MIRI. The mPTP located between the inner and outer mitochondrial membranes has a vital role in regulating the level of mitochondrial membrane potential and maintaining a stable potential difference [3], and mPTP opening is thought to be the terminal link of MIRI [4]. Therefore, regulating mPTP opening by effective interventions is essential to prevent and ameliorate MIRI. Basic research and clinical trials have learned that in MIRI, opioids effectively attenuate the development of MIRI pathology [5-7]. Numerous studies have shown that opioids improve mitochondrial stability and reduce ischemia-reperfusion injury in ischemia-reperfused myocardium by modulating the opening of mPTP. There is increasing interest in the specific mechanisms by which opioids attenuate MIRI.

Therefore, this paper reviews the molecular biological structure of mPTP in MIRI and the possible mechanisms involved in the occurrence of MIRI and delves into the possible mechanisms of action of opioids to improve MIRI by regulating mPTP opening, which is intended to provide new valuable ideas for the myocardium of ischemia-reperfusion injury.

2. Role and Structure of mPTP

Mitochondria are organelles with a bilayer membrane, the outer membrane is highly permeable, and the inner membrane is less permeable. Since the myocardium requires high energy and mitochondria provide 95% of the energy to cardiomyocytes [8], mitochondria play a significant physiological role in MIRI. It was found that the level of mitochondrial inner membrane permeability depends on the magnitude of mPTP opening. mPTP selectively allows the passage of non-specific substances and protons with molecular weight less than 1.5 kd through the mitochondrial inner membrane. The opening of mPTP leads to alteration of mitochondrial inner membrane permeability, followed by the imbalance of ion concentration difference and the potential difference between inner and outer membrane, decreased sodium-potassium pump activity, and blocked Na^+-K^+ transport across the membrane, which in turn triggers mitochondrial dysfunction, decreased mitochondrial membrane potential, cytochrome C (Cyt-C) release [9], initiation of caspase apoptotic cascade reaction leading to apoptosis, and MIRI occurrence. The flow of ions may also cause the formation of osmotic pressure between the mitochondria and the intracellular compartment, resulting in mitochondrial matrix hyperosmolarity, which swells the mitochondria and leads to damage.

mPTP is a group of protein complexes between the inner and outer mitochondrial membranes and is a non-specific channel. The molecular composition of mPTP is not fully understood. However, most scholars believe that the voltage-dependent anion channel (VDAC) in the outer membrane, adenosine translocator protein (ANT) in the inner membrane, and mitochondrial cyclophilin D (CypD) are important regulatory components of mPTP. Recently, it was prop-osed that the subunit of ATP synthase is involved in forming the pore component of mPTP in the mitochondrial inner membrane [10]. However, many studies have updated the above idea [11-14]. Among them, Baines [11] used RNA interference to knock down one or three alleles of VDAC in fibroblasts, and VDAC gene deletion cells under conditions such as calcium overload and oxidative

stress led to cell death as in wild-type fibroblasts, suggesting that VDAC may not be an essential component of mPTP; and, Kokoszka et al. [13] found that ANT1 and ANT2 genes. In addition, Kokoszka et al. found that murine hepatocytes deficient in both ANT1 and ANT2 genes could still undergo cell death after ischemia-reperfusion. mPTP pore opening in ANT1-deficient cells required higher concentrations of Ca^{2+} to be induced and was no longer regulated by ANT ligands than in wild-type cells. However, ANT1 overexpression did not induce mPTP pore opening but caused reactive oxygen species (ROS)-dependent upregulation of Bax expression and cell death mediated by its activation. The research results suggested that ANT only has a regulatory effect on mPTP pore opening, but it may also be involved in cell death that is not dependent on mPTP pore opening.

3. Biological Mechanisms Involved in the Development of MIRI by mPTP

It was shown that during myocardial ischemia mPTP is in a closed state, and the initial phase of reperfusion is characterized by large amounts of ROS and factors such as Ca^{2+} open mPTP, triggering mitochondrial membrane potential decay and dephosphorylation, leading to cardiomyocyte death. Abdallah Y et al. [15] demonstrated that perhaps Ca^{2+} is more closely related to mPTP opening. Their finding in MIRI rat cardiomyocytes that calcein (calcein) exits from mitochondria during the reperfusion period leads to a decrease in mitochondrial membrane potential and an overload of intracellular Ca^{2+} and ROS, leading to cell death. The Ca^{2+} blocker carotenoid (carotene) was found to block mPTP opening and ROS production thus, whereas the application of ROS scavengers did not achieve myocardial protection. It is suggested that a more critical factor affecting mPTP opening is intracytoplasmic Ca^{2+}. When mitochondrial mPTP opens pathologically due to external causes, intracellular levels of lactate dehydrogenase (LDH) and creatine kinase (CK) increase and superoxide dismutase (SOD) and glutathione Peroxidase activity decreases, leading to increased intracellular ROS and malondialdehyde (MDA) production, increased Cl^-, and the opening of VDAC channels in the outer mitochondrial membrane, enhancing the uptake of Ca^{2+} by mitochondria, with the opening of VADC2 channels playing an important role[16]. The large amount of Ca^{2+} in mitochondria induces mPTP opening. At the same time, CypD prolonged mPTP opening time and Ca^{2+} exocytosis via mPTP increases, leading to intracellular Ca^{2+} overload and reduced ATP production, causing the collapse of mitochondrial membrane potential, eventually leading to cell death. Meanwhile, Bax and Bak, members of the Bcl-2 family, induce Cyt-C release and initiate the caspase apoptotic cascade [17], damaging cardiomyocytes. After the application of mPTP-specific opener, canthaxanthin, after ischemia, the measurement of LDH, SOD, MDA and interleukin-6 (IL-6) in animals and the area of myocardial infarction in rats revealed that the area of myocardial infarction was larger in rats after the application of mPTP-specific opener compared with the standard group [18]. It shows that the opening of mPTP is a critical cause and fundamental factor of MIRI, and blocking mPTP opening can reduce reperfusion injury.

4. Biological Mechanisms by which Opioids Ameliorate the Development of MIRI

Opioids have been widely used clinically for the treatment of pain. Related experiments have confirmed that the use of opioids can also treat MIRI and reduce the area of reperfused injured myocardium. Animal experiments have shown that morphine treatment can effectively reduce apoptosis and myocardial reperfusion damage after ischemia and reperfusion in rats [19]. The results of increased myocardial infarct area following the opioid er naloxone application also demonstrate that opioids can reduce the extent of MIRI cell injury, improve myocardial function, and protect reperfused cardiomyocytes [20]. Opioids activate the opioid receptor activation downstream pathway in vivo to exert cardioprotective effects, where the opioid receptor system

includes δ, κ and μ opioid receptors and their endogenous opioid ligands, among which δ and κ opioid receptors are closely associated with cardioprotection. Studies have shown that activation of δ2 opioid receptors by opioids increases cardiac resistance to reperfusion injury, and the use of selective δ2 opioid receptor blockers can block the protective effects of opioids[21]. Early studies suggested that κ receptors were not associated with cardioprotection, but recent experiments have found that activation of κ2 receptors has no effect on cardiac tolerance to reperfusion and that activation of κ1 receptors prevents cardiac reperfusion injury [22]. However, evidence that μ receptors exert the same cardioprotective effect in animal and human tissues is mixed [21]. WU [23] demonstrated that Morphine effectively reduced MIRI infarct size. However, recent studies have shown that short-term high-dose application of opioids increases myocardial oxidative stress and antagonizes the infarct-protective effects of the drug in rats, as seen with prolonged opioid use [24]. Kunecki et al. [25] found that Morphine improved systolic blood pressure and normal diastolic function of the human myocardium in a dose-dependent manner. In the case of acute ischemia-reperfusion injury, different timing of morphine treatment will lead to different outcomes, with 90 minutes of reperfusion application as the dividing line, where ischemia-reperfusion time less than 90 minutes of morphine application will reduce the infarct size and more than 90 minutes of morphine application will increase the infarct size [26]. Therefore, the correct and rational use of opioids has a crucial role in myocardial protection.

4.1 Morphine Improves MIRI by Inhibiting mPTP Opening

Morphine is a pure monomeric opioid alkaloid, isolated in the early 19th century, mostly used clinically for analgesia and mainly associated with mu-opioid receptors. Morphine and its related derivatives act as exogenous opioid receptor agonists and can exert myocardial protective effects through pretreatment and post-treatment mechanisms [27-28]. Morphine effectively reduces infarct size in rats after myocardial ischemia/reperfusion injury [23,29]. The pathway through which Morphine exerts its cardioprotective effects may be through.

4.1.1 Morphine Improves MIRI by Blocking mPTP Opening through Modulation of Endoplasmic Reticulum Stress

The protein kinase R-like endoplasmic reticulum kinase (PERK) pathway is an essential component of the endoplasmic reticulum stress (ERS) signalling pathway, which affects cellular adaptation and survival under stressful conditions. Studies have shown that the PERK/EIF2α/ATF4 pathway plays an essential role in the protection of interstitial hypoxic cells [30], suggesting that the PERK pathway plays a crucial role in myocardial ischemia-reperfusion injury. Zhao Miao et al.[31] showed that Morphine inhibited the expression of glucose-regulated protein 78 (GRP78) and glucose-regulated protein 94 (GRP94), p-PERK and CHOP protein levels in oxidatively stressed myocardial H9c2 cells and significantly enhanced GSK-3β phosphorylation in oxidatively stressed myocardial H9c2 cells to inactivate them (GSK-3β activity is associated with (GSK-3β activity is closely related to a variety of diseases), thus blocking the opening of mPTP and thus achieving myocardial protection [32]. It is suggested that Morphine inhibits ERS through the PERK pathway, inactivates GSK-3β, blocks mPTP opening, attenuates myocardial mitochondrial damage by ischemia-reperfusion and protects reperfusion-injured cardiomyocytes.

The endoplasmic reticulum is a storage site for zinc ions in cells, and the stability of zinc ion concentration, i. e. zinc homeostasis, is essential for maintaining normal physiological functions in the body. Zinc homeostasis imbalances can lead to immunodeficiency, growth disorders, hyposexuality, dermatitis, neurological dysfunction [33] and cardiovascular diseases such as ischemic cardiomyopathy, arteriosclerosis, and ischemic reperfusion injuries [34-35]. External

stimuli can cause ERS leading to the release of zinc ions from the endoplasmic reticulum [36], an imbalance in zinc homeostasis, and ultimately cell death, so maintaining zinc homeostasis is critical. It has been demonstrated that Morphine and exogenous zinc ions can block mPTP opening by inhibiting GSK-3β activity through AKT and can significantly inhibit reperfusion-induced ERS and exert myocardial reperfusion protection [37], suggesting that Morphine and zinc ions regulate endoplasmic reticulum stress to block mPTP opening has a vital role in myocardial reperfusion protection. The effect of Morphine on GRP78 protein expression during reperfusion was observed by administering Morphine and the zinc ion chelator TPEN to cardiomyocytes during reperfusion, and this effect of Morphine was inhibited by the zinc ion integrator TPEN. Suggesting that Morphine inhibits reperfusion-induced ERS via zinc ions; also, in observing the effect of Morphine on mPTP opening in cardiomyocytes, the effect of Morphine was found to be inhibited by zinc ion chelator [38]. The results of several tests suggest that Morphine regulates ERS with the participation of zinc ions, and Morphine inhibits ERS by maintaining zinc homeostasis, thus preventing mPTP opening and exerting myocardial protection by reperfusion; whether AKT/GSK-3β is an essential mechanism of mitochondrial-endoplasmic reticulum "cross-talk" needs more experimental evidence.

4.1.2 Morphine Improves MIRI by Inhibiting mPTP Opening Through the NO/cGMP/KATP Pathway

NO plays a protective role against cardiac ischemia-reperfusion [39]. NO activates protein kinase G (PKG) by acting on guanylate cyclase (GC) to induce the production of cGMP [40], which acts as a downstream signalling protein of cGMP to activate ATP-sensitive potassium channel (KATP channel) channels [41], where KATP channels are considered to be a critical link in myocardial protection, and experiments have demonstrated that the application of KATP agonists can stimulate myocardial Na^{+}-Ca^{2+} exchange, shorten the action potential time course of cardiomyocytes, reduce calcium inward flow, and reduce calcium overload during myocardial ischemia and early reperfusion, thus producing myocardial protection [42]. Studies have shown that Morphine stimulates the synthesis of various NO synthases and promotes NO synthesis [43]. In a related study, the myocardial protective effect of Morphine was found to be blocked by the injection of the NO synthase blocker L-NAME [44]. Morphine pretreatment did not reduce the area of myocardial infarction in inducible NO synthase (iNOS) knockout mice [45]. It has also been shown that activators of KATP channels can enhance the analgesic and anti-injurious effects of opioids to some extent [46]. It is inferred that Morphine has a protective effect on the myocardium through NO/cGMP and downstream protein kinase pathway [47], but the mechanism of whether Morphine can exert myocardial protective effects through NO/cGMP/KATP modulation of mPTP opening is not precise, so it is essential regarding the study to elucidate the mechanism of myocardial protective effects induced by Morphine modulation of NO/cGMP/KATP signalling pathway.

4.2 Remifentanil Improves Miri by Inhibiting mPTP Opening

Remifentanil is a member of the Fentanyl family, with rapid onset of action after injection and rapid disappearance of effects, and is a short-acting opioid. Remifentanil can effectively inhibit stress response, reduce caspase-3 expression, increase Bcl-2/Bax expression [48] and maintain hemodynamic stability. Remifentanil can improve ischemia-reperfusion injury in various organs [49-51]. Remifentanil has been shown to improve ischemia/reperfusion injury in the liver by activating dorsal vagal neurons [50]. Recent experiments have demonstrated that Remifentanil can improve MIRI by inhibiting the IL-48 signalling pathway [51]. Remifentanil has a cardioprotective effect, and it is hypothesized that its mechanism of action may be through.

4.2.1 Rifentanil Improves MIRI by Indirectly Exciting the Vagus Nerve to Inhibit mPTP Opening

It was found that sympathetic excitation in the heart after ischemia-reperfusion caused intracellular Ca^{2+} overload, leading to myocardial injury [52]. Miura et al. [53] found in 2001 that protection of ischemic myocardium by Remifentanil might be related to reducing adrenaline release by inhibiting sympathetic excitation. In 1999, Yao et al. first found that the vagal neurotransmitter acetylcholine (ACh) protects the myocardium by activating mitochondrial ATP-sensitive potassium channels (mitoKATP) at the cellular level. Moreover, Rourke [54] found that activated mitoKATP during ischemia-reperfusion reduced the number of mPTP openings and inhibited the decrease in mitochondrial membrane potential, thereby improving ischemic myocardial function, which opens up the possibility that the vagus nerve protects the myocardium by inhibiting mPTP opening through activation of KATP channels. Subsequent findings from the Katare [55] experiment further prove that the vagus nerve improves MIRI by inhibiting mPTP opening by reducing mitochondrial swelling and rupture. It can be inferred that Remifentanil may protect cardiomyocytes from MIRI improvement by preventing mPTP opening through indirect excitation of the vagus nerve.

4.2.2 Rifentanil Inhibits mPTP Opening by Reducing ROS Production to Improve MIRI

Restoration of perfusion is commonly chosen clinically to treat the ischemic myocardium, but the re-established oxygen supply may be another layer of the blow to the myocardial cells. Mitochondria are the prominent organelles that produce oxygen radicals. In the event of ischemia-reperfusion, the mitochondrial structure is changed, and the normal oxidative phosphorylation pathway is inhibited, which reduces the efficiency of oxygen radical scavenging and allows oxygen radicals to leak from the mitochondria into the cytoplasm. The highly reactive intermediate product ROS is generated by the chain reaction of oxygen radicals in vivo. A large amount of ROS production leads to mPTP opening, mitochondrial membrane potential depletion and apoptotic cell death. Studies suggest that Remifentanil attenuates MIRI possibly by attenuating ROS generation related to [56]. Luccinetti [57] In an experiment to determine the effect of different anesthetic drugs on ROS-mediated recovery of post-ischemic left ventricular work (LV) in rats induced by Intralipid post-treatment, it was found that Remifentanil in the absence of Intralipid post-treatment, Remifentanil improved LV function. In the presence of Intralipid post-treatment, Remifentanil increased its myocardial protective benefit. Therefore, Remifentanil itself has a protective effect on ischemic myocardium and provides additional protection to the ROS-mediated heart. Its mechanism of action may attenuate MIRI by attenuating ROS generation to inhibit mPTP opening.

4.3 Fentanyl Improves MIRI by Inhibiting mPTP Opening

Fentanyl is a commonly used anesthetic drug in clinical practice, and its application is more common than Remifentanil. Therefore, it is essential to elucidate the myocardial protective effect of Fentanyl. Fentanyl has been shown to protect the type 2 diabetic myocardium [58]. Fentanyl plays a vital role in ischemia-reperfusion cardiomyocyte apoptosis [59]. Among them, although Fentanyl is a μ-opioid receptor agonist, its exertion of myocardial protection may be accomplished through δ and κ receptors [60]. The mechanism of action may be.

4.3.1 Fentanyl Improves MIRI by Increasing Adenylate Release to Inhibit mPTP Opening

Adenosine, a compound consisting of N-9 of adenine and C-1 of D-ribose linked by a β-glycosidic bond, has the chemical formula C_{10} H_{13} N_5 O_4; adenosine can directly enter the myocardium through phosphorylation to produce adenosine acid, which is involved in myocardial

energy metabolism, and also involved in reducing Ca^{2+} production, dilating coronary vessels and increasing blood flow. There are three types of adenosine receptors, A1, A2 and A3. The myocardial protective effect of adenosine combined with the A2 receptor has been studied more thoroughly. In the ischemia-reperfusion model, reoxygenation caused the number of intracellular autophagosomes to exceed the number of autolysosomes, but the results were reversed after adenosine A2 receptor agonists were used, moreover, after using adenosine A2 receptor agonist before reperfusion protected cell survival through anti-apoptotic and anti-autophagic effects, improved ventricular systolic dysfunction, and significantly reduced myocardial infarct area [61], suggesting that adenosine has a vital role in protecting ischemia-reperfusion injured myocardium. The lack of local oxygen supply after myocardial ischemia interrupts oxidative phosphorylation and reduces ATP production because mitochondria cannot transfer electrons to oxygen through the electron transport chain. H^+ cannot cross the inner mitochondrial membrane, and the transmembrane potential collapses. The mitochondria can only hydrolyze the residual ATP to maintain the transmembrane potential. Thus, adenosine decreases dramatically after the onset of hypoxia, opening mPTP through a series of pathways [62], leading to myocardial cell injury. Kato [63] found in an experiment in which the Langendorff rat heart underwent ischemia for 30 minutes, with 60 minutes of reperfusion, that rats given Fentanyl before induction of ischemia were more likely to be reperfused than control rats given Fentanyl 60 minutes after reperfusion. The mechanical function of the rat heart after ischemia was improved compared to the control group (no Fentanyl drug was given before the start of the experiment). The ability of Fentanyl to improve mechanical function in the ischemic heart was eliminated after continued administration of naloxone and the adenosine A1 receptor antagonist DPPCX. Thus, it is suggested that Fentanyl may improve MIRI by increasing adenylate release and inhibiting mPTP opening.

4.3.2 Fentanyl Improves MIRI by Promoting the Release of Atrial Peptides to Inhibit mPTP Opening

Fentanyl promotes the synthesis and secretion of atrial peptides by cardiomyocytes [64-65]. Atrial peptide, an endocrine hormone, is an atrial linear peptide. It is present in granules within atrial myocytes, regulates the body's water balance, and affects blood pressure. Atrial peptides are stored as inactive central atrial peptides in their original form or the granules of atrial myocytes and are degraded by enzymes to produce biologically active atrial peptides when the atria experience stimuli such as increased sodium levels [66]. Atrial peptides can improve MIRI by reducing Ca^{2+} overload through the carbon monoxide-cyclic ornithine pathway [67], and also improve SOD activity, reducing the production of malondialdehyde, a product of lipid peroxidation reactions, and reducing mPTP opening, thereby reducing ROS damage to cardiac myocytes [68]. Therefore, it is inferred that the improvement of MIRI by Fentanyl may be achieved by promoting the release of atrial peptides to inhibit mPTP opening.

5. Conclusion and Outlook

In summary, mPTP opening is a pathological factor contributing to the development of myocardial ischemia-reperfusion injury. Opioids modulate mPTP opening levels through related pathway proteins to inhibit mPTP opening and thus reduce MRIR mortality.

MIRI is an intricate pathophysiological process involving multiple genes, molecules and cellular tissues, and no drug is effective in treating MIRI with minimal side effects. However, there are still some issues that need to be addressed, such as the clinical focus on how to apply opioids to treat MIRI, but not on the immediate or short-term effects on patients' cardiac function after drug treatment; there are many targets that can reduce reperfusion injury, and there is a wide range of

opioids. It is unclear whether other concomitant diseases such as hypertension and diabetes affect the myocardial protective effect of opioid receptors; or whether the clinical use of opioid formulations should be further optimized to avoid adverse effects of opioids due to individual patient differences. Therefore, there is much room for development in elucidating how opioids can be used to treat MIRI patients. Long-term follow-up studies on patients in clinical practice, refinement of the opioid mechanism of action, comprehensive and systematic grasp of the dynamic changes of myocardial ischemia-reperfusion patients' conditions and the effects of opioid intervention, selection of specific therapeutic regimens, and development of scientific evaluation methods are of great significance to carry out opioid prevention and treatment of the myocardial ischemia-reperfusion injury. The mechanism of myocardial protection of opioids will have an essential role in the prevention, treatment and prognosis of MIRI.

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