A Review of Pharmacological Preconditioning for Hepatic Ischemia-Reperfusion Injury

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Abstract: Hepatic ischemia/reperfusion injury (HIRI) is a pathophysiological condition that occurs when the liver's blood supply is interrupted, resulting in organ hypoxia. It commonly happens when blood supply to the liver is reduced during liver resection due to prolonged obstruction of blood flow, shock, trauma, or heart failure. Prolonged hepatic ischemia followed by reperfusion, which occurs following a liver transplant, causes serious harm and contributes to increased morbidity and death. Several HIRI treatments, including pharmacological preconditioning, ischemic preconditioning, and remote ischemic preconditioning, have been proposed based on the further study on hepatic ischemia-reperfusion injury. Pharmacological preconditioning has demonstrated promising benefits in the prevention of liver injury in experimental models and a few randomised controlled human studies. The current state of pharmacological preconditioning for hepatic ischemia and reperfusion injury is discussed in this study.

Keywords*:* Ischemic Preconditioning; Ischemia-Reperfusion Injury; Hepatectomy; Liver Transplant; Drug

Introduction

Ischemia-reperfusion injury (IRI) is a joint experimental and clinical finding that tissue ischemia with insufficient oxygen supply followed by successful reperfusion triggers a broad and complex array of inflammatory responses involving multifactorial metabolic mechanisms pathways, ultimately leading to severe ischemia-reperfusion injury, circulatory dysfunction, organ failure, and death. Ischemia-reperfusion injury to the liver is a type of injury that occurs when the liver is deprived of oxygen and nutrients (HIRI) is a multi-factorial pathologic process that leads to post-ischemic organ failure and cell death.

Following liver surgery, there is an increased risk of death, resulting in an increase in morbidity and mortality. For irreversible acute and chronic liver disorders, a liver transplant has been the most effective treatment option so far. The primary cause of primary non-function or insufficiency of the transplanted liver after liver transplantation is ischemia-reperfusion damage. It is also the most common reason for liver transplantation and mortality. As a result, liver transplantation research is a prominent topic.

Ischemic preconditioning (IPC) is described as a brief period of ischemia followed by tissue reperfusion in order to increase ischemic tolerance for a prolonged length of ischemia. The adaptive pathophysiological process in the targeted organ allows IPC to reduce the size of IRI. Ischemic preconditioning can lower the severity of the ischemia-reperfusion injury and increase the success rate of liver transplantation.

Ischemic preconditioning has been proven to be a promising technique for improving postoperative outcomes after liver

resections in a number of experimental investigations and a few clinical series. Furthermore, many pharmacological intervention and preconditioning methods, such as remote preconditioning, heat shock, and hyperbaric oxygen, have been developed to reduce the functional impairment associated with ischemia-reperfusion injury. The primary mechanisms of pharmacological preconditioning for liver ischemia/reperfusion injury are currently: (1) reducing cellular calcium excess; (2) reducing oxidative stress; (3) reducing inflammatory factor production; and (4) modulating apoptosis, pyroptosis, or autophagy. The majority of HIRI pretreatment medicines reduce tissue and cell damage by one or more of the mechanisms listed above, enhance liver tissue and cell resistance to ischemia-reperfusion (IR), maintain liver function, and prevent postoperative liver damage.

1. Substances that are anti-inflammatories

Although the inflammatory response is protective in the repair of tissue damage, an overabundance of it can harm tissue and organ function. Activated Kupffer cells produce a lot of reactive oxygen species, proinflammatory cytokines, chemokines, and adhesion molecules during HIRI. During liver resection, neutrophils aggregate in ischemic parts of the liver, promoting the inflammatory response of liver parenchyma cells, thanks to ROS-activated inflammatory pathways.

1.1Antagonizers of the adrenergic receptor

Mohammed et al. proposed that carvedilol can selectively antagonise α1ARs and non-selectively β_1ARs and β_2ARs as an adrenergic receptor antagonist[1], inhibit G protein-coupled receptor signalling pathway and reduce the expression of protein kinase C. level, thereby reducing the release of NF-κB and reducing the inflammatory response. CF102 is a highly selective α3 adrenergic receptor antagonist. Ohana et al. [2] believed that CF102 exerted a practical anti-inflammatory effect by down-regulating the expression of the PI3K/NF-κB signalling pathway.

1.2Dipeptidyl peptidase-4 inhibitor

Sherif et al. [3] discovered that vildagliptin, a dipeptidyl peptidase-4 inhibitor, lowers HIRI, primarily by inhibiting high mobility group protein 1 (HMGB-1). TNF- levels also reduce the expression of the TLR4/NF-B signalling pathway, which helps to reduce inflammation. By activating the Nrf-2/HO-1 pathway, Abdel-Gaber et al. [4] discovered that sitagliptin might enhance the expression of Nrf-2 mRNA and the content of HO-1 and so have an anti-inflammatory impact.

1.3Anesthetics

Yang et al. [5] found that remifentanil, as an opioid receptor agonist, could activate β-arrestin and reduce the inflammatory response of HIRI. Dexmedetomidine, an α2 receptor agonist, commonly used in clinical anaesthesia, can trigger the presynaptic α2A receptor on Kupffer cells' surface, inhibiting the expression of norepinephrine, inhibiting the inflammatory response, and reducing HIRI during hepatectomy.

1.4Endogenous active substances

Not only exogenous drugs can reduce HIRI damage, but many endogenous active substances can also play an important protective role. The Ang II/AT1R pathway, as a critical hypoxic/ischemic organ damage regulatory axis, activation of AT1R increases oxidative stress and the expression of inflammatory cytokines. Ye et al. [6] also found that pretreatment with galectin-1 (Gal-1), mainly expressed in macrophages, neutrophils, dendritic cells, and other cells, can increase anti-inflammatory cells. The expression of factor IL-10, while significantly attenuating the expression of pro-inflammatory cytokines and chemokines (CXCL-1, CXCL-10) such as TNF-α, IL-1β, IL-6 and IFN-γ, and reducing the inflammatory response.

In addition to the drugs included in the above categories, new drugs are continually being demonstrated to exert anti-inflammatory effects during HIRI. Kamel et al. [7] proposed that the angiotensin-converting enzyme inhibitor perindopril can alleviate the impact of Nrf-2-related signalling pathways, TLR4/NF-κB, JAK1/STAT-3, PI3k/Akt/mTOR and other signalling pathways. Yu et al. [8] found that L-tetrahydropalmatine can directly reduce the production of inflammatory

cytokines TNF-α and IL-6, further inhibiting the ERK/NF-κB signalling pathway and playing a protective role in the process of IR.

2. Medications to reduce cellular calcium overload

When IR occurs, the production of adenosine triphosphate (ATP) is reduced, the sodium-potassium pump activity is decreased, and the intracellular Ca2+ concentration is abnormally increased, that is, calcium overload. In addition, the damage to mitochondrial structure and function caused by cellular ischemia and hypoxia can also cause intracellular calcium overload. Calcium overload mainly induces cell death or apoptosis by activating calcium-dependent enzymes such as neutral protease and protein kinase C [1]. The current common drugs specifically reduce the cellular calcium overload during HIRI by protecting the structure and function of mitochondria. Neda et al. [2] proposed that silibinin can neutralise a large amount of ROS to maintain mitochondrial membrane integrity, reduce mitochondrial membrane fusion, reduce calcium overload, and reduce HIRI while regulating the expression of OPA1 and MFN1 genes. Gu et al. [11] [3] confirmed through experiments that ursodeoxycholic acid lysophosphatidylethanolamide could protect mitochondria, maintain ATP production, balance mitochondrial fission and fusion, reduce the reduction of mitochondrial fission and fusion calcium overload, and inhibit mitochondria-mediated apoptosis pathway and play a role in lowering HIRI.

3. Medications to reduce oxidative stress

Under physiological conditions, the reactive oxygen species (ROS) produced by hepatocytes maintain a dynamic balance with the superoxide dismutase (SOD) they contain. In the process of IR, Kupffer cells and neutrophils generate a large amount of ROS. The SOD produced by the body cannot be removed entirely, resulting in mitochondrial dysfunction, destruction of protein, cell membrane integrity and lipid peroxidation to produce propanediol. Aldehydes and other lipid peroxides. Therefore, scavenging excess ROS or increasing SOD expression can inhibit the occurrence of oxidative stress during IR, thereby alleviating HIRI.

De Almeida et al. [6] confirmed that methylene blue (MB) could exert its reducing properties at low concentrations, replacing oxygen molecules as the electron acceptor of xanthine oxidase in the electron transfer of IR, thereby reducing the amount of ROS.

4. Multi-mechanism medicines

Nobiletin, a natural flavonoid, is a beneficial antioxidant with anti-inflammatory and anti-cancer activities. In recent years nobiletin has received extensive attention due to its various medicinal properties and biological effects. Dusabimana et al. found that nobiletin can activate the SIRT1/FOXO3α signalling pathway to induce autophagy. Recent studies have shown that liver-selective MMP-9 inhibitors can reduce HIRI and accelerate liver tissue regeneration.

In the latest study, PPAR-γ agonists, the diabetes treatment drugs, were also found to play a protective role during liver ischemia/reperfusion. Oral administration of PPAR-γ agonists 1-3 days before liver surgery can effectively alleviate HIRI by activating the FAM3A-ATP-Akt signalling pathway, reducing oxidative stress and reducing the inflammatory mediator NF-κB . In addition, petrolatum can also reduce oxidative stress and inflammation by up-regulating the expression of PPAR-γ, regulating the downstream NF-κB-p65 and JAK2/STAT1 pathways .

Irisin, a newly discovered hormone, appears to be a novel and potential HIRI treatment. This kind of protein, which is released by skeletal and cardiac muscle after exercise, has many protective benefits in HIRI. After hepatic I/R, exogenous irisin treatment improved liver function, reduced liver necrosis and cell apoptosis, and lowered inflammatory response[14]. In hepatic I/R, exogenous irisin significantly reduced the expression of the mitochondrial fission related proteins dynamin-related protein 1 (drp-1) and fission 1 (Fis-1). Exogenous irisin therapy also boosted mitochondrial content as well as peroxisome proliferative activated receptor (PPAR) co-activator 1 (PGC-1) and mitochondrial transcription factor (TFAM) expression, all of which are associated to mitochondrial biogenesis. Irisin also reduced oxidative stress in the hepatic I/R by upregulating the production of uncoupling proteins (UCP) 2. Exogenous irisin therapy reduced hepatic I/R injury by inhibiting mitochondrial fission, boosting mitochondrial biogenesis, and alleviating oxidative stress, according to the

findings.

Conclusion

Ischemia-reperfusion damage is a serious side effect of liver surgery that is linked to a high rate of morbidity and mortality. Many studies have shown that pharmacological preconditioning can protect the liver by significantly reducing or preventing reperfusion injury throughout the last few years. However, most of these researches have been conducted on animals, and despite encouraging outcomes in experimental models, the majority of the findings cannot be applied to humans. Despite the fact that I/R injury appears to be reduced in terms of biochemical indices, most trials, particularly in the clinical situation, have failed to show any reduction in morbidity and mortality. As a result, the positive impacts on biochemical indicators must be translated into better clinical outcomes and validated in larger human investigations. More criteria, such as the patients' age, the pathology of the liver, the duration of ischemia, and the amount of the surviving liver, must also be investigated. On the following points, pharmacological preconditioning research and application still need to be improved: (1) The medication pretreatment study is currently in the early stages of development. (2) Based on the mechanism of action and pharmacokinetic characteristics of different drugs, what method and when to administer the medication during the perioperative period of liver surgery can exert the best protective effect of the drug is still being explored in the clinical application; (3) Whether pretreatment drugs with differing mechanisms of action and pharmacokinetic characteristics can exert the best protective effect of the drug is still being explored in the clinical application.

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