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Ischemia reperfusion injury and its therapy: An overview

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Abstract
Ischemia reperfusion (IR) injury is manifested in many ways from safer transient arrhythmias to fatal multiple organ dysfunction syndrome. Reperfusion injury is the damage of tissue that is caused when blood flow is restored to a region after certain period of ischemia Myocardial stunning, transplantation failure and organ dysfunction are some of its clinical outcomes. Several approaches, such as low-temperature reperfusion and ischemic preconditioning, are proven to be beneficial in animal models of IR injury. The purpose of this review article is to summarize its pathophysiology, clinical presentation as well as therapeutic strategies to limit ischemia-reperfusion injury.

Keywords: Ischemia reperfusion (IR) injury, pathophysiology, ischemic preconditioning

Introduction
Ischemia refers to lack of blood supply to a tissue/organ. Restricted blood flow to an organ deprives oxygen, resulting in tissue/organ damage. Reperfusion refers to restoration of blood supply to a previously ischemic tissue. Reperfusion injury or ischemia reperfusion (IR) injury is the damage of tissue that is caused when blood flow is restored to a region after certain period of ischemia. Ischemic period creates a situation that produces further tissue damage on reperfusion instead of regaining normalcy. Tissue damage is mainly attributed to oxidative damage as well as inflammatory process [1]. This condition is mostly seen in cases of organ transplantation, stroke, coronary angioplasty, thrombolytic therapy, cardiopulmonary bypass and hypovolemic shock leading to either local or systemic inflammatory responses [2]. However, it may even result in multiple organ damage. IR injury may also affect remote non ischemic organs at times.

Pathophysiology of IR Injury
Ischemic events decreases cellular oxidative phosphorylation and the ATP production goes down. This in turn alters membrane ATP-dependent ionic pump function resulting in the entry of water, sodium and calcium into the cell. Under physiologic conditions, hypoxanthine is converted to xanthine by the enzyme xanthine dehydrogenase [3]. During ischemia, xanthine dehydrogenase undergoes a conformational change to xanthine oxidase and intracellular accumulation of hypoxanthine occurs. Xanthine oxidase converts hypoxanthine into toxic reactive oxygen species (ROS) upon reperfusion.
Reduction of ATP causes impairment in mitochondrial function and there occurs translocation of bax, apoptotic bcl2 family member protein, from the cytosol to the outer mitochondrial membrane. This results in swelling of mitochondria leading to the outflow of cytochrome c which activates cytochrome c effector caspases and apoptosis commences.
A pro inflammatory state is induced during ischemic period posing risk upon further reperfusion. Ischemia contributes to increased expression of proinflammatory gene products including leukocye adhesion molecules, cytokines, endothelin, thromoxane A_2 etc.Reactive oxygen species produced from hypoxanthine directly impairs cellular membranes by lipid peroxidation as well as stimulate leukocyte activation, chemotaxis and adherence to endothelium [4].
IR produces activation of complement especially anaphylatoxins, C3a and C5a, and complement components, iC3b and C5b-9. C5a induces production of the cytokines monocyte chemo attractant protein 1, tumor necrosis factor a, interleukin-1, and interleukin-6. C5b-9 activate endothelial nuclear factor-kB to increase leukocyte adhesion molecule transcription and expression.

C5b-9 also promotes leukocyte activation and chemotaxis by inducing endothelial interleukin-8 and monocyte chemoattractant protein 1 secretion. Thus, complement reduce blood flow to an organ during ischemia by changing vascular balance and enhancing leukocyte endothelial adherence [5].

Leukocytes interact with the vascular endothelium and it is instigated by increased endothelial P-selectin surface expression induced by IR, which interacts with P-selectin glycoprotein 1 of leukocyte. interaction of leukocyte b2 integrins, such as CD11a/CD18 or Mac-1 with endothelial intercellular adhesion molecule 1 results in leukocyte adherence. Leukocyte transmigration into the interstitial compartment is facilitated by platelet–endothelial cell adhesion molecule 1, which is constitutively expressed along endothelial cell junctions. Activated leukocytes release toxic ROS, proteases and elastases, resulting in increased microvascular permeability, edema, thrombosis and parenchymal cell death.

Recently Zhiqiang Ye *et al.* [6] reported that some circular RNAs were differentially expressed in liver IR mouse models and they play roles in biological process, cellular component, and molecular function. It has also been hypothesized that by causing leukocytosis, subsequent microvascular occlusion, increased vascular endothelial growth factor (VEGF), and inflammation contribute to the development of vascular abnormalities resulting in retinal ischemia, which becomes the initiating event in neurodegeneration and neovascularization [7].

Clinical presentations of Ischemia – Reperfusion Injury

IR injury is manifested in many ways from much safer transient arrythemias to fatal multi organ dysfunction syndrome. Usually, even after successful removal of occlusion of a blood vessel, the blood flow is restored partially. This process is termed as “no reflow” phenomenon triggered by multiple etiologies like increased leukocyte endothelial cell adhesion, platelet–leukocyte aggregation, and decreased vasodilation. Myocardial stunning, transplantation failure and organ dysfunction are some of its clinical outcomes.

Liver IR injury sometimes occurs in liver transplantation, complex liver resection, hemorrhagic shock, and severe liver trauma surgery due to long ischemic time or other reasons. IR injury often leads to liver congestion, progressive thrombosis, and necrosis of organs, resulting in the failure of operation [8-9].

Therapeutic Strategies to limit IR Injury

Several approaches, such as low-temperature reperfusion and ischemic preconditioning, are proven to be beneficial in animal models of IR injury. But, these techniques are hard and strenous to conduct in clinical surgeries. Preconditioning with erythropoietin protects against subsequent IR injury in rat kidney [10].

Ischemic Preconditioning

Ischemic preconditioning is the process of exposing tissues to brief periods of ischemia to ensure protection from prolonged duration of ischemia [11]. Possible mechanisms responsible for the protective actions might owe to activation of protein kinase C from the stimulation of phospholipase C or D. This resuts in protein kinase C–dependent phosphorylation of ATP-sensitive potassium channels and thus, cellular energy stores gets elevated.

Antioxidant Therapy: Includes the use of superoxide dismutase, catalase, mannitol, allopurinol, vitamin E, *N*-acetylcysteine, iron chelating compounds, angiotensin-converting enzyme inhibitors, or calcium channel antagonists.

Anticomplement Therapy

This is achieved by complement inhibition, complement depletion, or in complement-deficient animals.

Antileukocyte Therapy

This is mainly focussed on inhibition of inflammatory mediator release or receptor engagement, leukocyte adhesion molecule synthesis, or leukocyte–endothelial adhesion to inhibit leukocyte adhesion molecule synthesis [4]. Transcription factors regulating leukocyte adhesion molecule synthesis, such as nuclear factor-kB are targets for many of the commonly used antiinflammatory drugs, including glucocorticoids, aspirin, salicylates, gold salts, and D-penicillamine. Antisense oligodeoxynucleotides and transcription factor decoys also used to inhibit leukocyte adhesion molecule and cytokine expression.

Montelukast, a strong and specific LTD4 receptor antagonist, when used against skeletal muscle reperfusion injury was found to have prevented cell damage at a significant level in the histological and biochemical examinations, suppressed the formation of malonaldehydes, and increased the antioxidant capacity [12].

Anti-VEGF therapies when started before any significant vascular pathology, might be beneficial to reducing the neuronal damage in ischemic diseases, such as diabetic retinopathy [13].

Novel therapeutic targets

PPARγ

PPARγ is expressed greatly in liver and plays an important role in liver IR injury protection. PPARγ activity is upregulated in liver IR injury. Studies in mouse revealed that PPARγ expression is increased after an IR injury episode providing protection to hepatocytes against apoptosis [14]. FAM3A belonging FAM3 gene family [15], a target gene for PPARγ owing for its protection in Liver IR injury. FAM3A is found to enhance ATP synthesis and the released ATP activate P2 receptors to elevate the amount of cytosolic free calcium and activate calmodulin, resulting in the activation of the PI3K-Akt signaling pathway in hepatocytes. In particular, oral administration of PPARγ agonists before liver surgery or transplantation to activate hepatic *FAM3A* pathways significant potential for lessening human liver IR injury [16].

miRNAs

They are short length non coding RNAs having 19-24 nucleotides. miR-122 is abundantly expressed in hepatocytes was found to involve in liver IR injury. Inhibiting hepatic miR-122 expression is one potential method for ameliorating liver IR injury.

SIRT1 and other targets

The activation of SIRT1 take part in important metabolic as well as physiologic actions like stress resistance, metabolism, apoptosis and energy balance in heart ischemia injury and cardiometabolic disease [17]. SIRT1 activats FoxO1, PGC1α and HIF2α or inhibits NF-κB transcription factors, thereby effective against oxidative stress associated with IR injury.

Recently, hydrogen and carbon monoxide gases were both

reported to reduce reactive oxygen species and attenuate IR injury. The effect was mainly due to increased expression of inflammatory cytokines such as tumor necrosis factor-α, interleukin-6, intracellular adhesion molecule-1, nuclear factor-κB etc. that were attenuated by the dual treatment [18].

Conclusions

IR injury arises when the blood supply to tissue is cut off. Lack of oxygen leads to accumulation of metabolic intermediates. With the start of reperfusion these reactions proceed with a sudden elevation in oxygen radicals. The incidence of IR injury is seen during mainly organ transplantation, coronary angioplasty, thrombolytic therapy, etc. leading to either local or systemic inflammatory responses. Though low-temperature reperfusion and ischemic preconditioning, are proven to be beneficial in animal models of IR injury, but are hard to be performed in clinical surgeries. Many novel available therapuetic targets to combat IR injury has to be investigated further for their successful outcome clinically.

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