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SIGNALING MECHANISMS OF ISCHEMIA-REPERFUSION INJURY: AN OVERVIEW

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ABSTRACT

Myocardial ischemia is a condition in which heart tissue receives inadequate blood flow, followed by inadequate oxygen and nutrient supply. However, reperfusion of the previously ischemic myocardium is often followed by detrimental changes in myocardial tissues, known as ischemia-reperfusion injury. The cellular effect of ischemia, reactive oxygen species, janus kinase/signal transducer and activator of transduction, mitochondrial permeability transition pore, ATP and inflammatory cascade involves in pathophysiology of ischemia reperfusion injury. In this review, we discussed the basic signalling mechanisms involved in ischemia-reperfusion injury.

KEYWORDS: Reperfusion, JAK-STAT, ATP, MPTP.

INTRODUCTION

Myocardial ischemia develops when coronary blood supply to myocardium is reduced, either in terms of absolute flow rate or relative to increased tissue demand. A pivotal feature of ischemia is that oxygen supply to the mitochondria is inadequate to support oxidative phosphorylation.[1,2,3,4,5,6,7] Myocardial ischemia and reperfusion leads to "ischemia/reperfusion injury" characterized by the development of contractile dysfunction, arrhythmias, and tissue necrosis (infarction). The re-flow of blood to ischemic myocardial tissue triggers necrosis and apoptosis in the myocytes.[8,9,10,11] Myocardial ischemia reperfusion injury occurs during the invasive treatments such as, thrombolysis[12,13,14], angioplasty [15,16], coronary by-pass surgery[8,17] and heart transplantation.[18,19] The apoptotic process is initiated after the onset of ischemia, and enhanced during reperfusion. Therefore it is thought that inhibition of apoptosis can attenuate the IR injury.[20,21] The pathogenesis of IR

such as high oxidative stress, Ca^{2+} overloading, loss of membrane phospholipids, neutrophil mediated endothelial dysfunction, progressive decrease in microvascular flow and depletion of the high energy phosphate store.[22,23] Oxidative stress is mostly related to the increased formation of reactive oxygen species (ROS), leads to lipid peroxidation. These changes are considered to the change membrane permeability and configuration in addition to producing functional modification of various cellular proteins.[24] Oxidative stress can cause to some cellular defects such as decreasing of the sarcolemmal Ca^{2+} ATP-ase pump and Na+-K+ ATP-ase activities. These alterations lead to a decrease in the Ca^{2+} effluxes and an increase in the Ca^{2+} influxes, respectively.[25,26,27,28,29] Oxidative stress has also been reported to suppress the sarcoplasmic reticulum Ca^{2+} ATP-ase pump and thus inhibits Ca^{2+} sequestration from the cytoplasm in cardiomyocytes results in intracellular Ca^{2+} overload and cell death.[30] It has been noted that activation of polymorphonuclear neutrophils (PMN) leads to coronary endothelium injury.[31] PMN accumulation in the extravascular compartment is also facilitated by interleukin 8 (IL-8) released from hypoxic tissues, resulting in a chemotactic gradient that directs neutrophils from the intravascular space towards the hypoxic interstitium.[32] The present review has discussed basic mechanisms involved in the pathophysiology of ischemia reperfusion injury in myocardial dysfunction followed by cell death.

MECHANISMS OF ISCHEMIA-REPERFUSION INJURY

Ischemia leads to reversible damage and irreversible damage. Its duration of time can give the idea of this type of damage. If its duration is less than 40 min, cellular and functional alterations are reversible and can be treated. If it is between 40-50 min, there is a certain progressive functional loss and irreversible damage, if it is more than 50 min, some events occur, which resembles re-oxygenation or reperfusion injury. The early reperfusion is an undoubted precondition for the survival of ischemic myocardium. However, reperfusion is a road map for cellular injury. The various signalling mechanisms of myocardial ischemia-reperfusion injury (I/R) are.

Free Oxygen Radicals

The adenine nucleotide catabolism during ischemia leads to intracellular accumulation of hypoxanthine, which subsequently generates reactive oxygen species (ROS) upon reperfusion (Fig. 1). During ischemia, cellular ATP is degraded to form hypoxanthine. Under normal condition, hypoxanthine is oxidized by xanthine dehydrogenase to xanthine, but during

ischemia, xanthine dehydrogenase is converted to xanthine oxidase. Unlike xanthine dehydrogenase, which uses nicotinamide adenine dinucleotide as its substrate, xanthine oxidase uses oxygen and therefore, during ischemia, is unable to catalyze the conversion of hypoxanthine to xanthine, resulting in a buildup of excess tissue levels of hypoxanthine. When oxygen is reintroduced during reperfusion, conversion of the excess hypoxanthine by xanthine oxidase results in the formation of ROS[33,34], including superoxide anions (O^{2-}) hydroxyl radicals (OH-), hypochlorous acid (HOCl), hydrogen peroxide (H_2O_2), and peroxynitrite. ROS directly damage cellular membranes through lipid peroxidation. Further, ROS stimulate leukocyte activation and chemotaxis by activating plasma membrane phospholipase A_2 to form arachidonic acid, an important precursor for synthesis of eicosanoids such as thromboxane A_2 and leukotriene B_4. Moreover, ROS stimulate leukocyte adhesion molecule and cytokine gene expression *via* activation of transcription factors such as nuclear factor-kB (NF-kB) lead to myocardial damages.[35,36,37,38] (Fig.3)

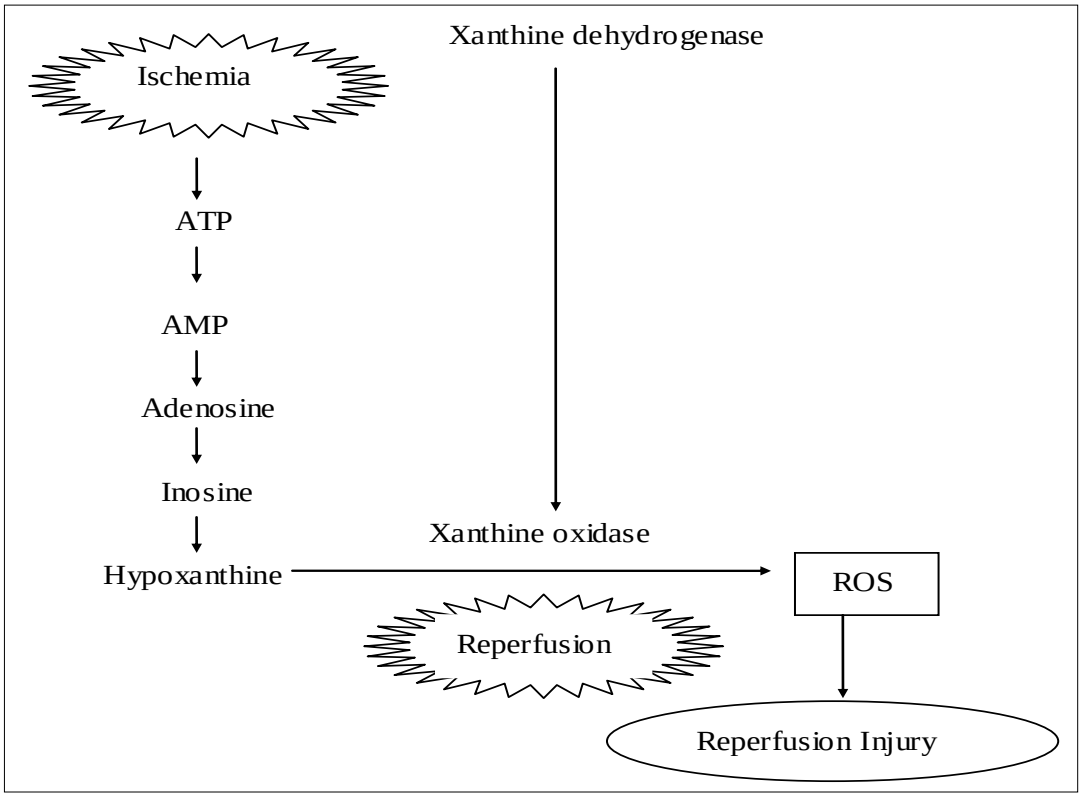

Fig. 1: Formation of ROS in ischemia-reperfusion injury

ATP- adenosine triphosphate, AMP- adenosine monophosphate ROS- reactive oxygen species

Neutrophil Activation in the Reperfusion Injury

Cardiac ischemia-reperfusion injury triggers an acute inflammatory response in which neutrophils via chemotactic attraction infiltrate the myocardium and worsen the condition of the already injured tissue. Endothelial cells, in response to specific stimuli like ROS release chemo-attractants. These includes leukotriene B4, monocyte chemo-attractants protein (MCP), adhesion molecules such as intercellular adhesion molecule 1 (ICAM 1), vascular cell adhesion molecules (VCAM) and selectins, leading to neutrophil attraction, sequestration and adhesion to the microvasculature.[39,40,41] Accumulation and sequestration of neutrophils in the coronary microcirculation can lead to the occlusion of the microvasculature and thereby interferes with blood flow in the reperfused region ultimately lead to myocardial injury (Fig. 3).[42]

Contractile dysfunction and reperfusion arrhythmias

The deleterious effects of ischemia-reperfusion injury are reversible contractile dysfunction known as myocardial stunning and impairment of blood flow at microvascular level. Myocardial stunning is the contractile dysfunction of heart that persists after reperfusion despite the absence of irreversible damage and despite restoration of normal or nearly normal coronary flow.[43,44] Reperfusion arrhythmias may be a cause of sudden death after relief of coronary ischemia and are frequent in patients undergoing thrombolytic therapy.[45] It has been noted that reperfusion of the myocardium ischemia lead to ventricular tachycardia in rats[46] (Fig.3).

ATP involvement in Energy depletion

Energy depletion is other harmful consequences of ischemia as a result of defective synthesis of adenosine triphosphate (ATP) and degradation of energy rich phosphates, that is, ATP via adenosine diphosphate (ADP) and adenosine monophosphate (AMP) to adenosine and finally hypoxanthine. Normally, hypoxanthine is converted to xanthine by the enzyme xanthine dehydrogenase in the presence of nicotinamide adenine dinucleotide (NAD). However, under ischemic conditions, xanthine dehydrogenase undergoes a conformational change to xanthine oxidase which is capable of producing highly ROS (Fig. 1). This conformational change is also promoted by increased intracellular calcium (Ca^{2+}) leads to myocardial cellular injury[47,48,49,50,51,52] (Fig. 1, 3).

Cellular acidosis, calcium overload and MPTP opening

During ischemia, the reduced O_2 supply causes an increase in the rate of glycolysis, generating H+ and lactate and decreasing intracellular pH. The Na^+/H^+ exchanger overloads the cytosol with Na^+ as the excess H^+ are extruded, causing the reversal of the Na^+/Ca^{2+} exchanger, which extrudes excess Na^+, but overloads the cytosol with Ca^{2+}. The depletion of ATP during ischemia prevents the activity of pumps such as the Na^+/K^+ ATPase, as well as active Ca^{2+} excretion which prevents the re-establishment of normal cellular ionic homeostasis.[53] Furthermore, there is an increase in ROS production if the first minute of reperfusion is very high as O_2 is re-introduced into damaged mitochondria. Mitochondrial Ca^{2+} overload and increased ROS can result in opening of the mitochondrial permeability transition pore (MPTP) and initiates the translocation of BAX (apoptosis regulator also known as Bcl-2 like protein), from the cytosol to the outer mitochondrial membrane which leads to myocardial damages. This causes mitochondrial swelling and induces the efflux of cytochrome C and other pro-apoptotic factor via opening of the permeability transition pore into the cytosol where cytochrome C activates effector caspases and initiates apoptosis[54,55] (Fig. 3).

Activation of compliment system

Ischemic-reperfusion results in local activation of compliment system and leads to production of compliment factors C3a, C5a, and membrane attack complex (MAC). C5a exerts numerous pro-inflammatory effects such as chemotaxis of neutrophils, release of proteases, production of oxygen radicals which may further amplify the inflammatory response by initiating production of TNF, IL-1, and IL-6 and monocyte chemo-attractants protein. Moreover C_5b-9 isoform of compliment factors playing a major role in IR mediated myocardial tissue injury.[39,42]

Leukocyte activation

We have found from the previous study that ischemia followed by reperfusion induced ROS and further ROS stimulate leukocyte activation and chemotaxis by activating synthesis of eicosanoids such as thromboxane A2 and leukotriene B4.[48] ROS also stimulates leukocyte adhesion molecule and cytokine gene expression via activation of transcription factors such as nuclear factor kB (NF kB).[56] Leukocyte activation release proteases and elastases, which result in increased microvascular permeability, edema, thrombosis, and myocardial cell death[57] (Fig. 3).

Adenosine monophosphate (AMP)-activated protein kinase

Many studies have demonstrated that myocardial ischemia triggers activation of AMP protein kinase pathway by generation of ROS.[58,59] AMP protein kinase is a serine/threonine kinase which is composed of α catalytic, β and γ regulatory subunits as a heterotrimeric protein.[60] As an energy sensor, AMP protein kinase is activated by a depletion of ATP which induces the activation of catabolic mechanism and phosphorylates anabolic enzymes to inhibit their synthesis for maintaining the ongoing intracellular oxygen and nutrients homeostasis (Fig. 1).

JAK-STAT

The janus kinase/signal transducer and activator of transduction (JAK/STAT) pathway is a newly discovered intracellular signal-transducing pathway that is activated by oxygen radicals, various cytokines, and growth factors in ischemic heart diseases. Recent studies have demonstrated that myocardial ischemic injury induced rapid activation of this pathway.[61] The JAK/STAT pathway is now recognized as an important membrane-to-nucleus signalling pathway, originally identified as a major signal transduction pathway of the cytokine superfamily is known to be activated by several hypertrophic agonists.[62,63,64] In response to ischemic stress, phosphorylation of JAK occurs followed by tyrosine phosphorylation and dimerization of cytosolic STAT monomers. The STAT dimers readily translocate to the nucleus, bind to the promoter regions of the DNA and regulate transcription of genes.[64,65] It has been noted that the activation of JAK-STAT pathway is involved in the IR injury[63] (Fig. 2)

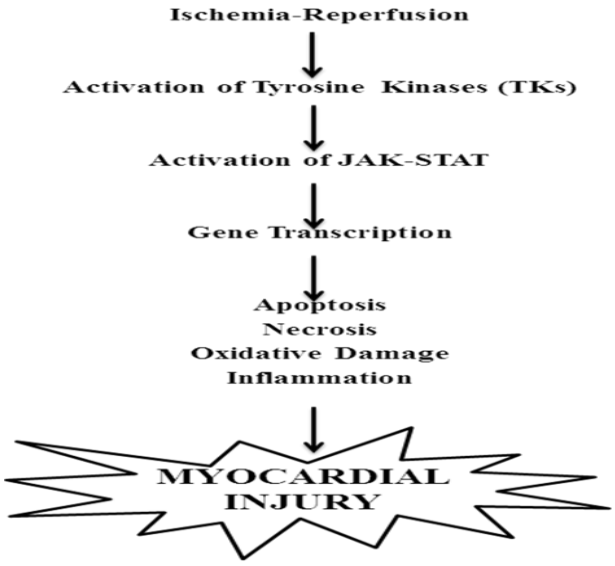

Fig. 2: Diagrammatically representation of JAK-STAT in ischemic-reperfusion injury

JAK-STAT indicates Janus Kinase/Signal Transducer and Activator of Transduction

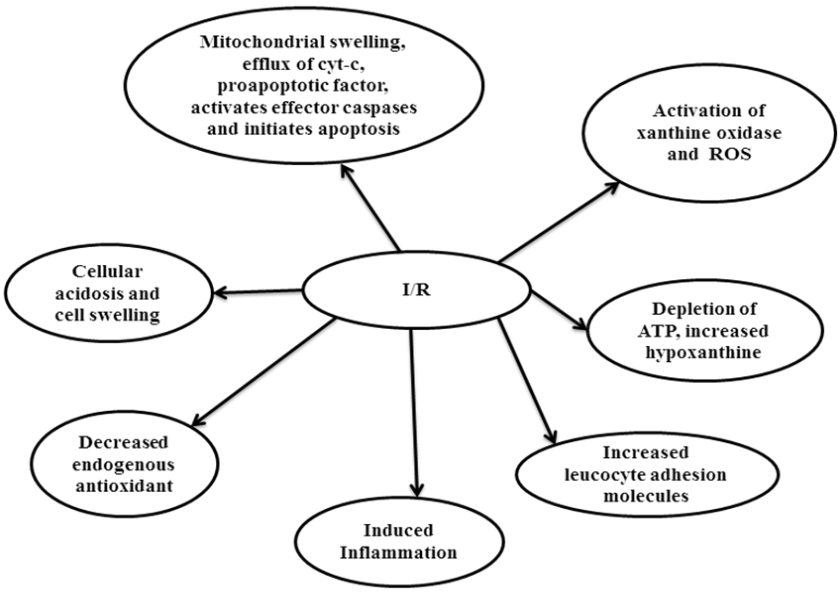

Fig. 3: Schematic diagrammatic representation of the pathophysiology of Ischemia-Reperfusion (I/R) injury.

CONCLUSION

Ischemia/Reperfusion injury produced due to local and systemic inflammatory response characterized by oxidant production, complement activation, leukocyte–endothelial cell adhesion, transendothelial leukocyte migration, platelet/leukocyte aggregation, increased microvascular permeability, decreased endothelium-dependent relaxation and depletion of ATP. It is noted that occurrence of I/R myocardial injury during the surgery clinically results multiple organ dysfunction and cardiovascular complications due to high oxidative stress. Our review is in-lighting the basic pathophysiology and mechanisms of I/R injury. In addition, studies are obligatory to recognize the major signaling mechanisms involved in I/R injury, which may open a novel vista to use pharmacological interventions to limit lethal reperfusion injury during cardiac surgery. On the basis of this review, it may be concluded that I/R-injury may formulate the heart susceptible to increased infarct size and enhanced oxidative stress.

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