



Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj



Review Article

Role of cardiac renin angiotensin system in ischemia reperfusion injury and preconditioning of heart

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ARTICLE INFO

Article history:

Received 19 April 2016
Accepted 21 June 2016
Available online xxx

Keywords:

Myocardial ischemia–reperfusion injury
Ischemia preconditioning
ACE inhibitor
ACE2 activator
Angiotensin II antagonist

ABSTRACT

Ischemic heart disease (IHD) is the second leading cause of morbidity and mortality. According to American Heart Association, cardiovascular disease (CVD) is the leading cause of acute myocardial infarction, congestive heart failure, cardiac arrest and arrhythmias. Ischemia is a state of oxygen deprivation in tissues, whereas reperfusion is restoration of blood flow in ischemic tissues. Myocardial damage of tissue during reperfusion after ischemia insult is known as myocardial ischemia–reperfusion (I/R) injury. It induces damage to cardiac muscle via increasing an excessive expression of oxygen, sodium and calcium ions which are responsible for the activation of proteases and cell death. Heart renin angiotensin system (RAS) plays an important role in the myocardial ischemia and reperfusion injury. Angiotensin (1–7) is responsible for vasodilation and angiotensin II for vasoconstriction. Therefore, in this article we reviewed that myocardial I/R injury get upregulated by angiotensin II that leads to increased infarct size and can be reduced by the use of ACE inhibitors, ACE2 activators and angiotensin II antagonist.

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1. Introduction

Cardiovascular disease (CVD) or blood vessel disease, is the leading cause of death worldwide.¹ IHD causes damage to heart muscle via deposition of cholesterol plaques on the wall of coronary arteries and reducing the availability of nutrients like glucose.^{2,3} Ischemia is defined as an insufficient supply of the nutrient and oxygen to the cardiac muscle. During ischemia, the level of glutathione, phosphocreatine and ATP are reduced while hypoxanthine level gets elevated. Altered ion distribution, i.e. increase in intracellular Ca^{2+}/Na^{2+} , cellular swelling, cytoskeleton disorganization and acidosis of cells occur.⁴ During reperfusion injury, blood flow supply returns to the cardiac muscle that causes release and activation of intracellular Ca^{2+} channel, formation of cellular edema and damage to lipid membrane.^{5,6}

The renin–angiotensin system which is composed of renin, angiotensin converting enzyme (ACE), angiotensin I and angiotensin II, is localized in different areas of heart such as atria, conduction system, valves, coronary vessels, ventricles, fibroblasts and myocytes.^{7,8} ACE 2 system is found in venous endothelial cells,

arterial smooth muscle cells, cardiac myocytes, myofibroblasts, thoracic aorta, carotid arteries and veins.^{9–11} Myocardial angiotensin receptors were discovered in 1980s. These receptors are the supporter of local renin angiotensin system and intracardiac renin angiotensin system. They play a very crucial role in cardioprotection. Major effector peptide in renin angiotensin system is angiotensin II (vasoconstrictor), whose excess production increase the blood pressure and leads to the damage of various organs like brain, kidney and blood vessels.¹² Angiotensin II antagonist and angiotensin converting enzyme inhibitors (captopril and enalapril) have cardioprotective effect by reducing the blood pressure and infarct size.^{13,14}

Cardiac angiotensinogen are glycoprotein of α_2 -globulin class, synthesized in the cardiac muscle. Gene expression of angiotensinogen has been found in the mice and rats. Lower concentration of angiotensinogen is found in the ventricles as compared to heart atria. It has been reported that cardiac angiotensinogen mRNA level in rat and mice liver is approximately 5% and 1%. Glucocorticoid hormone treatment increases the production of hepatic angiotensinogen in the rat heart. Dzau in 1987 observed that dietary sodium raises the level of mRNA angiotensinogen in rat tissue, which could be suppressed after ACE inhibitor treatment.^{15–17}

Cardiac renin is a proteolytic enzyme which was discovered in 1898, by Robert Tigerstedt in Sweden. It has been documented that

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<http://dx.doi.org/10.1016/j.ihj.2016.06.010>

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there is an increased gene expression of renin in both mice and rat heart. An estimated 2% mRNA level is found in rat kidney and the submaxillary gland of mice.^{18–20}

Cardiac angiotensins are hormonal peptides, formed by the proteolytic reaction of angiotensinogen and renin. Angiotensins are of two types, angiotensin I and angiotensin II. Angiotensin I have no biological role on heart renin angiotensin system. They are precursor of angiotensin II and angiotensin III.^{21,22} Angiotensin II is an effector hormone which plays a major role in heart renin angiotensin system. It leads to hypertension by increasing vasoconstriction and retention of fluid and sodium in the body.²³ Angiotensin II is also responsible for stimulation of inflammatory mediators such as NAD(P)H oxidase, phospholipase A₂ and JAK/STAT pathway. De Leeuw in 1999 reported that angiotensin converting enzymes treatment decreases angiotensin II level.^{24,25}

Cardiac angiotensin converting enzymes (ACE) are metallopeptides which are commonly distributed on epithelial and endothelial cells surface. ACE inhibitors have been reported to exhibit protective effect on cardiovascular disease.²⁶ They are involved in the treatment for hypertension, myocardial infarction and congestive heart failure (CHF) as they inhibit angiotensin II formation.²⁷ Angiotensin converting enzyme 2 (ACE2) is an exopeptidase with zinc membrane which help in the conversion of angiotensin I and angiotensin II to angiotensin 1–9 and angiotensin 1–7. Angiotensin 1–7 is a vasodilator that further converts into angiotensin 1–5 via ACE.^{28–30}

2. Myocardial ischemia/reperfusion injury

Myocardial ischemia/reperfusion injury was first discovered by Jennings et al. in 1960. It develops when coronary blood supply to myocardium is reduced. Restoration of blood flow to ischemic heart is necessary for maintaining heart physiology.^{31,32} The non-lethal episodes of ischemia and reperfusion prior to global myocardial ischemic insult have proved to reduce myocardial injury, which is termed as preconditioning. Reperfusion can elicit a cascade of adverse events that paradoxically causes injury of tissue.³³ During reperfusion after ischemic stress, hypoxanthine is oxidized by xanthine oxidase which produces reactive oxygen species (ROS).³⁴ Ischemia followed by reperfusion is a stronger cause of apoptosis than sustained ischemic insult. Ischemia due to an anaerobic metabolism causes catabolism of adenine nucleotide and leads to depletion of adenosine triphosphate (ATP).³⁵ At the time of reperfusion, xanthine oxidase metabolizes the hypoxanthine to xanthine and forms uric acid that leads to the formation of huge amount of reactive oxygen species, i.e. superoxide anion (O²⁻), hydrogen peroxide (H₂O₂) and hydrogen radical (OH⁻).³⁶

Myocardial IR injury usually causes inflammation on the cardiac muscle and leads to hypoxia. This phenomena damages tissues by activating leukocytes, cytokines, reactive oxygen species and frequently develops during heart transplantation, infarction and sepsis.^{37,38}

3. Purpose of inflammatory cascade in myocardial ischemia/reperfusion (I–R) injury

Ischemia is defined as an insufficient supply of the nutrient and oxygen to the cardiac muscle. During ischemia, the level of glutathione, phosphocreatine and adenosine triphosphate (ATP) are reduced and hypoxanthine level gets elevated. Altered ion distribution, i.e. increase in intracellular Ca²⁺/Na²⁺, cellular swelling, cytoskeleton disorganization and acidosis of cells occur³⁹ (Fig. 1).

Myocardial ischemia injury leads to the inhibition of oxidative phosphorylation that decreases the level of adenosine diphosphate (ADP) and elevates adenosine monophosphate (AMP). AMP further forms adenosine that gets converted into inosine and hypoxanthine.^{40,41} Further hypoxanthine forms xanthine via xanthine dehydrogenase and accounts for the activation of reactive oxygen species (ROS).³⁴ Inhibition of Na⁺/K⁺ ATPase and formation of ionic homeostasis (increases of Na⁺ and Ca⁺ ions) activates protease, i.e. calpains and phospholipases which are responsible for direct apoptosis cell death.^{42,41} It also release cytokine C in the cytoplasm then activates effectors caspases and ruptures sarcolemmal membrane⁴³ (Fig. 2).

During reperfusion injury, re-energization of mitochondria generate reactive oxygen species.^{44,45} It is documented that cell membrane damage during reperfusion is caused due to peroxidation of lipid and oxidizing agents such as peroxynitrite and hydroxyl radical.^{44,46} Both reactive oxygen species and restored pH are responsible for the opening of mPTP during reperfusion injury. Activation of mPTP accelerates the release of cyt C and caspases to the ruptured sarcolemmal membrane that further leads to apoptosis cell death⁴⁷ (Fig. 3). During reperfusion followed after ischemia, blood supply results in anaerobic metabolism, cardiac muscles rupture, cytokines damage, micro-circulation clots and accumulation of free radical in myocardium⁴⁸ (Fig. 4).

4. Role of heart RAS in I/R injury and ischemic preconditioning (IPC)

Renin angiotensin system (RAS) plays an important role in myocardial ischemic and reperfusion injury (I/R). Cardiac RAS system consist of angiotensinogen, Ang I, Ang II, ACE, ACE 2,

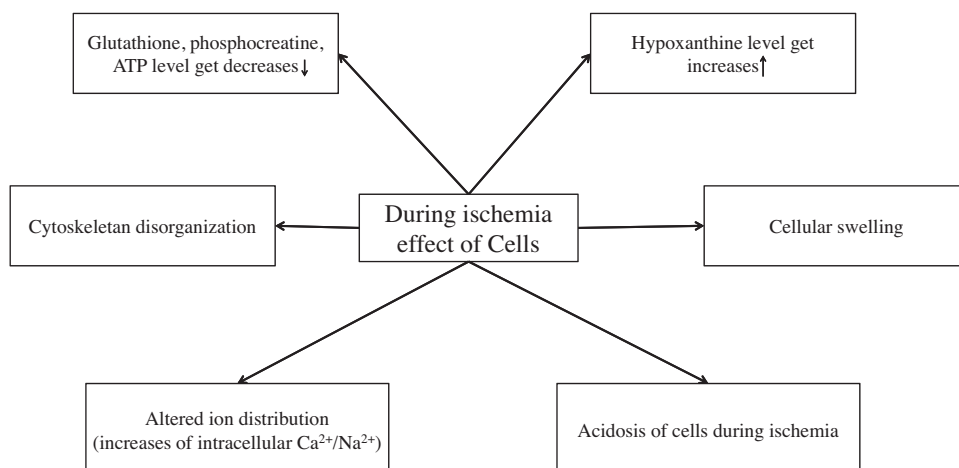


Fig. 1. Cellular myocardial ischemia injury.

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