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Mini-review

Cellular mechanisms against ischemia–reperfusion injury induced by the use of anesthetic pharmacological agents

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ABSTRACT

Ischemia–reperfusion (IR) cycle in the myocardium is associated with activation of an injurious cascade, thus leading to new myocardial challenges, which account for up to 50% of infarct size. Some evidence implicates reactive oxygen species (ROS) as a probable cause of myocardial injury in prooxidant clinical settings. Damage occurs during both ischemia and post-ischemic reperfusion in animal and human models. The mechanisms that contribute to this damage include the increase in cellular calcium (Ca^{2+}) concentration and induction of ROS sources during reperfusion. Pharmacological preconditioning, which includes pharmacological strategies that counteract the ROS burst and Ca^{2+} overload followed to IR cycle in the myocardium, could be effective in limiting injury. Currently widespread evidence supports the use of anesthetics agents as an important cardioprotective strategy that act at various levels such as metabotropic receptors, ion channels or mitochondrial level. Their administration before a prolonged ischemic episode is known as anesthetic preconditioning, whereas when given at the very onset of reperfusion, is termed anesthetic postconditioning. Both types of anesthetic conditioning reduce, albeit not to the same degree, the extent of myocardial injury. This review focuses on cellular and pathophysiological concepts on the myocardial damage induced by IR and how anesthetic pharmacological agents commonly used could attenuate the functional and structural effects induced by oxidative stress in cardiac tissue.

Contents

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1. Introduction

There are common clinical situations in which ischemia (lack of or decreased organ blood flow and O_2 supply) occurs. Cell injury can be induced not only during the ischemic period; it may also be accentuated during the reperfusion process (ischemia–reperfusion injury, IR) [1]. Currently, mechanisms of IR have attracted great interest and are included in the pathophysiology of several clinical conditions such as myocardial infarction, stroke, major trauma, surgery, organ transplant and shock due to different sources [1,2]. Several mechanisms have been proposed as mediators of the damage induced by IR, such as complement system and leukocyte activation, increased free radical concentration, the reduction of oxidative phosphorylation, endothelial dysfunction and the activation of pathways of apoptosis, necrosis and/or autophagy [3,4]. The study of the pathophysiological mechanisms of IR has allowed the development of different experimental strategies that can lead to a reduction in organ damage due to the IR cycle and explore potential therapeutic targets.

This review includes the pathophysiological events that explain the cellular mechanisms induced by IR injury and describes the evidence regarding the protective role that several drugs commonly used in anesthesia perform against this injury.

2. Role of oxidative stress in ischemia–reperfusion injury

Oxidative stress is defined as an imbalance between the generation of reactive oxygen species (ROS) and the antioxidant defense systems with the potential generation of cellular damage [5]. Reactive oxygen species concentration may increase due to a decrease in the antioxidant enzymes activities or by the depletion of antioxidants [6]. In cell metabolism, oxygen can form reactive intermediates such as superoxide, hydrogen peroxide and the hydroxyl radical before it is reduced to water. In turn, the reactive nitrogen species include mainly nitric oxide, peroxynitrite and nitrogen dioxide, formed during the homolytic decomposition of peroxynitrous acid [7].

Oxidative stress occurrence has been extensively investigated in ischemic and reperfusion (IR) injury of the myocardium [8,9]. Cellular effects of ROS are partially mediated by the activation of pro-oxidant and pro-inflammatory pathways in the myocardium, such as nuclear factor (NF)-kappaB, AMPK and STAT-3 [10]. Nuclear factor-κB exists mainly in the cytosol as a preformed trimeric complex consisting of the inhibitor protein IκB and p50/p65 dimer protein. Reactive oxygen species induce redox changes that result in the phosphorylation of the β-subunit of IκB, thereby activating their proteolytic digestion. Thus, p50/p65 subunits can translocate to the nucleus binding to DNA, and initiate the transcriptional process. These super families of transcription factors have been implicated in the regulation of immune cell maturation, cell survival, and inflammation in many cell types, including cardiac myocytes [11]. NF-κB regulates the expression of cardiac genes downstream that program multiple cascades of signal transduction in a variety of physiological and pathophysiological states, such as apoptosis, cell survival, cell growth, cell division, innate immunity, cell differentiation, and cell stress responses (hypoxia, ischemia and stretch). This evidence supports the concept that NF-κB may be an important therapeutic target for cardiovascular diseases [12].

The pathophysiology of cardiovascular IR injury includes a pro-oxidant imbalance that does not counteract with the antioxidant defense mechanisms available. This high ROS concentration can lead to cellular damage through various mechanisms including the direct damage to biomolecules (e.g. lipids, proteins and DNA) or indirect damage through the activation of pro-apoptotic pathways. Specifically, ROS liberated during I/R promotes membrane damage through lipid peroxidation. Some of the most highly reactive aldehydes produced endogenously are 4-hydroxy-2-nonenal (4-HNE), malondialdehyde, acrolein, crotonaldehyde and methylglyoxal. Aldehydes are well-studied products of lipid peroxidation, with the α,β-unsaturated being the most cytotoxic by reacting with phospholipids, proteins and DNA. However, their effects are not only toxic but rather homeostatic as they participate in signal transduction pathways [13]. Reactive oxygen species generated during IR react with to polyunsaturated fatty acids to form aldehydes like 4-HNE, which inactivates proteins and DNA by forming hybrid covalent chemical addition compounds called adducts. The ensuing chain reaction results in cellular dysfunction and tissue damage including a wide spectrum of events ranging from electron transport chain dysfunction to apoptosis [14]. In addition, 4-HNE directly depresses contractile function, enhances ROS formation, modulates cell signaling pathways, and can contribute to many cardiovascular diseases including myocardial IR injury and arteriosclerosis [15]. Recent studies have identified that mitochondria are both a primary source and a target of lipid peroxidation products, with specific emphasis on aldehydes in cardiomyocytes and how these affect the electron transport system and Ca^{2+} balance [16]. These effects occur through a variety of mechanisms, including cross-linking of the lipid tails, which limits phospholipid mobility in the bilayer. Of singular importance, the inner mitochondrial membrane contains cardiolipin, a highly unsaturated phospholipid specifically localized to this compartment, which is particularly prone to peroxidation. The presence of cardiolipin in the inner membrane ensures the efficient function of mitochondrial components such as the electron transport chain complexes and adenine nucleotide transporter among others [17]. Acrolein, the simplest unsaturated aldehyde, has also recently been identified as a product of lipid peroxidation formed in response to increased oxidative stress [18]. Acrolein binds to cysteine and lysine residues on proteins and has been suggested to be a mediator of oxidative damage in a variety of human diseases. Despite the well-known reactivity of unsaturated aldehydes, their effects on cardiac function were only recently described. Several reports show that acrolein induces cardiac dysfunction and selective myofilament impairment, in addition to modifying proteins involved in energy metabolism, which possibly affects their function [19,20].

Althoug these observations do not constitute direct evidence that lipid peroxidation products are involved in the pathogenesis of these diseases, they do suggest clinical scenarios by which these

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