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Review Article

Cytoprotective role of heme oxygenase-1 in liver ischemia reperfusion injury

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Abstract: Ischemia/reperfusion (I/R) injury is the main cause of graft dysfunction and failure in vascular occlusion both during liver surgery and during liver transplantation. The pathophysiology of hepatic ischemia-reperfusion includes a number of mechanisms including oxidant stress that contribute to various degrees to the overall organ damage. Heme oxygenases (HO) are essential enzymes which degrade heme into biliverdin-IXalpha, free divalent iron, and carbon monoxide (CO). Due to its anti-inflammatory, anti-apoptotic and, as recently described, anti-viral properties. The inducible HO isoform HO-1 is an important molecule which could find its way into therapy of acute and chronic liver injuries including acute liver failure, alcoholic or viral hepatitis, chronic inflammation, fibrosis, cirrhosis, and hepatocellular carcinoma are life threatening diseases and as a consequence might result in the necessity of liver transplantation. Liver transplantation is limited by ischemia/reperfusion (I/R) injury, which is characterized by hypoxia and nutrient deficiency resulting in oxidative stress, apoptosis and immune activation. Induction of HO-1 and application predominantly of CO have been shown to interfere with liver I/R injury and to improve recipient and graft survival. HO-1 and its reaction products of heme degradation has been linked to cytoprotection, and as an inducible form of HO, serves a vital metabolic function as the rate-limiting step in the heme degradation pathway, and affords protection in models of liver I/R injury. HO-1 system is an important player in liver I/R injury condition, and may offer new targets for the management of this condition. This review aims to summarize cytoprotective role of heme oxygenase-1 (HO-1) and its products within the liver.

Keywords: Heme oxygenase, ischemia/reperfusion injury, oxidative stress, cytoprotection, liver

Introduction

The heme is a ubiquitous molecule containing an active iron center that carries a high affinity for molecular oxygen and can donate electrons. The high affinity for oxygen allows for reversible binding, transport, and storage of oxygen in hemoglobins and myoglobin.

Heme oxygenase (HO) is ubiquitous and essential enzymes for all eukaryotic organisms that depend on aerobic oxidation and electron transport via heme-containing proteins [1, 2]. The HO system is the rate-limiting step in the conversion of heme into biliverdin, carbon monoxide (CO) and free iron (Fe^{2+}). There are three distinct HO isoforms (HO-1, HO-2, and HO-3) identified to date, HO-1 is the inducible form of the enzyme, also known as heat shock protein (hsp) 32, constitutively expressed HO-2, and a related but less well characterized HO-3. Under physiological conditions, HO-2 is the major HO isoform found in mammalian tissues, particularly in brain and testis. In contrast, HO-1 expression is relatively low, with the exception of spleen in which its levels are constitutively high. Upregulation of HO-1 may be among of the most critical cytoprotective mechanisms that are activated during times of cellular stress, such as inflammation, ischemia, hypoxia, hyperoxia, hyperthermia or radiation [3], and is thought to play a key role in maintaining antioxidant/oxidant homeostasis during times of cellular injury [4].

HO-1 is a single transmembrane inducible protein found in endoplasmic reticulum, caveola, nuclei and mitochondria. It is ubiquitously present in mammalian tissues such as liver, spleen, pancreas, intestine, kidney, heart, retina, prostate, lung, skin, brain, spinal cord, vascular smooth muscle cells and endothelial cells. The

human HO-1 gene is located on chromosome 22q12; it is approximately 14 kb long and contains 5 exons [5]. Control of HO-1 transcription is complex and tightly regulated, with differences in expression found between tissues, as well as between species [6]. Its expression is relatively low under physiological conditions, except in the spleen where the action of HO-1 is critical to the recycling of iron from senescent erythrocytes [7]. Many studies indicated that the induction of HO-1 plays a significant protective role against inflammatory processes and oxidative tissue injury [8-10]. More recent findings have led to a re-definition of the HO pathway as not only an anti-oxidative mechanism but also a more complex and coordinated cytoprotective system [11]. This report summarizes the current understanding of the HO-1 cytoprotective functions during liver I/R injury. The implications for possible therapeutic manipulation of HO in liver I/R injury are elucidated.

Ischemia/reperfusion injury in liver

Interruption of blood supply results in ischemic injury which rapidly damages metabolically active tissues. Paradoxically, reintroduction of blood flow obtained following ischemia initiates a cascade of events that can potentially worsen the original injury. This effect is known as reperfusion injury [12]. The liver is composed of labile cells that are very susceptible to I/R injury [13]. Multiple factors have been shown to be involved in the process of liver I/R injury. The primary pathophysiological events of this injury involve microcirculatory flow disturbances caused by the production of reactive oxygen species (ROS). Tissue ischemia and oxidative stress activate families of protein kinases that converge on specific transcriptional factors that regulate the expression of inflammatory genes. The resulting gene products include enzymes [e.g. inducible nitric oxide synthase (iNOS), phospholipase A2, and cyclooxygenase-2 (COX-2)], cytokines [e.g. tumor necrosis factor α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6)], prostaglandins (e.g. PGE-2), and adhesion molecules [e.g. intracellular adhesion molecule (ICAM-1), E-selectin] [14-18]. These initiate local inflammation, which is further amplified by the recruitment of circulating leukocytes [16], which appear to be key effector cells in causing tissue injury. Furthermore, I/R injury induces widespread endothelial cell apoptosis and the loss of endothelial cells in the vessels serving the organ results in thrombosis [15, 16] directly in the liver [19]. This injury observed during I/R is believed to trigger a systemic inflammatory response leading to multiple organ failure [20, 21], which frequently involves the liver and lungs [22, 23]. Liver I/R injury is a complex, multifactorial pathophysiological process, dependent upon an understanding of which the optimal therapeutic approach is aimed at ameliorating I/R injury. Heme complexes derived from cytochrome P-450, catalase, and superoxide dismutase (SOD), could all effectively catalyze Oxygen Free Radical (OFR) formation [24]. Activation of anti-oxidant enzymes, such as catalase, SOD, and glutathione reductase are also known to decrease during IRI [25]. Clearly, by preventing heme from extracellular and intracellular sources to produce OFR, the heme degradation by HO-1 may exert an important cytoprotective effect. HO-1 system might be one of the most promising approaches among the potential therapeutic options.

Roles of HO-1 in ischemia/reperfusion injury in liver

HO-1 is a bona fide 32-kDa stress protein (Hsp32), variously manifested in endothelial, epithelial, smooth muscle and other cell types. HO-1 plays a protective role in many disease models *via* its anti-inflammatory, antiapoptotic, and anti-proliferative actions [26]. The hepatic microvasculature is a unique and well organized system of microvessels, which are composed of parenchymal hepatocytes and a variety of non-parenchymal cells, such as sinusoidal endothelial cells, Kupffer cells [27] and Ito cells. Cytochrome P450 [28] is a major contributor to production of bilirubin derived from nonhemoglobin sources in the liver [29]. HO-1 is expressed at low to undetectable levels in hepatocytes and is expressed mainly in Kupffer cells under basal conditions. However, HO-1 undergoes a rapid transcriptional activation in both Kupffer cells and hepatocytes in response to noxious stimuli [30]. A physiological role for HO-1 gene expression has also been demonstrated in HO-1 deficient mice and in one case of human genetic HO-1 deficiency. Both murine and human HO-1 deficiencies have systemic manifestations associated with iron metabolism, such as hepatic overload (with signs of a chronic hepatitis) and iron-deficiency anemia (with paradoxical increased levels of ferritin)

[31]. Determining the role that HO-1 plays in such regulatory mechanisms has become increasingly relevant in recent years because its induction has been shown to prevent ethanol-induced inflammation in the intestine [32] and liver [33], as well as in the prevention of oxidative damage to hepatocytes [34]. These results demonstrate that HO-1 is implicated in cytoprotection and may be an effective agent for the treatment of liver I/R injury.

Basic functions of heme degradation products

The heme catabolism by HO-1 produces carbon monoxide (CO), free iron, and biliverdin that is subsequently converted to bilirubin by biliverdin reductase [35]. HOs are rate-limiting enzymes in the heme catabolism. Three HO isozymes have been identified: HO-1, HO-2 and HO-3. HO-1 is an inducible enzyme, while the other two are expressed constitutively [36]. Three degradation products of the heme metabolism are considered to be beneficial due to their immunomodulatory, anti-apoptotic, and vasoactive properties and is up-regulated in their inflamed tissue.

Carbon Monoxide (CO)-CO is one of the three products of heme degradation by HO-1 and has profound effects as a signaling molecule that culminates in anti-inflammatory, antiapoptotic, and vasodilating effects [37, 38]. Despite its potential toxicity, has recently caused a great interest because of its function as a signaling molecule with vasodilatory effects mediated by cGMP, and its antiapoptotic and anti-inflammatory effects [39]. CO can travel freely throughout intracellular and extracellular compartments and exert a wide spectrum of modulating physiological effects on multi-systems [40]. A number of studies have revealed that CO mediates potent cytoprotective and anti-inflammatory effects in models of I/R injury of the heart, lung, kidney, and liver [41, 42]. Some studies demonstrate that the efficacy of CO gas inhalation for the prevention of cold intestinal I/R injury using a small intestinal transplantation model, in which CO is able to effectively inhibit an early up-regulation of proinflammatory mediators such as IL-6, IL-1, TNF-α, ICAM-1, iNOS, and COX-2 [43].

Bilirubin-HO degrades heme into equimolar quantity of biliverdin. Biliverdin is, in turn, very rapidly converted to bilirubin by the enzyme biliverdin reductase [44]. Biliverdin and its reduced product, bilirubin, scavenge various ROS and are hence considered potent antioxidants [45, 46], which have been shown to confer cytoprotection against oxidative stress conditions in various cell types [47]. Biliverdin is found to exert a beneficial influence on many diseases, including atherosclerosis, inflammatory, autoimmune, degenerative diseases, and cancer, in which it serves as a highly lipophilic antioxidant [48]. It can slightly reduce ethanol-induced lipid peroxidative injury by decreasing MDA content [49]. In addition, Takamiya et al [50] have demonstrated that HO-1 stabilizes mast cells (MCs) in order to exercise an anti-inflammatory action through bilirubin. In addition, biliverdin can modulate leukocyte infiltration by altering the expression of adhesion molecules, and to inhibit complement in vitro [51].

Free iron (Fe^{2+})-The third product, despite its cytotoxic pro-oxidant effects, induces an overexpression of ferritin, which in turn has strong antioxidant effects through the depletion of free iron and also by other less characterized effects that result in the induction of tolerogenic dentritic cells [52]. Iron is released in equimolar amounts when heme is degraded to yield biliverdin and CO. As iron, like other transition metals, catalyzes the formation of reactive oxygen intermediates, most notably the hydroxyl radical (Haber-Weiss or Fenton reaction), it is obvious that this by-product may offset the antioxidative properties of bile pigments if it is formed in sufficient amounts. Ferritin, representing a cellular storage system for iron, is an acute-phase reactant that is regulated essentially by the same stress events as HO-1, including iron, heme, UV irradiation, and hypoxia/reoxygenation [53]. Since free iron can participate in Fenton reaction, resulting in the membrane/tissue damage, HO-1-dependent release of free iron leads to the rapid expression of the iron-sequestering protein, ferritin as well as an iron ATPase pump that actively removes intercellular iron from the cell [54]. Maintenance of low iron pools by increased ferritin levels plays a central role in cellular anti-oxidant defense and cytoprotection mechanisms. Indeed, gene therapy-induced overexpression of the ferritin heavy chain (H-ferritin) protected rat livers from IRI, and prevents hepatocellular damage upon transplantation into syngeneic recipients. The protective effect of H-ferritin was associated with the inhibition of endothelial cell and hepa-

tocyte apoptosis. Thus, ferritin seems to confer cytoprotection against oxidative challenge. There is no elaborate information about the roles of iron and ferritin in liver I/R injury, but in such a mechanism they could still be operative.

Conclusion

Liver I/R injury is a complex, multifactorial pathophysiological process. Despite its complexity, the HO-1 system may play an important role in various pathophysiological conditions owing to its antioxidative, anti-inflammatory, antiapoptosis, and potent cytoprotective properties. Thus, pharmacological modulation of the HO-1 system may represent an effective and cooperative strategy to mitigate liver injury. HO-1 amplifies multiple intracellular cytoprotective mechanisms against a variety of cellular insults. The anti-oxidant function of HO-1 is not only heme degradation, but also biliverdin/bilirubin production. Ferritin upregulation also provides antioxidant function. CO, the last by-product of HO-1, exerts important anti-inflammatory and antiapoptotic effects via p38 MAPK activation, and may also modulate the vascular tone, which leads to diminished platelet aggregation and depressed fibrinogenesis. More importantly, regulating the HO-1 system with different agents has already been demonstrated as important for attenuating I/R injury in other organs including the brain, liver, and kidney [55]. Due to a paucity of clinical studies looking at the influence of liver I/R injury on patient outcome, it is unlikely that we will find the answer from a retrospective review of clinical studies, and we will need to undertake large prospective trials. Until then, clinical practice should reflect on the scientific evidence, and on the basis of the experimental evidence presented, hepatic surgeons should proceed cautiously in patients with liver I/R injury.

Future prospects

In a clinical setting, however, the inducible HO-1 system still has several limitations. The different effects of HO-1, which are neither exclusively cytoprotective nor exclusively cytotoxic, should be further investigated. The HO-1 induced cytoprotection might be restricted to a narrow threshold of overexpression. As outlined in this review, CO may represent a candidate for the treatment of transplanted patients against IRI. However, its therapeutic window must be carefully considered, because the inhalation of high levels can be toxic or even be lethal. Biliverdin and reduced bilirubin may also represent possible candidates for clinical application. We have recently demonstrated that biliverdin had a protective effect in stringent rat liver models of IRI, as evidenced by an improved portal blood flow/bile production and a reduction in hepatocellular damage. It also improved the survival rate in a syngeneic rat orthotopic liver transplantation (OLT) model after prolonged cold ischemia [56]. However, because bilirubin in excess can cause neurotoxicity and can act as a lytic agent binding to erythrocyte membranes, the therapeutic window of biliverdin must be examined in detail prior to its clinical use. From the above, the question arises if HO-1 or its products can be used clinically. Although CO is toxic, beneficial results can be obtained with relatively low doses for appropriate length of time. In rodents, the administration of biliverdin or bilirubin in the first few weeks of life did not reveal much toxicity. Recent experimental evidence indicates that they are not only non-toxic at physiological concentrations in normal cells; they may also have important anti-oxidant, anti-inflammatory, or anti-apoptotic properties [57]. Based on this review, which reveals that HO-1 is associated with both processes of IRI, we can conclude that HO-1 can attenuate liver I/R injury. HO-1, therefore, seems to stand out as a potential key therapeutic target to maintain graft function. However, despite the progress in understanding disease mechanisms in animal models, our knowledge of the human pathophysiology in warm or cold ischemia-reperfusion injury is poor. Thus, the limited mechanistic understanding of an intervention strategy and the limited insight into the various human pathomechanisms are a combination that makes success in the clinic unlikely. Therefore, more translational studies are needed to improve our understanding of the mechanisms of liver cell injury, inflammation, and regeneration particularly not only in humans but also in animal models. In addition, more and improved antioxidant strategies need to be developed and mechanistically tested. Overall, it appears that therapeutic interventions that target multiple antioxidants pathways may be more promising strategies than attempt to improve the antioxidant capacity of cells by a single

compound acting as free radical scavenger. In summary, the therapeutic role of HO-1 must undergo further critical analysis due to its limitations.

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Disclosure of conflict of interest

None.

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