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Heme oxygenase-1 system and gastrointestinal inflammation: A short review

Xiao Zhu, Wen-Guo Fan, Dong-pei Li, Hsiangfu Kung, Marie CM Lin

Abstract

Heme oxygenase-1 (HO-1) system catalyzes heme to biologically active products: carbon monoxide, biliverdin/bilirubin and free iron. It is involved in maintaining cellular homeostasis and many physiological and pathophysiological processes. A growing body of evidence indicates that HO-1 activation may play an important protective role in acute and chronic inflammation of gastrointestinal tract. This review focuses on the current understanding of the physiological significance of HO-1 induction and its possible roles in the gastrointestinal inflammation studied to date. The ability to upregulate HO-1 by pharmacological means or using gene therapy may offer therapeutic strategies for gastrointestinal inflammation in the future.

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Key words: Heme oxygenase-1; Gastrointestinal inflammation

INTRODUCTION

Heme oxygenase (HO) is the rate-limiting enzyme in heme catabolism, a process which leads to the generation of equimolar quantities of carbon monoxide (CO), Fe$^{2+}$ and biliverdin. Three distinct HO isoforms (HO-1, HO-2 and HO-3) have been identified to date, which are the products of different genes. HO-2 is constitutively and most highly expressed in neuronal tissues contributing to cell homeostasis, whereas HO-1, also referred to as heat shock protein-32 (Hsp32), is an inducible enzyme and expressed at a relatively low level in most tissues. HO-3 has been found only in the rat brain, but no activity in humans.

Unlike the constitutively expressed HO-2, HO-1 is exquisitely sensitive, not only to heavy metals, but also to all kinds of stimuli and agents that cause oxidative stress and pathological conditions. Induction of the HO-1 protein has been reported to protect against a variety of stress conditions such as ischemia, hemorrhagic shock, heat...
shock\textsuperscript{[5]}, hypoxia\textsuperscript{[6]}, and reactive oxygen species (ROS)\textsuperscript{[8]}. In fact, there has been no other enzyme described to date that is affected by so many stimuli of diverse nature as HO-1\textsuperscript{[1]}. The strong adaptive response of HO-1 to various stimuli suggests that pharmacologic modulation of HO-1 system may represent an effective and cooperative strategy to intervene in protection against inflammatory processes and oxidative tissue injury. HO-1 is expressed constitutively in normal gastric, intestinal and colonic mucosa\textsuperscript{[9,10]} and up-regulated in their inflamed tissues\textsuperscript{[13]}. What implications of HO-1 are in gastrointestinal inflammation and injury? In this review, we focus on this subject, and elucidate the mechanisms and some potential clinical applications to gastrointestinal inflammation.

**UPREGULATION OF HO-1 IN GASTROINTESTINAL TRACT**

Interestingly, expression of HO-1 is usually increased in gastrointestinal inflammation and injury. This was shown in gastric ulcers\textsuperscript{[11]}, colitis\textsuperscript{[12,13]}, radiation enteritis\textsuperscript{[14]} inflammatory bowel disease (IBD)\textsuperscript{[15]} of animal models or patients. Moreover, HO-1 is expressed constitutively in normal gastrointestinal tract (GIT)\textsuperscript{[6,10]}.

The GIT is lined by a simple epithelium that separates the hostile processes of digestion and absorption that occur in the intestinal lumen from the aseptic environment of the internal milieu by defensive mechanisms.\textsuperscript{[15]} GIT undergoes constant oxidative stress, inflammation and cell cycle/apoptosis. The normal expression and up-regulation of HO-1 indicate that activation of HO-1 could act as a natural defensive mechanism to alleviate inflammation and tissue injury in the GIT\textsuperscript{[5,11,18]}.

**ROLE OF HO-1 IN GASTROINTESTINAL INFLAMMATION AND INJURY**

HO-1 is commonly regarded as a potent anti-inflammatory enzyme and has anti-inflammatory properties. For example, HO-1 upregulated by hemin\textsuperscript{[16]}, heme\textsuperscript{[26]} and cobalt-protoporphyrin\textsuperscript{[27]} can ameliorate experimental colitis. Conversely, administration with HO inhibitor (tin mesoporphyrin, SnMP) results in exacerbation of experimental colitis along with a reduction in HO-1 activity\textsuperscript{[12]}.

In addition, the mechanism of action of 5-aminosalicylic acid (5-ASA, an anti-colitis agent used clinically) is attributed in part to the up-regulation of HO-1 enzyme expression and activity\textsuperscript{[22]}. Moreover, some agents including glutamine\textsuperscript{[23,24]}, tranilast\textsuperscript{[25]}, RDP58\textsuperscript{[26,27]}, Octreotide\textsuperscript{[26,27]}, lansoprazole\textsuperscript{[28-30]}, Ketamine\textsuperscript{[31]} Polaprezinc (PZ, an anti-ulcer drug)\textsuperscript{[32]} and gliotoxin\textsuperscript{[33]} may contribute to the preservation of gastrointestinal mucosa in some experimental models, such as colitis, radiation enteritis, and acute gastric mucosal lesions. This protective effect is partly mediated by the induction of HO-1 expression.

Nuclear factor-erythroid 2-related factor 2 (Nrf2) has been known to be a transcriptional factor which plays a crucial role in cytoprotection against inflammation. The severity of colitis induced by dextran sulphate sodium (DSS) in Nrf2-deficient mice is found to be associated with decreased expression of HO-1\textsuperscript{[34]}.

These results demonstrate that HO-1 may be implicated in cytoprotection and may be an effective agent for the treatment of diseases characterized by mucosal inflammation in GIT.

**MECHANISMS OF ACTION**

HO-1 seems to have an important protective role in acute and chronic inflammation of GIT. HO-1 is the key enzyme in heme degradation and plays a key role in regulating the intracellular heme level. HO-1 activity means rapid removal of free heme, which is shown to be cytotoxic. Thus, HO-1 is associated with a protective response and contributes to the preservation of GIT mucosa (Figure 1).

**CO AND GASTROINTESTINAL INFLAMMATION**

Almost all CO produced \textit{in vivo} comes from the degradation of heme by HO. \textit{Evidence indicate that CO mediates many of the biological actions of HO-1}\textsuperscript{[35]}. Otterbein \textit{et al.}\textsuperscript{[36]} demonstrate that CO can inhibit the production of proinflammatory cytokines [tumor necrosis factor (TNF)-\textalpha, interleukin (IL)-1\textbeta, and macrophage inflammatory protein-1\textbeta] and stimulate the synthesis of the anti-inflammatory cytokine interleukin-10. Other studies also suggest that CO implicates in mediating the anti-inflammatory actions\textsuperscript{[37,38]}.

Hegazi \textit{et al.}\textsuperscript{[39]} have shown that CO at a low concentration mitigates chronic intestinal inflammation in a T helper-type-1 cell-mediated mouse model of murine colitis in IL-10-deficient mice and protect against the development of postoperative ileus (POI) and necrotising enterocolitis in rodents and swine\textsuperscript{[40,41]}. Moreover, Scott \textit{et al.}\textsuperscript{[42]} demonstrate that low-dose inhaled CO selectively attenuates the remote intestinal inflammatory response.
elicited by hindlimb ischemia-reperfusion. And pre-treatment with CO-releasing molecules (CO-RMs) markedly reduced intestinal muscularis inflammation induced by surgical manipulation of the small intestine\(^{[4]}\). The anti-inflammatory actions of CO can be in large measure mediated through p38 mitogen-activated protein kinase (MAPK) pathway\(^{[36,37]}\).

The knowledge of the role of CO in gastrointestinal inflammation is limited, but such a mechanism could be operative in GIT. Recently, Chin et al\(^{[45]}\) pointed out that CO has been ascribed an additional novel role as a host defense molecule agent against microbes (bactericidal agent).

### BILIVERDIN/BILIRUBIN AND GASTROINTESTINAL INFLAMMATION

HO-1 catalyzes the rate-limiting step in heme degradation to biliverdin. Biliverdin is, in turn, converted into bilirubin by biliverdin reductase at the expense of nicotinamide adenine dinucleotide phosphate (NADPH). Biliverdin and bilirubin are reducing species and hence potential antioxidants\(^{[46,47]}\). Several studies have demonstrated that the administration of biliverdin and/or bilirubin is potently cytoprotective in a variety of pathophysiological events, including ischemia-reperfusion injury, and transplant rejection\(^{[48,49]}\). In addition, bilirubin is also known to modulate immune effector functions and suppress inflammatory response\(^{[50]}\).

Treatment with biliverdin can significantly decrease mRNA expression of inducible nitric oxide synthase (iNOS), cyclooxygenase 2, and intercellular adhesion molecule-1 as well as the inflammatory cytokines IL-6 and IL-1\(\beta\), and decreased neutrophil infiltration into the jejunal muscularis in rat syngeneic small intestinal transplants\(^{[51]}\). Hayashi et al\(^{[52]}\) demonstrate that the effects of HO-1 induction on leukocyte adhesion could be mimicked by bilirubin. In addition, the study of Lee et al\(^{[53]}\) show that bilirubin exerts anti-inflammatory effects in vitro.

The data indicate that this product of HO reaction play an important role in the anti-inflammatory effects of HO-1. However, there has been no report about the measurement of tissue levels of biliverdin/bilirubin in human GIT, and even the role of the biliverdin/bilirubin pathway has not been clarified in experimental model of gastrointestinal inflammation.

### Fe\(^{2+}\) AND GASTROINTESTINAL INFLAMMATION

Fe\(^{2+}\), the third product of heme decomposition, can be potentially toxic, but it can upregulate an iron-transporter pump that removes intracellular Fe\(^{2+}\) from the cell\(^{[54]}\) and induces the expression of ferritin, an iron storing protein\(^{[55]}\). Expression of ferritin is originally reported to protect endothelial cells against oxidant damage in vitro\(^{[56]}\). In addition, over-expression of H-ferritin (heavy chain ferritin) has also been shown to protect cultured endothelial cells from undergoing apoptosis and protect livers from transplant-associated ischemia-reperfusion injury\(^{[58]}\). Increased ferritin protein levels induced by lansoprazole in endothelial cells and macrophages can reduce NADPH-dependent ROS formation, indicating that ferritin may account for the gastric protection of lansoprazole\(^{[59]}\).

Although the roles of the iron and ferritin in the overall cytoprotective effect of HO-1 are not clear, presumably both contribute in a crucial manner to the overall antioxidant effect following increased HO-1 expression in a variety of situations\(^{[57]}\). Further work is clearly needed in this area.

The exact mechanisms underlying the anti-inflammatory functions of the HO-1 in gastrointestinal inflammation have not been fully elucidated. However, the signaling action of CO combined/or complemented by the antioxidant properties of biliverdin/bilirubin and the sequestration of iron by ferritin could all contribute to suppression of inflammation\(^{[58]}\). It becomes clear that upregulation of HO-1 and/or exogenous administration of one or more of its products would be therapeutic strategies for gastrointestinal inflammation.

### HO-1 AND iNOS

The inducible isoform of nitric oxide synthase (iNOS) can produce sustained high quantities of nitric oxide (NO), which may be involved in the mucosal injury associated with IBD. Indeed, upregulation of iNOS or NO release has been demonstrated in both ulcerative colitis and Crohn’s disease\(^{[59,60]}\). HO-1 inducers, cadmium and bismuth salts, heme, and nitric oxide (NO) donors, act at the transcriptional level inhibiting iNOS mRNA expression in vitro\(^{[51]}\). Wang et al\(^{[53]}\) investigated the possible role of HO-1 in experimental colitis in rats. Their data show that HO-1 plays a protective role in the colonic damage, and this effect probably result in part from inhibition of iNOS expression in colonic tissues. Moreover, Dijkstra et al\(^{[62]}\) demonstrate opposite regulation of iNOS and HO-1 in intestinal epithelial cells in response to cytokine exposure and oxidative stress. These findings suggest that HO-1/CO and iNOS/NO system may act together in a complex, dynamic, and adaptable association in gastrointestinal inflammation, which remain to be elucidated further.

### HO-1 PROMOTER POLYMORPHISM

HO-1 is known as an oxidative stress responsive protein that is upregulated by multiple stimuli, which has been proposed to provide an important cellular response that protects cells against oxidative damage. However, humans differ quantitatively in their ability to mount an HO-1 response.

An HO-1 gene promoter microsatellite (GT)(n) dinucleotide repeat polymorphism is associated with...
regulation of HO-1 in response to inflammatory stimuli. Short GT repeats (< 25) are associated with highly significant up-regulation of HO-1 in response to inflammatory stimuli[40,64]. The investigators have studied the association between the HO-1 genotype and gastrointestinal inflammation. They investigated the variants of HO-1 promoter region in 179 patients with Crohn’s disease, 110 with ulcerative colitis and 56 control patients without inflammation. The data show that (GT)(n) di-nucleotide repeats of the HO-1 promoter region have no significance for the pathophysiology and disease course of IBD[43]. In gastrointestinal tumors, a potential impact of the (GT)(n) repeat polymorphism has been demonstrated[66]. But in gastrointestinal inflammation diseases which usually associate tumors, it remains to be verified.

CONCLUSION

Chronic inflammatory disorders in GIT have been linked with an increased risk of the development of gastrointestinal tumors[65]. It is well known that HO-1 is involved in inflammation and have protective effects in GIT against inflammation and oxidative injury; thus, the modulation of HO-1 through pharmacological means or the use of gene therapy may offer therapeutic strategies for gastrointestinal inflammation and more importantly, to prevent gastrointestinal cancer. A comprehensive understanding of the underlying mechanisms for the observed effects of HO-1 in gastrointestinal inflammation will be necessary in the future.

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