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# Therapeutic Potential of Hemooxygenase-1 in Cardiovascular Diseases

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***Abstract*** **: Cardiovascular diseases are responsible for 1 of every 2.9 deaths in the United States of America, revealing the burden of the disease is very high. Because of the high mortality rate and escalating cost in health care for the disease, it is of important and urgent and immediate need to treat and prevent cardiovascular diseases effectively and potentially. Heme oxygenase-1 enzyme (HO-1) speed up the heme oxidation reaction to produce iron, biliverdin, and carbon monoxide. Inspite of the fact that HO-1 is demonstrated at reasonable levels in innumerable tissues under normal conditions, it is highly inductive in response to variety of patho-physiological stresses. Various studies have demonstrated that HO-1induction to preserve cells and tissues is an adaptive defense system against injury in innumerable disease settings. HO-1 is popping up as a remarkable effective therapeutic target for cardiovascular disease treatments.**

## INTRODUCTION

Heme-oxygenase an emerging molecule has arrived. Cardiovascular diseases are responsible for 1 of every 2.9 deaths in the United States of America, revealing the burden of the disease is very high. Because of the high mortality rate and escalating cost in health care for the disease, it is of important and urgent need to treat and prevent cardiovascular diseases effectively and potentially. Heme oxygenase-1 enzyme (HO-1) speed up the heme oxidation to produce iron, biliverdin, and carbon monoxide. Inspite of the fact that HO-1 is demonstrated at reasonable levels in innumerable tissues under normal conditions, it is highly inductive in response to variety of patho-physiological stresses. Various studies have demonstrated that HO-1induction to preserve cells and tissues is an adaptive defense system against injury in innumerable disease settings. HO-1 is popping up as a remarkable effective therapeutic target for cardiovascular disease treatments.

### Ho-1 suppresses the pathogenesis of inflammatory diseases

The first genetic deficiency of HO-1 in human was reported during a young boy in 1999 and a second case was reported recently in a young woman . These 2 patients died during a small age, of only 6 and fifteen years old. These cases demonstrated inflammatory phenotypes which incorporates elevated expression of inflammatory markers like C-reactive protein, ferritin, and Von Wille brand factor. They additionally had coagulopathy, nephritis, chronic inflammation, and accumulated status to atherosclerosis. The human HO-1 deficiency reveals a vital immune modulatory role of HO-1 and highlights the essential function of HO-1 in human health and sickness. Upon antigen recognition, T cells are activated, endureing profound phenotypical modifications and expand logarithmically to provide an outsized pool of antigen specific effector T cells. These will migrate into the location of inflammation and eliminate microorganism pathogens. Coronary heart condition (CHD) remains a significant health issue within the United States of America and developing countries.. CHD could be a results of manifestations of induration of the arteries. arteriosclerosis lesions in coronary arteries will result in blockage of blood flow and subsequent anaemia of the guts, that then ends up in myocardial infarction. It's clear from all the evidences that inflammation plays a key role within the pathologic process of atherosclerosis, as well as initiation and progression, and

therefore atherosclerosis is recognized as a chronic disease. Methods targeting inflammation is also of therapeutic edges within the bar and treatment of atherosclerosis and cardiovascular disease.That, HO-1 acts as a protecting gene in humans was initially advised by the association of a HO-1 genetic deficiency with the premature death of a six-year-old boy UN agency succumbed to a complex inflammatory syndrome. This approach has been used to block HO-1 activity and revert moderate pathology related to type Crigler-Najjar type-1 syndrome. However, for those inflammatory diseases were induction of HO-1 expression would be fascinating this approach might not wield the expected results, as people fourteen with affordable level of HO-1 inducibility would most likely not respond with efficiency to the present therapy. There are specific pathological conditions, such restenosis that develop following coronary stenting, whereby the therapeutic effects could also be accomplished by short-run expression of HO-1.

**Potential targets for Therapeutic Applications**
**(I)HO-1 in myocardial infarction**

A task for HO-1 in cardiac homeostasis was 1st concerned during a study showing that HO-1 expression within the heart is inflated in response to hyperthermia. A follow-up study showed that ischemia/reperfusion considerably enhances HO-1 expression within the porcine heart, suggesting a possible role of HO-1 within the defense against patho physiological stress. Since HO-1 and its byproducts mediate countless cyto-protective effects like anti inflammation, inhibitor, and anti-apoptosis, HO-1 might play a task in promoting graft survival after transplantation. Abdominal aortic aneurysm (AAA) could be a comparatively common and sometimes fatal condition that primarily affects older patients. It's a number one reason behind sudden death in men older than fifty five years. Reduced oxygen content from blood creates a condition during which the restoration of circulation ends up in inflammation and aerobic harm from reactive oxygen species (ROS). In fact, aerobic stress plays a serious role within the patho-physiology of cardiac disorders. Thus, each the direct and indirect protecting and stimulatory effects on the vascular bed create HO1 a promising target for the development of treatment techniques in cardiovascular disorders.

**(II) Heart transplantation**

Most effective medical care for coronary failure at end-stage is that the Heart transplantation . However, patients want immune-suppression for all times long remedy to stop chronic and acute rejection by immune system for function and allograft survival. Existing immune-suppressive drug treatments are effective for acute however not for chronic rejection and are connected with noteworthy aspect effects which has diabetes, dyslipidemia and excretory organ toxicity. In sight of the actual fact that HO-1 and their byproducts mediate infinite cytoprotective effects like anti-oxidant, anti-inflammation, and anti-apoptosis, HO-1 may play a really vital role in promoting graft survival after the transplantation. Curiously, Ohmann et al. Recently found that HO-1 polymorphisms with higher expression of HO-1 correlate with a reduced risk of late post-transplantation infection in paediatric heart. Though it's clear that HO-1 protects heart graft in animal models, the role of HO-1 in human heart transplants is somewhat controversial and so warrants more study.

**(III) HO-1 in abdominal aortic aneurysm**

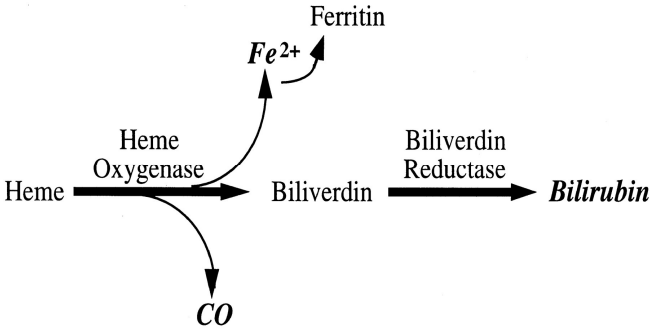
Abdominal aorticaneurism (AAA) is a comparatively common and typically fatal condition that primarily affects older patients . It's a number one explanation for sudden death in men older than fifty five years.AAA could be a localized dilatation of the abdominal aorta exceeding the standard diameter (~2 cm) by over five hundredth, that is characterised by chronic aortic wall inflammation, loss of medial SMCs, and animal tissue degradation and transforming. AAA is related to maturity, male gender, cigarette smoking, atherosclerosis, cardiovascular disease, and a genetic disposition Screening studies in Europe show that 5% of men sixty five years ancient have AAAs of three cm or additional. within the U.S., the prevalence of AAAs 2.9 to 4.9 cm in diameter ranges from 1.3% in men forty five to fifty four years older to 12.5% in men seventy five to eighty four years older. With an aging population, the incidence and prevalence of AAA is definite to go up. Taken along, with the anti- oxidative, anti-inflammatory drug, and anti-apoptotic activities of HO-1, HO-1 includes a important potential to prevent/attenuate the development/ progression of AAA. The role of HO-1 within the pathologic process of AAA definitely warrants any investigation.

**Mechanism of Action**

**(I) Increase in the level of Heme Oxygenase-1 and Heme Oxygenase Activity**

The degradation and catabolism of heme is currently thought about complicated in cellular defense as a result of 2 completely different reasons. Firstly, the pro-oxidant heme is removed. Secondly, the rise within the production of bilirubin and CO is currently useful and demanding to

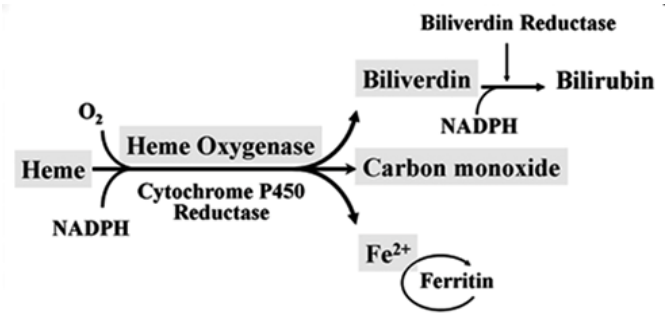
cellular defense systems. Iron, that stimulates the free radical formation, is straight away bound by protein. Therefore, CO and bilirubin a revital to the protection that happens from exaggerated levels of Ho-1 protein and HO activity. Chronic induction in HO-1 protein could have each advantageous and fatal effects. The role of Ho, example, within the resistance to H2O2 and heme toxicity was measured within the urinary organ animal tissue cells. Followed and so adapted by long-run exposure to H2O2, urinary organ animal tissue cells displayed a two-fold increase within the basal Ho activity and increase within the level of HO-1 macromolecule, that was thought-about useful and advantageous. Long-term exposure to each the stressors resulted, within the adaptation of some resistance to more complicated challenges of oxidizing agent stress in these cells (da silva et al.1996). Hence forth, it shows that the resistance that is made up, showing, that, it's effective, high and elevated levels of HO-1 macromolecule should be gift before the onset of the chronic sickness.




The acute sharp sudden induction within the levels of HO-1 has been shown to possess an advantageous impact as a result of the speedy and sudden decrease within the quantity of unwanted heme. (Sacerdoti et al 1989) initial reported the advantages of this acute impact, representing innumerous that the treatment with stannous chloride (SnCl2) prevents the onset of high blood pressure. Heme arginate or to be precise heme, used clinically for the porphyria treatment (Kordac et al.,1989) has been shown to possess a advantageous affect on chronic induction of HO-1 and lower the blood pressure in hypertensive rats ( Schwartzman et al., 1990; Martasek et al.,1991; Ndisang et al.,2003; Wang et al.,2006).

**Chronic effects**

It shows that resistance enhanced with time of exposure, suggesting that, to be effective, enlarged levels of HO-1 protein should be present before the onset of chronic sickness.




**Cardiovascular Drugs and Drug Developments Targeting Heme Oxygenase**

**(I) Gene Expression**

A wide range of compounds are used to up-regulate the expression of Ho-1 and therefore the activity of HO. In the treatment of type of diseases like atherosclerosis, hypertension, and vascular injury in individuals. Henceforth, the adverse and long results of expression of HO-1 and its effect on the synthesis pathway of heme should be kept in mind before clinical application. Recent studies have shown some well-known and normally used drug agents that modulate the expression of HO-1 in vascular cells.

**(II) Aspirin**

Aspirin is widely famous to decrease the incidence of thrombotic occlusive events, like myocardial infarction and stroke, by inhibiting the plateletcox-2 activity. Aspirin the degree of amount of Ho-1 increased and also the activity of HO in an exceedingly dose-dependent manner in cultured epithelium cells obtained from umbilical vein of humans. Pretreatment of cells with aspirin or bilirubin protected the epithelium cells from H2O2-mediated toxicity (Grosser et al.,2003). It has been recently studied that aspirin-triggered lipoxin evoked the expression of epithelium HO-1 protein counting on the time and concentration. it's studied that this technique is mediated by the activation of the G protein-coupled lipoxin A4 receptor (Nascimento-Silva et al.,2005). It's been shown that aspirin-triggered lipoxin induces HO-1 in human epithelium cells which this increase within the HO-1 protein is accountable for the anti-inflammatory property of those lipid mediators (Becker et al.,2003; Nascimento-Silva et al.,2005). However, the dose of aspirin that are utilized in these studies represented is more than that that are used clinically.

**(III) Amino Acid Apolipoprotein A-I L-4F and D-4F Mimetic Peptides.**

The recent development of compounds like 4-F is a well documented (Navab et al.,2005) and these peptides show equal efficiency whether they are made from D-or L-amino acids (Van Lenten et al.,2007). Recent developments show that rats were made diabetic by streptozocin treatment displayed high aortic oxidative stress and endothelial sloughing that was ameliorated by administration of D-4F. D-4F increased levels of aortic HO-1 protein, HO activity, and extracellular superoxide dismutase while decreasing superoxide levels (Kruger et al.,2005;Peterson et al.,2007).

**(IV) Probucol**

Probucol, is an antioxidant drug, which reduces the risk of restenosis (Heinecke,2006). The protective effect of probucol depends on its ability to inhibit the oxidation of lipid and also on its ability to induce the HO-1. Probucol drug inhibits the accumulation of macrophage, thereby stimulates the re-endothelialization, and inhibits the proliferation of vascular smooth muscle cells. These processes are mediated through the induction of HO-1, an activity which is not shared by vitamin E (Choi et al.,2004;Wu et al.,2006), which, along with other antioxidants, has failed to protect against atherosclerotic disease. A striking exception is probucol, which retards atherosclerosis in carotid arteries and restenosis of coronary arteries after angioplasty (Wu et al.,2006). These findings indicate the contribution of HO-1 in the actions of probucol.

**(V) Losartan**

HO-1 is demonstrated in medial smooth muscle and adventitial cells in normo tensive rat aorta and is markedly increased in adventitial and endothelial cells in angiotensin II-induced hypertensive rat aorta (Ishizaka et al.,1997). This up-regulation in blood pressure, and thus HO-1, was reduced to levels comparable to those of controls by treatment with losartan (Ishizaka et al.,1997). Losartan markedly reduced pulmonary pressure and inhibited vascular remodeling in volume-overloaded left-to-right shunt rats, resulting in the down-regulation of HO-1 mRNA expression (Yuan et al.,2005).

**(VI) Immunosuppressive Drugs**

Cyclosporin is a powerful stimulator of oxidative stress signaling, which leads to transformation of growth factor-β production, Nitrous Oxide degradation, endothelial dysfunction, hypertension, and post-transplant nephropathy. Down-regulation of HO-1 expression by cyclosporin-A can be one method underlying the cyclosporin-A induced toxicity (Rezzani et al.,2005) and induction of HO-1 can prevent this. Carvedilol-mediated induction of HO-1 has been reported to lower the oxidative stress and to correct the altered cellular signaling mediated by oxidative stress in cyclosporin-A-induced post-transplant hypertension (Calo et al.,2002).

**Therapeutic opportunities**

As described above, across its enzymatic products HO-1mediates innumerable cellular functions in protecting cells and tissues against inflammation and oxidative stress. Numerous studies have demonstrated the protective function of HO-1 in innumerable cardiovascular diseases. In light of the socioeconomic burden of cardiovascular disease, the therapeutic potential of HO-1 is of particular interest. Thus, induction of HO1 pharmacologically or by other means might be a promising therapeutic intervention for preventing and treating these inflammatory cardiovascular diseases. Expression of HO-1 should be recognized as a central event in the control of inflammation and immunity. Most of the systems involved in the effects mediated by HO-1 remain to be established. In the process of unveiling these one will most probably gain better understanding on the control of inflammatory and immune reactions.

**Future prospective**

The studies reviewed above suggest that PDE-5 inhibitors have remarkable promise for further development as novel drug therapies for MI, cardiac hypertrophy, cardiomyopathy, heart failure, stroke, neuro degenerative diseases and, potentially, other circulatory disorders. Infact, there is an ongoing National Institutes of Health multi centre trial (RELAX: Evaluating the Effectiveness of Sildenafil at Improving Health Outcomes and Exercise Ability in People with Diastolic Heart Failure;NCT00763867) of patients with heart failure. There is a functional significance of the HO1 system in the vascular bed and the potential therapeutic applications of HO1gene transfer in cardio vascular disease. Moreover, it has been proposed that moderate, tightly controlled HO1 expression by gene therapy should provide protection against variety of toxic insults including reactive iron released in heme degradation.

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