Targeted Pharmacological Heme-Oxygenase-1 Induction as a Therapy for Diabetes

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Abstract

Diabetes has emerged as a major threat to health worldwide. The exact mechanisms underlying the disease are unknown; however, there is growing evidence that excess generation of reactive oxygen species (ROS), causes oxidative stress in various organs. In diabetic patients, oxidative stress is closely associated with chronic inflammation and plays a key role in the pathogenesis of micro- and macrovascular diabetic complications. Redox reactions associated with carbon monoxide (CO) metabolism play key roles in intra- and inter-cellular signaling. Cells produce significant amounts of CO as a product of cellular metabolism, largely from heme degradation catalyzed by microsomal heme oxygenases (HOs) generating CO, biliverdin, bilirubin and iron. This review focuses on the importance of both HO-1/CO system in the pathophysiology and therapy of inflammation associated with diabetes. Research on these pathways will open new perspectives for the rational design of drugs against diabetic diseases.

Keywords: Diabetes; Oxidative stress; Reactive oxygen species; Heme-oxygenase-1; Carbon monoxide

Introduction

Diabetes is a chronic disease characterized by elevated blood sugar levels resulting from either a lack of insulin production or resistance to insulin. About 230 million people worldwide had diabetes in 2010. The global figure of people with diabetes is projected to increase to 333 million in 2025, and 430 million in 2030 [1]. The majority of diabetes patients are not insulin-dependent and able, at least initially, to produce the hormone. This type of diabetes mellitus (DM) is termed type 2 diabetes. Insulin resistance is a fundamental aspect of the etiology of type 2 diabetes. Subjects with diabetes have an increased risk of ischemic heart disease, atherosclerosis and nephropathy [2,3]. Obesity, which is a major public health concern worldwide, increases the risk of type-2 diabetes [3]. Type 2 diabetes is caused by a combination of insulin resistance coupled with insufficient production of insulin to overcome the insulin resistance [4]. Oxidative stress plays a key role in the pathogenesis of micro- and macrovascular diabetic complications. There is now convincing evidence that redox reactions associated with CO metabolism play key roles in adaptive processes of tissues towards oxidative stress. Cells and tissues produce significant amounts of CO from heme degradation catalyzed by microsomal heme oxygenases (HO).

Heme Proteins as Signaling Molecules

Heme proteins play a major role in various biological functions and most of the reactions involving heme are redox reactions of heme iron. Heme is released from hemoproteins during red blood cell (RBC) destruction and is metabolized by heme oxygenases (HO). Three isoforms of HO have been characterized: an inducible form (HO-1), which is up-regulated, especially in the spleen and liver, in response to various types of stress, and two constitutive forms (HO-2 and HO-3). HO-1 generates signaling molecules through the catalysis of heme-carbon monoxide (CO), biliverdin, bilirubin and iron. This review focuses on the importance of both HO-1/CO system in the pathophysiology and therapy of inflammation associated with diabetes. Research on these pathways will open new perspectives for the rational design of drugs against diabetic diseases.
oxidative processes increases with age and with disease as a result of the deterioration of normal physiological control [6]. There is now convincing evidence that redox reactions associated with NO and CO metabolism play key roles in intra- and inter-cellular signaling, and in adaptive processes of tissues towards stress [7]. It is now well recognized that HO-mediated heme degradation has multiple roles, including antioxidant and iron reutilization functions. HO generates the effector molecules biliverdin/bilirubin, carbon monoxide, and free iron/ferritin.

Oxidative and Nitroxidative Stress in Diabetes

Given the multiplicity of their functions, mitochondria are a logical target for the study of metabolic diseases. Skeletal muscle is the major site of insulin-stimulated glucose use in the body, and the dysregulation of mitochondria is closely associated with insulin resistance in skeletal muscle and thus with the pathogenesis of type 2 diabetes. Inside mitochondria, electrons from reduced substrates move from complexes I and II of the electron transport chain through complexes III and IV to oxygen, forming water and causing protons to be pumped across the mitochondrial inner membrane. The electron transport system is organized so that the level of ATP can be precisely regulated [8].

The increased superoxide anion production is associated with oxidative processes. HO-2 has three cysteine residues that are thought to modulate PMN activity and the evolution of inflammation [23]. The inducible form of HO, HO-1, occurs at a high level of expression in the spleen and other tissues that degrade senescent red blood cells, including specialized reticulo-endothelial cells of the liver and bone marrow. HO-1 is also present in myeloid cells. These cells comprise monocytes, macrophages and dendritic cells, which play crucial regulatory roles in the innate and adaptive immune system. As the liver plays a crucial role in the body’s iron homeostasis (e.g. via secretion of the iron regulatory hormone: hepcidin) and in systemic inflammation, hepatic HO-1 may be important for the regulation of both systems. In an organ such as the liver, the induction of HO-1 expression is an important aspect of the anti-inflammatory, anti-apoptotic response to cellular stress. The gene coding for HO-1 is highly regulated [18,19]. HO-1 is emerging as a great potential therapeutic target for treating cardiovascular diseases. In the vascular system, HO-1 and heme degradation products perform essential physiological functions [20]. There appears to be a relationship between HO-1 expression and the signaling pathways that modulate inflammatory response [21]. Nitrated fatty acids (NO2-FA) resulting from interactions between NO and eicosanoids have distinct anti-inflammatory signaling properties. Nitrated linoleic acid potently induces HO-1 expression by an NO- and PPARγ-independent mechanism in human aortic endothelial cells [22]. These pathways may converge via the generation of nitrated unsaturated lipids that influence PMN activity and the evolution of inflammation [23].

Heme oxygenase-1: HO-1

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Heme oxygenase-2: (HO-2)

HO-2 is constitutively expressed in selected tissues (brain, liver, and testes) and is involved in signaling and regulatory processes. HO-2 has three cysteine residues that are thought...
to modulate the affinity for heme, whereas HO-1 has none [24]. Within the normal liver, HO-2 is constitutively expressed within hepatocytes, Kupffer cells, endothelial cells and Ito cells. In the central nervous system, it has been demonstrated that HO-2 can function as an \( \text{O}_2 \) sensor in the brain, and the \( \text{O}_2 \)-CO-H\(_2\)S cascade rapidly mediates hypoxia-induced cerebral vasodilation [25].

**Heme oxygenase-3: (HO-3)**

The existence of a third HO isoform, HO-3, was reported in the rat. HO-3 was shown to be the product of a single transcript of 2.4kb encoding a protein of 33kDa. The HO-3 transcript was found in a series of organs including spleen, liver, kidney and brain [26]. The function of HO-3 remains unclear, but it has been cloned from rat brain, suggesting a neural function. This enzyme is structurally similar to HO-2, but is less efficient at degrading heme.

**Incidence of Endogenous HO-1 Activation**

The incidence of endogenous HO-1 activation has been studied in experimental and clinical procedures. HO-1 activity provides a possible antioxidative function by accelerating the removal of heme to limit oxidative stress sustained through heme-iron dependent mechanisms. The effects of CO and bilirubin indirectly reproduce the incidence of HO activation. Great attention has been paid to the protective role of CO and carbon monoxide-releasing molecules (CORMs) in vascular diseases. Indeed, CO and CORMs exert anti-inflammatory and anti-oxidant actions on different organs [27,28]. Bilirubin appears to be a more potent antioxidant than biliverdin. Nonetheless, there is evidence that the direct and indirect antioxidant effects of both bile pigments contribute to the beneficial profile of the HO-1 pathway. Individuals with Gilbert’s syndrome have polymorphism in the bilirubin UDP-glucuronosyltransferase (UGT1A1) promoter and are protected against a number of factors associated with cardiovascular complications. This polymorphism results in slower glucuronidation and therefore diminished excretion of bilirubin, leading to elevated bilirubin levels in the plasma.

Recent studies have revealed that HO-1 mediates the adiponectin-induced anti-inflammatory response; adiponectin inducing an HO-induction [29]. Adiponectin, an adipokine predominantly secreted from adipocytes, plays a modulatory role in various pathophysiological conditions. Apart from its well characterized role in glucose and fatty acid metabolism, adiponectin has received special attention in recent years due to its protective role in inflammation. Moreover, chronic HO-1 induction also modifies the phenotype of adipocytes in obesity from large, cytokine-producing adipocytes to smaller, adiponectin-producing adipocytes [30]. Emerging evidence indicates that links exist between HO activity and the changes in energy metabolism that occur during the development of certain diseases. Experimental evidence suggests that excessive amounts of free fatty acids and high glucose produce hypertrophied adipocytes resulting in detrimental perturbations in both mitochondrial and endoplasmatic reticulum function. These effects are associated with the increased generation of ROS, activation of the inflammatory cascade and insulin resistance. The levels of HO-1 expression, HO activity and its products, CO and bilirubin, are decreased in humans and in animal models of type-2 diabetes [31]. In conclusion, the induction of HO-1 appears to modulate metabolic syndrome, obesity, and insulin resistance, and recent data provide evidence for the involvement of the HO–adiponectin-EET axis in adipogenesis and adipocyte signaling both in vitro and in vivo [32].

**Heme-Oxygenases Inducers (Table 1)**

A lot of natural agents have been recognized for their capacity to induce HO-1 in different tissues. Most of these compounds are characterized by a phenolic structure, similar to that of alpha-tocopherol, and present antioxidant properties.

| Name                        | Chemical Structure |
|-----------------------------|--------------------|
| Curcumin and analogues      | ![Curcumin Structure](image.png) |

**Table 1:** Chemical structures of heme oxygenase inducers.
| Resveratrol (trans-3,4,5-trihydroxystilbene) | ![Resveratrol](image1) |
|--------------------------------------------|-----------------------|
| Quercetin (Flavonoids: flavonoids, isoflavones, flavonones, catechins, anthocyanins) | ![Quercetin](image2) |
| Organosulfur compounds | | ![Diallyl sulfide (DAS)](image3) |
| | | ![Diallyl disulfide (DADS)](image4) |
| | | ![Diallyl trisulfide (DATS)](image5) |
| Isothiocyanates: Glucosinolates (beta-thioglucoside N-hydroxysulfates) | ![Isothiocyanates](image6) |
| Lithospermic Acid B (phenolic acid from tanshen: rhizome of Salvia Milthiorrhiza Bunge) | ![Lithospermic Acid B](image7) |
| 1,2,3,4,6-Penta-O-galloyl-beta-D-glucose (PGG) | ![1,2,3,4,6-Penta-O-galloyl-beta-D-glucose (PGG)](image8) |
| Scopoletin          | ![Scopoletin](image1) |
|---------------------|----------------------|
| Fraxetin            | ![Fraxetin](image2) |
| Caffeic acid phenetyl ester (CAPE) | ![CAPE](image3) |
| **Pharmacological Inducers of OH-1** | |
| Carnosol            | ![Carnosol](image4) |
| Dimethylfumarate    | ![Dimethylfumarate](image5) |
| Isothiocyanate-cysteine | ![Isothiocyanate-cysteine](image6) |
| Cobalt protoporphyrin (CoPP): CoPP IX | ![CoPP IX](image7) |
| Tricycles containing nonenolizable cyano enones (TCEs) | ![SUN4599](image1) |
|-----------------------------------------------------|-------------------|
| Celecoxib                                            | ![Celecoxib](image2) |
| Naproxinod                                          | ![Naproxinod](image3) |
| Hemin                                               | ![Hemin](image4) |
| NO-releasing compounds: e.g. Sodium Nitroprusside    | ![Sodium Nitroprusside](image5) |
Natural heme-oxygenase-1 inducers

A number of natural antioxidant compounds contained in foods and plants have been demonstrated to be effective non-cytotoxic inducers of the response protein HO-1 in various cellular models. Most of these compounds that induce HO-1 are characterized by phenolic structures and it is speculated that Nrf2 is involved in this induction of HO-1 [33]. The effects of various concentrations of a natural polyphenolic stilbene, resveratrol, on HO activity and HO-1 protein expression in different experimental conditions have been tested. Resveratrol is a non-flavonoid compound produced naturally by plants including grapes, peanuts, cranberries and blueberries. Resveratrol is the major polyphenol in red wine and has been shown to prevent or slow the progression of a wide variety of diseases [34]. The most extensively investigated HO-1 inducer is another natural compound, curcumin (diferuloylmethane). The effects of curcumin are associated with cellular protection against ROS. The level of HO-1 expression was found to be highest with curcumin, followed by demethoxycurcumin and bis-demethoxycurcumin. It has been suggested that the presence of methoxyl groups in the ortho-position on the aromatic ring are essential to enhance HO-1 expression [35].

Pharmacological interest approach of HO-1 inducers

Manipulation of the Nrf2/HO-1 pathway has been shown experimentally to protect against a variety of conditions characterized by oxidative damage and inflammation. Pharmacologically-active compounds have been used to target Nrf2/HO-1. Potent activators of the Nrf2/HO-1 pathway (i.e. carnosol, cobalt protoporphyrin, dimethyl fumarate) have been shown to modulate inflammation in mouse microglial cells [36]. Metalloporphyrins, particularly cobalt protoporphyrin (CoPP) can increase the expression of HO-1. CoPP affects the expression of antioxidant genes and recent data indicate that CoPP reduces mitochondrial production mediated by Foxo1 [37]. A large number of clinical and experimental pharmacological compounds have been shown to induce HO-1, via NO metabolism. The different statins with established antiatherogenic or slow the progression of a wide variety of diseases [34]. The major polyphenol in red wine and has been shown to prevent or slow the progression of a wide variety of diseases [34]. The most extensively investigated HO-1 inducer is another natural compound, curcumin (diferuloylmethane). The effects of curcumin are associated with cellular protection against ROS. The level of HO-1 expression was found to be highest with curcumin, followed by demethoxycurcumin and bis-demethoxycurcumin. It has been suggested that the presence of methoxyl groups in the ortho-position on the aromatic ring are essential to enhance HO-1 expression [35].

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