ANTIOXIDANTS & REDOX SIGNALING
Volume 4, Number 4, 2002

Forum Review

Heme Oxygenase-1: Molecular Mechanisms of Gene Expression in Oxygen-Related Stress

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ABSTRACT

Disturbances of intracellular redox equilibrium may alter eukaryotic gene expression patterns in the manifestation of an adaptive stress response. The inducible heme oxygenase-1 gene, *ho-1*, responds dramatically to changes in cellular redox potential provoked by multiple agents (oxidants, xenobiotics, reactive oxygen species, nitric oxide, and ultraviolet-A radiation) as well as deviations in oxygen tension in excess or deficit of normal physiological levels. This dual response to hyperoxic and hypoxic states renders *ho-1* an intriguing model system for studying oxygen-regulated gene expression. The complexation or depletion of reduced glutathione apparently represents an underlying mechanism by which oxidants trigger the response. Chelatable iron levels also influence the induction of *ho-1* as evidenced by the inhibitory effects of iron-chelating compounds. Redox-sensitive protein kinase cascades (*e.g.,* mitogen-activated protein kinases) participate in *ho-1* regulation. Recent progress in understanding *ho-1* transcription has identified two distal enhancer regions (E1, E2) in the mouse *ho-1* gene that mediate the response to many inducing conditions. This review will examine the potential roles of iron, glutathione, and reactive oxygen species in the upstream events leading to *ho-1* activation following oxygen related stress. *Antioxid. Redox Signal.* 4, 625–632.

INTRODUCTION

THE HEME OXYGENASE-1 (*ho-1*) gene provides a unique model for studying the mechanism(s) by which alterations in cellular redox potential result in gene expression (Fig. 1). The transcriptional up-regulation of the *ho-1* gene follows cellular exposure to agents, such as hydrogen peroxide (H_2O_2) (45, 47), ultraviolet-A (320–380 nm) radiation (45, 47), sodium *m*-arsenite ($NaAsO_2$) (45), heme (3), proinflammatory cytokines (16, 62, 77), bacterial endotoxins (15, 16, 77, 78), growth factors (24, 50), and tumor promoters (40, 49), that directly or indirectly generate intracellular reactive oxygen species (ROS). HO-1 expression thus acts as a general marker of oxidative stress (7). Furthermore, *ho-1* responds to fluctuations in oxygen (O_2) tension in excess (hyperoxia) or deficit (hypoxia) of normal physiological tension (54, 56, 69, 81). Hyperoxia generates an oxidative stress by elevating mitochondrial ROS production relative to normoxia (29). Although increased ROS production typically occurs with reoxygenation after hypoxia, recent controversial evidence suggests that hypoxia itself may increase mitochondrial ROS production in some cell types (17, 25, 91, 92).

The induction of HO-1 by ROS-generating systems occurs in association with the depletion of intracellular reduced glutathione (GSH), and may be enhanced by the chemical depletion of GSH (52). Also, HO-1 induction responds to thiol (-SH)-reactive substances that complex with GSH, including $NaAsO_2$, diethyl maleate, heavy metals, and nitric oxide (NO) (7, 14, 23, 30, 35, 45, 59, 82, 88). Consistent with a role for GSH in HO-1 induction, the antioxidant compound and GSH precursor *N*-acetyl-L-cysteine (NAC) may counter HO-1 induction in many systems (12, 15, 24, 28, 35, 78, 81). Intracellular (nonprotein) iron levels influence HO-1 expression by oxidative, hyperoxic, or hypoxic states, as illustrated by the attenuation of the response in the presence of iron chelators (27, 46, 75, 81, 90). Iron sensitizes cells to oxidant exposure,

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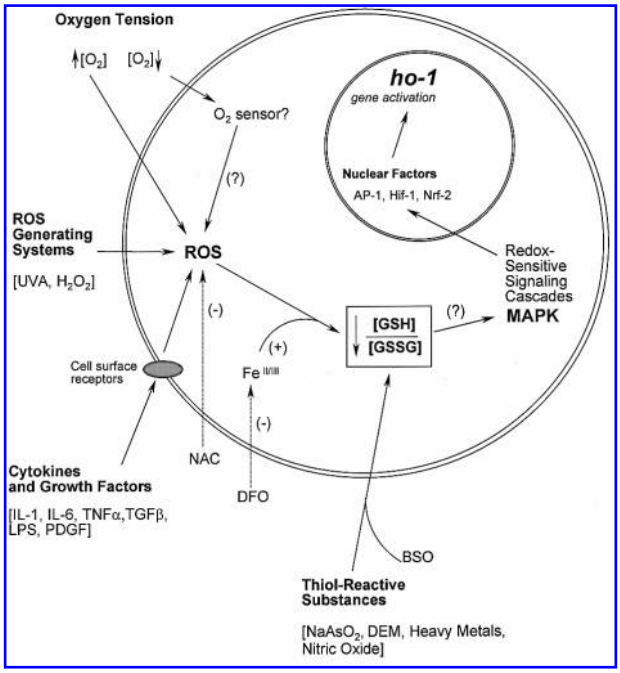

FIG. 1. Redox regulation of heme oxygenase-1 (*ho-1*) gene expression. Schemata represents a cell defined by its plasma membrane (large concentric circles) containing a nucleus (integrated circles). The conditions that activate *ho-1* are grouped into four broad categories: (a) fluctuations in oxygen tension, hyperoxia or hypoxia; (b) exposure to reactive oxygen species (ROS)-generating systems; (c) receptor-mediated cell stimulation by cytokines and growth factors; and (d) exposure to thiol (-SH) reactive substances. The general activation sequence consists of the modulation of intracellular ROS production, a decrease in the intracellular ratio of reduced glutathione to oxidized glutathione, the activation of redox-sensitive signaling components, and finally, the activation of nuclear transcription factors associated with the *ho-1* transcriptional response. The abbreviations used in the diagram include: AP-1, activator protein-1; BSO, D,L-buthionine-(*S,R*)-sulfoximine; DEM, diethyl maleate; DFO, desferrioxamine; $Fe^{II/III}$, ferrous/ferric iron; GSH/GSSG, ratio of intracellular reduced glutathione to oxidized glutathione; Hif-1, hypoxia-inducible factor-1; *ho-1*, heme oxygenase-1; H_2O_2, hydrogen peroxide; IL-1, interleukin-1; IL-6, interleukin-6; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; $NaAsO_2$, sodium-*m*-arsenite; NAC, *N*-acetyl-L-cysteine; Nrf, NF-E2 related factor; O_2, molecular oxygen; [O_2], oxygen tension; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor-β; TNFα, tumor necrosis factor-α; UVA, ultraviolet-A (320–380 nm) radiation.

and acts as a catalyst in free radical reactions, including the peroxidation of membrane lipids, and the Fenton reaction that produces the highly reactive hydroxyl radical (·OH) (10, 11). In addition to prooxidant properties, iron may have direct roles in the transcriptional and posttranscriptional regulation of gene expression (34, 48, 93).

This review describes the regulation of the *ho-1* gene by altered states of oxygen tension; examines the roles of GSH, chelatable iron, and intracellular ROS in mediating these responses; and summarizes current knowledge of the underlying signal transduction pathways and transcriptional apparatus.

EXPRESSION OF *HO-1* UNDER ALTERED STATES OF OXYGEN TENSION

Molecular oxygen (O_2), a vital factor in aerobic metabolism, serves as the terminal electron acceptor and substrate for cytochrome *c* oxidase. The utilization of O_2 for respiration has potentially toxic consequences, as partially reduced forms of oxygen may leak from the mitochondrial electron transport chain. Aerobic organisms have evolved a host of enzymatic and chemical antioxidant defenses to counter the toxic effects of O_2 metabolites under normal physiological O_2 tensions (33). Abnormal O_2 concentrations, such as hypoxia or hyperoxia, may exert stress on ordinary metabolism, resulting in adaptive responses.

Hypoxia

Hypoxia may occur in biological systems as a consequence of restricted oxygen intake or transport during high-altitude exposure, asphyxiation, impaired lung function, carbon monoxide (CO) poisoning, or various pathophysiological states, including arteriosclerosis, fibrosis, and neoplasia (39). In the cardiovascular system, a restriction of blood flow (ischemia or stroke) may reduce O_2 delivery to tissues. The systemic vasculature responds to acute hypoxia by dilation. In contrast, chronic hypoxia may constrict the pulmonary vasculature, leading to pulmonary hypertension (53, 60).

Hypoxia may trigger signaling cascades leading to gene expression events, although the initiating event or "oxygen sensor" remains obscure (13). Various models have suggested that the O_2 sensing apparatus may consist of hemoprotein(s) [mitochondrial cytochrome *c* oxidase, cytochrome p450, an NAD(P)H oxidase, or perhaps other cytosolic hemoprotein(s)], which alter ROS production as a consequence of O_2 tension (13, 31, 42, 84, 99). The direction of ROS flux during hypoxia is also a matter of current controversy. Recent evidence suggests that hypoxia increases ROS production in certain cell types (*i.e.,* cardiomyocytes) (17, 25, 91, 92). Downstream of the enigmatic oxygen sensor, the signal transduction pathways triggered by hypoxia that regulate such gene expression phenomenon may involve redox-sensitive protein components (protein kinases, phosphatases, and nuclear factor oxidoreductases) (43, 51, 96). The transcription factors known to mediate gene regulation during hypoxia include the hypoxia inducible factor-1 (HIF-1) and the activator protein-1 (AP-1) (36, 56, 85, 96). HIF-1 consists of a heterodimer of basic-helix loop helix proteins: HIF-1α, which is stabilized by hypoxia, and HIF-1β, also known as the aryl hydrocarbon nuclear translocator (ARNT) (85). AP-1 consists of Jun family proteins that homo- or heterodimerize with other members of the Jun or Fos families (20). The oxidant inducible transcription factor nuclear factor-κB is typically activated in the reoxygenation phase after hypoxia (80).

The exposure of mammalian cells to hypoxia *in vitro* triggers cell type-specific alterations in protein expression patterns. HO-1 appears to represent a major hypoxia-inducible protein in mammalian cells. Hypoxia regulates the expression of other proteins possibly involved in cellular adaptation, including glucose-regulated proteins (GRPs) (41, 79, 83), drug detoxification enzymes (NADPH:quinone oxidoreductase,

and γ-glutamyl-cysteinyl-synthetase) (72, 96), glycolytic enzymes (87), constitutive and inducible nitric oxide synthases (NOS) (8, 58, 74), cytokines and growth factors (erythropoietin, vascular endothelium growth factor) (31, 71, 86), metallothionein (70), early response gene products (c-Fos, c-Jun) (9, 68), and the growth arrest- and DNA damage-inducible proteins (GADD45 and GADD153) (76). Heacock and Sutherland characterized the hypoxic response in mouse mammary tumor cells (EMT6/Ro) and Chinese hamster ovary (CHO) cells, and identified induced proteins, designated as oxygen regulated proteins (ORP; M_R 260, 150, 100, 80, and 33 kDa) (37, 38). The synthesis rate of these ORPs increased during hypoxia, against a background of impaired cellular protein synthesis, and then declined during reoxygenation (94). The high-molecular-weight ORPs correspond to various GRPs (GRP-170, GRP-94, GRP-78), (41, 79, 83), whereas ORP33 corresponds to HO-1 (69). A distinct series of hypoxia-associated proteins (M_R 56, 47, 39, 36, 34 kDa) (32, 100) appeared in bovine and human vascular (aortic and pulmonary) endothelial cell culture.

Recent studies have clearly demonstrated the HO-1 response to hypoxia in certain cells of vascular origin. Exposure of rat aortic vascular smooth muscle cells (VSMC) to hypoxia induced *ho-1* transcription and mRNA accumulation (56, 64). This response to hypoxia also occurred in rat pulmonary endothelial (PAEC), but not in rat pulmonary artery vascular smooth muscle. Comparative analysis of these cell types demonstrated that different modes of transcription factor binding activities underlie these responses. HO-1 mRNA induction in PAEC occurred in association with increased AP-1 DNA binding activity, whereas the response in VSMC was shown to involve predominately HIF-1 (36, 56).

The importance of HIF-1 in *ho-1* gene activation was further corroborated using mutant Hepa cells deficient in HIF-1β. In contrast to wild-type cells, the mutant cells did not exhibit HO-1 mRNA accumulation in response to hypoxia (56). Interestingly, hypoxic activation of the *ho-1* gene in CHO cells is apparently independent of HIF-1 as demonstrated in mutant CHO cells deficient in HIF-1α (95). Taken together, these results suggest that although HIF-1 mediates the hypoxic induction of HO-1 in some cell types (*i.e.*, VSMC), it may not be the sole obligatory factor.

Ryter *et al.* observed the induction of HO-1 protein levels and enhanced HO enzymatic activity in aortic endothelial cells of bovine origin (BAEC) subjected to hypoxia, which persisted at high levels during subsequent reoxygenation. The endothelial HO-1 induction response to hypoxia was abolished by treatment with iron-chelating agents (desferrioxamine and *ortho*-phenanthroline) or high concentrations of NAC, and enhanced by loading the cells with iron prior to the hypoxia (81). These results argue for a prooxidative role for iron in the HO-1 response to hypoxia. In human dermal fibroblasts, HO-1 mRNA accumulation during hypoxia could also be attenuated by metal chelators, but not NAC (75). Hypoxia modulates iron regulatory protein activity, and thus alters intracellular iron metabolism with reciprocal changes in ferritin and transferrin receptor synthesis (34). Although no direct evidence exists for such an iron-protein-dependent mechanism regulating *HO-1* mRNA stability, the possibility cannot be excluded (75).

Motterlini *et al.* demonstrated a decrease in the ratio of reduced glutathione to oxidized glutathione (GSH/GSSG) in BAEC during the hypoxic induction of HO-1. The authors propose that the GSH depletion is caused by *S*-nitrosothiol formation from the reaction of GSH with NO, which in turn originates from the prior hypoxic activation of iNOS in these cells. Consistent with this hypothesis, inhibitors of iNOS, NO scavengers, and the GSH precursor NAC inhibit the induction of HO activity by hypoxia, whereas treatment with *S*-nitrosoglutathione augments the response (67). Direct NO donation with sodium nitroprusside potentiates the hypoxic response in BAEC (Ryter, unpublished observation). Flavonoid compounds have also been noted to modulate HO-1 expression under hypoxia. For instance, quercetin inhibits the response (81), whereas the spice-derived antioxidant curcumin potentiates the response (66). Cultured rat neonatal cardiomyocytes also respond to hypoxia with elevated levels of HO-1 (12). As with endothelial cells, high concentrations of NAC attenuate the phenomenon (12).

In vivo, exposure to 7% O_2 induced HO-1 mRNA accumulation in rat lung, liver, heart, and aorta (56). Chronic hypoxia and pulmonary arterial banding, shown to increase right ventricular pressure, induced HO-1 mRNA in both ventricles of the rat heart (44).

Recent evidence implicates HO-1 as an inducible mechanism for protection against hypoxic lung injury *in vivo*. HO-1 null mice (*ho-1*$^{-/-}$) develop right ventricular dilation and right myocardial infarction, during chronic hypoxia (10% O_2), relative to wild-type mice that sustain the treatment (97). In this model, no difference in pulmonary hypertension appeared between the lungs of wild-type or *ho-1*$^{-/-}$ mice (97). In contrast, the elevation of HO-1 protein by chemical inducers ($NiCl_2$ or hemin) prevented the development of pulmonary hypertension in the rat lung as a consequence of chronic hypoxia treatment (19). Transgenic mice overexpressing HO-1 specifically in the lung displayed resistance to the inflammatory and hypertensive effects of hypoxia (61).

The induction of stress proteins, including HO-1, by hypoxia in vascular systems may represent an adaptive response to vascular oxidative injury. By altering *ho-1* and NOS gene expression, hypoxia potentially modulates the availability of gaseous second messengers CO and NO. Fluxes in CO production would have consequences in the regulation of vascular function(s), including dilation, expression of vasoconstrictors, inhibition of platelet aggregation, and smooth muscle proliferation (63–65).

Hyperoxia

Hyperoxia, or elevated O_2 tension, also precipitates a stress response in mammalian cells and tissues. The condition arises through the forced administration of O_2 for critical care. Hyperoxia causes oxidative lung injury, generally associated with the increased intracellular production of ROS. Exposure of adult rats to hyperoxia (95% O_2) increased HO-1 mRNA, protein, and enzymatic activity in the rat lung (54). Elevation of lung HO activity was also observed in neonatal rats exposed to hyperoxia for 3 days (21). The transcriptional activation of *ho-1* by hyperoxia was demonstrated *in vitro* using cultured cells of lung origin (epithelial cells, fibro-

blasts, macrophages, and smooth muscle cells) (54). In human cells lines, the activation of HO-1 by hyperoxia could be augmented by prior loading with iron or heme, and diminished in the presence of iron-chelating agents (27, 90). Whereas hyperoxia and hypoxia are two opposite states with respect to O_2 availability, they apparently share mechanistic similarities in the requirement for iron in *ho-1* gene activation. Interestingly, the antioxidant NAC appears ineffective at blocking hyperoxia-induced HO-1 expression (90).

HO-1 and HO-2 potentially contribute to pulmonary defenses against high O_2 levels. Overexpression of HO-1 in lung epithelial cells causes growth arrest, but confers resistance against O_2-mediated cytotoxicity (55). Overexpression of HO-1 in rat fetal lung cells also conferred resistance against hyperoxia (89). Gene transfer of *ho-1* to the lungs provides antiinflammatory and antiapoptotic defense in rat lungs subjected to high O_2 tension (73). HO-2 knockout mice display increased susceptibility to hyperoxia compared with their wild-type counterparts, and accumulate iron in their lungs (22).

SIGNALING INTERMEDIATES AND TRANSCRIPTIONAL APPARATUS

The molecular signaling pathways regulating hypoxic *ho-1* gene activation are still unclear. Kacimi *et al.* have implicated p38 mitogen-activated protein kinase (MAPK) in the hypoxic *ho-1* activation pathway in cardiomyocytes. SB203580, an inhibitor of p38 MAPK, blocked the *ho-1* response to hypoxia, whereas inhibitors of the extracellular regulated kinase (ERK) pathway (PD98059), or of tyrosine kinase (tyrphostin), had no effect (43). Roles for ERK (18, 26) and/or p38 MAPK, (6, 18, 26) have been proposed in the activation of *ho-1* by other inducing chemicals, including $NaAsO_2$ (26), heavy metals (6), and NO (18). The artificial overexpression of MAPK kinase kinases (MEKK1, TAK1, and ASK1) induced *ho-1* in HEPG2 cells (98). The resolution of upstream events in *ho-1* activation is complicated by cell type-specific and inducer-dependent variations, and may be confounded by an incomplete understanding of the specificities of chemical inhibitors.

Deletion mutagenesis studies of the murine *ho-1* gene 5′ flanking sequence linked to reporter gene constructs have revealed two transcriptional enhancer sequences located at −4 kb (E1; originally referred to as SX2) and −10 kb (E2; AB1) of the transcriptional start site (1, 2, 4). In addition to essential functions in maintaining basal promoter activity, these elements mediate the induction of *ho-1* to a wide variety of inducing chemicals, including heavy metals, 12-*O*-tetradecanoylphorbol 13-acetate, endotoxin, heme, and H_2O_2 (1, 2, 4, 15). Both enhancer elements contain repeated essential *cis*-acting DNA motifs designated as stress responsive elements (StRE) with the consensus sequence (T/CGCTGAGTCA). Intrinsic to the StRE appears several overlapping consensus sequences for transcription factor binding sites: AP-1: (TGA(C/G)TCA); v-maf oncoprotein (TGCTGAGTCAGCA); and the Cap'n'Collar/basic-leucine zipper family of proteins (CNC-bZIP) (T/C)GCTGA(G/C)TCA(C/T). The latter sequence is very similar to the antioxidant responsive element (GCNNNGTCA) (5).

Deletion mutagenesis studies have identified the requirement for E1 and the participation of E2 enhancer regions in the regulation of *ho-1* during hyperoxia in RAW 264.7 cells, mediated by the intrinsic AP-1 elements in these regions. The induction response to hyperoxia required the cooperation of STAT (signal transducer and activator of transcription) elements located within the proximal promoter region (57). Hyperoxia caused increased DNA binding activity of AP-1 and STAT (STAT1, STAT3, STAT5) transcription factors in RAW 264.7 cells. In contrast, in VSMC that exhibit strong activation of *ho-1* transcription in response to hypoxia, neither E1 nor E2 responds to hypoxia (56). The hypoxic response in VSMC is associated with increases in HIF-1α and β protein levels, and requires a distinct sequence at −9 kb (hypoxia responsive element) that contains two functional binding sites for HIF-1 (56).

SUMMARY

HO performs a simple metabolic function in the breakdown of heme, with multiple possible physiological consequences. It is now commonly accepted that HO-1 exerts a protective or adaptive effect in the context of oxidative stress or oxygen toxicity. Furthermore, CO, a by-product of HO activity, has taken center stage as a controversial toxic molecule with possible physiological function in the nervous and cardiovascular systems. In the bewildering array of chemical and pathological conditions that trigger HO-1 expression, several common themes emerge. Cellular glutathione status may act as a cellular "sensor" whose equilibrium, when disturbed in favor of consumption or depletion, triggers HO-1 expression by activating redox-sensitive signaling components. Intracellular iron in chelatable nonheme form participates in HO-1 expression under not only oxidative but hyperoxic and hypoxic states. Recent work in the field has identified distinct promoter elements where the signals generated by multiple diverse agents can converge to activate a common transcriptional response. Current efforts attempt to unravel the signal transduction pathways involving redox-sensitive protein kinase and phosphatase activities that regulate *ho-1* under altered states of oxygen tension. The knowledge of how *ho-1* is regulated by diverse stimuli in various disease contexts may be useful information for the development of therapeutic strategies.

ABBREVIATIONS

AP-1, activator protein-1; BAEC, bovine aortic endothelial cells; CHO, Chinese hamster ovary cells; CO, carbon monoxide; ERK, extracellular signal-regulated kinase; GRP, glucose-regulated protein; GSH, glutathione reduced form; GSSG, glutathione oxidized form; HIF-1, hypoxia inducible factor; HO-1, heme oxygenase-1; HO-2, heme oxygenase-2; H_2O_2, hydrogen peroxide; iNOS, inducible nitric oxide syn-

thase; MAPK, mitogen-activated protein kinase; $NaAsO_2$, sodium-*m*-arsenite; NAC, *N*-acetyl-L-cysteine; NO, nitric oxide; NOS, nitric oxide synthase; O_2, molecular oxygen; ORP, oxygen-regulated protein; PAEC, pulmonary artery endothelial cells; ROS, reactive oxygen species; STAT, signal transducer and activator of transcription; StRE, stress response element; VSMC, vascular smooth muscle cells.

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Received for publication August 16, 2001; accepted October 25, 2001.

This article has been cited by:

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