Endoplasmic Reticulum Stress Stimulates Heme Oxygenase-1 Gene Expression in Vascular Smooth Muscle

ROLE IN CELL SURVIVAL*

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Heme oxygenase-1 (HO-1) is a cytoprotective protein that catalyzes the degradation of heme to biliverdin, iron, and carbon monoxide (CO). In the present study, we found that endoplasmic reticulum (ER) stress induced by a variety of experimental agents stimulated a time- and concentration-dependent increase in HO-1 mRNA and protein in vascular smooth muscle cells (SMC). The induction of HO-1 by ER stress was blocked by actinomycin D or cycloheximide and was independent of any changes in HO-1 mRNA stability. Luciferase reporter assays indicated that ER stress stimulate HO-1 promoter activity via the antioxidant response element. Moreover, ER stress induced the nuclear import of Nrf2 and the binding of Nrf2 to the HO-1 antioxidant response element. Interestingly, ER stress stimulated SMC apoptosis, as demonstrated by annexin V binding, caspase-3 activation, and DNA laddering. The induction of apoptosis by ER stress was potentiated by HO inhibition, whereas it was prevented by addition of HO substrate. In addition, exposure of SMC to exogenously administered CO inhibited ER stress-mediated apoptosis, and this was associated with a decrease in the expression of the proapoptotic protein, GADD153. In contrast, the other HO-1 products failed to block apoptosis or GADD153 expression during ER stress. These results demonstrated that ER stress is an inducer of HO-1 gene expression in vascular SMC and that HO-1-derived CO acting in an autocrine fashion to inhibit SMC apoptosis. The capacity of ER stress to stimulate the HO-1/CO system provides a novel mechanism by which this organelle regulates cell survival.

Heme oxygenase (HO) catalyzes the rate-limiting step in the oxidative degradation of heme to biliverdin, iron, and carbon monoxide (CO) (1). Subsequently, biliverdin is rapidly converted to bilirubin by biliverdin reductase. Three distinct isoforms of HO, HO-1, HO-2, and HO-3, have been described (2–4). However, recent work suggests that HO-3 may be a pseudogene derived from HO-2 transcripts (4). The HO-2 isoform is constitutively expressed and is present in high concentrations in the brain and testes (5). In contrast, HO-1 is ubiquitously distributed and strongly induced by oxidative, nitrosative, osmotic, and hemodynamic stress (6–10). Induction of HO-1 by these biochemical and biomechanical stimuli provides an important cellular defense mechanism against tissue injury (7, 9, 11–14). Several postulated mechanisms account for the beneficial effects of HO-1. HO-1 results in the catabolism of the pro-oxidant heme to bile pigments biliverdin and bilirubin, which are potent antioxidants capable of scavenging peroxy radicals and inhibiting lipid peroxidation (15, 16). In addition, HO-1 induction is accompanied by increased ferritin activity, which exerts an additional antioxidant effect by chelating free iron (17). Finally, HO-1 liberates the diatomic gas CO that possesses significant anti-inflammatory and anti-apoptotic properties (18–20).

The endoplasmic reticulum (ER) is a dynamic membranous organelle that plays a critical role in the folding, transport, and processing of newly synthesized proteins (21, 22). Numerous infectious agents, environmental toxins, and adverse metabolic conditions interfere with protein folding leading to ER stress. To protect against ER stress, the ER has evolved highly specific signaling pathways collectively termed the unfolded protein response (UPR). Three ER-resident transmembrane proteins, the kinase and endoribonuclease IRE1, the PERK kinase, and the basic leucine-zipper transcription factor ATF6, have been identified as proximal sensors of ER stress (23). Activation of these sensors results in the up-regulation of genes encoding ER chaperone proteins such as GRP78 that increase protein folding activity and prevent protein aggregation. In addition, the UPR results in translation attenuation to reduce the load of protein synthesis and to prevent further accumulation of unfolded proteins. Finally, when ER function is severely impaired, apoptosis is induced. This apoptotic event is triggered by the activation of the proapoptotic transcription factor GADD153 and/or by the activation of ER-associated caspase-12 (24–26).

Because HO-1 is induced by several forms of cellular stress, the present study examined whether ER stress regulates HO-1 expression. We now report that ER stress is a novel inducer of HO-1 in vascular smooth muscle cells (SMC). Interestingly, the activation of the HO-1 gene by ER stress does not occur via the...
conventional UPR-responsive element but rather through the antioxidant-responsive element (ARE). In addition, we have shown that HO-1-derived CO functions in an autocrine manner to suppress apoptosis. The HO-1/CO system may represent an important adaptive mechanism to promote cell survival during periods of ER stress.

**MATERIALS AND METHODS**

**Materials**—Collagenase, elastase, SDS, Triton X-100, HEPES, cycloheximide, actinomycin D, EDTA, Tween 20, penicillin, streptomycin, dithiothreitol, iron, sucrose, Nonidet P-40, brefeldin A, homocysteine, thapsigargin, and minimum essential medium were purchased from Sigma. Phenylmethylsulfonyl fluoride, aprotinin, leupeptin, and pepstatin A were from Roche Applied Science. Biliverdin, bilirubin, zinc protoporphyrin-IX, and tin protoporphyrin-IX were from Frontier Scientific Purphyrin Products (Logan, Utah). MG132 and proteasome inhibitor I were from Calbiochem; glyceraldehyde-3-phosphate dehydrogenase, or 18 S RNA.

**protein and protein levels were determined by Northern and Western blotting, respectively.**

A polyclonal HO-1 antibody and an anti-KDEL monoclonal antibody that recognizes GRP78 were from StressGen Biotechnologies Inc. (Victoria, Canada); anti-GADD153, Nrf2, lamin B1, and β-actin polyclonal antibodies were from Santa Cruz Biotechnology Inc. (Santa Cruz, CA). A polyclonal HO-1 antibody was from Oncogene (San Diego, CA). [α-32P]CTP (3000 Ci/mmol) was from PerkinElmer Life Sciences.

**Cell Culture**—Vascular SMC were isolated by elastase and collagenase digestion of rat thoracic aortas and characterized as described previously (27). SMC were cultured serially in minimum essential medium supplemented with 10% serum, 2 mM l-glutamine, 5 mM TES, 5 mM dithiothreitol, 0.5 mM phenylmethylsulfonyl fluoride, 10 mM EDTA, 0.5 mM phenylmethylsulfonyl fluoride, 10 mM EDTA, and 0.4% Nonidet P-40. Samples were incubated for 10 min, and centrifuged at 14,000 g. Supernatant containing the nuclear proteins was resolved by SDS-PAGE, and Nrf2 levels were determined by Western blotting using Nrf2 antibody.

**Preparation of Nuclear Extract and Nrf2 Analysis**—Cells were harvested in ice-cold lysis buffer (10 mM HEPES, pH 7.9, 10 mM KCl, 0.1 mM EDTA, 0.5 mM phenylmethylsulfonyl fluoride, 10 μg/ml aprotinin, 10 μg/ml leupeptin, 10 μg/ml pepstatin A, 0.5 mM dithiothreitol, and 0.4% Nonidet P-40). Supernatants were incubated for 10 min, and centrifuged at 14,000 g for 3 min at 4 °C. The resulting nuclear pellet was resuspended in extraction buffer (20 mM HEPES (pH 7.9), 0.4 M NaCl, 1.0 mM EDTA, 1 mM dithiothreitol, 0.5 mM phenylmethylsulfonyl fluoride, 10 μg/ml aprotinin, 10 μg/ml leupeptin, 10 μg/ml pepstatin A, and 10% glyceralde)

**Results**—For the means ± S.E. Statistical analysis was performed with the use of a Student’s two-tailed t test and an analysis of variance when more than two treatment regimens were compared. p < 0.05 was considered statistically significant.

**RESULTS**

**Treatment of vascular SMC with brefeldin A, a well established inducer of ER stress that inhibits the translocation of proteins from the ER to the Golgi apparatus (32), stimulated HO-1 mRNA and protein expression in a concentration-dependent manner (Fig. 1A).** The induction of HO-1 by brefeldin A was delayed, with marked increases in HO-1 mRNA and protein appearing after 24 h of brefeldin A exposure (Fig. 1B). Homocysteine, which promotes protein misfolding in the ER by interfering with disulfide bond formation (21), also induced HO-1 protein expression (Fig. 2A). Similarly, thapsigargin, which induces ER stress by inhibiting ER Ca²⁺-ATPase (33), stimulated the expression of HO-1 protein (Fig. 2B). In addition, proteasomal inhibition, a known stimulus for UPR activation (34), induced HO-1 expression. Incubation of SMC with proteasome inhibitor MG-132 and proteasome inhibitor I increased HO-1 protein expression (Fig. 2B). The induction of ER stress by all of these agents was confirmed by the significant increase in the level of GRP78 (Fig. 2, A and B).

**In the next series of experiments the molecular mechanism by which ER stress induces HO-1 expression was examined.** Incubation of SMC with the protein synthesis inhibitor cycloheximide or the transcriptional inhibitor actinomycin D...
and HO-1 and GRP78 protein were determined by Western blotting. Brefeldin A (BF), homocysteine (Hcy; 3 mM), or thapsigargin (Thaps; 4 μM) for 24 h, and HO-1 and GRP78 protein were determined by Western blotting. B. SMC were exposed to the proteasome inhibitors, MG-132 (0–30 μM) or proteasome inhibitor 1 (PI-1; 0–30 μM) for 24 h, and HO-1 and GRP78 protein were determined by Western blotting. Similar findings were observed in three separate experiments. HO-1 mRNA and protein were blocked by MG-132 (0–30 μM) or proteasome inhibitor 1 (PI-1; 0–30 μM) for 24 h (Fig. 3B). However, the stability of HO-1 transcripts was unaffected by brefeldin. To determine whether increases in HO-1 expression in response to ER stress involve transcriptional activation of the gene, SMC were transiently transfected with a HO-1 promoter construct and promoter activity was monitored. Cadmium, an established activator of the HO-1 promoter (31), induced an ~6-fold increase in promoter activity (Fig. 3C). Brefeldin A and the proteasome inhibitor MG-132 also stimulated more than a 2-fold increase in promoter activity (Fig. 3C). Furthermore, the expression of Nrf2 induced a significant increase in HO-1 promoter activity (Fig. 3C). Interestingly, mutation of the AREs attenuated basal activity and abolished the response to cadmium, brefeldin A, proteasome inhibition, and Nrf2 (Fig. 3C). These results indicated that ER stress activates HO-1 transcription via the ARE.

Electromobility shift assays using an ARE probe corresponding to the mouse HO-1 promoter detected a complex that was significantly increased in intensity by the ER stress inducers, brefeldin A, thapsigargin, and homocysteine (Fig. 4A). Because the transcription factor Nrf2 appears crucial for ARE-mediated gene expression (Fig. 3C) (35), we investigated whether ER stress stimulated the binding of Nrf2 to the ARE. Indeed, supershift electromobility shift assay reactions using an antibody directed against Nrf2 retarded the migration of the ARE protein complex (Fig. 4B) (35). Therefore, the activation of Nrf2 by homocysteine (Fig. 4B) and other ER stress agents was corroborated by the nuclear accumulation of Nrf2.

In subsequent experiments the functional role of HO-1 during ER stress was examined. Treatment of SMC with homocysteine resulted in a significant increase in the rate of apoptosis as reflected by annexin V binding (Fig. 5). However, the addition of the HO inhibitors, zinc protoporphyrin-IX or tin protoporphyrin-IX, increased homocysteine-mediated apoptosis by ~2-fold. These findings suggested that the induction of HO-1 by ER stress may function in an autocrine manner to inhibit SMC apoptosis. Subsequently, we determined which of the HO-1 products mediates this cytoprotective effect. Incubation of SMC with brefeldin A or thapsigargin for 24 h resulted in a significant increase in caspase-3 activity that was reversed by the exogenous administration of CO (200 ppm) (Fig. 6A). Similarly, the stimulation of DNA fragmentation by brefeldin A, thapsigargin, or homocysteine was prevented by CO (Fig. 6, B and C). In contrast, the addition of the bile pigments, biliverdin or bilirubin, or free iron had no effect on DNA laddering (Fig. 6D). Furthermore, increasing endogenous
CO production via the exogenous addition of hemin blocked brefeldin A-mediated DNA fragmentation (Fig. 6E).

Finally, we investigated the effect of CO on specific pathways that promote apoptosis during ER stress. In particular, we examined whether CO regulates the activity of caspase-12 or the expression of GADD153 because both these proteins have been implicated in the induction of apoptosis by ER stress (24–26). Incubation of vascular SMC with brefeldin A stimulated the processing of procaspase-12. Western blot analysis demonstrated a significant decline in procaspase-12 levels following 24 h of brefeldin exposure (Fig. 7A) that paralleled the onset of apoptosis. However, the application of CO (200 ppm) had no effect on the activation of caspase-12 by brefeldin A (Fig. 7A). In contrast, CO markedly attenuated the increase in GADD153 protein expression induced by brefeldin A or homocysteine (Fig. 7B). Moreover, CO blocked the time-dependent induction of GADD153 mRNA by homocysteine (Fig. 7C). The other HO-1 products failed to inhibit GADD153 expression (data not shown).

**DISCUSSION**

In the present study, we identified ER stress as a novel inducer of HO-1 gene expression in vascular SMC. We found that HO-1 is induced by a diverse set of conditions that cause ER stress, including inhibition of protein transport, calcium depletion, homocysteine exposure, and protein accumulation. Furthermore, we discovered that the induction of HO-1 inhibits SMC apoptosis during ER stress via the release of CO. These findings implicate the HO-1/CO system as a critical modulator of cell survival during periods of ER stress.

Our finding that ER stress stimulates HO-1 gene expression in SMC extended an earlier study showing that thapsigargin induces a marked rise in HO-1 mRNA in primary neuronal cells (36). In addition, the induction of HO-1 by homocysteine in cultured cells is also consistent with the increase in HO-1 expression observed in a murine model of hyperhomocysteine-
ER Stress Induces HO-1 Gene Expression

**Fig. 7** Effect of carbon monoxide on endoplasmic reticulum stress-mediated apoptotic pathways in vascular SMC. A, SMC were treated with brefeldin A (BF, 1 μM) for 24 h in the presence or absence of carbon monoxide (CO; 200 ppm), and the processing and activation of caspase-12 was monitored by Western blotting. B, SMC were treated with BF (1 μM) or Hcy (3 mM) for 24 h in the presence or absence of CO (200 ppm), and GADD153 protein expression was monitored by Western blotting. C, SMC were treated with Hcy (3 mM) for various times (0–24 h) in the presence or absence of CO (200 ppm), and GADD153 mRNA expression was monitored by Northern blotting. Similar findings were observed in three separate experiments.

**mia (37).** In contrast, ER stress fails to stimulate HO-1 expression in cultured hepatoma cells (38). The dissimilar results between these studies may reflect differences in cell type, culture conditions, or duration and extent of ER stress. Interestingly, a recent report (39) found that ER stress promotes hyaluronan deposition and leukocyte adhesion to SMC, demonstrating that SMC represent a physiologically relevant cellular target of ER stress.

ER stress induces HO-1 expression in a concentration- and time-dependent manner. The induction of HO-1 by ER stress is dependent on de novo RNA synthesis and does not involve alterations in HO-1 mRNA stability. Transient transfection experiments indicate that ER stress stimulates the transcriptional activation of the HO-1 gene. However, the activation of HO-1 transcription by ER stress does not occur via the classical mammalian UPR element (5'-CCAAT-N5'-CCACG-3'). A computer search of the entire 15 kb of the 5'-flanking region of the mouse HO-1 gene failed to detect any candidate UPR elements. Similarly, computer analysis of a BAC clone sequence (GenBank accession number Z82244) containing the entire human HO-1 gene and greater than 20 kb of the 5'-flanking region did not reveal a UPR element (38). Instead, ER stress induces HO-1 transcription via the ARE. Electromobility shift assays found increased ARE binding in nuclear extracts from SMC exposed to ER stress. Moreover, when the ARE element is mutated, the stimulation of HO-1 promoter activity by ER stress is completely abrogated.

Many nuclear transcription factors have been reported to bind to the ARE. However, recent work indicates that the transcription factor Nrf2 plays a critical role in ARE-dependent HO-1 gene expression (35). Consistent with this, we found that stimulation of HO-1 promoter activity in vascular SMC by Nrf2 is dependent on the presence of AREs in the promoter. Furthermore, we detected Nrf2 binding to the HO-1 ARE in SMC following exposure to ER stress. Under normal conditions, Nrf2 is retained in the cytoplasm via its binding to the cytosolic protein Keap1 (40). However, changes in cellular redox potential and/or phosphorylation of Nrf2 lead to the release of Nrf2 from Keap1 and its translocation to the nucleus, resulting in ARE-mediated gene transcription (40, 41). Interestingly, we observed that ER stress induces the accumulation of Nrf2 in the nucleus of vascular SMC. This finding is supported by a recent study showing that ER stress triggers the nuclear import of Nrf2 in embryonic fibroblasts (42). The activation of Nrf2 appears to involve the ER signaling protein, PERK, which has been shown to phosphorylate and activate Nrf2 in response to ER stress conditions (43). Collectively, these data suggest a model where PERK activation in response to ER stress stimulates the phosphorylation and nuclear translocation of Nrf2 where it complexes with the ARE in the HO-1 promoter to trigger gene expression.

HO-1 exerts important cytoprotective actions in response to numerous cellular insults, (7, 9, 11–14). In the present study, we have shown that HO-1 also counteracts the damaging effect of ER stress. The induction of HO-1 by ER stress contributes to cell survival because inhibition of HO activity augments apoptosis, whereas addition of a HO substrate prevents apoptosis during ER stress. The anti-apoptotic effect of HO-1 is likely mediated via the release of CO because the exogenous administration of CO mimics the cytoprotection afforded by HO-1. In contrast, the other HO-1 products do not protect cells from undergoing apoptosis. CO has no effect on the activation of the ER-specific caspase-12 by ER stress, but it markedly blunts the expression of the proapoptotic transcription factor, GADD153. Interestingly, cells with a targeted deletion of Nrf2 exhibit elevated levels of GADD153 and reduced survival following ER stress relative to wild-type cells (41, 42). It is tempting to speculate that HO-1-derived CO synthesis contributes to the repression of GADD153 expression and increased survival in the wild-type cells.

Recent studies indicate that ER stress may also activate the intrinsic (mitochondrial) and extrinsic (death receptor) signaling pathways to trigger apoptosis (44–46). Given that CO has been shown to block both these signaling pathways (19, 20, 47), it is likely that CO inhibits ER stress-mediated apoptosis via multiple mechanisms. Thus, the induction of HO-1 and the release of CO during ER stress may represent an important survival response in providing cells additional time to execute the UPR and restore ER function. In addition, HO-1-derived CO leads to cell cycle arrest (28, 48), which might allow the cell to concentrate resources on alleviating stress rather than on growth and division.

The ability of HO-1-derived CO to block ER stress-mediated apoptosis may be of clinical significance. ER stress has been implicated in the pathogenesis of a variety of diseases. Cell death following ER stress is believed to contribute to the progression of neurodegenerative disorders such as Alzheimer and Parkinson disease and to the loss of pancreatic β cells in diabetes (49–51). Furthermore, ER stress may underlie cell death following ischemia-reperfusion (52). In addition, damage to vascular cells by ER stress in hyperhomocysteinemic states promotes the development of atherosclerosis (53–56). Thus, approaches that target HO-1 or CO to sites of ER stress offer a promising therapeutic modality in treating a variety of disorders related to ER stress.

In conclusion, the present study has demonstrated that ER stress induces HO-1 gene expression in vascular SMC and that HO-1-catalyzed CO formation inhibits apoptosis during ER...
stress. In addition, it has shown that the anti-apoptotic effect of CO is associated with a decrease in GADD153 expression. The HO-1/CO system represents a potentially new therapeutic target in ameliorating diseases associated with ER stress.

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