Mechanism of heme oxygenase-1 gene induction by curcumin in human renal proximal tubule cells

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Hill-Kapturczak, Nathalie, Vijayalaksmi Thamilvelvan, Feiyan Liu, Harry S. Nick, and Anupam Agarwal. Mechanism of heme oxygenase-1 gene induction by curcumin in human renal proximal tubule cells. Am J Physiol Renal Physiol 281: F851–F859, 2001. First published August 9, 2001; 10.1152/ajprenal.00140.2001.—Heme oxygenase-1 (HO-1) catalyzes the rate-limiting step in heme degradation, releasing iron, carbon monoxide, and biliverdin. Induction of HO-1 occurs as an adaptive and protective response to several inflammatory stimuli. The transcription factor activator protein-1 (AP-1) has been implicated in the activation of the HO-1 gene. To elucidate the molecular mechanism of HO-1 induction, we examined the effects of diferuloylmethane (curcumin), an inhibitor of the transcription factor AP-1. Surprisingly, curcumin by itself was a very potent inducer of HO-1. Curcumin has anti-inflammatory, antioxidant, and renoprotective effects. To evaluate the mechanism of curcumin-mediated induction of HO-1, confluent human renal proximal tubule cells were exposed to curcumin (1–8 μM). We observed a time- and dose-dependent induction of HO-1 mRNA that was associated with increased HO-1 protein. Coincubation of curcumin with actinomycin D completely blocked the upregulation of HO-1 mRNA. Blockade of nuclear factor-κB (NF-κB) with an IkBα phosphorylation inhibitor attenuated curcumin-mediated induction of HO-1 mRNA and protein. These data demonstrate that curcumin induces HO-1 mRNA and protein in renal proximal tubule cells. HO-1 induction by curcumin is mediated, at least in part, via transcriptional mechanisms and involves the NF-κB pathway.

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6-responsive elements as well as other transcription factors have been reported in the promoter region of the HO-1 gene (15, 33), suggesting a potential role for these transacting factors in modulating HO-1 gene expression. The present investigation was designed to evaluate the signaling pathways involved in the activation of the human HO-1 gene by various oxidant stimuli. We therefore explored the role of curcumin, an inhibitor of the transcription factor AP-1, in human proximal tubule cells. Surprisingly, curcumin by itself was a potent inducer of HO-1 mRNA and protein.

Curcumin, a major constituent of the food spice turmeric, exhibits potent antioxidant, anticarcinogenic, and anti-inflammatory properties (1, 50, 53). Curcumin has a long history of medicinal use in India and Southeast Asia for a variety of inflammatory conditions and other disease pathologies (8). Curcumin inhibits lipid peroxidation and scavenges superoxide anions, hydroxyl radicals, and NO (8, 18, 53, 57). Curcumin has been shown to be cytoprotective in several models of oxidant-induced renal injury (18, 31, 55, 61). The mechanism of the cytoprotective effects of curcumin, however, is not well understood. It has been suggested that the anticarcinogenic and anti-inflammatory properties of curcumin may be due to its ability to inhibit cellular gene expression regulated by transcription factors such as Egr-1 and AP-1 (29, 45, 56).

In an attempt to elucidate the molecular mechanism and the signaling pathway involved, we examined the effects of N-acetylcysteine (NAC), deferoxamine (DFO), tyrosine kinase inhibitors, actinomycin D and cycloheximide, and an inhibitor of the NF-κB pathway on curcumin-mediated HO-1 induction in human renal proximal tubule cells.

**EXPERIMENTAL PROCEDURES**

**Reagents.** Tissue culture media, serum, and supplements were obtained from Clonetics (Walkersville, MD). Actinomycin D, anti-human ferritin antibody, cycloheximide, curcumin, DFO, hemin, NAC, and nordihydroguaiaretic acid (NDGA) were obtained from Sigma (St. Louis, MO). Rabbit polyclonal antibody against rat HO-1 was from StressGen Biotech (Vancouver, BC). BAY 11–7082, a blocker of inhibitor IκB phosphorylation and degradation, was from Biomol Research Laboratories, (Plymouth Meeting, PA). Tyrosine kinase inhibitors, herbimycin and genistein were obtained from Calbiochem (San Diego, CA).

**Cell culture.** Human renal proximal tubule cells (HPTC; Clonetics) were grown in renal epithelial basal medium supplemented with fetal bovine serum (FBS; 5%), gentamicin (50 μg/ml), amphotericin B (50 μg/ml), insulin (5 μg/ml), transferrin (10 μg/ml), triiodothyronine (6.5 ng/ml), hydrocortisone (0.5 μg/ml), epinephrine (0.5 μg/ml), and human epidermal growth factor (10 ng/ml), at 37°C in 95% air-5% CO2. These cells have been shown to be positive for γ-glutamyltranspeptidase, an enzyme marker for proximal tubule cells. We also confirmed the presence of morphological features of proximal tubule cells, by electron microscopy, in HPTC grown on Transwell cell culture filters. HPTC exhibited microvilli, abundant mitochondria, lysosomes, and endocytotic vacuoles. Studies were performed on HPTC cultures over a range of no more than four to five passages. HK-2 cells (ATCC), an immortalized human proximal tubule epithelial cell line from normal adult kidney (51), were grown in keratinocyte-serum-free medium supplemented with 5 ng/ml recombinant epidermal growth factor and 40 μg/ml bovine pituitary extract (GIBCO BRL, Rockville, MD). Cells were grown in 100-mm tissue culture plates and studied as a confluent monolayer in all experiments. Twenty-four hours before stimulation, media were changed in HPTC to complete media containing 0.5% FBS.

**Northern analysis.** Total cellular RNA was extracted from cultured cells using the method of Chomczynski and Sacchi (16). The RNA was electrophoresed on 1% agarose-formaldehyde gels, blotted onto nylon membranes, and hybridized to a 32P-labeled cDNA probe for human HO-1. To control for loading and transfer of RNA, the blots were reprobed with a cDNA probe for human glyceraldehyde-3-phosphate dehydrogenase (GAPDH). Autoradiography was performed with the use of intensifying screens at ~80°C. Densitometry was performed using National Institutes of Health Image 1.60 software on a Power Macintosh computer.

**Immunoblot analysis.** For ferritin immunoblots, cells were washed and collected in a solution of 8 mM Na2HPO4, 1.5 mM KH2PO4, 2.7 mM KCl, and 140 mM NaCl, and centrifuged at 1,000 g for 2 min. The pellet was resuspended in potassium phosphate buffer, pH 7.4, containing 10 mM EDTA, sonicated for 20 s, and centrifuged at 10,000 g, and then the supernatant was collected for Western blot analysis. For HO-1 immunoblots, cells were washed twice with ice-cold PBS and lysed in Triton lysis buffer. Protein concentrations were determined by bicinchoninic acid assay (Pierce, Rockford, IL). Samples (20 μg) were separated in a 10 (for HO-1) or 15% (for ferritin) SDS-polyacrylamide gel and then transferred onto a polyvinylidene difluoride membrane. The membranes were incubated for 1.5 h with a rabbit polyclonal antibody against rat HO-1 (1:500 dilution) or anti-human ferritin antibody (1:2,000) followed by incubation with peroxidase-conjugated goat anti-rabbit IgG antibody (1:20,000 dilution) for 1 h. Labeled protein bands were examined using chemiluminescence (Pierce).

**Data analysis.** Data are expressed as means ± SE. Statistical analysis of HO-1 mRNA levels in the different groups was performed using ANOVA and the Student-Newman-Keuls test. All results were considered significant at P < 0.05.

**RESULTS**

Curcumin induces HO-1 mRNA and protein expression in human renal proximal tubule cells. Curcumin has previously been shown to inhibit the transcription factor AP-1 (45, 56). AP-1 has been implicated in the activation of the HO-1 gene (7, 15). Therefore, we determined the effects of curcumin on stimulus-mediated HO-1 induction in HPTC. Interestingly, curcumin alone induced HO-1 mRNA and protein in HPTC. A 4-h exposure of HPTC to curcumin at concentrations of 1.0, 2.0, 4.0, and 8.0 μM resulted in a dose-dependent increase (up to 12-fold) of HO-1 mRNA (Fig. 1A). Immunoblot analysis demonstrated that induction of HO-1 mRNA by curcumin (8.0 μM) was accompanied by a fivefold increase in HO-1 protein (Fig. 1B). Induction of HO-1 mRNA was observed as early as 2 h, and peaked at 6 h, in the presence of curcumin (8.0 μM) (Fig. 1C). Ethanol (0.01%, vehicle) alone did not induce HO-1 mRNA. Curcumin (8.0 μM, 4 h) also resulted in a significant induction of HO-1 mRNA in HK-2 cells, an immortalized human proximal
tubule cell line (Fig. 1D). No cytotoxicity was observed by using the above concentrations of curcumin for up to 24 h.

**Induction of HO-1 mRNA by curcumin requires RNA synthesis.** To evaluate the mechanism of curcumin-mediated HO-1 induction, confluent HPTC were cotreated with 8 μM curcumin and 4 μM actinomycin D, a transcriptional inhibitor, or 20 μM cycloheximide, an inhibitor of protein synthesis, for 4 h. Actinomycin D completely blocked curcumin-mediated HO-1 mRNA induction (Fig. 2). Cycloheximide had no significant effect on the upregulation of HO-1 mRNA steady-state levels in response to curcumin (Fig. 2). These data suggest that HO-1 induction by curcumin is dependent on RNA synthesis and is not dependent on de novo protein synthesis.

Curcumin-induced HO-1 gene expression is not dependent on increased mRNA stability. To examine whether increased HO-1 gene expression was a result of increased mRNA stability, confluent HPTC were preincubated with curcumin followed by the addition of actinomycin D. Cells were incubated with 8 μM curcumin for 4 h, washed, and exposed to media containing 4 μM actinomycin D in the absence or presence of an additional dose of 8 μM curcumin. RNA was isolated and processed at 0.5, 1, 2, 4, 8, 16, and 24 h, respectively. No significant change in the half-life of HO-1 mRNA was observed in the actinomycin D-treated cells in the presence or absence of the second dose of curcumin (Fig. 3). These data indicate that the half-life of curcumin-mediated HO-1 mRNA induction is ~1.8 h and is not dependent on increases in mRNA stability.

**Curcumin induces ferritin protein expression in HPTC.** Previous studies have shown that, in several instances, induction of HO-1 is coupled to the induction of ferritin, which safely sequesters the iron released during heme degradation (3, 11, 41). Therefore, we examined the effects of 8 μM curcumin on ferritin induction. Immunoblot analysis demonstrated a 2.6-fold induction of light-chain ferritin after a 72-h exposure to curcumin in HPTC (Fig. 4). A modest increase in heavy chain ferritin was also observed, represented by the band at ~21 kDa (Fig. 4).

**Antioxidants and tyrosine kinase inhibitors do not inhibit curcumin-mediated induction of HO-1 mRNA.** NAC, an antioxidant, has been reported to block induction of HO-1 by the cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-1α in endothelial cells (59). In addition, we have previously reported that DFO, an iron chelator, inhibited HO-1 induction by oxidized LDL and hyperoxia in endothelial cells (3, 23).
We examined the effects of the above agents on curcumin-mediated induction of HO-1 mRNA. HPTC were pretreated with 500 μM DFO overnight or 50 μM and 1 mM NAC for 1 h. Cotreatment of DFO or NAC with 8 μM curcumin for 4 h had no effect on curcumin-mediated HO-1 mRNA induction (Fig. 5A). Therefore, induction of HO-1 by curcumin appears to be through a mechanism independent of overt oxidative stress and the generation of reactive oxygen species.

The tyrosine kinase pathway has also been implicated in the induction of HO-1 by hemin, cadmium, and sodium arsenite (37). However, the tyrosine kinase inhibitors herbimycin A (1 μM) and genistein (1 and 10 μM), at concentrations in the range of the IC50 for tyrosine kinases, failed to block the induction of HO-1 mRNA by curcumin (8 μM, 4 h) (Fig. 5B), suggesting that the tyrosine kinase pathway is not involved in curcumin-mediated HO-1 induction.

The NF-κB pathway is involved in curcumin-mediated induction of HO-1 mRNA and protein. At high concentrations (20–60 μM), curcumin is an inhibitor of NF-κB, and at lower concentrations (<10 μM) it selectively inhibits AP-1 (6, 35, 45). NF-κB is normally present in the cytosol, where it is bound to an inhibitory protein component, IκB (35). IκB undergoes phosphorylation, ubiquination, and degradation when activated, thereby releasing active NF-κB, which then translocates into the nucleus (9, 20). Coincubation of HPTC with curcumin (8 μM) and BAY 11-7082 (10 μM), an inhibitor of IκB phosphorylation (46), abolished curcumin-mediated induction of HO-1 mRNA (Fig. 6, A and B) and protein (Fig. 6C). BAY 11-7082 (10 μM) alone had no effect on HO-1 induction.

NDGA, another AP-1 inhibitor, has been shown to inhibit TNF-α activation of vascular cell adhesion molecule (VCAM)-1 expression in human dermal microvascular endothelial cells (6). Therefore, the effect of NDGA on HO-1 mRNA in HPTC was also examined. Similar to curcumin, NDGA (10 μM, 4 h) alone induced HO-1 mRNA, and coincubation with BAY 11-7082 (10 μM) blocked the NDGA-mediated induction of HO-1 mRNA in HPTC (Fig. 6D). Therefore, the NF-κB pathway appears to be involved in NDGA- as well as curcumin-mediated induction of HO-1 in human renal epithelial cells.

DISCUSSION

There is considerable evidence to support the involvement of reactive oxygen species in the pathogenesis of renal tubular injury from ischemia-reperfusion and nephrotoxins (10, 44, 52, 63). While measures of free radical generation and lipid peroxidation are increased, a variety of antioxidants and several oxidant scavenging enzymes have been shown to attenuate the course of renal injury (10, 63). In such states of increased oxidative stress, cells and tissues gear up inherent defense systems as an adaptive response. One such antioxidant response in renal tubules exposed to...
injurious stimuli is the robust and dramatic induction of HO-1. Induction of HO-1 occurs in several models of acute renal injury and plays a cytoprotective role (41, 42, 54). Studies using chemical inducers or inhibitors as well as studies in HO-1-knockout mice provide evidence for a protective role of HO-1 in renal injury (42, 54). The induction of HO-1 has been recognized as a characteristic cellular response to a diverse array of potentially injurious stimuli in several nonrenal biological systems as well (15, 43, 65). Besides its heme-degrading function, several of the by-products of the HO-1 catalyzed reaction have been shown to have antioxidant, anti-inflammatory, as well as antiapoptotic effects (25, 40, 43, 48, 65).

The molecular mechanisms underlying HO-1 induction are complex and tightly regulated at the level of transcription. In the case of the mouse HO-1 gene, Alam and colleagues (7, 15) have implicated AP-1 and related transcription factors in the activation of the HO-1 gene after oxidant stressors. In an attempt to evaluate the role of AP-1 in the induction of the HO-1 gene in human proximal tubule cells, we were surprised to find that low doses of curcumin, an AP-1 inhibitor, upregulated HO-1 mRNA and protein. Motterlini et al. (39) have recently reported the induction of HO-1 by curcumin in bovine endothelial cells. Furthermore, they have observed that prior induction of HO-1 by curcumin rendered significant resistance of cells to glucose oxidase-induced cell damage after a hypoxic stimulus (39). The observation that an inhibitor (curcumin) of a transcription factor (AP-1) induces expression of HO-1 is similar to the findings of Hartsfield et al. (26). They have reported dramatic induction of HO-1 with pyrrolidine dithiocarbamate (PDTC), an inhibitor of NF-κB, while they were studying the involvement of the NF-κB pathway in NO-mediated induction of HO-1. In addition, these authors have demonstrated that PDTC-mediated induction of HO-1 occurred via AP-1 (26).

Fig. 5. Effect of antioxidants, N-acetylcysteine (NAC) and defereroxamine (DFO), and tyrosine kinase inhibitors, herbimycin (Herb) and genistein (Gen), on curcumin-mediated induction of HO-1 mRNA. A: confluent monolayers of HPTCs were pretreated with DFO (500 μM) overnight or NAC (50 μM and 1 mM) for 1 h followed by cotreatment of DFO or NAC with curcumin (8 μM) for 4 h. B: confluent monolayers of HK-2s were pretreated with Herb (1 μM) or Gen (1 and 10 μM) for 30 min followed by the addition of curcumin (8 μM) for 4 h. Total RNA was isolated, electrophoresed, transferred to a nylon membrane, and hybridized with a 32P-labeled human HO-1 cDNA probe. The membrane was stripped and reprobed with a human GAPDH cDNA probe to control for loading and transfer. Results are representative of 3 independent experiments.

Fig. 6. Effect of IκB phosphorylation inhibitor, BAY 11-7082, on curcumin and nordihydroguaiaretic acid (NDGA)-mediated induction of HO-1 expression. A: confluent monolayers of HPTCs were coincubated for 4 h in serum-free medium containing curcumin (8 μM) in the presence or absence of BAY 11-7082 (10 μM). Total RNA was isolated, electrophoresed, transferred to a nylon membrane, and hybridized with a 32P-labeled human HO-1 cDNA probe. The membrane was stripped and reprobed with a human GAPDH cDNA probe to control for loading and transfer. B: results representative of 3 independent experiments and the densitometric analysis of the HO-1/GAPDH message are shown. *P < 0.01, control vs. curcumin alone, vs. curcumin+BAY 11-7082 and vs. BAY 11-7082 alone. C: HPTCs were incubated in serum-free medium containing curcumin (8 μM) in the presence and absence of BAY 11-7082 (10 μM) for 12 h. Western blot analysis was performed as described in EXPERIMENTAL PROCEDURES. D: HPTCs were incubated in serum-free medium containing NDGA (10 μM) in the presence and absence of BAY 11-7082 (10 μM) for 4 h. Total RNA was processed, and Northern analysis was performed as described above.
Curcumin, a polyphenolic compound, belongs to the bioflavonoid family and exhibits potent antioxidant, anticarcinogenic, and anti-inflammatory properties (1, 8, 18, 50, 53, 57). The beneficial effects of curcumin have been well documented in both renal and nonrenal models of oxidant injury (18, 31, 55, 60, 61). However, the exact mechanism of the beneficial effects is not clearly known. Curcumin inhibits lipid peroxidation and scavenges superoxide anions, hydroxyl radicals, and NO (18, 53, 57). Curcumin and a related bioflavonoid, quercetin, have also been shown to decrease immune- and nonimmune-mediated renal injury in ischemia reperfusion (55). When used either alone or in combination with mycophenolate mofetil, quercetin and curcumin reduce renal injury and attenuate expression of proinflammatory cytokines (55). More recently, curcumin has been shown to induce the expression of HO-1 in both normal and obstructed rat kidneys (31), providing in vivo application to the use of curcumin as a relevant HO-1 inducer. The localization of such induction in the kidney has not been reported yet and would be of interest. Our studies have also demonstrated the induction of ferritin by curcumin. Although we have not evaluated the mechanism of this induction, in most instances ferritin is coinduced with HO-1 (11, 41, 62). However, inhibition of HO-1 activity does not always result in decreased ferritin content (2, 12), suggesting that increased ferritin can occur via mechanisms independent of iron release from the HO-1 reaction. Given that curcumin induces HO-1, it is tempting to speculate that the antioxidant and anti-inflammatory properties exhibited by curcumin may be mediated, at least in part, through HO-1 induction.

At the cellular level, curcumin has been reported to inhibit expression of genes such as inducible NOS, VCAM-1, E-selectin, and others via suppression of the AP-1 transcription factor (6, 13, 14, 29). AP-1 proteins, such as intercellular adhesion molecule-1, VCAM-1, and E-selectin. Significant anti-inflammatory effects have also been observed in vivo with a related compound (46). Reversible activation of stress-activated kinases p38 and JNK-1 and activation of tyrosine kinases such as intercellular adhesion molecule-1, VCAM-1, and E-selectin. Significant anti-inflammatory effects have also been observed in vivo with a related compound (46). Reversible activation of stress-activated kinases p38 and JNK-1 and activation of tyrosine kinase have also been shown with these compounds (46). The authors suggest that these compounds do not act as global inhibitors of cytokine-induced phosphorylation events but selectively inhibit phosphorylation of IkBα (46). In the present studies, inhibition of NF-κB, using one of the novel inhibitors of IkBα phosphorylation, which inhibited cytokine-induced expression of adhesion molecules such as intercellular adhesion molecula-1, VCAM-1, and E-selectin. Significant anti-inflammatory effects have also been observed in vivo with a related compound (46). Reversible activation of stress-activated kinases p38 and JNK-1 and activation of tyrosine kinase have also been shown with these compounds (46). The authors suggest that these compounds do not act as global inhibitors of cytokine-induced phosphorylation events but selectively inhibit phosphorylation of IkBα (46). In the previous studies, inhibition of NF-κB, using one of the novel inhibitors of IkBα phosphorylation, BAY 11-7082 (10 μM), completely blocked curcumin-mediated HO-1 mRNA and protein induction. It is interesting that curcumin, on the one hand, induces HO-1 via a proinflammatory transcription factor (NF-κB) but, on the other hand, exhibits antioxidant and anti-inflammatory properties, further emphasizing the functional significance of HO-1 as an adaptive response to inflammation.

In an effort to identify regulatory sequences that control curcumin-mediated HO-1 induction in HPTC, we have evaluated up to −4.5 kb of the human HO-1 promoter region (containing consensus binding sites for AP-1 and NF-κB). This fragment responds partially to known inducers of the gene (e.g. heme and cadmium) but lacks the cis-acting elements necessary for cur-
Cumin-mediated induction of HO-1 (data not shown). The absence of a response with the −4.5-kb human HO-1 promoter region to curcumin is further corroborated by the failure of this fragment to respond to other stimuli that directly increase de novo HO-1 gene transcription, i.e., oxidized lipids, hydrogen peroxide, hypoxia, and iron/hypoxia (5, 23). Based on the results of our present study, which implicates NF-kB as a potential transcription factor involved in cumin-mediated HO-1 induction, it is possible that an important NF-kB site(s) outside of the −4.5-kb promoter region may be responsible for HO-1 gene induction. Further studies using chromatin structure analysis to delineate the regions around the human HO-1 gene that control cumin-mediated HO-1 induction would be of interest.

The tyrosine kinase pathway has also been implicated in the induction of HO-1 by hemin, cadmium, and sodium arsenite (37). Bioflavonoids, such as quercetin and curcumin, have a common polyphenolic structure and, in addition to inhibiting transcription factors, are also broadly acting inhibitors of both cytosolic and membrane tyrosine kinases. Curcumin has been shown to inhibit the activities of cellular kinases, including protein kinase C and tyrosine protein kinase, and to be a potent inhibitor of the initiation, promotion, and progression of several types of human cancers (49). In the present studies, the tyrosine kinase inhibitors herbimycin and genistein had no effect on cumin-mediated HO-1 induction, suggesting that this pathway is not involved.

Changes in cellular oxidative stress are critical in the induction of the HO-1 gene by several stimuli. However, similar to the observations of Motterlini et al. (39), we have not observed any inhibition of cumin-mediated HO-1 induction by the antioxidant NAC. These results are similar to the mechanism of HO-1 gene induction by transforming growth factor-β that seems to be independent of changes in the cellular redox state (28). In addition, unlike the effects of DFO on oxidized LDL (3)- or hyperoxia (23)-mediated induction of HO-1, we have not observed any effect of DFO on cumin-mediated HO-1 induction. These data suggest that the induction of HO-1 may not always represent an index of changes in the cellular redox status and that other non-redox-related pathways may exist and need further elucidation.

In summary, curcumin induces HO-1 mRNA and protein as well as ferritin protein in HPTCs. HO-1 induction by curcumin is mediated, at least in part, via transcriptional mechanisms and most likely involves the NF-kB pathway. The beneficial effects of curcumin may, in part, be mediated through an increase in HO-1 gene expression, and further studies to explore this correlation are necessary in models of renal injury.

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REFERENCES


