Genetic suppression of HO-1 exacerbates renal damage: reversed by an increase in the antiapoptotic signaling pathway

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Olszanecki R., Rezzani R., Omura S., Stec DE., Rodella L., Botros FT., Goodman AI., Drummond G., Abraham NG. Genetic suppression of HO-1 exacerbates renal damage: reversed by an increase in the antiapoptotic signaling pathway. Am J Physiol Renal Physiol 292: F148—F157, 2007. First published August 29, 2006; doi:10.1152/ajprenal.00261.2006.—Apoptosis has been shown to contribute to the development of acute and chronic renal failure. The antiapoptotic action of the heme oxygenase (HO) system may represent an important protective mechanism in kidney pathology. We examined whether the lack of HO-1 would influence apoptosis in clipped kidneys of two-kidney, one-clip (2K1C) rats. Five-day-old Sprague-Dawley rats were injected in the left ventricle with clipped kidneys of two-kidney, one-clip (2K1C) rats. Five-day-old Sprague-Dawley rats were injected in the left ventricle with 5 × 10^6 colony-forming units/ml of retrovirus containing rat HO-1 antisense (LSN-RHO-1-AS) or control retrovirus (LXSN). After 3 mo, a 0.25-mm U-shaped silver clip was placed around the left renal artery. Animals were killed 3 wk later. Clipping the renal artery in LSN-RHO-1-AS rats did not result in increased HO-1 expression. In contrast to LXSN animals, 2K1C LSN-RHO-1-AS rats showed increased expression of cyclooxygenase 2 (COX-2) and higher 3-nitrotyrosine (3-NT) content as well as increased expression of the proapoptotic protein Apaf-1 and caspase-3 activity. Clipping the renal artery in LXSN rats resulted in increased expression of the antiapoptotic proteins Bcl-2 and Bcl-xl, while clipping the renal artery in LSN-RHO-1-AS rats did not change Bcl-2 levels and decreased the levels of Bcl-xl. Treatment of LSN-RHO-1-AS rats with cobalt protoporphyrin resulted in induction of renal HO-1, which was accompanied by decreases in blood pressure, COX-2, 3-NT, and caspase-3 activity, and increased expression of anti-apoptotic molecules (Bcl-2, Bcl-xl, Akt and p-Akt) in the clipped kidneys. These findings underscore the prominent role of HO-1 in counteracting apoptosis in this 2K1C renovascular hypertension model.

Heme oxygenase; hypertension; 2K1C; apoptosis; oxidative stress

HEM E OXYGENASE (HO) CATALYZES the rate-limiting step in heme degradation, producing iron, carbon monoxide (CO), and biliverdin, which is rapidly converted to bilirubin. Two major HO isoforms, the products of two distinct genes, have been described: HO-1, an inducible isoform, and HO-2, a constitutively expressed isoform. HO-1 is induced by heme and a variety of nonheme stimuli, including heavy metals, reactive oxygen species (ROS), nitric oxide (NO), ANG II, endotoxin, and cytokines (1, 2). In general, upregulation of HO-1 serves as an adaptive and beneficial response to these stimuli.

Induction of HO-1 has been shown to play a cytoprotective role in renal injury secondary to rhabdomyolysis (32), ischemia-reperfusion injury (31), glomerulonephritis (16), renal transplant rejection (7), and nephrotoxins (e.g., cisplatin) (4). Under these conditions, the protective effects of HO were related to degradation of the toxic free-heme moiety and stimulation of efflux of prooxidant iron from the cells, and also to the biological actions of bilirubin, a potent antioxidant (41) and CO, a vasodilatory and anti-inflammatory molecule (38).

Recently, inhibition of apoptosis has been proposed as a new mechanism for HO-mediated cytoprotection. Several lines of evidence point to the antiapoptotic role of HO. The absence of the HO-1 gene significantly increases the susceptibility of fibroblasts to stressful or toxic insult (34), while, on the other hand, fibroblasts (20) and neurons (14) overexpressing HO-1 are resistant to stress-mediated cell death. Furthermore, both pharmacological HO-1 induction and HO-1 gene overexpression render human renal epithelial cells resistant to cisplatin-induced apoptosis (39). HO-1–/– mice have been shown to exhibit increased susceptibility to renal apoptosis and necrosis after treatment with cisplatin (39). Intriguingly, the mechanism(s) by which HO-1 exerts its antiapoptotic effect, whether it is principally through the action of CO (13), the regulation of cellular iron (20), or the generation of bilirubin (17), is still a matter of debate. Recent reports underscore the role of enhanced apoptosis in the development of various acute and chronic renal diseases (25, 30, 46). Thus we hypothesize that the antiapoptotic action of the HO system may represent an important protective mechanism in kidney pathology.

In the two-kidney, one-clip (2K1C) model of renovascular hypertension, clipping one of the renal arteries decreases perfusion pressure to the clipped kidney, which stimulates renin release, increases ANG II production, and causes a rise in blood pressure. The role of renal apoptosis in the 2K1C model has not been established; however, clipping the renal artery results in renal atrophy associated with cortical hypoxia (50) and increased renal production of ROS (29), both known as potent triggers of apoptosis (19, 42).

Recently, we have shown that prolonged pharmacologically mediated upregulation of HO-1 ameliorates the development of hypertension in 2K1C rats and prevents atrophy of the clipped kidney by mechanisms involving antioxidant and anti-inflammatory actions as evidenced by decreases in renal 3-nitrotyrosine (3-NT) and cyclooxygenase (COX-2) expression, respectively (11). We hypothesize that the antiapoptotic action may represent an important mechanism...
of HO-1-dependent cytoprotection in the clipped kidneys of 2K1C rats.

The objective of the present study was to elucidate whether the lack of HO-1, achieved with retroviral transfer of rat antisense HO-1 (LSN-RHO-1-AS) to Sprague-Dawley rats, would affect blood pressure and expression of selected pro- and antiapoptotic molecules in clipped kidneys in the 2K1C model and whether the changes elicited by the lack of HO-1 might be reversed by the chemical induction of HO-1 in LSN-RHO-1-AS rats. We report that the retroviral transfer of LSN-RHO-1-AS increased blood pressure and apoptosis, an effect reversed by induction of HO-1 in this animal model of renovascular hypertension.

MATERIALS AND METHODS

Generation of HO-1-AS transgenic rats. Genetic suppression of HO-1 was accomplished by delivery of the HO-1 gene in antisense orientation using retroviral gene transfer of rat HO-1-AS to newborn Sprague-Dawley (SD) rats as described previously (52). Each experiment required nine pregnant rats (Charles River Labs, Wilmington, MA) to deliver a total of ~80 littersmates. Male rats (~50%) were separated and used for viral delivery. The concentrated retroviruses (3–5 × 10^9 cfu/ml) were prepared as previously described (52) and injected intraventricularly at day 5 (20 μl) and at day 12 (40 μl). Following injection, the rats were allowed to recover and were returned to their mothers for continued weaning. Transgenic rats underexpressing the HO-1 gene were kept in a pathogen-free environment. The animals were weaned at 21 days and housed in their own cages. To test suppression of HO-1 expression in LXS N- and LSN-RHO-1-AS-transduced animals, thoracic aortas were removed from 1-mo-old rats and analyzed (Fig. 1). We measured the basal levels of HO-1/HO-2 expression and HO activity as well as changes in these parameters after the use of the HO-1 inducers heme (1 mg/100 g body wt) and SnCl₂ (1 mg/100 g body wt).

Treatment of animals. All experiments were approved by the Institutional Animal Care and Use Committee and conducted under the guidelines for the Care and Use of Laboratory Animals published by the Office of Science and Health Reports, National Institutes of Health. Experiments were conducted in 12- to 13-wk-old male SD rats (350–375 g body wt).

Preparation of 2K1C model. At least twice before surgery, systolic blood pressure was measured without anesthesia, using the tail cuff method. Animals were anesthetized with pentobarbital sodium, and a U-shaped silver clip with an internal gap of 0.25 mm was placed around the left renal artery. Five groups of age-matched rats were studied: sham-operated LXS N animals, 2K1C LXS N rats, sham-operated LSN-RHO-1-AS animals, 2K1C LSN-RHO-1-AS rats, and 2K1C LSN-RHO-1-AS rats treated with cobalt protoporphyrin (CoPP) for 3 wk (5 mg/100 g body wt, administered subcutaneously in weekly injections). Each group contained 18 animals; a total of 90 rats were used. There was no mortality in the rats receiving CoPP. Following surgery, blood pressure was measured twice a week for 3 wk.

On the day before death, rats were housed in metabolic cages for urine collection. Animals were killed on day 21 after the surgery. Blood samples were collected in K_3EDTA tubes, which were centrifuged at 2,500 g for 10 min at 4°C to separate the plasma and stored at −20°C.

Tissue preparation. Kidneys were immediately collected, weighed, and frozen at −80°C until use. Tissues were homogenized (4 ml/g wet wt) in homogenization buffer (pH 7.4) consisting of 0.25 M sucrose, 0.5% Nonidet P-40, and 10 mM EDTA in TBS (20 mM Tris and 150 mM NaCl, pH 7.4) containing a cocktail of protease inhibitors (Sigma, St. Louis, MO) and Halt, a phosphatase inhibitor cocktail (Pierce Biotechnology, Rockford, IL). The homogenates were centrifuged at 10,000 g for 10 min at 4°C. The cell-free supernatant (10,000 g supernatant) was used for Western blot analyses or activity assays. Protein concentration was determined using the Bradford method (Bio-Rad, Hercules, CA).

Plasma creatinine concentration. Plasma creatinine levels were measured using a commercial kit (Sigma) according to the manufacturer’s instructions.

Western blot analysis. Western blot analysis of protein expression was performed as previously described (10). Briefly, cell-free homogenates (10,000-g supernatant) of kidney preparations (20 μg protein) were separated by SDS-PAGE and transferred to a PVDF Immobilon-P membrane (Amersham Pharmacia, Piscataway, NJ) using a semidry transfer apparatus (Bio-Rad, Hercules, CA). The membranes were incubated with 5% milk in 10 mM Tris–HCl, pH 7.4, 150 mM NaCl, 0.05% Tween 20 (TBST) buffer at 4°C overnight. After washing with TBST, the membranes were incubated with one of the
LACK OF HO-1 AND APOPTOSIS IN 2K1C RATS

Results

HO-1 protein expression and HO activity in LSN and LSN-RHO-1-AS rats. We determined the levels of HO-1 and HO-2 protein levels, using Western blot analysis, as well as overall HO activity (Fig. 1, A–C). The effects of HO upregulation using heme and SnCl₂ were also measured in both control and AS-treated rats. Following treatment with the AS gene, HO-1 protein levels decreased to 26.5 ± 11.1% of the levels found in controls (P < 0.05) (Fig. 1, A and B). Following HO induction by heme, there was an almost 7-fold increase in HO-1 protein in control rats and >12-fold increase in the AS-treated rats (P < 0.0005 for each). As shown in Fig. 1C, the reduction in HO-1 protein following treatment with the AS gene resulted in diminished HO activity compared with controls (P < 0.05). Similarly, the increased level of HO-1 protein following treatment with either heme or SnCl₂ restored HO activity in both control and AS-treated rats (P < 0.05 vs. corresponding controls).

Development of hypertension and kidney atrophy in LSN-RHO-1-AS rats. In sham LSN-RHO-1-AS rats, blood pressure did not change throughout the study. However, blood pressure increased starting on day 9 after clipping in 2K1C LSN-RHO-1-AS rats (Fig. 2). Seventeen days after clipping, systolic blood pressure in 2K1C LSN-RHO-1-AS rats was significantly higher than that of sham rats (151 ± 1 vs. 132 ± 2 mmHg, respectively, P < 0.05). This increase in blood pressure was associated with an increase in plasma creatinine levels (40.3 ± 2.8 vs. 29.3 ± 3.9 μmol/l, P < 0.05) and a decrease in creatinine clearance (1.5 ± 0.2 vs. 2.8 ± 0.4 ml/min, P < 0.05). Blood pressure was maintained at significantly lower levels (P < 0.05) in CoPP-treated compared with nontreated 2K1C LSN-RHO-1-AS animals (Fig. 2). Clipping-induced renal atrophy (~37% decrease in weight) was potentiated in LSN-RHO-1-AS rats compared with LSNXN animals (Fig. 3). Left kidney weights were higher in LSNXN (1.016 ± 0.08 g) compared with LSN-RHO-1-AS (0.621 ± 0.03 g) animals. This effect was prevented by the administration of CoPP (right kidney weight from LSN-HO-1-CoPP animals was 1.321 ± 0.11 g compared with 1.264 ± 0.07 g for sham right kidney weight). Reversal of HO activity and HO-1 gene expression was achieved by the superinduction of HO-1 using the pharmacological inducer CoPP. This resulted in a reversal of the decrease in kidney size (P < 0.001). In all experimental animals, there was an increase in kidney size; for example, the right kidney from LSNXN and HO-1-AS rats (1.83 ± 0.14 g) was not significantly different in weight from sham or CoPP right kidneys.

Measurement of apoptosis. For the detection of DNA fragments by TUNEL methodology and visualization of apoptotic nuclei in renal tissue, we used a TdT-FragEL DNA Fragmentation Detection Kit (EMD Biosciences, San Diego, CA). The materials were used according to the instructions of the manufacturer. For quantitative analysis, the percentages of apoptotic cells were calculated in 10 fields for each sample by an independent observer, using an optical polarized light microscope at a final magnification of ×200.

Casppase activity assay. Caspase-3 activity was determined by colorimetric assay (ApoTarget kit, BioSource International, Camarillo, CA) following the manufacturer’s protocol. Briefly, tissue cell lysates were prepared in cell lysis buffer (Tris-buffered saline containing detergent), and protein concentrations in samples were estimated using the Bradford method. Then, 200–300 μg of protein lysate/sample were mixed with 200 μM substrate (DEVD-pNA for caspase-3) in 2X reaction buffer and incubated at 37°C overnight in the dark. Developed color was measured at 405 nm in a Benchmark microplate reader (Bio-Rad). Blank readings were subtracted from each sample before calculation. Caspase activity was expressed in absorbance units (OD 405 nm) per milligram of protein.

Statistical analysis. Results are presented as means ± SE for the number (n) of replicate determinations. Statistical significance between experimental groups was determined by using a t-test or one-way ANOVA followed by the Fisher’s least significant difference multiple-comparison test; P < 0.05 was considered significant. Blood pressures were analyzed by using repeated measures ANOVA followed by the Fisher’s least significant difference multiple-comparison test; P < 0.05 was considered significant.
**HO-1 and HO-2 protein expression.** Clipping the renal artery caused significant induction of HO-1 protein in the kidneys of LXSN but not LSN-RHO-1-AS animals (Fig. 4A). Importantly, treatment with CoPP caused a significant induction of HO-1 protein ($P < 0.05$) in the kidneys of 2K1C LSN-RHO-1-AS rats (Fig. 4B). Neither renal artery clipping nor treatment with CoPP influenced renal levels of HO-2 protein (Fig. 4, A and B).

**COX-2 and NT expression.** COX-2 protein expression was significantly higher in sham LSN-RHO-1-AS rats compared with sham LXSN animals. Clipping the renal artery caused induction of COX-2 protein in the kidneys of LXSN animals; however, it did not reach the levels of COX-2 in the kidneys of LSN-RHO-1-AS rats (Fig. 5A). To estimate oxidative stress, we measured 3-NT levels. The 3-NT levels were significantly higher in sham LSN-RHO-1-AS rats compared with sham LXSN animals. Clipping the renal artery caused an increase in the 3-NT signal in the kidneys of LXSN animals; however, the levels of 3-NT in 2K1C LXSN were significantly lower than those in 2K1C LSN-RHO-1-AS rats (Fig. 5A). Importantly, treatment with CoPP caused a significant decrease in both COX-2 protein and 3-NT levels in the kidneys of 2K1C LSN-RHO-1-AS rats (Fig. 5B).

**Measurement of DNA fragmentation and apoptotic nuclei.** Apoptotic nuclei were visualized in the renal cortex and medulla by labeling DNA fragments using TUNEL assay. A dark brown signal indicated positive staining of apoptotic nuclei. The number of apoptotic cells in sham LXSN kidneys was negligible (Fig. 6, A–C) compared with sham with genetically decreased HO-1 (LSN-RHO-1-AS) (Fig. 6, D–F). However, the number of apoptotic cells was increased in clipped kidneys (Fig. 6, G–I) and, furthermore, the number was significantly decreased by CoPP (5 mg · body wt$^{-1}$ · wk$^{-1}$ for 3 wk) in HO-1 and HO-2 expression.

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**Fig. 4.** A: Western blot and densitometric analysis showing HO-1 and HO-2 expression in clipped kidneys of LXSN and LSN-RHO-1-AS rats compared with sham animals. B: Western blot and densitometric analysis showing effect of treatment with CoPP (5 mg · 100 g body wt$^{-1}$ · wk$^{-1}$ for 3 wk) on HO-1 and HO-2 expression in clipped kidneys of genetically decreased HO-1 LSN-RHO-1-AS rats. Values are means ± SE; $n = 4$/group. *$P < 0.05$ vs. sham.
exacerbated in clipped kidneys from HO-1-AS animals (Fig. 6, J–L vs. D–F, and calculated in Fig. 7). Importantly, the number of apoptotic nuclei in the clipped kidneys from animals with genetically suppressed HO-1 and HO activity (LSN-RHO-1-AS) was reduced ($P < 0.05$) by the superinduction of HO-1 as a result of CoPP administration (Fig. 6, M–O).

Caspase-3 activity. Caspase-3 activity did not differ between sham LXSN and sham LSN-RHO-1-AS rats (Fig. 8). Clipping the renal artery resulted in a significant increase in caspase-3 activity in LXSN and LSN-RHO-1-AS rats; however, the rise in activity was significantly higher in LSN-RHO-1-AS animals (Fig. 8). Importantly, the induction of HO-1 by CoPP strongly abrogated the increase in caspase-3 activity in LSN-RHO-1-AS rats. Expression of selected pro- and antiapoptotic molecules. Proapoptotic Apaf-1 protein expression was significantly higher in sham-operated and 2K1C LSN-RHO-1-AS rats compared with sham-operated and 2K1C LXSN animals, respectively (Fig. 9). There was no difference in the expression of antiapoptotic Bcl-2 protein between sham LXSN and LSN-RHO-1-AS rats. Clipping the renal artery caused a significant increase of Bcl-2 in the kidneys of LXSN animals, but not in the kidneys of LSN-RHO-1-AS rats (Fig. 10A). Moreover, clipping caused a significant decrease in Bcl-xl in the kidneys of LSN-RHO-1-AS rats (Fig. 10A). Importantly, CoPP, a potent inducer of HO-1, caused a significant increase in both Bcl-2 and Bcl-xl as well as in Akt and phospho-Akt levels in the clipped kidneys of LSN-RHO-1-AS rats (Figs. 10B and 11, respectively).

**DISCUSSION**

We report several important findings in this study. First, suppression of HO-1 in vivo via genetic probes, using retroviral transfer of the rat HO-1 gene in the antisense orientation,
Fig. 6. Apoptotic nuclei in renal cortex and medulla of clipped kidneys from LXSN and LSN-RHO-1-AS rats visualized by labeling DNA fragments, using TUNEL assay.
exacerbated atrophy and enhanced apoptosis in the clipped kidney in this animal model of renovascular hypertension. Second, induction of HO-1 by CoPP effectively ameliorated the development of hypertension and prevented renal atrophy in rats transduced with antisense HO-1. Third, both suppression of proapoptotic and induction of antiapoptotic molecules were involved in the HO-1-mediated cytoprotection in the clipped kidneys of LSN-RHO-1-AS rats.

We have shown that retrovirus-mediated gene transfer is an effective approach for manipulating HO-1 expression levels and HO activity in vitro and in vivo and that the model of LSN-RHO-1-AS rats represents a valuable tool for studying the biological role of HO-1 (36, 52). In the present study, transduction of rat HO-1 in the antisense orientation to newborn rats led to decreased HO-1 protein expression and HO enzyme activity compared with animals injected with empty vector. Moreover, there were important differences in terms of renal HO-1 induction between rats transduced with antisense HO-1 and those injected with empty vector. Clipping the renal artery induced HO-1 in the kidneys of LXSN rats but not in the kidneys of rats transduced with rat antisense HO-1. Importantly, the LSN-RHO-1-AS rats responded to the chemical inducer CoPP with induction of renal HO-1.

HO-1 has been shown to play a vital role in protecting the kidneys against various noxious stimuli (5, 40). For example, induction of HO-1 has been shown to preserve renal function and to decrease the expression of inflammatory molecules in the glycerol model of acute renal failure (33, 47). In ischemia-reperfusion injury, heat preconditioning or CoPP administration induced HO-1, preserved kidney graft function, and prevented postperfusion apoptosis after cold preservation (48).

In the present study, kidney damage evoked by clipping the renal artery was inversely related to renal HO-1 expression, being more severe in rats transduced with antisense HO-1 compared with rats transduced with empty vector. Importantly, the use of CoPP as an exogenous inducer of HO-1 ameliorated the development of hypertension and attenuated renal atrophy in 2K1C LSN-RHO-1-AS rats (Figs. 2 and 11, respectively). These results underscore the essential cytoprotective role of the HO system in the clipped kidney of 2K1C renovascular hypertensive rats.

The role of HO-1 in renovascular hypertension has not been widely studied. Previously, Wiesel et al. (51) showed that the absence of HO-1 leads to more severe renovascular hypertension and kidney ischemic damage in 1K1C mice. Recently, we reported that induction of HO-1 with CoPP ameliorates, while inhibition of HO activity by SnMP aggravates, the development of hypertension and renal atrophy in 2K1C rats (11). However, the mechanisms by which HO-1 induction proves beneficial in renovascular hypertension are still a matter of debate.

In many experimental models, HO-1 was shown to counteract oxidative stress and inflammation (3, 5, 34, 35), at least partly by the prevention of free heme from participating in prooxidant reactions (8) as well as by the generation of bilirubin, a potent antioxidant (41), and CO, an anti-inflammatory molecule (38). We have shown previously that induction of HO-1 by CoPP abrogated oxidative stress and inflammatory reactions in clipped kidneys of 2K1C rats, as evidenced by decreases in free heme and NT levels and a decrease in COX-2 expression, respectively (11). In the present work, we demon
strate that the lack of HO-1 enhanced clipping-induced renal oxidative stress and inflammatory reactions, as evidenced by the elevated nitrotyrosine and COX-2 levels (Fig. 4, A and B). Noteworthy is the fact that both effects were abrogated by the induction of HO-1 with CoPP (Fig. 4 B). Clearly, antioxidant and anti-inflammatory effects contribute to the beneficial action of HO-1 in the 2K1C model of renovascular hypertension.

The novel findings of the present study are that apoptosis may contribute to kidney damage after renal artery clipping and that the lack of HO-1 enhances proapoptotic pathways in the clipped kidneys of 2K1C rats. Numerous studies have implicated the contribution of apoptosis in various acute and chronic renal disorders (25, 30, 46); however, the contribution of apoptosis to kidney damage and the development of renovascular hypertension has not been determined thus far. In the present work, we demonstrate that clipping the renal artery...
increased caspase-3 activity in the kidneys and that this increase was exacerbated by the genetically decreased HO-1 in LSN-RHO-1-AS rats compared with rats transduced with empty vector (Fig. 7). Importantly, CoPP, the potent HO-1 inducer, completely abrogated the increase in caspase-3 activity. Activation of caspase-3 is considered an indication of relatively advanced apoptosis and represents an effector mechanism common to extrinsic and intrinsic apoptotic pathways (18, 28). Thus the question arises as to what molecular mechanisms upstream of caspase-3 activation could be regulated by the HO system. Higher levels of Apaf-1 in rats lacking HO-1 suggests a link between HO-1 and the intrinsic mitochondrial pathway of apoptosis (37, 53). The intrinsic pathway of apoptosis involves permeabilization of the outer membrane of mitochondria with release of proapoptotic proteins, such as cytochrome c (12, 24). The binding of cytochrome c with Apaf-1 leads to activation of procaspase-9, which, in turn, activates effector caspases, such as 3, 6, and 7 (49, 54).

We conclude that genetic suppression of HO-1 via retroviral transfer of the rat HO-1 gene in the antisense orientation exacerbates kidney damage and enhances apoptosis in the clipped kidneys of rats in this 2K1C model of renovascular hypertension and that both effects can be effectively ameliorated by the HO-1 inducer CoPP. This study also identifies suppression of proapoptotic and induction of antiapoptotic molecules as a new mechanism of HO-1-mediated cytoprotection in clipped kidneys of 2K1C rats.

REFERENCES


9. Botros FT, Laniado-Schwartzman M, Schwartzman ML, Stier CT Jr, Goodman AI, Abraham NG. Expression in rats lacking HO-1, but not in the rats transduced with empty vector. Importantly, induction of HO-1 with CoPP strongly increased the expression of Bcl-2, Bcl-xl, Akt, and phosphorylated Akt in the clipped kidneys of LSN-RHO-1-AS rats (Figs. 10B and 11).


