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Forum Review

Prooxidant and Antioxidant Functions of Nitric Oxide in Liver Toxicity

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ABSTRACT

In response to tissue damage and inflammation induced by a variety of xenobiotics including acetaminophen, carbon tetrachloride, ethanol, galactosamine, and endotoxin, as well as disease states such as viral hepatitis, and postischemic and regenerative injury, the liver produces large quantities of nitric oxide. Indeed, nearly all cell types in the liver including hepatocytes, Kupffer cells, stellate cells, and endothelial cells have the capacity to generate nitric oxide. Thus, these cells, as well as infiltrating leukocytes, may indirectly augment tissue injury. In many models of liver damage, nitric oxide and its oxidation products such as peroxynitrite contribute to the injury process by directly damaging the tissue or by initiating additional immunologic reactions that result in damage. In some models, nitric oxide donors or peroxynitrite can mimic the cytotoxic actions of liver toxins. Moreover, agents that prevent the generation of nitric oxide or antioxidants that bind reactive nitrogen intermediates, or knockout mice with reduced capacity to produce nitric oxide, are protected from xenobiotic-induced tissue injury. In contrast, there have been reports that blocking nitric oxide production enhances xenobiotic-induced tissue injury. This has led to the concept that nitric oxide either inactivates proteins critical for xenobiotic-induced tissue injury or acts as an antioxidant, reducing cellular levels of cytotoxic reactive oxygen intermediates. Whether or not nitric oxide or secondary oxidants generated from nitric oxide act as mediators of tissue injury or protect against toxicity is likely to depend on the precise targets of these reactive nitrogen intermediates, as well as levels of superoxide anion present and the extent to which tissue injury is mediated by reactive oxygen intermediates. In addition, as toxicity is a complex process involving a variety of cell types and many soluble mediators, the contribution of each of these factors must be taken into account when considering the role of nitric oxide as a determinant of tissue injury. Antioxid. Redox Signal. 3, 261–271.

INTRODUCTION

ONE OF THE HALLMARKS OF TISSUE INJURY is an inflammatory response, a process characterized by the accumulation of phagocytic cells at sites of damage. These cells, which include neutrophils and macrophages, produce a wide array of inflammatory mediators that are crucial for microbial killing. These mediators also play important roles in maintaining tissue homeostasis and in initiating repair processes. However, it is becoming increasingly apparent that in excessive amounts, inflammatory mediators, which include proteolytic enzymes, reactive oxygen and nitrogen intermediates, as well as proinflammatory cytokines and bioactive lipids, also have the capacity to contribute to tissue damage (57–60, 74). This can occur because these mediators directly damage the tissue and amplify the inflammatory response. A key mediator released by activated macrophages that has been implicated in toxicity is

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nitric oxide. A number of laboratories have shown that large amounts of this highly reactive nitrogen intermediate are produced during tissue injury associated with inflammation (13, 64, 73). Indeed, in many of these systems, modulating nitric oxide production can modify tissue injury. The agent inducing injury, its target tissue, and local concentrations of reactive oxygen intermediates are important determinants of whether or not nitric oxide production plays a protective or pathologic role in tissue injury.

NITRIC OXIDE PRODUCTION BY LIVER CELLS

As nearly all orally ingested xenobiotics pass through the liver via the portal circulation, it is not unexpected that this tissue is a major target organ for toxicity. Many chemicals are also metabolized to toxic intermediates in the liver, and this contributes to tissue injury. A major response of the liver to xenobiotic-induced toxicity is apoptosis and necrosis (56, 57). Nitric oxide produced by cells in the liver has been implicated in both of these processes; however, the source of this free radical is not clear.

Xenobiotic-induced toxicity is associated with increases in the number of macrophages in the liver (89). A number of studies have demonstrated that these cells are functionally active; that is, when compared with normal resident liver macrophages or Kupffer cells, they display increased phagocytosis and chemotaxis and release an array of inflammatory cytokines. They also produce increased quantities of reactive oxygen intermediates and reactive nitrogen intermediates (29, 61, 63). In the normal liver, Kupffer cells represent ~30% of the liver sinusoidal cells and comprise 80–90% of all macrophages in the body (57), and thus, changes in the number of functionally active hepatic macrophages would be expected to have profound consequences on the functioning of the liver. Indeed, proof that macrophage activity is important in mediating toxicity comes from studies demonstrating that agents that suppress macrophage activity such as the rare earth metal gadolinium chloride, reverse or reduce xenobiotic-induced liver damage (13, 65, 77).

A question arises as to the contribution of macrophage-derived nitric oxide to xenobiotic-induced hepatotoxicity. Macrophages produce nitric oxide in response to cytokines and bacterially derived products via the high-output inducible form of nitric oxide synthase (NOS2) (64). In the absence of stimulation, liver macrophages produce only low levels of nitric oxide. Following treatment with lipopolysaccharide (LPS), γ-interferon (γ-IFN), or the combination of LPS and γ-IFN, these cells release large quantities of this reactive nitrogen intermediate, a response that is blocked by nitric oxide synthase inhibitors such as N^G-monomethyl-L-arginine (NMMA), N^ω-nitro-L-arginine methyl ester (NAME), and aminoguanidine (8, 29, 59, 64). Interestingly, the ability of liver macrophages to produce nitric oxide is enhanced by cytokines known to be important in inflammation including tumor necrosis factor-α, granulocyte-macrophage-colony stimulating factor, macrophage-colony stimulating factor, and interleukin-1β (63). These latter findings are important because the presence of these mediators in the liver *in vivo* during xenobiotic–induced inflammation is likely to control the state of macrophage activation. When incubated with the protein kinase C activator, 12-*O*-tetradecanoylphorbol 13-acetate, a potent inducer of the macrophage respiratory burst, Kupffer cells synthesize peroxynitrite, an even more potent oxidant than nitric oxide, which has been implicated in tissue injury (57).

The sites at which activated macrophages accumulate in the liver provide additional evidence that these cells contribute to cytotoxicity and liver injury. This is readily apparent when acetaminophen-induced hepatotoxicity is examined (61, 62, 65). Acetaminophen is a mild analgesic and antipyretic agent known to cause centrilobular hepatic necrosis at toxic doses. It is well recognized that reactive acetaminophen metabolites bind to centrilobular hepatic proteins inducing cellular damage (4, 34, 91). However, during acetaminophen toxicity, large numbers of activated macrophages also accumulate in centrilobular regions directly at sites of tissue injury (61). The release from these cells of high concentrations of nitric oxide, as well as other soluble mediators including tumor ne-

crosis factor-α, interleukin-1, and reactive oxygen intermediates mediate toxicity. Selective reduction of macrophage activity by gadolinium chloride abrogates acetaminophen-induced toxicity, strongly supporting a role of this cell type in toxicity (65, 77). That nitric oxide is also crucial for hepatotoxicity is evidenced by the fact that aminoguanidine, a selective NOS2 inhibitor that does not alter acetaminophen metabolism, prevents acetaminophen-induced hepatic necrosis and increases in serum transaminase levels (29, 30).

It should be emphasized that macrophages are not the only cell type in the liver capable of producing nitric oxide. In early studies using animal models, immunohistochemical techniques localized NOS2 in sinusoidal endothelial cells, as well as hepatocytes following acute endotoxemia (23, 63, 66). Hepatocytes are the largest and most abundant cell type in the liver. They play a major role in detoxification of chemicals, glutamine, and urea and in cholesterol biosynthesis, as well as in ammonia and bilirubin metabolism (46). As the source of acute-phase proteins, they are also involved in the host response to tissue injury and inflammation (55). A number of studies have shown that hepatocytes produce nitric oxide and its oxidation products, and this is thought to contribute to altered hepatic functioning in liver injury following exposure to xenobiotics (17, 18, 30). Hepatocytes were among the first cell types characterized for nitric oxide production (17, 84, 85). A variety of inflammatory mediators including endotoxin and tumor necrosis factor-α, interleukin-1, and γ-IFN induce nitric oxide biosynthesis in these cells (17, 18, 84). Endotoxin and various cytokines have been reported to act synergistically to up-regulate expression of NOS2 (14, 31, 32, 85), whereas steroids down-regulate its expression (19, 31). Hepatocytes are also highly responsive to toxicants in terms of nitric oxide production. For example, hepatocytes isolated from endotoxemic rats release increased amounts of nitric oxide in response to inflammatory mediators (52). In addition, during acetaminophen toxicity, NOS2 is localized in hepatocytes in centrilobular regions (30). Hepatocytes isolated from both untreated and acetaminophen-treated rats also express NOS2 and readily synthesize nitric oxide in response to inflammatory mediators. Interestingly, hepatocytes from acetaminophen-treated animals are primed to respond to inflammatory mediators and produce significantly more nitric oxide in response to inflammatory mediators, further supporting the idea that nitric oxide derived from these cells contributes to acetaminophen-induced liver toxicity (30).

NOS2 can also be induced in hepatic stellate (Ito) cells and endothelial cells. Using a rat model, Helyar et al. (40) demonstrated that isolated stellate cells produce nitric oxide in response to LPS and γ-IFN, as well as tumor necrosis factor-α and macrophage-colony stimulating factor. A marked enhancement of nitric oxide production was observed in stellate cells isolated from endotoxemic rats (40). Similarly, Rockey and Chung (93) demonstrated that interleukin-1β stimulates stellate cell nitric oxide production. These investigators also showed that periportal-based liver damage induced by ligation of the common bile duct stimulates expression of NOS2 mRNA in stellate cells. Like stellate cells, endothelial cells from rat liver also produce nitric oxide in response to cytokines and LPS, an effect that is enhanced after toxicant administration to animals (28, 56, 63, 64). In these cells, granulocyte-macrophage-colony stimulating factor, macrophage-colony stimulating factor, and interleukin-1β synergize with LPS and γ-IFN to induce nitric oxide production.

At the present time, the precise roles of stellate cell- and endothelial cell-derived nitric oxide in normal hepatic functioning and tissue injury are unknown. Both of these cell types increase in number following treatment of rats with endotoxin (28, 40, 56, 63, 64) and may contribute to localized nitric oxide production during acute endotoxemia. As stellate cells are important in the production of extracellular matrix and vitamin A storage, nitric oxide may play a role in modifying these functions. Nitric oxide also controls contractility of stellate cells (93), a function that appears to be important in regulating hepatic blood flow (40, 47, 86, 94). In this regard, Sakamoto et al. (94) demonstrated that interleukin-1β is also a potent relaxing agent for cultured rat stellate cells. Diffusion of hepatic endothelial nitric oxide into

stellate cells may be important in regulating blood flow in the hepatic microcirculation. It is possible that during inflammation, nitric oxide released by endothelial cells increases vascular permeability, thereby facilitating extravasation of leukocytes into the surrounding tissue, a process that is important in tissue injury, inflammation, and/or wound healing (98).

NITRIC OXIDE AND APOPTOSIS IN THE LIVER

Once produced by cells of the liver, a question arises as to potential mechanisms by which nitric oxide modulates toxicity. During endotoxemia in rats, morphologic changes in centrilobular hepatocyte structure occur that are indicative of cells undergoing apoptosis or programmed cell death (56, 64, 66). Thus, hepatocytes undergo hypertrophy, vacuolization, and chromosomal emargination. Much work on nitric oxide has concentrated on its effects on cell proliferation and apoptosis (37, 39, 40, 50, 63, 64, 66, 67, 81). Exogenously added nitric oxide and nitric oxide produced endogenously are known to suppress cellular proliferation in a number of different cell types including those in the liver. For example, nitric oxide has been associated with reduced proliferation in hepatocytes, stellate cells, Kupffer cells, and endothelial cells (23, 28, 29, 40, 56, 63, 66). That reduced cell proliferation is due to endogenously generated nitric oxide is supported by the fact that this process is prevented by nitric oxide synthase inhibitors (23, 28, 40, 56, 63, 66). Inhibition of proliferation by nitric oxide is associated with apoptosis (66). A characteristic of apoptotic cells is the appearance of cytoplasmic DNA, which is caused by internucleosomal cleavage of nuclear DNA. This DNA appears as a 180-bp "ladder" when analyzed by agarose gel electrophoresis and is thought to be caused by the activation of endogenous nucleases (92). The DNA ladder pattern is evident in cultured hepatocytes isolated from endotoxemic rats and is enhanced in cells stimulated to produce nitric oxide (66), indicating that the hepatocytes are undergoing apoptosis. Nitric oxide synthase inhibitors prevent this process, again confirming that it is mediated by nitric oxide (66).

It should be noted that it is not just the nitric oxide-producing cell that is susceptible to inhibition of proliferation and apoptosis. Nitric oxide can freely diffuse across cell membranes, and in tissues it can affect surrounding cells. Most cells are susceptible to exogenously added nitric oxide either in the form of a saturated solution of nitric oxide or as a nitric oxide-donating compound. A number of studies have also demonstrated that coculture of non–nitric oxide-producing target cells with cells producing nitric oxide can induce apoptosis in the target. This has been demonstrated in cocultures of tumor cells and nitric oxide-producing macrophages (2), rat Kupffer cells and hepatoma cells (54), type II pneumocytes and alveolar macrophages (42), thymocytes and endothelial cells stimulated to express nitric oxide with cytokines and endotoxin (24), in primary cultures of neurons and nitric oxide-producing glial cells (83), in glial cells cocultured with retinal ganglion cells (79, 102), and in mixed cultures of mouse osteoblasts and bone marrow cells (79). In an *in vivo* mouse model, liver cell production of nitric oxide has been shown to inhibit hepatic tumor growth of B16 melanoma cells, suggesting that this may be a natural defense mechanism against cancer metastasis (108).

As indicated above, nitric oxide can trigger apoptosis in hepatocytes isolated from endotoxemic rats (66). If this is a critical mediator of toxicity *in vivo*, then it would be expected that treatment of rats with nitric oxide synthase inhibitors would reverse the structural alterations in the liver associated with endotoxemia, and this is what has been observed (66). However, in several animal models, nitric oxide synthase inhibitors have been shown either to have little effect or to actually potentiate endotoxemia (38, 67). For example, following treatment of mice with *Cornebacterium parvum* and LPS, inhibition of nitric oxide production with NMMA augments tissue damage (8, 38). In rats, the nitric oxide synthase inhibitor NAME, but not *S*-methylisothiourea, was found to aggravate liver damage (107), whereas the nitric oxide synthase inhibitor N^G-(1-iminoethyl)-L-ornithine increased hepatic injury with formation of oxidative DNA damage in LPS-treated rats (29). Enhancement of tissue damage by nitric oxide synthase inhibitors suggests that nitric oxide is hepatoprotective. Variations between

studies may be due to differences in the animal models and nitric oxide synthase inhibitors used, the methods used to assess liver damage, quantities of nitric oxide formed in the liver, and/or the extent to which tissue injury is mediated by oxygen radicals (89).

As indicated above for hepatocytes, many cell types have been reported to undergo apoptosis when stimulated to produce nitric oxide, and this includes both mouse and human macrophages (2, 12), tumor cells (45, 110), embryonic neurons (21), rat lung fibroblasts (111), pancreatic β cell lines (3, 45), adrenal vascular endothelial cells (72), vascular smooth muscle cells (27), and renal mesangial cells (53). Cells undergoing apoptosis in direct response to nitric oxide include neuronal cell lines (80), astrocytes (44), primary cultures of cerebellar granule cells (80), and cortical cultures (88). Nitric oxide by itself may not directly mediate apoptosis; a metabolite or oxidation product may be responsible for this activity. For example, nitric oxide can react with protein sulfhydryls and/or peptides such as glutathione to form nitrosothiols, and these proteins or metabolites may act as key mediators that direct cellular signaling to initiate apoptosis (99). They may also release nitric oxide intracellularly or transnitrosate critical thiols in proteins and modulate their function (71). Modifications of protein thiols may be critical events in the regulation of apoptotic cell death (75). Peroxynitrite, formed by the reaction of nitric oxide with superoxide anion, is able to nitrate tyrosine residues in proteins in the presence of transition metals (6, 90). The idea that peroxynitrite plays a role in the action of nitric oxide is based on the findings that nitrate-modified proteins can readily be detected in tissues during toxicity (6). Like nitric oxide, peroxynitrite has a very short half-life, and its ability to induce cell death will depend on its concentration and proximity to critical cellular targets (6). At the present time, it is unclear if cytotoxicity induced by peroxynitrite results from activated forms of the radical or decomposition products such as hydroxyl radicals (6). Due to the ubiquitous nature of superoxide anion, almost all cells have the capacity to produce peoxynitrite (44), although it is uncertain if endogenous production of this reactive metabolite mediates apoptosis. In cell types such as rat motor neurons, peroxynitrite may be critical for the process because both superoxide anion and nitric oxide appear to be required for the process (21). In several cell types, including rat thymocytes (95) and pancreatic acinar cells (97), exogenous peroxynitrite directly induces apoptosis. Peroxynitrite also induces apoptosis in human HL60 leukemia cells (113), colon tumor cells (96), megakaryocytic cell lines (5), rat PC12 cells (20), and bovine retinal pigmented epithelial cells (7).

The signaling pathways activated by nitric oxide to induce apoptosis are not well defined. Many targets for nitric oxide have been described, including those that are known to be critical components of the apoptotic process, and include cellular sulfhydryls, heme- and iron-sulfur-containing proteins (64). Nitric oxide inhibits enzymes in intermediary metabolism, including *cis*-aconitase and glyceraldehyde-3-phosphate dehydrogenase, and enzymes required for DNA synthesis, mitochondrial respiration, including complexes I–III (11, 64), and this may lead to apoptosis. Nitric oxide and its oxidation products also induce the release of mitochondrial-derived factors regulating apoptosis, activate caspases, and stimulate proteolytic cleavage of poly(ADP-ribose)polymerase, key factors regulating the apoptotic process (11, 41). Nitric oxide also activates guanylyl cyclase and increases intracellular cyclic GMP (cGMP), also a potentially important mediator of apoptosis. In several cell types, formation of cGMP and activation of cGMP-dependent protein kinases have been reported to be essential in nitric oxide-mediated apoptosis (22, 103). Other signaling proteins modulated by nitric oxide that are potentially important mediators of apoptosis include protein kinase C (82), p53 (76), and cyclic AMP dependent protein kinases (106).

As nitric oxide can be hepatoprotective, it is not surprising that, depending on the model, this reactive mediator can inhibit apoptosis. Kim et al. (50) first demonstrated that both nitric oxide generated endogenously and nitric oxide applied exogenously suppress tumor necrosis factor-α-, anti-FAS-, or growth factor deprivation-induced apoptosis. It has been suggested that, when nitric oxide is generated in cells, it can contribute to the late stages of cytokine-induced apoptosis (16, 68); exposure to nitric oxide prior to or together with cytokines

can inhibit apoptosis (51, 52, 67–79). Nitric oxide apparently acts by inhibiting tumor necrosis-α-induced signal transduction pathways, leading to apoptosis including production of ceramide, activation of the tumor necrosis factor-α receptor adapter protein TRADD, release of cytochrome *c*, and the activity of initiator and effector caspases (51, 52, 67–69). Nitric oxide can directly inhibit caspases such as caspase-3 presumably via *S*-nitrosylation (49). *S*-Nitrosylation of caspases and inhibition of apoptosis have been described in a number of cell types, including embryonic kidney cells (101), human leukemia cells (75), and embryonic endothelial cells (36). In hepatocytes, tumor necrosis factor-α-induced apoptosis is enhanced by inhibition of NOS2, and inhibited by sustained endogenous nitric oxide production following adenovirus-mediated NOS2 gene transfer into hepatocytes (67). The effects of nitric oxide on apoptosis are inhibited by suppressing the formation of cGMP, indicating that a cGMP-dependent mechanism may mediate the action of nitric oxide on caspase-3 (49). A similar mechanism has been reported in rat ovarian follicles (15) and dorsal root ganglion neurons (102). It should be pointed out that a large number of caspases are involved in apoptosis (92), and whether or not nitric oxide modulates this process may depend on localized concentrations of nitric oxide and which of these proteases are activated or inhibited in each cell type.

Large amounts of nitric oxide can lead to tissue damage, and cells respond by expressing proteins or oxidants and antioxidants for protection against free radical damage. By regulating cellular redox status, for example, with superoxide anion, cells can detoxify nitric oxide (6). Levels of enzymes such as superoxide dismutase and catalase (6) or peroxidases (1) may be important determinants of nitric oxide-induced cytotoxicity. As nitric oxide modulates cellular thiol redox status, this also is an important determinant of toxicity. Agents that either increase or decrease cellular thiols are known to modulate apoptosis. For example, increasing intracellular glutathione with *N*-acetylcysteine suppresses apoptosis induced by nitric oxide in human colon carcinoma cells (43), whereas a reduction in cellular glutathione has been reported to protect against apoptosis in vascular smooth muscle cells.

In hepatocytes, nitric oxide has been shown to induce heat shock protein 70 (Hsp70), an important member of the heat shock protein family (48). This was associated with inhibition of apoptosis (48). A number of studies have indicated that expression of NOS2 can be regulated by Hsp70 and that this protein protects against nitric oxide-mediated injury. In brain glial cells, Hsp70 induction decreases expression of NOS2 mRNA and enzyme activity (25), whereas in rat fibroblasts, transfection with Hsp70 suppresses cytokine- and LPS-induced NOS2 (25). Additional proteins thought to be important in protecting against nitric oxide include Bcl-2, p53, and heme oxygenase-1. Bcl-2 is a member of a family of apoptotic regulatory proteins, some of which suppress apoptosis (Bcl-2, Bcl-xL), whereas others (Bax, Bak) promote apoptosis (35). Dimerization of pro- and antiapoptotic members of this family can regulate cell survival (35). In B lymphocytes, nitric oxide stimulates expression of Bcl-2 and suppresses apoptosis (33), whereas in fibroblasts, transfection with Bcl-2 confers resistance to nitric oxide-induced apoptosis (109). Activation of p53 is known to trigger apoptosis; however, in human cells overexpressing NOS2, p53 accumulates without apoptosis, whereas transfection of p53 decreases production of NOS2 (26). Heme oxygenase-1 is the rate-limiting enzyme in heme catabolism, and in many different cell types, nitric oxide induces this enzyme (10). Heme is a highly toxic intracellular prooxidant, and its breakdown by heme oxygenase-1 is an important protective mechanism (87). Products of heme oxygenase-1, including carbon monoxide and bilirubin, have antioxidant potential (87, 100), and bilirubin can act as a peroxyl radical scavenger (100). Iron is also generated by this enzyme and, by virtue of its ability to generate free radicals in a Fenton-type reaction, can be cytotoxic (87). However, its binding by ferritin can effectively sequester this metal and limit toxicity.

SUMMARY

Nitric oxide and its oxidation products have been implicated in the toxicity of a variety of

xenobiotics, including endotoxin (66), acetaminophen (30), carbon tetrachloride (112), ethanol (78), and galactosamine (9). It has also been implicated in viral hepatitis (70), as well as postischemic liver injury (105). In many instances, nitric oxide damages tissues and contributes to liver injury. However, in other models nitric oxide protects against liver toxicity (38, 50). In either situation, its actions may be due to its ability to act as both an oxidant and an antioxidant. It can also regulate expression of proteins crucial for oxidant metabolism. Most cell types in the liver produce nitric oxide; further research is needed to define the role of each cell type in the process of xenobiotic-induced liver injury and the mechanisms by which nitric oxide regulates necrosis and apoptosis.

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ABBREVIATIONS

cGMP, cyclic GMP; Hsp70, heat shock protein 70; γ-IFN, γ-interferon; LPS, lipopolysaccharide; NAME, N^{ω}-nitro-L-arginine methyl ester; NMMA, N^{G}-monomethyl-L-arginine; NOS2, inducible nitric oxide synthase.

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