Mechanisms of hypothermic protection against ischemic liver injury in mice

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Hepatic hypothermia has been shown to have a protective effect on surgical resection of the liver (31). In 1953, Raffucci et al. (25) noted that dogs rendered hypothermic by total body cooling could survive 1 h of hepatic ischemia, whereas normothermic dogs all died within the same period of time. Since then, numerous methods of hypothermia have been developed and adapted for clinical application (11, 20, 31). Subsequently, hypothermic techniques are now performed in selected patients with large metastatic liver tumors and hepatocellular carcinoma associated with cirrhotic liver disease (12, 14, 32). However, the physiological mechanisms by which hypothermia confers protection against hepatic ischemia-reperfusion injury remain largely unknown. In the current studies, we investigated whether hypothermia protects against ischemia-reperfusion injury by altering the hepatic inflammatory response.

MATERIALS AND METHODS

Hepatic ischemia-reperfusion injury model. Male C57BL/6J mice (Jackson Laboratories, Bar Harbor, ME) weighing 23–27 g were used in all experiments. This project was approved by the University of Louisville Animal Care and Use Committee and was in compliance with the National Institutes of Health guidelines on the care and use of laboratory animals. Male littermate mice (C57BL/6J; Jackson Laboratories) weighing 23–27 g were used in all experiments. The mice were weighed daily and kept on a 12:12-h light-dark cycle. All surgical procedures were performed as described previously (11, 20, 31). The mice were anesthetized with an intraperitoneal injection of ketamine (100 mg/kg) and xylazine (5 mg/kg). After the surgical incision, the mice were placed on a heated warming pad to maintain normothermic body temperature. The surgical technique used in this study was a partial hepatic resection, which was performed by incising the skin and subcutaneous tissue, cutting the muscle, and exposing the liver. The liver was then freed from the surrounding peritoneal structures, and the liver was secured with nonabsorbable sutures. The surgical incision was then closed, and the mice were returned to their cages. The animals were allowed to recover for 24 h before the experiment was performed. The mice were then divided into experimental and control groups. The experimental group was subjected to hypothermic protection, whereas the control group was subjected to normothermic protection. The mice were then killed by exsanguination, and the liver was removed and weighed. The liver was then weighed, and the wet-to-dry weight ratio was calculated. The liver was then fixed in 10% formalin and embedded in paraffin. The liver was then sectioned and stained with hematoxylin and eosin for histological evaluation. The liver was then evaluated for histological changes such as necrosis, inflammation, and fibrosis. The liver was then weighed, and the wet-to-dry weight ratio was calculated. The liver was then evaluated for histological changes such as necrosis, inflammation, and fibrosis. The liver was then weighed, and the wet-to-dry weight ratio was calculated.

Surgical management of hepatic resectional surgery often requires hepatic inflow occlusion (Pringle maneuver) to reduce intraoperative bleeding. The resultant hepatic ischemia-reperfusion leads to an acute inflammatory response that may cause significant hepatocellular damage and organ dysfunction (13, 19). This inflammatory response is characterized by early production of the proinflammatory cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-1β, which are released by activated Kupffer cells immediately after hepatic ischemia-reperfusion (28, 30). These cytokines appear to propagate the inflammatory response by upregulating adhesion molecules on the hepatic vascular endothelium and increasing the production of CXC chemokines (4–6, 18). The cooperative effects of adhesion molecules and CXC chemokines results in the recruitment of neutrophils from the vascular space into the hepatic parenchyma (15). These activated neutrophils then cause hepatocellular damage by obstructing the microcirculation and releasing toxic substances such as reactive oxygen species and proteases (15, 16, 29). In experimental models, blockade of inflammatory mediators has proven effective against liver injury after hepatic ischemia-reperfusion (5, 6, 9, 26), suggesting that interventional therapies designed to suppress the inflammatory response during hepatic ischemia-reperfusion may reduce the morbidity of hepatic resectional surgery.

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Health guidelines. The animals were divided into three groups: sham control, normothermic hepatic ischemia-reperfusion, and hypothermic hepatic ischemia-reperfusion. Partial hepatic ischemia was induced as previously described (18). Briefly, mice were anesthetized with sodium pentobarbital (60 mg/kg im). A midline laparotomy was performed, and an atraumatic clip was used to interrupt blood supply to the left lateral and median lobes of the liver. The caudal lobes retained intact portal and arterial inflow and venous outflow, preventing intestinal venous congestion. After 90 min of partial hepatic ischemia, the clip was removed, initiating hepatic reperfusion. The animals received 0.2 ml of sterile saline subcutaneously, the wound was closed in layers with 4-0 silk, and the animal was allowed to recover. Sham control mice underwent the same protocol without vascular occlusion. Rectal temperature was measured by using an electronic thermometer with a probe (Fisher Scientific, Pittsburgh, PA) every 15 min after injection of anesthesia. In sham and normothermic groups, body temperature was maintained at 37°C by using a heating pad. In the hypothermic group, body temperature was not regulated. For assessment of hepatic reperfusion, 20 mg/kg Evans blue dye was injected intravenously 1 min before reperfusion. At the indicated times, postischemic livers were excised, weighed, and then homogenized in 2 ml PBS. The homogenate was diluted with 2 vol of formamide and incubated for 2 h at 60°C, followed by centrifugation for 30 min at 5,000 g. The absorbance of the supernatant was measured at 620 nm and 740 nm, and Evans blue concentration was determined by a standard curve. Correction for contaminating heme pigments was calculated by the formula E 620 − (1.426 × E 740 + 0.03). Final Evans blue dye concentration was expressed as nanograms Evans blue dye per gram liver tissue.

RT-PCR. Liver tissue was removed after 90 min of ischemia and 1 h reperfusion. Total RNA from liver tissue was extracted with TRIzol reagent (GIBCO-BRL, Rockville, MD). RNA (1 μg) was reverse transcribed to cDNA using random hexamers (Perkin-Elmer, Foster City, CA). cDNA products were amplified by PCR (30 cycles: 95°C for 60 s, 59°C for 90 s, and 72°C for 10 s). Primers for TNF-α, IL-1β, macrophage inflammatory protein (MIP)-2, and β-actin have been described elsewhere (1, 35). PCR products were electrophoresed in a 3.5% agarose gel, stained with ethidium bromide, and photographed.

Liver neutrophil accumulation. Liver myeloperoxidase (MPO) assay was performed on animals 8 h after reperfusion. Liver MPO content was assessed by methods described elsewhere (18). Briefly, liver tissue (100 mg) was homogenized in 2 ml of buffer A (3.4 mmol/l KH2PO4 and 16 mmol/l Na2HPO4, pH 7.4). After being centrifuged for 20 min at 10,000 g, the pellet was resuspended in 10 vol of buffer B (43.2 mmol/l KH2PO4, 6.5 mmol/l Na2HPO4, 10 mmol/l EDTA, and 0.5% hexadecyltrimethylammonium, pH 6.0) and sonicated for 10 s. After being heated for 2 h at 60°C, the supernatant was reacted with 3.3’5’-tetramethylbenzidine and the optical density was read at 655 nm.

Blood and tissue analysis. Blood was obtained by cardiac puncture 8 h after reperfusion for analysis of serum alanine aminotransferase (ALT) as an index of hepatic cellular injury. Measurements of serum ALT were made using a diagnostic kit (Sigma, St. Louis, MO). Serum levels of TNF-α, IL-1β, and MIP-2 were measured by sandwich ELISA according to the manufacturer’s instructions (R&D Systems, Minneapolis, MN). Ischemic lobes (or corresponding lobes in the sham group) were excised for tissue analysis. Liver edema was determined by organ wet-to-dry weight ratios. Tissues were fixed in 10% formalin and then embedded in paraffin for light microscopy. Sections were stained with hematoxylin and eosin for histological examination.

Western blot. Liver homogenates were sonicated on ice three times for 10 s and then centrifuged at 14,000 rpm for 30 min at 4°C. Supernatants were removed, and protein content was estimated using the Bradford method. Tyrosine phosphorylation of c-Jun NH2-terminal kinase (JNK) was determined by Western blot with a phosphospecific antibody (Cell Signaling Technology, Beverly, MA). Samples were separated by 10% SDS-PAGE, transferred onto a nitrocellulose membrane, and blocked with 5% milk in TWEEN-20 Tris-buffered saline (TTBS) for 1 h at room temperature. Blots were probed with the anti-phospho JNK in 5% BSA/TTBS overnight at 4°C, and antibodies were detected by using a peroxidase-conjugated secondary antibody in 5% milk/TTBS for 1 h at room temperature. Products were visualized by enhanced chemiluminescence. To verify equal loading of proteins in each lane, the blots were stripped and restained using an antibody that stains total JNK (Cell Signaling Technology). Western blot films were digitized, and activation of JNK (phosphorylated/total) was determined by image analysis with software from Adobe Systems (San Jose, CA).

Electrophoretic mobility shift assay. Nuclear extracts of liver tissue were prepared by the method of Deryckere and Gannon (7) and analyzed by electrophoretic mobility shift assay. Briefly, double-stranded nuclear factor (NF)-κB consensus oligonucleotide (Promega, Madison, WI) was end labeled with [γ-32P]ATP (3,000 Ci/μmol at 10 μCi/μl; Amersham, Arlington Heights, IL). Binding reactions containing equal amounts of nuclear protein extract (20 μg) and 35 fmol (~50,000 cpm, Cherenkov counting) of oligonucleotide were incubated at room temperature for 30 min. Binding reaction products were separated in a 4% polyacrylamide gel and analyzed by autoradiography.

Statistical analysis. All data are expressed as means ± SE. Data were analyzed with a one-way ANOVA with subsequent Student-Newman-Keuls test. Differences were considered significant when P < 0.05. To calculate percentage change, negative control values were subtracted from positive control and treatment group values.

RESULTS

Regulation of body temperature. Rectal temperature was monitored every 15 min during hepatic ischemia-reperfusion. Just before induction of anesthesia, the average rectal temperature of mice was 37.1 ± 0.05°C (Fig. 1). After injection of 60 mg/kg of pentobarbital, body temperature decreased in all mice. In mice regulated with a heating pad, body temperature was 33.8 ± 0.1°C at the initiation of hepatic ischemia. In mice without any thermoregulatory support, body temperature was 30.6 ± 1.3°C on hepatic ischemia. By the end of the ischemic period, regulated mice had a rectal temperature of 36.7 ± 0.4°C, whereas those with no thermoregulatory support had a rectal temperature of 25.9 ± 0.5°C. Mice in which body temperature was controlled maintained rectal temperatures in the range of 35–37°C for the duration of hepatic reperfusion. In mice in which body temperature was not controlled, rectal temperature was 24.9 ± 0.4°C 15 min after reperfusion and returned to temperatures in the range of 35–37°C within 4 h of reperfusion. Thus mice not receiving thermoregulatory support were signifi-
cantly hypothermic for nearly 4 h after induction of hepatic ischemia.

Effects of hypothermia on hepatic reperfusion. Because mice in which body temperature was not controlled were hypothermic for an extended time during reperfusion, we sought to determine if this reduction in body temperature affected the rate at which the liver reperfused. To address this issue, normothermic and hypothermic mice were injected intravenously with Evans blue dye just before reperfusion. The ischemic lobes were resected after 1, 5, 10, 20, and 30 min of reperfusion. The liver content of Evans blue dye increased at similar rates in normothermic and hypothermic mice and reached a maximum in both groups by 20 min (Fig. 2A). Macroscopically, reperfusion appeared to be more uniform in hypothermic mice compared with normothermic mice (Fig. 2B). These data suggest that the reperfusion rates were similar in normothermic and hypothermic mice but that hypothermia facilitates more uniform reperfusion.

Effects of hypothermia on inflammatory liver injury. To assess the effects of hypothermia on liver injury induced by ischemia-reperfusion, we measured serum levels of ALT and liver wet-to-dry weight ratios. After hepatic ischemia and 8 h reperfusion in normothermic mice, there was a significant increase in hepatocellular injury compared with the sham controls (Fig. 3A). Hypothermia reduced hepatocellular injury by 89% (P < 0.001). Similarly, normothermic ischemia-reperfusion induced a significant increase in liver wet-to-dry weight ratios compared with sham controls (Fig. 3B). Hypothermic mice had far less hepatic swelling, with a 91% reduction in liver wet-to-dry weight ratios compared with normothermic mice (P < 0.001). To further assess the effects of hypothermia on hepatic ischemia-reperfusion injury, sections of liver obtained from the ischemic lobe after ischemia and 8 h of reperfusion were evaluated for histopathological changes. In normothermic mice undergoing ischemia-reperfusion, liver sections were characterized by patchy areas of coagulative necrosis, especially in zones 2 and 3 of hepatic lobules (Fig. 4A). Neutrophils and red blood cells were numerous in the necrotic areas, and there was a marked destruction of sinusoidal structure consistent with the no-reflow phenomenon (21, 29). In contrast, hepatic architecture of hypothermic mice appeared normal; there was no evidence of hepatocyte necrosis and no inflammatory cell infiltrates (Fig. 4B). These data demonstrate that hypothermic mice are greatly protected from ischemia-reperfusion-induced hepatocellular injury.

The liver injury induced by ischemia-reperfusion is known to be mediated by the secretory products of activated neutrophils (16). To determine whether hypothermia reduced the hepatic recruitment of neutrophils, we measured the content of MPO in liver samples obtained after ischemia and 8 h of reperfusion. In normothermic mice, ischemia-reperfusion caused a significant increase in liver MPO content compared with sham controls (Fig. 5). In hypothermic mice this effect was completely abrogated, with liver MPO content reduced 99% from that of normothermic mice (P <
Hypothermia prevents the recruitment of neutrophils into the liver.

Effects of hypothermia on the production of proinflammatory cytokines and chemokines. The hepatic inflammatory response to ischemia-reperfusion is characterized by increased production of proinflammatory cytokines and the subsequent production of neutrophil-attracting chemokines (5, 6, 18). In an attempt to identify the mechanism by which hypothermia conferred its protective effects, we first assessed whether hypothermia altered the expression of mRNA for the cytokines TNF-α and IL-1β, and the chemokine MIP-2 in liver tissues obtained after ischemia and 8 h of reperfusion. As shown in Fig. 6, expression of TNF-α, IL-1β, and MIP-2 mRNA was increased in normothermic mice compared with sham controls. TNF-α and IL-1β mRNA expression in hypothermic mice was similar to sham controls, whereas MIP-2 mRNA in hypothermic mice was higher than in sham controls (Fig. 6). We next measured serum protein levels of TNF-α, IL-1β, and MIP-2. In normothermic mice, serum levels of TNF-α, IL-1β, and MIP-2 after ischemia-reperfusion were all significantly greater than serum levels in sham controls (Fig. 7). Hypothermia resulted in an 80% reduction in TNF-α (P < 0.001), a 76% decrease in IL-1β (P = 0.003), and a 92% reduction in MIP-2 (P < 0.001) compared with normothermic mice. Thus hypothermia appears to confer its protective effects by greatly suppressing the production of proinflammatory cytokines and chemokines.

Effects of hypothermia on activation of NF-κB, JNK, and activator protein-1. The expression of proinflammatory cytokines is controlled by a number of different signal transduction pathways. The transcription factor NF-κB is a primary regulator of a large number of cytokines and chemokines (24). We investigated whether the decreased cytokine and chemokine generation in hypothermic mice might be caused by suppressed activation of NF-κB. However, we found that NF-κB activation in hypothermic mice was not decreased compared with normothermic mice (data not shown). Because the expression of cytokines and chemokines is also controlled in part by c-Jun (33, 34), and
since other studies have suggested a role for JNK in the hepatic response to ischemia-reperfusion (3, 23), we investigated whether the activity of JNK was altered by hypothermia. As shown in Fig. 8, no activated (phosphorylated) JNK was detected in livers from sham controls. In livers from normothermic mice, both JNK isoforms 1 and 2 were activated after 1 and 4 h of ischemia but were increased minimally after 8 h of reperfusion (Fig. 8). In hypothermic mice, there was no activation of the JNK2 at any time point (Fig. 8). There did appear to be slight activation of JNK1 after 1 h of reperfusion, but there was no activation of this form at either 4 or 8 h after reperfusion (Fig. 8). To determine if this effect was specific for JNK or was a generalized effect on mitogen-activated protein kinases, we assessed the activation of two other mitogen-activated protein kinases, p38 and extracellular signal-regulated protein kinase (ERK). No phosphorylated p38 could be detected in any group (data not shown). Phosphorylated ERK was detected in both normothermic and hypothermic livers, but there was no difference between groups (data not shown). This suggests that hypothermia selectively suppresses the activation of JNK but not other mitogen-activated protein kinases.

Because JNK activation can lead to transcriptional activation of activator protein (AP)-1 (17), and since AP-1 is known to contribute to the gene expression of TNF-α and other proinflammatory mediators (33, 34), we assessed the activation of AP-1 in normothermic and hypothermic mice after hepatic ischemia-reperfusion. In normothermic mice, AP-1 activation was greatly increased after ischemia and 1 h of reperfusion compared with normothermic sham controls (Fig. 9A). Hypothermia completely abrogated this increase in hepatic AP-1 activation. There was a faster-migrating band observed in the sham and hypothermia groups. To determine the composition of this band, as well as that of the expected AP-1 band, supershift assays were performed. The faster-migrating band observed in the hypothermia group did not supershift on addition of antibodies to FosB, JunB, c-Jun, or JunD (Fig. 9B). The composition of the AP-1 complex in normothermic mice appeared to be composed of JunB, c-Jun, and JunD. These data suggest that suppressed activation of JNK and the resulting reduction in AP-1 activation may contribute to the protective effects of hypothermia on hepatic ischemia-reperfusion.

**DISCUSSION**

Hypothermia has been used to safely prolong hepatic ischemia resulting from inflow occlusion during resec-
tional surgery (31). Furthermore, hypothermia has been shown to reduce ischemia-reperfusion injury to the liver (11, 12, 14, 20, 25, 32). To date, the mechanism for the protective effects of hepatic hypothermia has been attributed to reduced metabolism and oxygen consumption. Early studies showed that total body cooling to a rectal temperature as low as 23°C for up to 12 h does not adversely affect liver function (10). Subsequently, it was shown that extracorporeal cooling of the liver to 25°C resulted in a 36% reduction in the oxygen consumption by the liver (22). More recent reports suggest that hepatic hypothermia reduces liver ATP levels, resulting in a prolongation of hepatocellular viability in ischemic tissues (8). Transcriptional activation and protein synthesis demand a great deal of energy, and thus hypothermia may attenuate transcriptional activation and protein synthesis by suppressing the cellular metabolic activity and oxygen demand. Kupffer cells are known to be activated by liver ischemia and are thought to initiate the hepatic inflammatory response through their production of proinflammatory cytokines and chemokines. However, hepatocytes are also a significant source of these mediators, and it is likely that hypothermia reduces the metabolic rate and energy requirement of Kupffer cells and hepatocytes during the initial phase of hepatic ischemia-reperfusion, thereby decreasing proinflam-

Fig. 7. Effects of hypothermia on serum levels of TNF-α, IL-1β, and MIP-2 after hepatic ischemia and 8 h of reperfusion. Serum samples were analyzed by ELISA. Values are means ± SE; n = 5/group.

Fig. 8. Effects of hypothermia on the activation of c-Jun NH₂-terminal kinase (JNK) in liver during ischemia-reperfusion injury. Lysates of liver tissues from independent mice were analyzed by Western blot and stained with phospho-specific antibodies to JNK (A, top). The blot was then stripped and restained for total JNK proteins (A, bottom). JNK1 (B) and JNK2 (C) activation was assessed by image analysis of digitized Western blots.
matory cytokine and chemokine production and suppressing the subsequent inflammatory response.

To the best of our knowledge, this is the first study to demonstrate that hypothermia suppresses the hepatic inflammatory response to ischemia-reperfusion. We found that mice that were hypothermic during the ischemic and early reperfusion periods had dramatically reduced production of the proinflammatory cytokines TNF-α and IL-1β and the CXC chemokine MIP-2. This hypothermia-induced suppression of these mediators resulted in almost complete abrogation of hepatic neutrophil accumulation. Furthermore, liver histology of hypothermic mice appeared almost completely normal, whereas normothermic livers displayed the typical signs of hepatocellular necrosis, sinusoidal collapse, and leukocyte accumulation. Correspondingly, hypothermia almost completely ameliorated the hepatic injury induced by ischemia-reperfusion. The liver injury induced by ischemia-reperfusion is greatly dependent on neutrophils (15, 16). Numerous studies have shown that prevention of neutrophil recruitment to liver by blockade of cytokines, chemokines, or adhesion molecules suppresses the development of tissue injury (5, 6, 9, 26). Our data suggest that hypothermia prevents the initiation of the inflammatory response in the liver by preventing the transcription of proinflammatory mediators.

The gene expression of the mediators studied here is controlled largely by the transcription factor NF-κB (24). However, hypothermia did not cause a reduction in NF-κB activation in liver, suggesting that hypothermia may affect other transcriptional regulators involved in the expression of TNF-α, IL-1β, and MIP-2. A likely candidate is AP-1, which is known to be involved in the transcription of proinflammatory mediators (33, 34). Hyperthermia greatly suppressed the activation of JNK1 and JNK2. Both of these isoforms are involved in the activation of AP-1, but JNK2 has been shown to have 10-fold greater activity for c-Jun phosphorylation (27). Interestingly, JNK2 phosphorylation was completely inhibited in hypothermic mice. Correspondingly, there was almost complete inhibition of AP-1 activation in the liver after ischemia-reperfusion. Thus it seems that reduced hepatic temperature somehow differentially affects NF-κB and AP-1. The activation of these two transcription factors has been documented in hepatic ischemia-reperfusion injury, and both share similar activation kinetics (38). Previous studies by us and others have suggested a central role of NF-κB in the hepatic inflammatory response to ischemia-reperfusion (35, 38). However, NF-κB activation is known to be necessary for hepatocyte regeneration (2), and thus a potential role of NF-κB in hepatoprotection has also been suggested. The role of AP-1 in the hepatic inflammatory response has not been rigorously investigated. Optimal gene expression of multiple cytokines and chemokines requires cooperative activation of both NF-κB and AP-1, suggesting that the reduced production observed during hypothermia may be due to the selective effect on AP-1. Furthermore, our studies suggest that selective inhibition of AP-1 may provide a potential therapeutic benefit for the hepatic inflammatory response induced by ischemia-reperfusion.

There is evidence that hypothermia reduces the production of reactive oxygen species induced by hepatic ischemia (36, 37). AP-1 is activated by oxidant stress, and it is possible that the hypothermia-induced reduction of reactive oxygen species may result in decreased...
AP-1 activation. However, NF-κB is also redox sensitive, and therefore reduced oxidant stress in hypothermic mice would be expected to reduce the activation of NF-κB. We did not observe any reduction in NF-κB activation in livers from hypothermic mice. Furthermore, adenosinergic expression of mitochondrial superoxide dismutase in liver greatly reduces hepatic ischemia-reperfusion injury in association with reduced activation of both AP-1 and NF-κB (39). Thus it appears unlikely that reduced generation of reactive oxygen species by hypothermia results in selective inhibition of AP-1 activation. The mechanism by which hypothermia suppresses JNK activation and subsequent activation of AP-1 warrants further investigation.

In summary, our data demonstrate that hypothermia during hepatic ischemia-reperfusion prevents the activation of the transcription factor AP-1 and subsequent production of proinflammatory cytokines and chemokines. These effects result in abrogation of liver neutrophil accumulation and hepatocellular damage. Our findings offer a new explanation for the beneficial effects of hypothermia on hepatic ischemia-reperfusion injury. Furthermore, they support the use of hypothermic therapy in the management of complex liver resectional surgeries that require extended occlusion times.

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