Chronic alcohol consumption accelerates liver injury in T cell-mediated hepatitis: alcohol disregulation of NF-κB and STAT3 signaling pathways

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Am J Physiol Gastrointest Liver Physiol 287: G471–G479, 2004. First published April 2, 2004; 10.1152/ajpgi.00018.2004.—Alcohol consumption is a major risk factor accelerating the progression of liver disease in patients with chronic hepatitis virus infection. However, the mechanism underlying the enhanced susceptibility of alcoholics to liver injury is not fully understood. Here, we demonstrate that chronic ethanol consumption increases the susceptibility of C57BL/6 mice to concanavalin A (Con A)-induced T cell-mediated hepatitis. Injection of a low dose of Con A (5 μg/g) causes severe liver damage in ethanol-fed mice as evidenced by a significant elevation of serum alanine aminotransferase levels, massive necrosis, and infiltration of leukocytes but only slightly induces liver injury in control pair-fed mice. In ethanol-fed mice, the activation and cytotoxicity of natural killer T cells, cells that play key roles in Con A-induced T cell hepatitis, are not significantly enhanced relative to pair-fed mice. Moreover, Con A-induced activation of hepatic NF-κB is increased, whereas activation of STAT1 and STAT3 is attenuated in ethanol-fed mice. Consistent with this result, the expression of chemokines and adhesion molecules [such as ICAM-1, macrophage inflammatory protein (MIP)-1, MIP-2, and MCP-1] controlled by NF-κB is upregulated, whereas STAT1-controlled expression of chemokines (such as MIG and IP-10) is downregulated in ethanol-fed mice compared with pair-fed mice. In conclusion, chronic alcohol consumption accelerates T cell-mediated hepatitis via upregulation of the NF-κB signaling pathway and subsequently enhances expression of chemokines/adhesive molecules and recruitment of leukocytes into the liver. Down-regulation of the antipapoptotic STAT3 signal may also contribute to alcoholic liver injury; concanavalin A: nuclear factor-κB; STAT3.

Worldwide, alcohol consumption is a major cause of chronic liver disease. Interestingly, only ~15–20% heavy drinkers develop alcoholic liver injury, suggesting that alcohol is a cofactor for developing chronic liver disease (14, 17). Accumulating evidence indicates that many genetic and acquired factors are implicated in the susceptibility of individuals to alcohol-induced liver injury (5, 12, 14, 27, 30). These factors include chronic viral infection, nutritional factors, dose and duration of alcohol consumption, drinking patterns, age when drinking began, genetic polymorphisms of cytokines and alcohol-metabolizing enzymes, gender, histocompatibility antigens, immunological factors, genetic predisposition to alcohol addiction, and hepatic iron overload (2, 5, 12, 14, 27, 30, 35, 39). In rodents, intragastric infusion of ethanol for 4–5 wk leads to steatosis, inflammation, and, to a lesser extent, fibrosis in the liver, whereas feeding Lieber-DeCarli liquid diet containing ethanol does not cause significant liver injury except steatosis in rats (15, 16, 28) but enhances endotoxin (26-) and galactosamine (41)-induced liver injury in mice and concanavalin A (Con A)- and endotoxin-liver injury in rats (6, 7). Here, we demonstrate that ethanol consumption significantly enhanced T cell-mediated hepatitis induced by Con A in mice. A low-dose injection of Con A induced significant elevations in serum transaminase levels, hepatic inflammation, and necrosis in ethanol-fed mice but not in pair-fed mice.

Con A injection has been widely used to study T cell-mediated hepatitis, whose manifestation closely resembles the pathology of a variety of human liver disorder (47). Accumulating evidence suggests that activation of a variety of cytokines and their downstream signals plays an important role in the development and progression of T cell-mediated liver injury in this model (46). TNF-α activation of the NF-κB signal (48, 50), IFN-γ activation of signal transducer, and activator transcription factor 1 (STAT1) (21) and IL-4 activation of STAT4 (22) have all been shown to play crucial roles in the development of liver injury in Con A-induced hepatitis. In contrast, IL-6 activation of STAT3 is protective against liver injury (21). After activation of various signals, a wide variety of chemokines and adhesion molecules are induced and consequently attract infiltrating granulocytes, resulting in massive inflammation and necrosis (4, 22, 43). Recently, it has been shown that natural killer T (NKT) cells are essential for Con A-induced T cell hepatitis via expression of Fas ligand (FasL), which directly kills hepatocytes (45). To understand the molecular mechanism by which alcohol consumption enhances Con A-induced hepatitis, we compared Con A injection-induced activation of NKT cells, signaling pathways, and the expression of various chemokines and adhesion molecules in pair- and ethanol-fed mice. Our results show that in ethanol-fed mice, Con A-induced activation of STAT1 and STAT3 signaling pathways is inhibited, whereas activation of the NF-κB signaling pathway is enhanced compared with pair-fed mice. Consistent with the observed upregulation in NF-κB activation, the expression of various chemokines and adhesion molecules controlled by NF-κB is enhanced in ethanol-fed mice, which may be an important mechanism contributing to the increase in susceptibility of ethanol-fed mice to T cell-mediated hepatitis induced by Con A.

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Materials and Methods

Materials. Anti-STAT1, anti-phospho-STAT1 (Tyr701), anti-phospho-STAT3 (Tyr705), anti-STAT3, anti-phospho-ERK1/2, anti-4B, and anti-phospho-1kB antibodies were obtained from Cell Signaling Technology (Beverly, MA).

Mouse models of chronic ethanol consumption and Con A-induced hepatitis. Male C57BL/6 mice weighing 20–25 g were fed a nutritionally adequate liquid diet containing 5% ethanol or a control diet in which ethanol was substituted isocalorically with dextrin maltose (BioServ, Frenchtown, NJ). Both diets were dispensed in glass liquid-diet feeding tubes (BioServ). Ethanol was introduced gradually by increasing the content by 1% (vol/vol) every 2 days until the mice were consuming diets containing 5% (vol/vol) ethanol for 2 or 4 wk. Subsequently, pair- and ethanol-fed mice were injected intravenously with Con A. After various time periods, mice were killed and liver injury was determined.

Initially, male C57BL/6J mice from the Jackson Laboratory (Bar Harbor, ME) were used in our studies. However, the ethanol-fed C57BL/6J mice gained less weight than pair-fed mice, and there was 15–20% mortality in the ethanol-fed group during the 4-wk feeding period. Similar mortality in ethanol-fed C57BL/6J mice was also reported previously (26). Although there was 15–20% mortality in the ethanol-fed C57BL/6J mice during the 4-wk feeding period, the surviving mice after 2- or 4-wk feeding with ethanol were more susceptible to Con A-induced liver injury compared with pair-fed mice (data not shown). Then we tested this model in male C57BL/6N mice from the National Cancer Institute (NCI) (Frederick, MD). Interestingly, ethanol-fed male C57BL/6N mice and pair-fed mice gained weight similarly, and none of them died during the 4-wk feeding period. Therefore, the data from the study of male C57BL/6N mice (NCI) were reported in this paper.

Isolation and culture of primary mouse hepatocytes. Mice weighing 20–25 g were anesthetized with pentobarbital sodium (30 mg/kg ip), and the portal vein was cannulated under aseptic conditions. The liver was subsequently perfused with an EGTA solution (in mM: 5.4 KCl, 0.44 KH2PO4, 140 NaCl, 0.34 NaHPO4, 0.5 EGTA, and 25 Tricine, pH 7.2) and DMEM (GIBCO-BRL, Gaithersburg, MD) and digested with 0.075% collagenase solution. The isolated hepatocytes were subsequently cultured in Hepato-ZYME-SFM media (GIBCO-BRL) and they were used to assay for NKT cytotoxicity.

Western blot analysis. Liver tissue extracts were prepared by homogenization in lysis buffer (30 mM Tris, pH 7.5, 150 mM sodium chloride, 1 mM phenylmethylsulfonyl fluoride, 1 mM sodium orthovanadate, 1% Nonidet P-40, 10% glycerol) at 4°C, followed by centrifugation at 16,000 rpm at 4°C for 10 min. After protein concentrations were quantified, the supernatants were mixed in Laemmli sample buffer containing 44.5 mM Tris-HCl, pH 8.2, 44.5 mM boric acid, 1 mM EDTA. After the gel was prerun at 100 V for 2 h, electrophoresis was performed at 270 V for 2 h at 4°C. The gels were then analyzed using the PhosphorImager ImageQuant program (Molecular Dynamics, Sunnyvale, CA).

EMSA. EMSAs were performed in 20-μl volumes with 20 mM Tris-HCl, pH 7.9, 1.5% glycerol, 50 μg/ml BSA, 1 mM DTT, 0.5 mM phenylmethylsulfonyl fluoride, 2 μg/ml Avidin (d-l-dc), 1 ng 32P-labeled probe, and 10 μg nuclear extract. Reactions were incubated at 25°C for 20 min and subsequently analyzed by electrophoresis through nondenaturing stock polyacrylamide gels (6 or 10%) in 0.5 × TBE buffer containing 44.5 mM Tris-HCl, pH 8.2, 44.5 mM boric acid, and 1 mM EDTA. After the gel was prerun at 100 V for 2 h, electrophoresis was performed at 270 V for 2 h at 4°C. The gels were then analyzed using the PhosphorImager ImageQuant program (Molecular Dynamics). The NF-κB binding site of the double-stranded oligonucleotide 5’-AGT TGA GGC GAC TTT CCC AGG-3’ was used as a probe to determine NF-κB binding.

Isolation of liver mononuclear cells and adoptive transfer. Pair- and ethanol-fed mouse livers were removed and pressed through a 200-gauge stainless steel mesh. The liver cell suspension was collected and suspended in RPMI 1640 media (GIBCO-BRL). After centrifugation at 50 g for 5 min, mononuclear cells (MNC supernatant) were separated from parenchymal cells (pellet). MNCs were then washed in PBS and resuspended in 40% Percoll (Sigma) in RPMI 1640. The cell suspension was gently overlaid onto 70% Percoll and centrifuged for 20 min at 750 g. MNCs were collected from the interphase, washed twice in PBS, and resuspended in RPMI 1640.

Adoptive transfer of hepatic MNCs into the liver was performed as described previously (22).

Cytotoxicity assay. The cytotoxicity of hepatic MNCs against primary mouse hepatocytes was measured using a 4-h AST release assay as described previously (22). Briefly, mice were treated with Con A for 2 h, then hepatic MNCs were isolated and subsequently added to cultured mouse hepatocytes at the indicated effector-to-target (E/T) ratios. After 4 h, the supernatant was harvested and AST activity was measured. The specific cytotoxicity was calculated as AST experimental − AST spontaneous/AST maximum − AST spontaneous × 100%.

Flow cytometric analysis of NKT cell activation in the liver after administration of Con A. To compare activation of NKT cells in pair- and ethanol-fed mice, hepatic MNCs were stained with anti-NK1.1, anti-CD3, and anti-Fas antibodies (PharMingen, San Diego, CA) and analyzed through a fluorescence-activated cell sorter (FACScalibur, Becton Dickinson, Mountain View, CA).

Statistical analysis. For comparing values obtained in three or more groups, one-factor analysis of variance was used followed by Tukey’s post hoc test. Statistical significance was taken at the P < 0.05 level.

Results

Chronic ethanol consumption potentiates T cell-mediated hepatitis induced by Con A. As shown in Fig. 1, injection of a low dose of Con A (5 μg/g) failed to induce significant liver injury in 2- or 4-wk pair-fed groups (Fig. 1, A and B). However, the same treatment caused severe liver damage in both 2- and 4-wk ethanol-fed groups, as evidenced by signif-
astic elevations in serum ALT and AST levels (Fig. 1, A and B) and massive necrosis in the liver (Fig. 1C). Similarly, injection of Con A (6 μg/g) did not induce significant liver injury in 4-wk pair-fed mice but significantly elevated serum ALT and AST levels in 4-wk ethanol-fed mice (Fig. 1D).

Cytotoxicity of hepatic MNCs against primary hepatocytes is not enhanced in ethanol-fed mice. The cytotoxicity of hepatic NKT cells against hepatocytes has been suggested to play an important role in Con A-induced liver injury (45). Therefore, we examined whether the cytotoxicity of hepatic MNCs against hepatocytes was enhanced in ethanol-fed mice as a potential mechanism for alcohol potentiation of T cell-mediated hepatitis. Three different groups of effectors/targets were compared. As shown in Fig. 2, MNCs from Con A-treated pair-fed mice, compared with MNCs from Con A-treated ethanol-fed mice, showed significantly higher cytotoxicity against both pair-fed (Fig. 2A) and ethanol-fed mouse hepatocytes (B) at a 50:1 E/T ratio. This indicates that the cytotoxicity of hepatic MNCs from ethanol-fed mice was reduced compared with MNCs from pair-fed mice. Figure 2, A and B, also showed that hepatocytes from ethanol-fed mice were more susceptible to MNC killing than from pair-fed mice. As shown in Fig. 2, A and B, pair-fed MNCs were cytotoxic against 45% of hepatocytes from ethanol-fed mice compared with only 29% of pair-fed mouse hepatocytes. Similarly, ethanol-fed liver MNCs caused cytotoxicity in 25% of ethanol-fed mouse hepatocytes and only 17% of pair-fed mouse hepatocytes. In Fig. 2C, the cytotoxicity of pair-fed mouse MNCs against pair-fed mouse hepatocytes and ethanol-fed mouse MNCs against ethanol-fed mouse hepatocytes was compared, indicating that the cytotoxicity between these two groups of effectors/targets was comparable. Taken together, these findings show that increased hepatic MNC cytotoxicity is not likely responsible for ethanol-induced potentiation of T cell-mediated hepatitis.

Next, the activity of liver MNCs from pair- and ethanol-fed mice via adoptive transfer was compared. As shown in Fig. 2D, adoptive transfer of liver MNCs from ethanol-fed mice induced lower levels of ALT elevation after Con A injection relative to adoptive transfer of pair-fed mouse liver MNCs. These findings suggest that chronic ethanol consumption enhances the sensitivity of liver MNCs to the effects of Con A administration (P < 0.05).

Effects of chronic ethanol consumption on NKT cells in Con A-induced hepatitis. Activation of NKT cells has been suggested to play an important role in Con A-induced liver injury (45). We wished to examine Con A activation of NKT cells in
Effects of chronic ETOH consumption on infiltration of leukocytes in T cell-mediated hepatitis. The activation of multiple signals has been implicated in the development and progression of T cell-mediated hepatitis (21, 22, 48, 50). Therefore, Con A-mediated activation of these signals between pair- and ethanol-fed mice was compared. As shown in Fig. 5A, injection of Con A induces activation of STAT1 and STAT3 in the livers of pair-fed mice, as evidenced by the detection of phosphorylated STAT1 and STAT3. Such activation was markedly suppressed in ethanol-fed mice. STAT1 protein expression was also induced after injection of Con A, which was less evident in the ethanol-fed group relative to the pair-fed group. Similar STAT3 protein expression was detected in both Con A-treated pair- and ethanol-fed groups. Furthermore, Con A injection also caused activation of ERK1/2 in the liver; such activation was significantly enhanced in the ethanol-fed group compared with the pair-fed group (Fig. 5A).

Next, NF-κB activation was determined by using gel mobility shift assay. As shown in Fig. 5B, Con A injection was shown to induce NF-κB binding in pair-fed mice, with peak effect occurring at 1 h, whereas significantly higher and prolonged NF-κB binding was observed in ethanol-fed mice. Consistent with the results of the gel mobility shift assay, Western blot analysis showed that IkB was rapidly phosphorylated after injection of Con A in pair-fed mice, and this phosphorylation was much higher and prolonged in ethanol-fed mice (Fig. 5C). The IkB protein was rapidly degraded 1 h after Con A injection and recovered to normal levels at 3 h in pair-fed mice (Fig. 5C). In ethanol-fed mice, injection of Con A also caused rapid degradation of IkB protein at 1 h, but the IkB protein was not completely recovered until 12 h later (Fig. 5C).

Effects of chronic ethanol consumption on expression of chemokines and adhesion molecules in T cell-mediated hepatitis. The above data demonstrate that ethanol consumption regulates activation of various signaling pathways during T cell-mediated hepatitis. Next, we examined whether Con
A-induced expression of various chemokines and adhesion molecules, which are controlled by these signaling pathways, is regulated in ethanol-fed mice compared with pair-fed mice. As shown in Fig. 6A, Con A injection induced expression of various chemokines and adhesion molecules in the liver, with peak effect between 1 and 6 h. Compared with pair-fed mice, Con A induction of VCAM-1, ICAM-1, Eotaxin-1, Eotaxin-2, macrophage inflammatory protein (MIP)-1α, MIP-1β, MIP-2, and MCP-1 in ethanol-fed mice was prolonged, whereas induction of MIG and IP-10 was decreased. To further confirm the prolonged induction of these chemokines and adhesion molecules, we compared and quantified their expression at the 12-h point after Con A injection. As shown in Fig. 6, B and C, induction of ICAM-1, MIP-1α, MIP-1β, MIP-2, and MCP-1 was significantly potentiated in ethanol-fed mice compared with that in pair-fed mice 12 h after injection of Con A, whereas induction of MIG was decreased.

**DISCUSSION**

In this paper, we demonstrated that chronic ethanol consumption markedly potentiates T cell-mediated hepatitis induced by injection of Con A in mice. Furthermore, it was determined that ethanol potentiation of T cell-mediated hepatitis is due mainly to enhancing the NF-κB signaling pathway and the subsequent induction of NF-κB-controlled chemokines and adhesion molecule expression in the liver. As shown in Fig. 5, B and C, NF-κB binding, IkB phosphorylation, and IkB degradation after Con A injection were significantly enhanced in ethanol-fed mice compared with pair-fed mice. Consistent with this finding, ICAM-1, MIP-1α, MIP-1β, MIP-2, and MCP-1 expression, which are controlled by NF-κB (11, 18, 37), are significantly prolonged in ethanol-fed mice after Con A injection compared with pair-fed mice. It has been reported (31, 32) that ethanol consumption causes activation of NF-κB and subsequent induction of chemokines and adhesion mole-
molecules in rodent livers as well as in monocytes from human patients with alcoholic hepatitis. For example, Nanji et al. (33) reported that intragastric feeding of an ethanol diet with fish oil or corn oil induced significant activation of NF-κB and induction of regulated on activation normal T-expressed and presumably secreted, MCP-1, MIP-1α, MIP-2, IP-10, cytokine-induced neutrophil chemoattractant, and ENA-78 in the livers of rats compared with feeding rats with an ethanol diet containing saturated fatty acids. The activation of NF-κB and induction of chemokines and adhesion molecules strongly correlated with liver inflammation and injury in this intragastric model (33). The activation of NF-κB in monocytes was also reported in human alcoholic liver disease (20). Additionally, the critical role of NF-κB activation in alcoholic liver injury has been clearly demonstrated through delivery of the adenoviral IκB super-repressor gene, which reduced early alcohol-induced liver injury in rats (49). However, the mechanisms underlying ethanol-mediated activation of NF-κB are not fully understood. Recent data (31, 44) show that alcohol exposure elevates TNF-α levels, which are mediated via multiple mechanisms including potentiation of LPS-activated ERK1/2-Egr-1 signal pathway, stabilization of TNF-α mRNA.

Fig. 4. ETOH consumption potentiates Con A injection-mediated infiltration of neutrophils and eosinophils in the liver. A: pair- and ETOH-fed mice were injected with Con A (5 μg/g) for 12 h. Liver sections were prepared and subjected to immunohistochemistry using anti-F4/80 antibodies to detect macrophages. B: liver sections in A were also immunostained with anti-MPO antibody to detect neutrophils. Ten fields were randomly selected, and positive cells were counted. Values are shown as means ± SE from 5 mice at each time point. *P < 0.05 compared with corresponding pair-fed groups. C: pair- and ETOH-fed mice were injected with Con A (5 μg/g) for 12 h. Hepatic eosinophil peroxidase activities were measured. Values are shown as means ± SE from 5 mice at each time point. *P < 0.01 compared with pair-fed group.

Fig. 5. Chronic ETOH consumption dysregulates STATs and NF-κB signaling pathways in T cell-mediated hepatitis induced by Con A. A: pair- and ETOH-fed mice were injected with Con A (5 μg/g) at various time points; total liver protein extracts were immunoblotted using various antibodies as indicated. B and C: activation of NF-κB was measured by using gel mobility shift analysis of NF-κB binding (B) and Western blot analysis of IκB phosphorylation (p-IκB) and IκB degradation (C). In B, 100-fold cold NF-κB probe was included in the gel shift binding assay. Data in A–C are representatives of 3 independent experiments with similar results.
(23, 24, 42), and induction of oxidative stress (1, 51). Hence, elevated levels of TNF-α could be an important mechanism contributing to NF-κB activation. Here, we showed that expression of TNF-α mRNA was significantly higher 3 h after injection of Con A in ethanol-fed mice compared with pair-fed mice (Fig. 6A), suggesting that ethanol potentiated NF-κB activation in T cell-mediated hepatitis, partly mediated via an increase in TNF-α production.

Activation of hepatic NKT cytotoxicity through expression of FasL against hepatocytes has also been shown to play an important role in Con A-induced liver injury (45). Our results in this paper showed that the cytotoxicity of hepatic NKT cells from ethanol-fed mice against hepatocytes from the same mice was similar to the cytotoxicity of hepatic NKT cells from pair-fed mice against hepatocytes from pair-fed mice (Fig. 2C), suggesting that ethanol potentiation of T cell-mediated hepatitis is not through enhancing NKT cell cytotoxicity. Further investigation showed that the cytotoxicity of ethanol-fed mouse liver NKT cells was lower than that of pair-fed mouse liver NKT cells, because the ability of ethanol-fed mouse liver NKT cells to kill the same target cells significantly decreased compared with NKT cells from pair-fed mouse liver. This is likely due to a downregulation of FasL expression in NKT cells after injection of Con A from ethanol-fed mice compared with pair-fed mice (Fig. 3, C and D). Moreover, hepatocytes from ethanol-fed mice were more susceptible to NKT cell killing compared with pair-fed mouse hepatocytes. Although the cytotoxicity of liver MNCs is not enhanced in ethanol-fed mice (Fig. 2), adoptive transfer of liver MNCs from ethanol-fed mice, compared with transfer of pair-fed liver MNCs, enhanced Con A-induced liver injury (Fig. 2D). Similarly, Cao et al. (7) reported that transfer of liver-associated T cells from ethanol-fed rats potentiated Con A-induced liver injury compared with cell transfer from pair-fed rats, which is likely mediated by enhanced TNF-α production. Taken together, these findings suggest that ethanol consumption may dysregulate liver MNCs, such as enhancing TNF-α production, and consequently T cell-mediated hepatitis is enhanced.

In contrast to potentiation of NF-κB signaling pathway, ethanol consumption decreased Con A-mediated activation of multiple STATs in the liver compared with pair-fed mice. As shown in Fig. 5A, injection of Con A caused activation of STAT1 and STAT3 in the livers of pair-fed mice, which was significantly decreased in ethanol-fed mice. Previously, it was shown that acute and chronic ethanol exposure inhibited IL-6 activation of STAT3 and IFN-γ activation of STAT1, which is partly mediated via activation of ERK1/2 and PKC (9, 10, 34). Here, we also showed that activation of ERK1/2 is significantly higher in ethanol-fed mice after Con A injection compared with pair-fed mice, suggesting that enhanced ERK1/2 activation could be involved in the downregulation of STAT activation in ethanol-fed mice. Activation of IL-6/STAT3 has been shown to protect against liver injury in Con A-induced T cell hepatitis (21); thus downregulation of STAT3 signaling may also contribute to ethanol potentiation of Con A-induced liver injury.

T cell-mediated immune responses have been implicated in the pathogenesis of a variety of human liver disorders (3, 19, 25) including autoimmune liver disease (29) and viral hepatitis (8, 38). Our findings here show that chronic ethanol consum-
tion potentiates Con A-induced T cell-mediated hepatitis in mice via dysregulation of cytokine signals such as stimulation of NF-κB signaling but inhibition of STAT signaling. Chronic alcohol consumption likely also dysregulates these cytokine signals and accelerates the development and progression of T cell-mediated injury in human liver diseases.

REFERENCES


