Glycine Accelerates Recovery from Alcohol-Induced Liver Injury

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ABSTRACT

Glycine prevents hepatic damage caused by hypoxia-reoxygenation, diminishes mortality due to endotoxin and minimizes alcoholic liver injury by decreasing blood ethanol. Our purpose was to investigate the effect of dietary glycine during recovery from early alcohol-induced injury, using a model that mimics the clinical presentation and histopathology with alcoholics. Male Wistar rats were exposed to ethanol continuously for 6 wk via intragastric feeding that resulted in typical histology of alcoholic liver injury, including steatosis, inflammation, necrosis and increased serum levels of aspartate aminotransferase and alanine aminotransferase. After cessation of ethanol, one group of rats received a control diet, the other a glycine-containing diet for 2 wk. During this period, all parameters studied tended to return to baseline values. However, serum aspartate aminotransferase and alanine aminotransferase recovered about 30% more rapidly in rats fed glycine. Further, the hepatic pathology score was also significantly lower in the glycine group than in controls (0.5 vs. 2.6). After 1 wk, steatosis was reduced significantly more in the glycine group (5.6%) than in controls (8.9%). Glycine also diminished numbers of infiltrating leukocytes and necrotic cells significantly more than in controls. This beneficial effect of glycine may be partly explained by the fact that glycine increased influx of chloride into Kupffer cells leading to diminished tumor necrosis factor-α production. These results indicate that a glycine containing diet expedites the process of recovery from ethanol-induced liver injury and may lead to its clinical application in alcoholic hepatitis.

It is well known that excessive intake of alcohol over a relatively long period leads to liver injury (Leelbach, 1966). Alcoholic liver disease affects millions of patients worldwide and is a major cause of death in urban American males (Diehl, 1989). The progression of alcoholic liver disease is characterized by steatosis, inflammation, necrosis and finally fibrosis and cirrhosis; when severe hepatitis occurs, death is a common outcome (Felver et al., 1990). Therefore, an effective, economical and simple treatment for reversal of liver injury when patients stop alcohol consumption could have a significant clinical impact. This study was designed to explore a possible new strategy to improve recovery from early alcoholic liver injury in the rat.

The establishment of a continuous intragastric feeding model in the rat by Tsukamoto and French (Tsukamoto et al., 1984) provides a reliable, clinically relevant animal model of alcoholic liver injury. With this model, not only is steatosis observed, but inflammation and pericentral necrosis also occur in about 2 to 4 wk. In this model of continuous enteral ethanol delivery, it was shown that early ethanol-induced liver injury was prevented by treatment with gadolinium chloride (GdCl₃), a selective Kupffer cell toxicant, indicating that Kupffer cells are involved in alcoholic liver disease (Adachi et al., 1994). When Gram-negative bacteria in the gut were reduced with antibiotics (Adachi et al., 1995) or lactobacillus administration (Nanji et al., 1994), early ethanol-induced liver injury was also diminished, implicating endotoxin in the pathogenesis of alcoholic liver disease. Elevated circulating endotoxin most likely activates Kupffer cells to release many potent effectors and cytokines (Decker, 1990), thus leading to alcohol-induced liver injury. This idea is supported by the fact that injury in this model was reduced with TNFα antiserum (Imuro et al., 1997b).

Glycine, a nonessential amino acid, has been shown to protect kidney proximal tubules (Miller et al., 1994) and hepatocytes (Nichols et al., 1994) against hypoxia. Glycine also prevented nephrotoxicity caused by cyclosporin A (Thurman et al., 1997). In a liver transplantation model, glycine added to the rinse solution reduced reperfusion injury and

ABBREVIATIONS: ALD, alcoholic liver disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GdCl₃, gadolinium chloride; LPS, lipopolysaccharide; NAD⁺, nicotinamide adenine dinucleotide; TNF-α, tumor necrosis factor-α; RT-PCR, reverse transcriptase polymerase chain reaction; [Ca²⁺], intracellular Ca²⁺; HEPES, N-[2-Hydroxyethyl]piperazine-N’-[2-ethanesulfonic acid.

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improved graft function and survival (Bachmann et al., 1995). Further, glycine improved the hepatic microcirculation and reduced injury in a low-flow, reflow model in the perfused liver (Zhong et al., 1996). Importantly, a diet containing glycine improved survival of rats in endotoxin shock, presumably by preventing activation of Kupffer cells, because TNFα production was decreased (Ikejima et al., 1996). In an in vivo study of ethanol-induced liver injury using the Tsukamoto-French model with a design where alcohol and glycine were given together, glycine minimized liver damage, but it also decreased ethanol in the stomach (Iimuro et al., 1996); therefore, it was not possible to determine if glycine directly acts on the liver or not. A reversal model designed by Nanji provides an alternative experimental design to evaluate the effect of glycine (Nanj et al., 1995). Using this model, alcoholic liver injury induced by 6 wk of ethanol exposure was reversed by 2 wk of treatment with an ethanol-free diet, mimicking the clinical situation. Accordingly, our purpose was to assess the effect of a glycine-rich diet on liver during the recovery phase of alcoholic liver injury after ethanol withdrawal, using this clinically relevant model.

Materials and Methods

Animals. Male Wistar rats (290–310 g) used in this study were housed in an American Association for Accreditation of Laboratory Animal Care-approved facility. All animals received humane care in compliance with institutional guidelines. An intragastric cannula was inserted into each rat as described by Tsukamoto and French (Tsukamoto et al., 1984). Briefly, cannulas were tunneled s.c. to the dorsal aspect of the neck and attached to infusion pumps by means of a spring-tether device and swivel, allowing complete mobility of the rats within metabolic cages. Animals were infused continuously with a high-fat liquid diet containing ethanol through an intragastric cannula for up to 6 wk.

Diets. The basic liquid diet was prepared according to Thompson and Reitz as described previously (Iimuro et al., 1996). It contained corn oil as fat (37% of total calories), protein (23%), carbohydrate (5%), minerals and vitamins, plus ethanol (35%). For the control diet, valine (2%, Sigma Chemical Co., St. Louis, MO) was added to the basic liquid diet to maintain nitrogen balance, and ethanol was replaced by dextrin-maltose. Valine was selected because it was previously shown that, unlike glycine, it did not prevent activation of Kupffer cells by endotoxin (Ikejima et al., 1997). Because it has been observed that 2% dietary glycine demonstrated better protective effects than 5% (Iimuro et al., 1996), the glycine containing diet was prepared by replacing valine with glycine (2%; Bio-Rad Laboratories, Hercules, CA).

Experimental protocol. Ethanol levels in the diet were gradually increased to 9 to 10 g/kg/day during the first week after surgery (e.g., 28–35% of total calories) based on the urine ethanol concentration. Values were between 10 and 12 g/kg/day during weeks 2 to 6. There were no significant differences in the amount of ethanol diet delivered to rats during 6 wk. Thereafter, animals were randomly assigned to two experimental groups (six per group), and given either control or glycine containing diets without ethanol for 2 wk. Rats in the glycine-treated group received 3.5 g/kg of glycine per day. Liver biopsies were taken at 6 wk of ethanol exposure, after 1 wk of recovery and at necropsy after 2 wk of recovery. Tissues samples were divided into two pieces; one was fixed in formalin the other frozen in liquid nitrogen and stored at −80°C.

Urine collection and assay for ethanol. Concentrations of ethanol in urine are representative of blood alcohol levels (Badger et al., 1993). Rats were housed in metabolic cages that separated urine from feces and urine samples were collected over 24 hr for each rat. Ethanol levels in urine were determined daily by measuring absor-

bance at 366 nm resulting from the reduction of NAD+ to the reduced form of nicotinamide adenine dinucleotide by alcohol dehydrogenase (Bergmeyer, 1988).

Blood collection and enzymatic assays. Blood was collected via the inferior vena cava at 6 wk of ethanol exposure, after 1 wk of dietary treatment, and at necropsy 2 wk after ethanol was terminated. Serum was stored at −20°C until AST and ALT were analyzed by standard enzymatic procedures (Bergmeyer, 1988).

Pathological evaluation. Formalin-fixed liver samples were embedded in paraffin and stained with hematoxylin and eosin to assess steatosis, inflammation and necrosis. Liver pathology was scored as described by Nanji et al. (1989) and was modified using a modification of previously published techniques (Arteel et al., 1996). Color detection ranges were set for white areas representing fatty vacuoles. The extent of fat accumulation in pericentral regions (zone 3) of the liver lobule was defined as the percent of the field area within the default color range determined by the software, avoiding the influence of lumina of central veins. Average measurements from each tissue section (five fields per section) were pooled to determine means.

Quantitation of infiltrating leukocytes and necrosis. The total number of infiltrating leukocytes (including neutrophils and mononuclear cells), hepatocytes and necrotic hepatocytes were counted in a 100 mm2 area with a magnification of 200×. Five areas per section were randomly selected and counted avoiding large lumina of vessels. Data were pooled to determine means.

TNFα mRNA in liver. For measurement of TNFα mRNA in frozen liver samples, standard RT-PCR techniques were used. Briefly, cellular RNA was isolated from homogenized liver preparations. Synthesis of cDNA was performed by addition of 1 mg of RNA in a reaction buffer with an oligo d (T)12–18 primer. After incubations,Reverse transcriptase was added and incubated with PCR primers specific for β-actin and TNFs (Clontech, Palo Alto, CA; Stratagene, La Jolla, CA). Synthesized cDNA was added to a PCR system, cycled, amplified and quantitated on electrophoresis gels. Densitometry was presented relative to the β-actin housekeeping marker gene.

Kupffer cell isolation and culture. Kupffer cells were isolated from normal male Wistar rats using techniques described previously (Ikejima et al., 1997). In brief, liver was digested with collagenase, excised and the Gilson capsule broken by shaking in Hanks’ balanced salt solution buffer. The suspension was filtered through sterile nylon gauze and the filtrate was centrifuged twice at 50 × g for 3 min to separate parenchymal from nonparenchymal cells. The supernatant was collected, and the nonparenchymal cell supernatant fraction was centrifuged at 500 × g for 7 min. The pellet was resuspended in buffer and gently layered on a density cushion of Percoll and centrifuged for 15 min at 1500 × g. The Kupffer cell fraction was collected and washed with Hanks’ balanced salt solution. Cells were seeded onto 25-mm glass coverslips and incubated in Dulbecco’s modified Eagle’s medium (GIBCO Laboratories Life Technologies Inc., Grand Island, NY) supplemented with 10% fetal bovine serum and antibiotics (100 U/ml of penicillin G and 100 μg/ml of streptomycin sulfate) at 37°C with 5% CO2. Nonadherent cells were removed after 1 hr by replacing the culture medium. All adherent cells phagocytosed latex beads, indicating that they were Kupffer cells (Doolittle et al., 1987). Cells were cultured for 24 hr before experiments.
Measurement of $^{36}$Cl chloride uptake by Kupffer cells. In the central nervous system, activation of glycine-gated chloride channel results in chloride influx (Langosch et al., 1990). Assays for uptake of $^{36}$Cl by Kupffer cells were conducted using an adaptation of the method described by Schwartz et al. (1986) and modified by Morrow and Paul (1988). In short, media bathing Kupffer cells was replaced with buffer (20 mM HEPES, 118 mM NaCl, 4.7 mM KCl, 1.2 mM MgSO$_4$, 2.5 mM CaCl$_2$, 10 mM glucose) and allowed to equilibrate for 15 to 30 min at room temperature after 24-hr culture. Coverslips were gently blotted dry and incubated for 5 sec in a Petri dish with 2 ml buffer containing 2 $\mu$Ci/ml $^{36}$Cl$^-$ in the presence or absence of glycine (1.0 mM). This concentration of glycine was chosen because it was similar to levels in blood where glycine exhibited protective effects (limuro et al., 1996). Chloride uptake was terminated by washing the coverslip with ice-cold buffer for 3 sec followed by a second wash for 7 sec. Protein was solubilized and determined using the method of Lowry et al. (1951), and radioactivity was counted by liquid scintillation spectroscopy in 5 ml of Ecoolume (ICN Pharmaceuticals Inc., Costa Mesa, CA) using a Beckman LC6000SC scintillation counter (Beckman Instruments Inc., Fullerton, CA).

Statistics. One-way repeated measures analysis of variance was used for the determination of statistical significance as appropriate. For comparison of pathological scores, the Mann-Whitney rank sum test was used. Data are presented as mean $\pm$ S.E.M. P < .05 was selected before the study as the level of significance.

Results

Experimental design, body weight and urine ethanol. Ethanol was administered for 6 wk. Thereafter, control or glycine-containing diets were given for 2 wk. A tendency for weight to decline slightly during the first week was observed, probably due to surgery. Thereafter, weights stabilized and then increased constantly until the end of 6 wk of ethanol administration. After ethanol was withdrawn and glycine or control diets were initiated, body weights were stable in both groups. There were no significant differences in body weight between the groups studied. A representative graph of urine ethanol concentrations measured daily during 6 wk of ethanol exposure is depicted in figure 1. As reported previously (Ikejima et al., 1996), ethanol levels fluctuate paradoxically in a cyclic pattern from 0 to $>$300 mg/dl in ethanol-fed rats, even though ethanol was infused at a continuous rate. Reasons for this phenomenon remain unknown.

![Fig. 1](representative plot of daily urine alcohol concentration of ethanol-fed rats. Urine alcohol concentrations were measured daily as described in “Materials and Methods.” Typical experiment.)

Serum enzymatic analysis. The average blood levels of AST and ALT before ethanol administration were 58 ± 5 and 29 ± 4 (U/liter), respectively. Six weeks of ethanol administration increased serum AST and ALT approximately 2.5-fold (table 1). One week of ethanol withdrawal led to a decrease in serum transaminases in both the control or glycine groups; however, serum enzyme levels were about 30% lower in rats consuming glycine-containing diets compared to controls (P < .05). Lower AST levels in the glycine group were also observed after 2 wk of recovery.

Pathological evaluation. Figure 2A is a photomicrograph of ethanol-induced liver injury after 6 wk of exposure to ethanol. Marked fatty accumulation and mild inflammation and necrosis were observed in this representative biopsy. The average pathological score after 6 wk of ethanol was 5.5 (table 1). After 1 wk of ethanol withdrawal, marked fatty changes were attenuated to moderate steatosis with mild inflammation and necrosis in the animals receiving control diet (fig. 2B). However, an even better recovery was observed in the glycine-treated group (fig. 2C), with animals exhibiting less steatosis, inflammation and necrosis. At this time point, pathology scores were reduced about 30% more in the glycine group than in controls (4.5 vs. 3.1, P < .05; table 1). The scores of livers from rats receiving control diet for 2 wk were 2.5 (table 1). In contrast, almost total reversal of liver injury was observed in the glycine fed animals; with an average pathological score of 0.5, values that were significantly lower than controls. The percentage of tissue area exhibiting steatosis in the liver using image analysis is also shown in table 1. Six weeks of ethanol exposure caused fatty accumulation in nearly 20% of the pericentral area, and steatosis in both groups was lowered significantly by removal of ethanol for 1 wk. The glycine-treated group, however, exhibited significantly less steatosis than the controls (5.6 vs. 9.8%, P < .05) after 1 wk.

Quantitation of infiltrating leukocytes and necrosis. The number of leukocytes (including neutrophils and mononuclear cells) in liver before ethanol exposure was 0.5/100 hepatocytes. After 6 wk of ethanol exposure, the total number of infiltrating leukocytes was increased about 7-fold (table 1). After 2 wk of glycine or control diet, the number of leukocytes in livers from glycine treated rats was 34% lower than the valine treated controls (P < .05), although inflam-

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$^a$ P < .05 compared to the control group.  
$^b$ P < .01 compared to the control group.  
$^c$ Represents pathology scores.  
$^d$ Represents numbers of infiltrating leukocytes/100 hepatocytes.  
$^e$ Represents numbers of necrotic cells/hepatocytes.
Information was reduced significantly in both groups due to ethanol withdrawal (table 1). Furthermore, the number of necrotic cells was reduced significantly (30%) more in the glycine group than in controls after one week of ethanol withdrawal (table 1).

**TNFα message RNA in liver.** Chronic enteral ethanol exposure caused a dramatic increase in TNFα mRNA in liver as expected (fig. 3). After 1 wk of ethanol withdrawal, TNFα mRNA was reduced 46% more in the rats fed glycine-containing diet than the animals receiving control diet.

**Effects of glycine on uptake of radiolabeled chloride by Kupffer cells.** Glycine activates a chloride channel in many cells. Further, radiolabeled chloride is used routinely in cells such as neurons to provide hard evidence for movement of chloride from the extracellular to intracellular space (Behne et al., 1988). Indeed, glycine (1.0 mM) caused a significant, 2.5-fold increase in 36Cl\(^{-}\) uptake in Kupffer cells (fig. 4).

**Discussion**

**Dietary glycine expedites recovery from alcoholic liver injury.** This study was designed to mimic the clinical situation where patients admitted to hospital with early alcoholic liver disease are withdrawn from alcohol. The major conclusion is that a glycine-rich diet expedites the process of recovery from early ethanol-induced liver injury in the rat. Elevated serum transaminase levels after 6 wk of ethanol exposure were reduced 30% more in rats receiving glycine diet during the next 1 and 2 wk of ethanol withdrawal, and the pathology score was also lowered significantly (32–80%) (table 1). Moreover, hepatic histology was almost normal in animals given a glycine-containing diet for two weeks. The
ability of glycine to accelerate recovery from early alcohol-induced liver injury was more at 1 than 2 wk of the recovery period (table 1).

Possible mechanism of action of glycine. Early alcoholic liver injury, characterized by steatosis, inflammation and necrosis, is mediated largely by Kupffer cells (Adachi et al., 1994; Knecht et al., 1995; Qu et al., 1996), resident macrophages of the liver and scavengers of gut-derived endotoxin LPS. Intake of alcohol increases blood levels of gut-derived endotoxin (Iimuro et al., 1997a), which, in turn, activates Kupffer cells (Nanji et al., 1989). Activated Kupffer cells then release mediators, such as TNFα and prostaglandin E2. The former is responsible for increased inflammation, necrosis and fatty accumulation in the injured liver (Iimuro et al., 1997b); the latter increases oxygen consumption that causes hypoxia in hepatocytes (Qu et al., 1996). Kupffer cells also contain voltage-dependent Ca2+ channels, and increases in [Ca2+] are necessary for endotoxin to induce synthesis of cytokines (Decker, 1990). A previous study showed that glycine blocked increases in [Ca2+]i due to LPS in Kupffer cells and reduced TNFα production (Ikejima et al., 1997). The ability of glycine to prevent the increase in [Ca2+]i was blocked in the absence of extracellular chloride or in the presence of strychine, a glycine receptor antagonist (Ikejima et al., 1997), supporting the hypothesis that glycine inhibits TNFα production through actions on [Ca2+]i by opening a glycine-gated chloride channel in Kupffer cells. Increased chloride influx most likely leads to inactivation of the Kupffer cells by hyperpolarizing the cell membrane, an idea supported by studies with voltage-sensitive dyes (Ikejima et al., 1997). In our study, influx of radiolabeled chloride into Kupffer cells was increased about 2.5-fold by glycine, consistent with this hypothesis. This inhibition of LPS-induced increases in [Ca2+]i by glycine is most likely responsible for reduced cytokine production. Indeed, TNFα mRNA was reduced dramatically by dietary glycine in this study (fig. 4), confirming a previous report (Ikejima et al., 1996). Therefore, it is concluded that glycine is beneficial in reversal of early alcohol-induced liver injury during recovery most likely by diminishing sensitivity of Kupffer cells to endotoxin.

Our study demonstrated that dietary glycine significantly reduced infiltrating leukocytes at 2 wk and necrotic cells at 1 wk. It was previously shown that TNFα was involved in these pathological changes, because antibodies to TNFα attenuated hepatic inflammation and necrosis (Iimuro et al., 1997b). It is, therefore, hypothesized that glycine reduced hepatic inflammation and necrosis in the present model by inhibition of TNFα production by activated Kupffer cells.

One of the main features of early ethanol-induced liver injury is steatosis, which was nearly totally reversed by glycine treatment during the 2 wk of ethanol withdrawal (fig. 3C; table 1). This profound reduction of steatosis by glycine might also be due to effects of glycine on Kupffer cells, leading to decreased TNFα production (Ikejima et al., 1996). For example, TNFα released by endotoxin-activated Kupffer cells (Martinez et al., 1992) stimulates lipid synthesis in the liver (Feingold and Grunfeld, 1987). Feingold and coworkers demonstrated that the synthesis of fatty acids in liver was increased 1 to 2 hr after TNFα administration, an effect that persisted for over 17 hr (Feingold and Grunfeld, 1987). Total hepatic triglyceride production was increased in TNFα-treated animals as measured by the incorporation of tritiated glycerol into hepatic serum triglyceride (Feingold et al., 1989). TNFα also stimulated peripheral lipolysis (Feingold et al., 1992), resulting in an increase in circulating free fatty acids, leading to increased delivery of lipid to the liver where it was reesterified (Wolfe et al., 1985). A decrease in lipoprotein lipase activity by TNFα is responsible for decreased clearance of triglyceride-rich lipoproteins, such as very low-density lipoproteins, leading to hyperlipidemia (Kawakami et al., 1982). Thus, it is concluded that dietary glycine reduces fat accumulation efficiently during the recovery phase after removal of ethanol by decreasing TNFα (Ikejima et al., 1996) and TNFα mRNA (fig. 4).

Clinical implications. When patients are admitted to the hospital with alcoholic hepatitis, alcohol is obviously withdrawn. It was demonstrated that early hepatic pathology was reversed more rapidly with diets containing glycine. Glycine is also suitable for patients who fail to abstain, because it will not only diminish existing liver injury, but will also reduce ethanol in the stomach (Iimuro et al., 1996). In severely ill patients, treatment with corticosteroids is recommended (Ramond et al., 1992); however, steroid treatment is contraindicated in patients with evidence of active infection or bleeding. There is currently no good evidence to support any other well-accepted forms of medical treatment in severe alcoholic liver disease (Morgan, 1996). Moreover, glycine has been given long-term to schizophrenics without toxic side effects (Rosse et al., 1989). Therefore, glycine, a nontoxic amino acid, might be a useful treatment during recovery from this devastating liver disease. Administration of glycine through diet is simple; therefore, it will be easily accepted by patients. Taken together, our data support the postulate that a glycine-rich diet may be a promising approach for treatment of early alcohol-induced liver disease.

References


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