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Biliary Decompression Reduces the Susceptibility to Ethanol-Induced Ulcer in Jaundiced Rats

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Summary

We investigated the gastric response to an ulcerogenic irritant and the change in gastric functions in an experimental rat model of obstructive jaundice, with or without biliary drainage. After biliary obstruction for 14 days, rats with ligated bile duct (BDL) were randomly divided into three groups: BDL group without biliary drainage, BDL followed by choledochoduodenostomy (CD) or a choledochovesical fistula (CVF). The gastric functions were evaluated 2 weeks after the surgery. Gastric damage, induced by orogastric administration of ethanol, was evaluated 30 min later using a lesion index and microscopic scoring was then performed on fixed stomachs. Basal gastric acid secretion was measured by the pyloric ligation method.The lesion index and maximum lesion depth did not differ in the BDL and sham groups, while they were significantly reduced in the CD group. Gastric acid output and secretory volume were reduced in the BDL group compared to the sham group, while these reductions were abolished in the CD group. Afferent denervation with capsaicin further reduced the ulcer index in the later group. Our data suggest that gastric mucosal susceptibility to injury is dependent on the normal flow of bile into the duodenal lumen, which appears to be a requirement for adaptive gastric cytoprotection.

Key words

Bile duct ligation • Choledochoduodenostomy • Gastric acid • Ulcer index • Myeloperoxidase

Introduction

Obstructive jaundice is often a clinical manifestation of pathological changes in the extrahepatic biliary system or the pancreas. Despite improvements in anesthesia and extensive perioperative management, surgery in patients with obstructive jaundice is associated with a high postoperative morbidity, and significant mortality compared to similar surgery in patients without jaundice (Pain *et al.* 1985, Clements *et al.* 1993a). These complications consist of primarily septic complications, hemorrhage, impaired wound healing and renal disorders (Allison *et al.* 1979, Armstrong *et al.* 1984, Dixon *et al.* 1994). Obstruction of the biliary tree and inability to excrete bile into the intestine cause all substances normally excreted into the bile to accumulate in the circulation. Many of these substances, including bile salts, have systemic toxic effects (Rege 1995). Biliary decompression remains the main therapeutic strategy for reducing the morbidity and mortality associated with

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definitive surgical treatment, although the results of this approach have been controversial (Pitt *et al.* 1985).

Postoperative gastrointestinal hemorrhage has been reported in 6-14 % of patients with obstructive jaundice (Blamey *et al.* 1983, Pain *et al.* 1985, Pitt *et al.* 1985, Dixon *et al.* 1994). Acute ulcer formation accompanied by massive hemorrhage is frequently due to operative stress, postoperative intragastric bile reflux and endotoxemia (Urakawa *et al.* 1987, Dixon *et al.* 1994). Animal models of biliary obstruction and drainage have supplemented knowledge of the basic pathophysiology of obstructive jaundice and its complications. Jaundiced animals are more prone to stress-induced gastric ulceration (Miyakawa *et al.* 1983) and cirrhotic rats exhibit increased susceptibility to gastric injury induced by irritants (Beck *et al.* 1992). The pathogenesis of acute gastric ulcers has been examined mainly with respect to aggressive factors, such as gastric acid and pepsin secretion (Silen *et al.* 1962). Some investigators have also studied the defensive mechanisms, such as gastric mucous secretion, gastric mucosal blood flow and the gastric mucosal barrier (Kameyama *et al.* 1984, Urakawa *et al.* 1987). Extreme decrease of gastric mucosal blood flow was found to be one of the exacerbating factors of acute ulceration in rats with obstructive jaundice (Sasaki *et al.* 1987).

There is increasing clinical and experimental evidence demonstrating the occurrence of systemic endotoxemia in obstructive jaundice (Rosoff and Goldman 1968, Clemente *et al.* 1977, Clements *et al.* 1996). Relief of biliary obstruction helps to reverse some of these complications and produces some improvement in the clinical condition (Gouma *et al.* 1987). However, controlled trials have not been convincing in highlighting the benefits of biliary drainage or in determining the best approach.

Using an experimental rat model of obstructive jaundice, we aimed to investigate the gastric response to an ulcerogenic irritant and the change in gastric functions when bile flow is diverted or internal biliary drainage is reestablished. The second aim was to evaluate the significance of re-flow of bile into the gastrointestinal tract when compared with drainage outside the gut.

Methods

Animals and surgery

Wistar albino rats of both sexes (175-250 g) were used. All experimental protocols were approved by the Marmara University School of Medicine Animal Care and Use Committee. Rats were anesthetized (100 mg/kg ketamine and 0.75 mg/kg chlorpromazine; intraperitoneally) during the surgical procedures. Bile duct ligation was performed by introducing a catheter (PE-50) into the proximal common bile duct and bending the lower end of the catheter to cause biliary obstruction (bile duct ligation; BDL group) (Diamond *et al.* 1991). Fourteen days after the ligation, internal biliary drainage was performed by dividing the ligature and inserting the distal end of the cannula either into the duodenum (choledocho-duodenostomy; CD group) or into the dome of the urinary bladder (choledochovesical fistula; CVF) through a purse string suture. A laparotomy was performed in the sham group.

Gastric functions were evaluated 2 weeks after the surgical procedures (bile duct ligation or internal biliary drainage). The rats were decapitated and trunk blood samples were collected in heparinized vials on ice and subsequently centrifuged at 4 ^{o}C. Plasma samples were stored at –70 ^{o}C for subsequent assay for liver function tests. Total (TBil) and direct bilirubin (DBil), aspartate transaminase (ASAT) and alanine transaminase (ALAT) were assayed using the standard techniques and the results were expressed in milligrams per 100 ml (Bil) or units per liter (ASAT and ALAT). Liver samples were fixed in 10 % aqueous neutral-buffered formaldehyde for the histological analysis of microscopical changes in the liver.

Perineural application of capsaicin to the vagus nerve

In order to test the involvement of vagal afferent nerves in the mucosal protective mechanism, topical capsaicin was applied on the vagal nerves. On the day of the bile duct ligation, a group of rats was anesthetized and pretreated with atropine sulfate (2 mg/kg, ip) to decrease the acute effects of capsaicin on the respiratory and cardiovascular systems. A 1 % solution of capsaicin (Sigma) or vehicle (10 % Tween 80 in oil) was applied to each vagus nerve in turn for 30 min. The total dose of capsaicin applied in each rat did not exceed 1 mg. After application, the area was rinsed with sterile saline. Before the experiment, rats were tested for impaired chemosensitivity by an eye-wiping test. In capsaicin-treated rats, the corneal afferents were no longer sensitive to a solution of 1 % NH_4OH (Raybould *et al.* 1992).

Induction of gastric damage and its histological assessment

Orogastric administration of ethanol (99 %, 5 ml/kg) was performed under brief ether anesthesia

following a 24-h fasting period. The animals were decapitated 30 min after the ethanol challenge, and the stomachs were rapidly removed, opened along the greater curvature, washed and examined macroscopically to measure the length of ulcers along their greatest diameters (ulcer index; mm). Stomachs were excised and fixed in 10 % aqueous neutral-buffered formaldehyde. Histological 5 μm thick sections were cut and stained with hematoxylin and eosin. All tissue sections were examined microscopically for characterization of histopathological changes. Microscopic gastric damage was assessed by using a semiquantitative scale (score 0, no damage; 1, superficial epithelial damage; 2, damage extending into deep foveolar cells; 3, damage involving the glandular area) (Eric and Susumu 1982) and the lesion-graded areas of each section were expressed as percentage of the total cross section area. Furthermore, using an ocular micrometer, the depth of injury (mm) in the maximum lesion area was compared with the total mucosa thickness, and was described as the "maximum injury depth" (%).

Measurement of gastric acid output and gastric secretory volume

Gastric secretory volume and acid output measurements were performed by the pyloric ligation method under light ether anesthesia (Günal *et al.* 1996). After recovering from anesthesia, the rats were allowed 3 h for the collection of acid in the awake state. After decapitation, the cardia was clamped and the gastric content was obtained by opening the greater curvature of the stomach. Following volume measurements, the collected specimen was titrated with 0.1 N NaOH.

Measurement of gastric emptying

Gastric emptying of a non-nutrient solution, methyl cellulose, was determined as described previously (Scarpignato *et al.* 1980, Günal *et al.* 1996). Briefly, 1.5 ml of methyl cellulose (1.5 %) containing a non-absorbable dilution marker phenol red (50 mg/100 ml), was given by an orogastric tube. After a 20-min constant period, the rats were decapitated, the stomachs were then homogenized in 100 ml of 0.1 N NaOH. The suspension was then allowed to settle (60 min) at room temperature, and 5 ml of the supernatant were added to 4 ml of 0.5 ml of trichloracetic acid (20 %; w/v). After centrifugation at 900x*g* for 20 min, the supernatant was added to 4 ml of 0.5 N NaOH, and absorbance of the sample was read at a wavelength of 560 nm with a UV spectrophotometer. Phenol red recovered from the stomachs of rats killed immediately after administration of the methyl cellulose solution served as the standard. The percentage of gastric emptying was calculated according to the following formula: [(1-amount of phenol red recovered from the test stomach)/average amount of phenol red recovered from standard stomachs] x 100.

Table 1. Liver enzymes evaluated on the 14th day following the following surgical procedures: in bile duct ligated rats (BDL) without any drainage, or in rats which had choledochoduodenostomy (CD), a choledochovesical fistula (CVF) or sham operations.

	ASAT U/l	**ALAT U/l**	**Total Bilirubin mg/100 ml**	**Direct Bilirubin mg/100 ml**
SHAM (n=10)	211.5±16.7	55.7±4.2	0.08±0.01	0.04±0.01
BDL (n=13)	1279.7±218.0***	240.7±46.3**	8.9±1.2***	6.6±0.8***
CD (n=6)	$623.0\pm153.2^{+}$	$122.7\pm26.7^{+}$	$1.8\pm0.5^{+++}$	$1.1\pm0.5^{+++}$
CVF (n=6)	$609.6\pm133.5^{+}$	276.6±48.8	$3.6\pm0.7^{+}$	$2.4\pm0.5^{+}$

*ASAT – aspartate transaminase; ALAT – alanine transaminase; ** $p<0.01$, *** $p<0.001$, compared to sham group; $^{+}$ $p<0.05$, $^{+++}$ $p<0.001$, compared to BDL group.*

Gastric luminal protein content

Gastric luminal protein content was measured by a modified Lowry method (Levine *et al.* 1990), as an indicator of mucosal permeability. Briefly, the gastric content that was accumulated after a 3-h pyloric ligation period was collected by a puncture of the greater curvature and was centrifuged at 900x*g* for 20 min. The supernatant was diluted with 20 mM K_2HPO_4 (Kpi). The sample was (50 μl) stirred with 1 ml of reg C solution and then reg D solution (0.1 ml). The absorbance of the sample was read on a spectrophotometer at 750 nm

wavelength. Afterwards, by using a standard curve, this absorbance value was converted to protein concentration mg/ml).

Statistics

All data are expressed as mean ± S.E.M. The statistical significance was determined using Student's t-test or ANOVA. Results were considered significant when P value was less than 0.05.

Results

The rats with ligated bile duct were clinically jaundiced and their liver enzymes were found to be elevated highly significantly on the 14th day of ligation (Table 1), when compared to the sham group. CD reversed the elevations in ASAT, ALAT and Bil levels ($p<0.05$-0.001), but the reductions in the enzyme levels of CVF rats were not as apparent as in the CD group ($p<0.05$).

Microscopically, BDL elicited inflammatory changes in the liver that were associated with the destruction of normal microscopical hepatic architecture. These changes included bile duct proliferation, fibrosis and porto-portal bridging in some areas. Similar changes were observed in the CD and CVF groups.

Gastric damage induced by ethanol

Intragastric administration of absolute ethanol produced lesions covering large areas of the stomach corpus. In the sham-operated, BDL and CVF rats, the calculated ulcer indices, evaluated macroscopically, did not differ from each other, while the ulcer index was significantly reduced in the CD group ($p<0.01$; Fig. 1a).

Microscopic evaluation of gastric lesions was presented as the ratio of the lesion area to the total section area (%). In the BDL group, the percentage of superficial lesion (grade 1) was significantly reduced when compared to sham group, in favor of increased percentage of severe damage of grade 2 and 3 (Fig. 1b). However, in the CD group, grade 2 and 3 lesions were significantly reduced as compared to the BDL group ($p<0.05$). Similarly, in the CVF group, grade 3 lesions were significantly reduced as compared to the sham or BDL groups. The ratio of maximum mucosal injury depth to the total mucosal thickness (%) was reduced significantly ($p<0.05$; Fig. 1c) in the CD and CVF groups as compared to the BDL group.

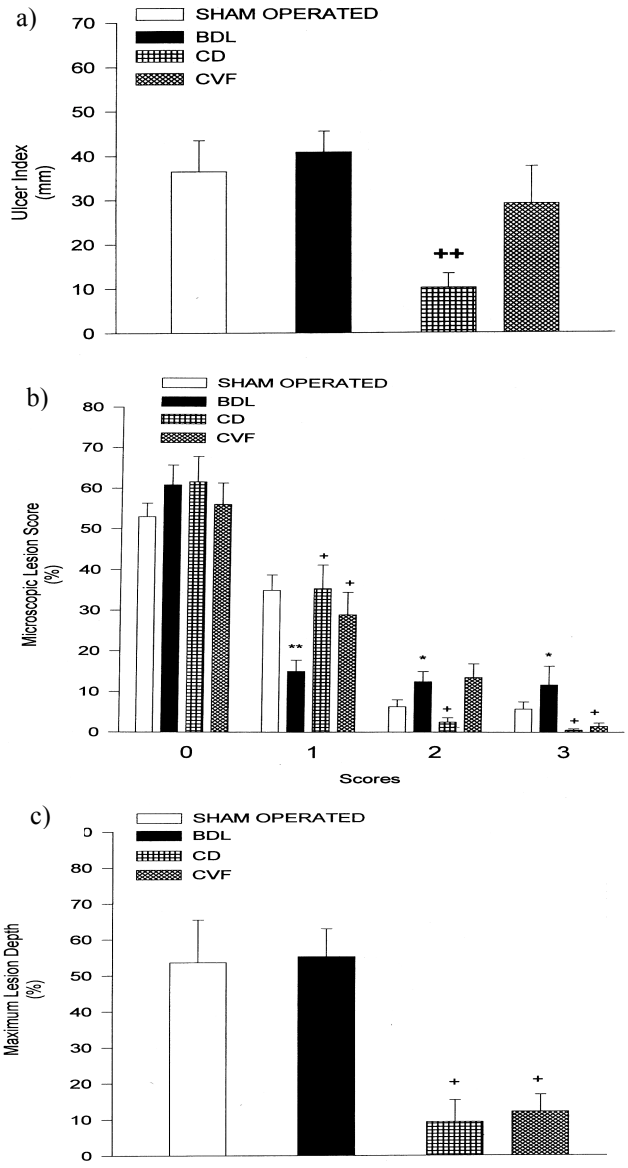

Fig. 1. *Gastric injury induced by orogastric absolute ethanol is expressed as macroscopic ulcer index* ***(a),*** *microscopic lesion score* ***(b)*** *and maximum lesion depth* ***(c)*** *in the bile duct of ligated rats (BDL; n=13) without any drainage or in rats which had choledochoduodenostomy (CD; n=6) or choledochovesical fistula (CVF; n=6) operations, compared with that in sham-operated rats (n=10). *p< 0.05, ** p<0.01, compared to the sham-operated group. +p<0.05, ++p<0.01, compared to the BDL group.*

Gastric acid output and gastric emptying

Gastric acid output was significantly reduced ($p<0.05$) in the BDL group as compared to the sham group (Fig. 2a). In the CD group, the reduction in acid output was found to be partially reversed, but did not

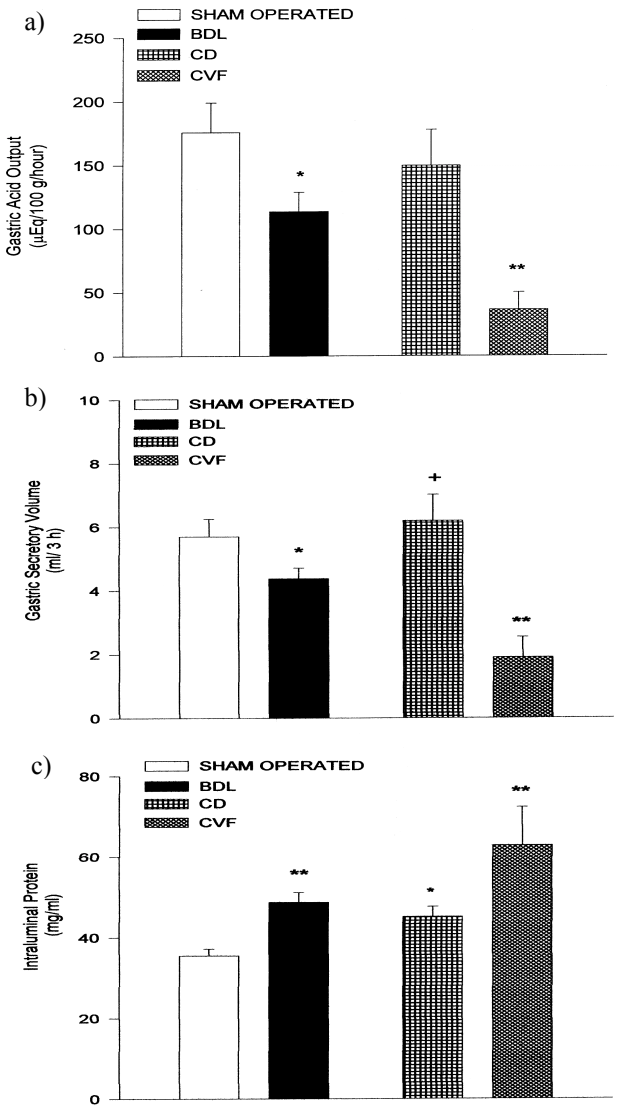

Fig. 2. *Gastric acid output* ***(a)****, secretory volume* ***(b)*** *and luminal protein content (mucosal permeability) in a 3-hour collection period* ***(c)*** *in rats with ligated bile duct (BDL; n=8) without any drainage or in rats which had choledochoduodenostomy (CD; n=6) or choledochovesical fistula (CVF; n=6) operations, compared with sham-operated rats (n=5). *p<0.05, **p<0.01, compared to the sham-operated group, + p<0.05, compared to the BDL group.*

differ from the BDL group. In the CVF group, the reduction in acid output was even more prominent ($p<0.01$, compared to the sham group) than that observed in the BDL group. Gastric secretory volumes measured with the pyloric ligation method corresponded to the gastric output values (Fig. 2b). In the BDL group, secretory volume was significantly reduced ($p<0.05$) and CD totally abolished this reduction ($p<0.05$, compared to BDL group). In the CVF group, gastric volume was significantly reduced, as observed in the gastric output values ($p<0.01$). Twenty-minute gastric emptying rates of sham-operated rats (62.9±7.8 %) did not differ from the rats in BDL (52.2±7.6 %), CD (58.8±5.9 %) or CVF (65.3±3.0 %) groups.

Gastric luminal protein content

As an indicator of mucosal permeability, the protein content that leaked from the interstitium and vascular compartment into the gastric pouch was measured (mg/ml). Mucosal permeability was significantly increased in the BDL, CD and CVF groups as compared to the sham-operated group ($p<0.01$; Fig. 2c).

Effect of perineural capsaicin on ethanol-induced gastric damage

In the BDL group after capsaicin-induced vagal afferent denervation, the calculated ulcer index was not different from that of the untreated group. The reduction of the ulcer index, observed upon the reflow of the bile into the intestine, was further enhanced by the ablation of the afferent nerves ($p<0.05$; Fig. 3).

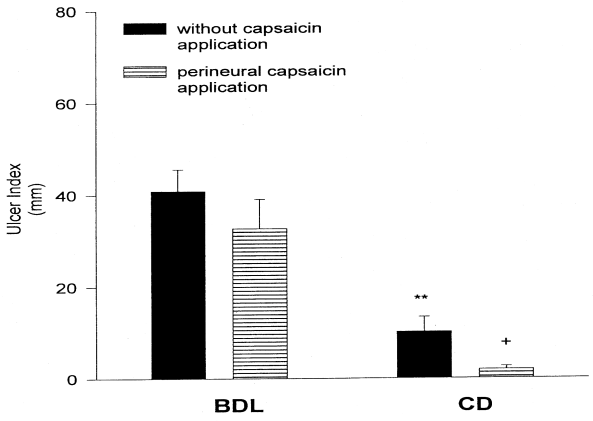

Fig. 3. *The effect of perineural capsaicin (1 %) application on the ethanol-induced ulcer index in bile duct ligated (BDL; n=8) rats and in rats which had choledochoduodenostomy (CD; n=8), compared with untreated BDL rats (n=13) and CD rats (n=6) groups. **p<0.01, compared to the BDL group without capsaicin application. +p<0.05, compared to CD group without capsaicin application.*

Discussion

It is well known that fatal upper gastrointestinal bleeding often occurs clinically in critically ill or postoperative patients and that its incidence becomes

even higher in patients with cirrhosis (Iwao *et al.* 1992), portal hypertension (McCormack *et al.* 1985) and obstructive jaundice (Blamey *et al.* 1983, Rege 1995). It is important to improve surgical treatment and to prevent these complications by clarifying the mechanisms of obstructive jaundice. The results of the present study demonstrate that rats after bile duct ligation did not exhibit enhanced mucosal damage after intragastric administration of absolute ethanol. However, the reversal of bile flow by either CD or CVF decreased the severity and depth of the mucosal lesions. Previous blockade of the normal flow of bile into the duodenum and the subsequent restoration had a protective effect on ethanol-induced ulcer formation, suggesting an "adaptive" gastric mucosal response to ulcerogenesis in obstructive jaundice. Adaptive cytoprotection was defined as the apparent resistance of the gastric mucosa to injury caused by a strong irritant such as 100 % ethanol or 100 mM taurocholate after brief exposure to a mild irritant such as 25 % ethanol or 5 mM taurocholate (Sasaki *et al.* 1986, Matsuo *et al.* 1989). It was proposed that adaptive cytoprotection requires intact vagal and sympathetic innervation as well as the endogenous prostaglandins (Kauffman 1991). The results of the present study have revealed that the reduction in ulcerogenesis does not appear to be related to an alteration in gastric secretory capacity.

Previous reports have referred to an increased gastric acid output, decreased gastric wall blood flow, and failed gastric mucosal barriers, on the basis of liver dysfunction, biliary diversion and portal blood flow disturbances (Sasaki *et al.* 1986, 1987, Urakawa *et al.* 1987). Disturbances in gastric mucosal microcirculation have attracted special attention in relation to gastric mucosal blood flow (Sasaki *et al.* 1987). It was shown that jaundiced and vagotomized rats exhibited a significant decrease of the ulcer index and improvement of the decreased gastric mucosal blood flow compared to the jaundiced group. In another study, it was concluded that, gastric mucosal circulatory disturbances in obstructive jaundice are the result of sympathetic nervous system hypofunction due to decreased noradrenaline content (Urakawa *et al.* 1987). They also demonstrated that the decrease of noradrenaline in the gastric mucosa was inhibited by exogenous PGE_2, which was indicated as one of the main factors of ulcer formation in obstructive jaundice. Mizumoto *et al.* (1986) have suggested that the increased plasma levels of bile acids play an important role in the mitigation of gastric mucosal defense mechanisms in obstructive jaundice directly through their toxic effects, since there was a 24-fold increase in total plasma levels of bile acids following ligation of the common bile duct.

In the present study, we investigated the influence of obstructive jaundice on acute gastric ulcerations in rats with special reference to the basal gastric secretory capacity. Bile duct ligation in rats reduced basal gastric acid output and volume, while leading to an increased mucosal permeability. These gastric mucosal alterations observed in jaundiced animals were totally abolished by the CD procedure, implicating that the increased levels of circulating bile acids may be responsible for the gastric secretory inhibition. However, inhibition in acid secretion was more pronounced in the CVF group, where the liver enzymes were found to be still elevated. In accordance with the high levels of the liver enzymes, circulating levels of bile salts are also still expected to be in high concentrations, since bile salts are known to be absorbed by bladder epithelial cells. Moreover, the catheter running the distance between the common bile duct and the urinary bladder may affect the resistance to flow, causing a back-flow of bile. It is recognized that biliary obstruction promotes bacterial translocation, which occurs when the emulsifying action of bile salts are absent from the gut lumen (Clements *et al.* 1993b). Bacterial translocation initiates the influx of endotoxins into the portal circulation. Endotoxins are known to increase gastric secretion (Rosoff and Goldman 1968) and hemorrhage from acute gastric erosions is associated with endotoxemia in patients with cirrhosis. However, in the present study bile duct ligation depressed gastric acid output, while in the CVF group, where the normal flow of bile was reestablished, enhanced reduction in gastric secretory capacity was accompanied by marked attenuation of ulcer formation. Taken together with the findings in the CD group, it may be suggested that the re-exposure of the gut mucosa to bile salts, enhances mucosal defense and reduces the magnitude of the injury by both macroscopic and microscopic assessment. This adaptive protection seems to be independent of basal gastric secretory capacity.

Local capsaicin application in the jaundiced animals did not influence ulcer formation. It is well known that in rats treated with the sensory neurotoxin capsaicin, there is deterioration of gastric ulcers induced by various stimuli (Evangelista *et al.* 1989), since the

sensory peptides have been hypothesized to participate in a capsaicin-sensitive "gastric defense mechanism" (Szolcsayi and Bartho 1981). On the other hand, it was also shown that pretreatment with capsaicin prevented the mucus depletion associated with exposure to ethanol and protected the gastric mucosa against damage (Kang *et al.* 1995). There is a growing body of evidence that some bile salts have cytoprotective effects (Ota *et al.* 1991). In the present study, the results revealed that capsaicin-treatment further reduced the ulcerogenesis beyond the protection promoted by bile re-flow. These results suggest that normal bile flow may be a requirement for adaptive cytoprotection, which appears to be independent of capsaicin-sensitive neurons.

A re-evaluation of the pathophysiological effects of biliary obstruction is essential, because appropriate preparation of patients with jaundice before invasive diagnostic and therapeutic procedures avoids complications and decreases the morbidity and mortality (Rege 1995). Patients with cirrhosis, portal hypertension and obstructive jaundice have an increased incidence of peptic ulcers (McCormack 1985, Beck *et al.* 1992), while the mechanisms involved remain unclear. The results of the present study suggest that aggressive factors such as acid secretion are less likely to be involved, focusing attention on gastric defensive factors such as the pre-epithelial mucus-bicarbonate layer (Guslandi *et al.* 1992). It was concluded that exposure of the gastric mucosa to a mild irritant causes the intraluminal release of protective products (Kauffman 1991) and that the normal free drainage of bile into the intestine seems to be necessary in the mediation of adaptive cytoprotection.

Despite the lack of information on the exact pathophysiological mechanisms, biliary decompression remains the main therapeutic strategy used in jaundiced patients. It is therefore important to establish these mechanisms in order to improve the postoperative prognosis. The beneficial effects of anti-endotoxic bile salts may not be attributed to their effects on the basal gastric secretory capacity. Relief of biliary obstruction, preferably into the gastrointestinal tract, may help to reverse the complications and produce improvement in the clinical condition.

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