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Intestinal flora translocation and overgrowth in upper gastrointestinal tract induced by hepatic failure *

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Subject headings hepatic failure; multiple organ dysfunction; bacterial overgrowth; bacterial translocation; intestinal flora

Abstract

AIM To explore the relationship between endoinfection caused by intestinal flora translocation and multiple-organ dysfunction in hepatic failure.

METHODS By using the quantitative bacteria culture, bacteria colony was counted in GI tract, bile duct and mesenteric lymphonodus in rat hepati c failure model.

RESULTS Intestinal flora migrated up to the upper GI tract and overgrew in stomach and jejunum in rats with hepatic failure. The number of bac teria colonies in the specimens of stomach, jejunum and ileum were 4.7×10^4/mL, 2.1×10^5/mL, 5.5×10^6/mL in experiment group and 4.6×10^2/mL, 6.1×10^1/mL, 2.4×10^3/mL in control group respectively ($P<0.05$). Bacteria in bile duct and mesenteric lymphonodus of hepatic failure rats were also cultured. Extensive damages of gastrointestinal mucosa caused by bacterial overgrowth were observed.

CONCLUSION Intestinal flora translocation and overgrowth in stomach and jejunum formed an endoinfectious source and caused obvious pathologic al injury of gastrointestinal mucosa, which play a very important role in develo ping abdominal distension, toxic intestinal expansion, alimentary tract haemorrhage and endotoxemia in patients with hepatic failure.

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INTRODUCTION

The patients with severe hepatic failure are predisposed to develop toxic intestinal expansion, alimentary tract haemorrhage, endotoxemia, spontaneous bacterial peritonitis, even septicemia[1-5]. It is necessary to investigate whether these complications are due to the intestinal bacterial overgrowth and intestinal flora translocation, and the mechanism and consequence of intestinal flora translocation in patients with hepatic failure.

MATERIALS AND METHODS

Animal model

Female Wistar rats (weighing 170 g - 220 g, supplied by the Experimental Animal Center of Tongji Medical University) were divided into two groups, five rats in each group. The experimental rats received hypodermic injection of thioa cetamide (TAA, 350mg/kg) once a day and 50g/L glucose in NS-10mL three times a day for three days. The experiment was performed in rats that developed II -III phase of hepatic encephalopathy. The control rats received hypodermic injection of 90g/L sodium chloride instead of TAA. After the rats were fasted for 12 hours, the experiments were made under strict sterile co ndition.

Bacteria colony counting in different gastrointestinal segment

After being anesthetized with pentobarbital, the stomach, 10cm proximal jejunum and 10cm terminal ileum of rats were cut off, and syringed with 1 mL sterile 90 g/L sodium chloride. The syringing solution was diluted and mixed with nutritive agar. After coagulation, it was turned over on a plat e and incubated at 37℃ for 24 hours.

Bacteria culture of biliary tract and mesenteric lymphonodus

Two cm bile duct and mesenteric lymphonodus of the rats were taken and homogenated with 1mL sterile 90g/L sodium chloride. Then the syrup was collected and mixed in a nutritive agar plate. It was cultured in the same manner as described above.

Bacteria culture of gastric juice in case of hepatic failure

Experiment was made in 5 patients with hepatic failure. Two of them had bleeding in alimentary tract. One mL gastric juice was drawn by gastric tube, then was taken to be cultured in the same manner as described above.

The pathological change of the gastrointestinal tract

At first we observed grossly gastrointestinal specimens in rats with hepatic failure. Then the specimens were fixed with 100mL/L formalin, embedded with paraffin, cut into slices, stained with HE and observed under light microscope.

RESULTS

Bacteria colony counting of stomach, jejunum and ileum in rats

With bacteria culture of the syringing solution, it was shown that intestinal flora migrated up to the upper GI tract apparently and bacteria overgrew in stomach and jejunum in the rats with hepatic failure while there were few bacteria in the upper GI tract in the control group rats. The number of bacteria colonies in stomach, jejunum and ileum of two groups are shown in Table 1.

Table 1 Bacteria colonies in different segments of GI tract in rats with hepatic failure (CFU/mL)

	No	Stomach	Jejunum	Ileum
Experimental group	5	4.7×10^{4a}	2.1×10^{5a}	5.5×10^{6a}
Control group	5	4.6×10^{2}	6.1×10^{1}	2.4×10^{3}

[a]$P<0.05$ *vs* control group.

Bacteria culture of biliary tract and mesenteric lymphonodus

Culture of biliary tract bacteria was positive in all experimental rats. The mean number of bacteria colonies in rats with hepatic failure was 159±116. The culture of mesenteric lymphonodus bacteria was positive in 4 of 5 experimental rats. The mean number of bacteria colonies was 21±19. Bacteria colony number in control rats was 0-11 and 0-4 respectively ($P<0.01$).

Bacteria culture of gastric juice in patients with hepatic failure

There was bacterial overgrowth in the gastric juice of patients with hepatic failure. Bacteria colony number was 3.3×10^{3}/mL to 7.5×10^{5}/mL.

Pathological change of the gastrointestinal tract

The stomach, jejunum, ileum and colon were dilated and the smooth muscle was flabby in experimental rats, especially in stomach. The gut lumen was full of fluid and gas. Blood stasis, erosions and bleeding spots in gastrointestine were easily found. Pathological changes were found under microscope such as thinning of mucosal lamina, degeneration and dropping off of epithelial cells, vascular congestion of submucosa and increasing of lymphocytes in mucosa and submucosa, villus structure change in the distal small intestine, and multiple erosions in stomach mucosa.

DISCUSSION

Bacteria translocation, the phenomina of bacteria migration from the gut lumen into the tissues of intestine and from distal GI tract to proximal, has been identified in the stress status after serious trauma or burn and hepatic failure. In that condition, intestinal flora can pass through the mucosa into the tissues outside bowel such as mesenteric lymphonodus, blood and even other organs in the body, and forms an endogenous infection source.

In normal condition, colon mucosa has an integrated mechanic barrier which can protect the mucosa from harmful irritation and invasion of normal intestinal flora. Though there are plenty of endotoxin and bacterial metabolic outcomes in colon, little can be absorbed into the body[3]. The mechanic barrier includes mucus, close junction of epithelial cells and special mucosal structure. In colon mucosa, no villus structure was found to have sticked out to the gut lumen, and the close arrangement of glands mininizes the contacting surface between the mucosa and the content in the gut lumen. Stomach protects istelf by secreting gastric acid to kill invading bacteria. In small intestine, villus sticking out to the lumen is helpful for degestion and absorption of food but harmful to the protection of itself from invasion of toxin and destruction of bacteria. Under normal condition, bacteria in chyme has been killed by gastric acid, and bacteria in colon can hardly goup into the upper small intestine mainly as a result of continous propulsive peristalsis of GI tract and scouring of secretary solution by small intestine, liver and pancreas, which contain a large number of antibodies and other bacteria inhabitors. So the exocrine function and GI motility are an important guarantee to maintain its normal flora.

It was confirmed in our experiment that bacteria migrated into the upper GI tract from colon and overgrew in stomach and proximal small intestine of the rats with acute hepatic failure induced by TAA. Bacteria colony number in jejunum of experimental rats was ten thousand times

that of control rats, and bacteria in stomach and ileum also increased distinctly. Bacteria in mesenteric lymphonodus and biliary tract were cultured, while bacteria increased apparently in stomach in hepatic failure patients. These results indicate that there was a bacteria translocation which can damage GI mucosa, and destruct villus structure and mucosal barrier. Both bacteria and gastric acid destroyed the mucosal barrier, resulting in erosions and bleeding of gastric mucosa. Lots of gas produced by migrating bacteria caused gastrointestinal distension.

The above results can explain why many pathological phenomena occurred in hepatic failure. In hepatic failure, the excitability of gastrointestinal nerve, muscle and gland changes, the movement and secretion of gastrointestine are inhabited. Bacteria in colon migrate rapidly up to the upper GI tract, and proliferate in the upper small intestine and make a great deal of metabolic products and toxins, which result in disruption of gastrointestinal mucosal barrier, damage of mucosal tissues, decrease of villus structure, degeneration and exfoliation of epithelial cells, and change of surface microcircumstance on gastrointestinal mucosa. Bacterial toxin stimulates the glands to secrete mucus and induces dysfunction of absorption which leads to watery stool and diarrhea. Gas resulting from bacterial overgrowth, low blood potassium, intestinal wall edema and ascites can cause abdominal distension, even toxic intestinal expansion. Translocated bacteria can directly injure gastrointestinal mucosa and induce erosion, ulcer and bleeding. In late hepatic failure, many patients develop refractory alimentary tract haemorrhage, which is known as bleeding due to hepato-gastrointestinal failure[4]. We believe that disruption of mucosal barrier and damage of mucosal tissue caused by bacterial overgrowth in stomach and proximal small intestine play a very important role in massive damages of gastrointestinal mucosa besides deficiency of blood coagulating factor, DIC and invasion of gastric acid.

In addition, bacterial overgrowth and high concentration toxin in jejunum are not only the direct cause of endotoxemia but also the foci of translocation lesion including bacteremia and infectious peritonitis. This can be confirmed by using oral or venous antibiotics which can partly prevent endogenous infection[5-7].

It is concluded that intestinal flora translocation and overgrowth in stomach and jejunum is an endogenous infectious source and causes obvious pathological damage of gastrointestinal mucosa, which play a very important role in leading to abdominal distension, toxic intestinal expansion, alimentary tract haemorrhage and endotoxemia in patients with hepatic failure.

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