学 位 論 文 の 要 旨

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学 位 論 文 名　Anti-tumor Effects of Cimetidine on Hepatocellular Carcinomas in Diethylnitrosamine-treated Rats

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論 文 内 容 の 要 旨

INTRODUCTION

Hepatocellular carcinoma (HCC) is currently the fifth most commonly occurring type of cancer and the third leading cause of death from cancer worldwide. Several drugs, e.g., ursodeoxycholic acid, glycyrrhizin, vitamin K2, acyclic retinoid, have been reported to be effective in preventing liver carcinogenesis. Nevertheless, HCCs still occur frequently at an annual rate of about 8% in Japan, particularly in patients with HCV cirrhosis. Interferon therapy prevents the incidence of HCC in patients with HCV-related cirrhosis, however, it is somewhat difficult to use in cases of uncompensated cirrhosis or serious complications, because of its many adverse effects. Thus, it is considered important to develop safe and more effective chemopreventive drugs for hepatocarcinogenesis.

Cimetidine, a commonly prescribed histamine H2 receptor antagonist, has been shown to have an anti-tumoral effect and demonstrated to be useful in some patients with malignancies, such as colon cancers, renal cell carcinomas, and malignant melanomas. However, there is no known clinical study of the anti-tumor effects of cimetidine in patients with HCC. In the present

study, we investigated the anti-tumor effects of cimetidine on chemically induced HCCs in rats.

MATERIALS AND METHODS

Four-week-old male Wistar rats (n=105) were divided into 4 groups. Those in groups A and B were administered diethylnitrosamine (DEN) intraperitoneally at 100 mg/kg of body weight every week for 6 weeks, during which rats in group A were given tap water and those in group B received cimetidine (100 mg/kg/day) in drinking water. Rats in groups C and D were administered saline instead of DEN, and given tap water and that with 100 mg/kg/day of cimetidine, respectively. The animals were killed at 7, 12, 22, and 32 weeks after the first administration of drugs. The numbers and size of the liver nodules were determined, and immunohistochemical studies were performed. Natural killer (NK) cell activity in spleen cells was also determined using a ^{51}Cr releasing assay and the proportion of NK cells among splenic lymphocytes was examined by flow cytometry.

RESULTS AND DISCUSSION

Liver nodules were observed only in groups A and B. The number of liver nodules in group B was less as compared to group A, with a significant difference at week 22 (26.8 ± 7.1 nodules/liver and 5.4 ± 2.2 nodules/liver, respectively, $p < 0.05$). Further, the maximum diameter of the largest nodule in group B was also smaller than that in group A, with a significant difference found at week 32 (31.3 ± 3.9 mm and 18.4 ± 2.1 mm, respectively, $p < 0.05$). Immunohistochemistry findings showed that the glutathione S-transferase placental form (GST-P)-positive areas, which indicated hepatic preneoplastic foci, were significantly smaller in group B as compared with group A at week 22 (14.1 ± 3.4% and 27.2 ± 3.9%, respectively, $p < 0.05$) and week 32 (15.1 ± 3.3% and 30.8 ± 3.9%, respectively, $p < 0.05$). Further, the number of proliferating cell nuclear antigen (PCNA)-positive hepatocytes tended to be lower in group B than in group A. In addition, Cimetidine treatment tended to enhance natural killer (NK) cell

activity in splenic lymphocytes, though flow cytometry revealed that the proportion of NK cells among total splenic lympocyte was not affected by that treatment. In summary, cimetidine was demonstrated to reduce the number and size of liver nodules, area of GST-P-positive preneoplastic foci, and number of PCNA-positive hepatocytes, probably by enhancing NK cell activity.

CONCLUSION

Our results showed that cimetidine has an inhibiting effect on hepatocarcinogenesis and are the first to show the anti-tumor effects of cimetidine on HCCs *in vivo*. Thus, this classic and safe drug may be suitable for the prevention and treatment of HCC, though additional studies are needed to elucidate the precise mechanism of its anti-tumor effects on HCCs.