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The Effect of Ketanserin Administration on Liver Regeneration after 60-70% Partial Hepatectomy

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S u m m a r y. The ability of the liver to regenerate after partial hepatectomy has been well known for many years. A large number of factors have been shown to affect liver regeneration. The role of serotonin on liver regeneration has recently been reported in cultured hepatocytes. In the present study, we investigated the effect of ketanserin, a 5-HT$_2$ receptor antagonist, on liver regeneration after partial hepatectomy in the rat. Ketanserin was administered at 6 mg/kg bodyweight at 2 hours before or 16 hours after partial hepatectomy and animals were killed at 24, 32, 40 and 48 hours after partial hepatectomy. Liver regeneration was evaluated by mitotic index in hematoxylin-eosin (HE) sections, [^{3}H]-thymidine incorporation into hepatic DNA and the immunochemical detection of monoclonal mouse anti-proliferating cell nuclear antigen (PCNA). The inhibitory effect of ketanserin was observed only when administered 16 hours after partial hepatectomy, while no inhibitory effect was observed when administered at 2 hours before partial hepatectomy. The results of this study indicate that ketanserin inhibits liver regeneration when applied at the time of hepatocyte progression to the S phase of the cell cycle, while when administered before partial hepatectomy does not affect the regenerative process.

INTRODUCTION

The ability of liver to regenerate is well known and it seems to be a protective mechanism against liver injury. The regenerative process depends on a great variety of circulating factors which trigger or suppress the proliferation of different cell types in order to highly regulate the reconstitution of liver tissue and preserve its metabolic functions (1,2).

Neurotransmitters are listed among the factors which influence liver regeneration. The role of catecholamines and especially norepinephrine in liver regeneration has been well studied. From the known data it seems that the action of norepinephrine is exerted through the a_1-adrenergic receptor and its plasma levels sharply increase from the first hour and high levels persist until 48 h after partial hepatectomy (3,4). The catecholamine stimulates DNA synthesis in a dose-dependent pattern only in the presence of EGF. The exact mechanism of norepinephrine's action is not known but it seems to be related to the regulation of EGF receptors, and EGF protein levels (5) as well as the offsetting of mitoinhibitory stimuli such as TGF-β1 (6).

The role of serotonin in liver regeneration after partial hepatectomy has recently been investigated in cultured rat hepatocytes. Serotonin induced a dose-dependent increase in DNA synthesis only in the presence of EGF (7). Serotonin receptor type 2 (5-HT$_2$) has been cloned from liver cells (8) and has been proposed to be the major type of serotoninergic receptor implicated in hepatocyte proliferation. The 5-HT receptors are transmembrane proteins coupled with G proteins and secondary messenger systems, with the exception of 5-HT$_3$ receptor, which is an ion channel (9). Ketanserin is a 5-HT$_2$ receptor antagonist which also possesses weak a_1-adrenoreceptor antagonistic activity (10).

In the present study, we investigated the influence of ketanserin in rat liver regeneration after 60-70% partial hepatectomy.

MATERIALS AND METHODS

Male Wistar rats (180-200 g) were subjected to 60-70% partial hepatectomy and assigned randomly to groups as follows: group I: 60-70% partial hepatectomy and intraperitoneal administration of normal saline, group II: 60-70% partial hepatectomy and intraperitoneal administration of ketanserin (6 mg/kg body weight) 2 h prior to partial hepatectomy and group III: 60-70% partial hepatectomy and intraperitoneal administration of ketanserin (6 mg/kg body weight) 16 h after partial hepatectomy. The animals of all groups were killed at 24, 32, 40 and 48 h after partial hepatectomy. The rate of liver regeneration was evaluated for all groups of rats by the tritiated thymidine incorporation into hepatic DNA, the mitotic index in HE sections and mitotic index by the immunochemical detection of PCNA.

RESULTS

Tritiated thymidine incorporation into hepatic DNA was at high levels at 24, 32 and 40 h after partial hepatectomy and sharply declined at 48 h in group I rats. The same temporal pattern of tritiated thymidine incorporation was also observed in group II of rats having administered ketanserin 2 h prior to partial hepatectomy. In group III, tritiated thymidine incorporation into hepatic DNA was markedly decreased at 24 h and was progressively increased thereafter.

Mitotic index in HE sections peaked at 32 h after partial hepatectomy in groups I and II. In group III, the index peaked at 40 h and the values were at low levels at 24 h and 32 h after partial hepatectomy.

The number of PCNA positive cells peaked at 24 h in groups I and II after partial hepatectomy. In group III, the numbers of PCNA positive cells were low at 24 h and 32 h, peaked at 40 h and remained at high levels thereafter.

DISCUSSION

Ketanserin had no apparent effect on liver regeneration when applied 2 h prior to partial hepatectomy. On the other hand, ketanserin administration at 16 h after partial hepatectomy arrested liver regeneration at 24 h and the regenerative process resumed after ketanserin elimination (half life of ketanserin is estimated 5-7 h (11) in rat) but in an asynchronized manner without the distinct peaks of liver regeneration that had been observed in normal rats (group I). The above findings imply that ketanserin might intervene in the regenerative process after 60-70% partial hepatectomy at the G1/S transition restrictive point or even at the late G1 phase of the cell cycle.

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