学 位 論 文 の 要 旨

氏名　　山本　徹

学 位 論 文 名	Hemoperfusion With a High Mobility Group Box 1 Adsorption Column Can Prevent the Occurrence of Hepatic Ischemia-Reperfusion Injury in Rats.
発 表 雑 誌 名 （巻，初頁～終頁，年）	Critical Care Medicine (in press)
著 者 名	Tetsu Yamamoto, Takashi Ono, Takashi Ito, Akira Yamanoi, Ikuro Maruyama, Tsuneo Tanaka

論 文 内 容 の 要 旨

INTRODUCTION

Liver ischemia-reperfusion (I/R) injury is an unavoidable process in several clinical situations, such as liver transplantation, liver resection with inflow occlusion. The sequelae of inflammatory processes responsible for organ damage following I/R have been extensively studied, but the precise mechanism of I/R injury is still not well understood.

High mobility group box 1 (HMGB1), a ubiquitous non-histone chromosomal protein, is passively released from necrotic cells and actively secreted by inflammatory cells. Once released into the extracellular space, HMGB1 acts as a signal of tissue damage and it can promote inflammation. Extracellular HMGB1 has recently been recognized as a mediator of hepatic ischemia-reperfusion (I/R) injury, however, the kinetics of HMGB1 during hepatic I/R and the role of HMGB1 in I/R injury still remain poorly understood. This study was designed to assess the localization and the kinetics of HMGB1 during hepatic I/R injury, and therapeutic effects with HMGB1 adsorption column in hepatic I/R injury were further evaluated.

MATERIALS AND METHODS

DESIGN: A prospective, randomized animal study. SUBJECTS: Male Sprague-Dawley rats. INVESTIGATION: The animals underwent 70% partial hepatic ischemia for 60 or 90 mins and were then reperfused. To investigate the HMGB1 levels in the serum and in the liver tissue, the animals were sacrificed at predetermined periods. The serum HMGB1 levels were measured by an ELSA method. The localization of HMGB1 in hepatocytes was assessed by immunohistochemical staining.

As a lethal model, global hepatic I/R was induced by portal triad cross-clamping for 30 mins. Hemoperfusion therapy using a cellulofine sulfate bead column (HMGB1 adsorption column) was performed during global hepatic ischemia. The protective effects of HMGB1 adsorption column were evaluated by animal survival rate and severity of the liver and the lung injury.

RESULTS AND DISCUSSION

First, the kinetics of HMGB1 were examined in hepatic I/R. During 60 min of 70% partial hepatic ischemia and the following reperfusion period, all animals survived until sacrifice. The serum HMGB1 level was not increased during ischemia, but was significantly increased immediately after reperfusion (45.4 ± 11.3 in I/R group and 0.4 ± 0.3 in sham group, $P < 0.05$). The cellular localization of HMGB1 was examined during hepatic ischemia. HMGB1 was predominantly localized in the nucleus of hepatocytes in a sham operation liver, while HMGB1 was partially translocated to the cytoplasm in the ischemic liver. These data suggest that MGB1 in the cytoplasm was released into the extracellular space in response to reperfusion, or HMGB1, which was released into the sinusoid in response to ischemia, was carried to the systemic circulation by the inflowing blood during reperfusion.

To examine the pathophysiological role of HMGB1 in hepatic I/R injury, we attempted to remove endogenous HMGB1 in I/R injury. In the lethal hepatic I/R injury model, adsorption of excess HMGB1 in the systemic circulation significantly improved animal survival at 24 hr after reperfusion. (90% in the treated group and 40% in control, log rank test, $p < 0.03$). The serum HMGB1 levels were significantly decreased in adsorption column group compared with

control at just after hemoperfusion treatment (62.7±13.8 ng/ml in adsorption column group and 108.5±12.2 in control column group, p =0.037). In this model, not only the liver but also the lung was injured. The HMGB1 adsorption column significantly reduced both the liver and the lung injury after 6 hours of reperfusion. The serum HMGB1 levels and the severity of liver damage were correlated. These findings indicate that serum HMGB1 should be kept at a low level to avoid organ damage following hepatic I/R injury.

In clinical settings, the serum HMGB1 levels can be elevated in patients who undergo liver transplantation or a major hepatectomy with Pingle's maneuver as well as patients with severe liver dysfunction, such as liver cirrhosis, fulminant hepatitis, or severe sepsis. The strategy aimed to remove HMGB1 by hemoperfusion with the HMGB1 adsorption column could be easily applicable to future clinical studies. Further investigation is thus required to assess the efficacy and the safety of the HMGB1 adsorption column for its clinical use.

CONCLUSIONS

HMGB1 plays an important role in the systemic as well as local pathogenesis of hepatic I/R injury. Therapies targeted to remove excessive serum HMGB1 with adsorption column might be beneficial and promising option in ischemia related liver injuries.