

論 文 内 容 要 旨

Decrease in major secondary bile acid, hyodeoxycholic acid, was the main alteration in hepatic bile acid compositions in a hypertensive nonalcoholic fatty liver disease model

(主要な 2 次胆汁酸であるヒオデオキシコール酸の減少が、高血圧を伴った非アルコール性脂肪性肝疾患モデルの肝臓での主な胆汁酸組成の変化である)

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Introduction

Recently, considerable attention has been paid to bile acid (BA) metabolism in nonalcoholic fatty liver disease (NAFLD). Nonetheless, studies on hepatic BA compositions in NAFLD are limited in the literature. This study investigated the effects of steatosis on hepatic BA composition in a hypertensive NAFLD model without obesity and DM. We compared the hepatic BA composition between hypertensive rats with and without steatosis.

Methods

Six- to 8-week-old female SHRs (hypertensive model) and Wistar Kyoto rat (WKY; normotensive model) were purchased from Charles River Laboratories (Osaka, Japan). SHRs were randomly assigned (n=6/group) to be fed for 5 weeks with either a normal chow diet (SHR-N) or a CD diet (SHR-CD). Likewise, WKYs were randomly assigned (n=6/group) to be fed for 5 weeks with either normal chow diet (WKY-N) or a CD diet (WKY-CD) (Oriental Yeast Co., Ltd.). After 5 weeks, rats were fasted overnight and anesthetized using sodium pentobarbital. Subsequently, the rats were killed by cardiac puncture to aspirate the blood, and the liver was excised. Hepatic BA analysis was performed using liquid chromatography–electrospray ionization–tandem mass spectrometry.

Results

Histopathological liver findings

The livers from the SHR-CD group showed severe steatosis. No steatosis was observed in the livers from SHR-N rats. The livers of the WKY-CD group showed mild steatosis. No steatosis was observed in the livers of the WKY-N group.

Analysis of hepatic BA compositions in the SHR-N and SHR-CD groups

In the SHR-CD group, the HDCA species exhibited the largest change in BA compositions. The level of HDCA species significantly decreased to 26.5 ± 33.4 nmol/g in the SHR-CD group (21.9% of that in SHR-N) compared with 121.0 ± 86.0 nmol/g in the SHR-N group, with a difference >90 nmol/g.

Analysis of hepatic BA composition in the WKY-N and WKY-CD groups

In the WKY-CD group, the CA species exhibited the largest change in BA composition. The level of CA species remarkably and significantly decreased to 81.8 ± 16.5 nmol/g in the WKY-CD group (46.7% of that in WKY-N) compared with 174.8 ± 27.9 nmol/g in the WKY-N group, with a difference >90 nmol/g.

Ratio of BA compositions in SHR-N and SHR-CD

In the SHR-CD group, the ratios of HCA species/HCA+beta-MCA species decreased significantly compared with those of the SHR-N group. In the SHR-CD group, the HDCA species/HDCA+HCA species ratio decreased nonsignificantly compared with that of the SHR-N group.

Discussion

The key finding of this study was that the decrease in HDCA species was the main alteration in a hypertensive NAFLD animal model. This finding suggested that the main effect of steatosis on hepatic BA composition in a hypertensive NAFLD model was to decrease HDCA species. In addition, no reduction of HDCA species was observed in the WKY-CD group. Accordingly, we speculated that the decrease in HDCA species in the SHR-CD group was more closely associated with hypertensive steatosis than with a CD diet.

We found that the HDCA species/HDCA+HCA species ratio decreased in the SHR-CD group compared with that in the SHR-N group, but the difference did not reach statistical significance. Its finding of the present study suggested that the transformation of HCA species to HDCA species was down-regulated in the SHR-CD model. HDCA species are synthesized from HCA species in the intestine by the intestinal microbiota. Thus, it was strongly suggested that decreased HDCA species in the SHR-CD group was caused by dysbiosis.

The results of this study are not consistent with those of previous studies. Obesity and DM have recently been shown to have an effect on BA composition. The reason for this discrepancy was thought to be that hepatic BA compositions in NAFLD might vary with comorbidities such as obesity and DM. Our results may have more important implications than the findings of the above-mentioned previous studies because we focused on the hypertensive NAFLD model and demonstrated simple findings about hepatic BA compositions in NAFLD.

Conclusions:

We demonstrated that the decrease in HDCA species was the main alteration in a hypertensive NAFLD model. It was suggested that the decrease in HDCA species in the SHR-CD group was caused by dysbiosis.