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学 位 論 文 内 容 の 要 旨

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Cholic acid administration modulates intestinal microbiota composition and parameters
for metabolic diseases in rats

（コール酸の摂取はラット腸内細菌叢の組成および代謝性疾患のパラメーター
を変化させる）

Causal relationship between imbalanced gut microbiota induced by high-fat (HF) diet administration and the development of metabolic diseases has been studied intensively. However, the relationship has not been fully understood. Under these conditions bile acid has been attracting a lot of attention, because secretion level of bile acid increases on a HF diet and also bile acid has a strong antimicrobial activity. Previous study conducted in my laboratory has demonstrated that the short-term (10 days) bile acid administration can regulate the gut microbiota composition in a similar way to that observed on a HF diet. However, it is not yet clear whether bile acid is involved in the development of metabolic diseases.

In this study, to elucidate the possibility that bile acid is not only an important regulator of the gut microbiota composition but also a responsible host factor for triggering metabolic diseases, long-term feeding trials of rats were conducted, where rats were fed HF diet (22 weeks) and cholic acid-supplemented diet (CA diet, 13 weeks) as test groups, and normal diet as control group. Their cecal microbiota compositions were characterized by pyrosequencing of the V3-V4 region of the 16S rRNA gene. Fecal bile acid compositions were analyzed during diet feeding period. At that time, the host health or disease status was monitored using oral glucose tolerance test, intestinal permeability and inflammatory markers.

1. Effects of long-term high-fat diet administration on bile acid profile, cecal microbiota composition and metabolic disease development

Long-term HF diet feeding significantly increased body weight and secretion level of bile acids. Most of the increased bile acids were converted into secondary bile acids including deoxycholic acid (DCA). However, these changes did not affect the microbiota composition at phylum level, while some genera including *Blautia*, *SMB53*, *Dorea* and *Bacteroides* were significantly increased in HF diet group. Long-term HF

diet feeding did not impair the glucose tolerance and the gut barrier function. There was also no effect of HF diet on serum biomarkers for liver inflammation or damage such as aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP). The gut microbiota and bile acid composition modulated by HF diet feeding seemed not to trigger metabolic disease development under the experimental conditions.

2. Impact of long-term cholic acid administration on cecal microbiota composition, bile acid profile and metabolic disease development

While there was no significant difference in the body weight and weight of fat tissues, a significant reduction of serum adiponectin level was observed in CA group. The adiponectin is known to show insulin-sensitizing, anti-inflammatory and anti-apoptotic effects. The administered CA was gradually converted into DCA with time course. DCA is one of the most potent antimicrobial secondary bile acids. In response to the change, CA group showed a significant increase in phylum Firmicutes ($p=0.002$) and a significant decrease in phylum Bacteroidetes ($p=0.001$) with concomitant decrease in the diversity of the bacterial community compared to the control group. While there was no effect of CA on glucose tolerance, the mucosal permeability in the intestine was significantly higher in the CA group than that in control group. These alterations may modulate immune reactions in the host because impaired barrier function in the intestine allows the movement of components of the gut microbiota, such as lipopolysaccharide, peptidoglycan and bacterial DNA, across the epithelium. Levels of both AST and ALT were significantly increased in the CA group. Interestingly, the concentration of ALT was associated with the increase of DCA. The increased levels of AST, ALT and ALP (despite not significant; $p=0.051$) were positively correlated with the relative abundances of the genera *Blautia*, *Anaerotruncus* and *Ruminococcus* (except correlation of AST and ALT with *Ruminococcus*). These results suggested the possibility that the increase of DCA associated with the increase of specific genera in the gut microbiota is involved in the induction of liver damage.

In conclusion, while no manifestation of disease status, CA-supplemented diet provoked up-regulation of several liver injury parameters with increased mucosal permeability as well as the alterations of both bile acid profile and gut microbiota composition. Therefore, bile acid is considered a possible candidate to trigger the development of hepatic disorders.