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学位論文審査の要旨

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学位論文題名

Improvement of bile acid-induced disorders by synbiotics
(胆汁酸誘導性病態に及ぼすシンバイオティクスの改善作用)

This dissertation consists of 90 pages, 18 figures, 7 tables, 3 chapters with 1 accompanied publication.

Bile acid (BA) contributes to digestion and/or absorption of hydrophobic nutrients due to its amphipathic nature. Altered BA metabolism is observed in some metabolic disorders not only in dyslipidemia but also in other diseases such as arteriosclerosis and hyperglycaemia. A high-fat diet consumption increases BA secretion and aging raises the ratio of cholic acid (CA)/chenodeoxycholic acid in the primary BAs. Instrumental analysis revealed that BAs exist at the range of 10^{-3} to 10^{-6} M in the blood, intestinal contents and feces, which can be used as a biomarker to evaluate health conditions. In our previous observation, dietary supplementation with CA in rats can be a reasonable model of non-communicable disease (NCD) that reflects BA metabolism in aging and high-fat diet consumption. The aim of the study is to investigate whether a dietary intervention with a synbiotic material ameliorates the CA-induced NCD. Some aspects of the CA-induced NCD were also clarified.

1. Combination of soy pulp and *Bacillus coagulans* lilac-01 improves intestinal bile acid metabolism without impairing the effects of prebiotics in rats fed the CA-supplemented diet

Intestinal bacteria are responsible for the production of secondary BAs. Also, an increase in the production of secondary BAs modulates the intestinal microbiota due to the bactericidal effects and raises the risk of carcinogenesis in the liver and colon. The ingestion of *Bacillus coagulans* improves constipation via the activation of bowel movement to promote defecation in humans, which may alter the BA metabolism in the intestinal contents. We studied whether *B. coagulans* lilac-01 and soy pulp as a prebiotics influence both BA metabolism and health conditions in the CA-supplemented diet-fed rats. In the CA-fed rats, soy pulp significantly increased the production of secondary BAs, such as DCA and ω -muricholic acid although the ingestion of soy pulp alleviated problems the CA-induced disorders such as decrease in plasma adiponectin and disruption of gut

permeability. When combined soy pulp with *B. coagulans*, the synbiotics ingestion successfully suppressed the increased production of secondary BA in the CA-fed rats compared to soy pulp itself, without impairing the beneficial effects of soy pulp. It is possible that a combination of prebiotics and probiotics can be used to avoid an unnecessary increase in the secondary BA production in the large intestine in maintaining beneficial functions of prebiotics.

2. Ingestion of the synbiotics improves hepatic lipid accumulation induced by the CA supplemented diet

The dietary supplementation with CA for 13 weeks induces fatty liver in the rats in our previous study. Based on this observation, we investigated the influence of the synbiotics on the CA-induced liver lipid accumulation in a shorter period. We observed hepatic lipid accumulation, increased gut permeability, and reduction of plasma adiponectin concentration at week 2 in the rats fed the CA diet. The consumption of the synbiotics normalized the CA-induced lipid accumulation accompanied by an increase in fecal lipid excretion. The synbiotics in combination of *B. coagulans* and soy pulp reduced gut permeability regardless of the CA-supplementation to the diet. These results indicate that the synbiotic material is applied to avoid development of fatty liver and disruption of gut permeability.

3. Increase of ileal permeability induced by taurocholic acid

The CA supplementation increased the fecal DCA and portal taurocholic acid (TCA) concentration in the previous experiments. It is possible that TCA is involved in the increase of gut permeability although some reports show deterioration of gut permeability by DCA. We examined whether TCA attenuates gut permeability by using isolated intestinal tissues. As a result, an existence of TCA in the luminal side increased permeability only at distal part of ileum. There was no effect of luminal TCA on the permeability in the other parts of small intestine, indicating that BA incorporation into the epithelial cells is involved in the TCA-induced increase of ileal permeability.

In conclusion, synbiotics can be used as a supplement to alleviate the BA-induced disorders including fatty liver without increase in the secondary BA production that often observed by prebiotics consumption. The CA-induced NCD is considered to be a new experimental model to evaluate the effect of dietary intervention and food components on health maintenance.

Therefore, we acknowledge that the author is qualified to be granted the Degree of Doctor of Philosophy in Agriculture from Hokkaido University.