Summary

Title: Studies on the prebiotic effect of 1-kestose on the physiology
（1-ケストース摂取による腸内環境の調節を介した生理作用に関する研究）

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Accumulating studies have indicated links between the gut microbiota and health and diseases. Development of insulin resistance is observed when intestinal barrier-protecting *Bifidobacterium* is reduced and endotoxin is increased. Low levels of butyrate-producing microbiota are frequently observed in patients' gut and experimental animals with type 2 diabetes. This dissertation aims to determine the prebiotic effects of 1-kestose on health and diseases. Specifically, it investigates the threshold of the 1-kestose prebiotic effect to stimulate beneficial bifidobacteria and whether 1-kestose has the potential to mitigate glucose tolerance in type 2 diabetes and the development of insulin resistance in rats. In this context, the prebiotic effect is defined as stimulating and activating beneficial gut microbiota, which brings host health benefits. Also, insulin resistance is defined as the reduced ability of both cellular glucose uptakes and inhibition of endogenous glucose production in response to the action of insulin from the bloodstream.

To determine the threshold dose of dietary 1-kestose that increased cecal bifidobacteria levels in rats, rats were fed experimental diets containing 0% to 0.3% 1-kestose for four weeks. Also, to test the hypothesis that dietary 1-kestose leads to beneficial effects on type 2 diabetes metabolic status, type 2 diabetes model rats were fed the 1-kestose supplemented diet for 16 weeks. Lastly, to assess the effect

of 1-kestose on plasma insulin level and their association with the gut microbiota composition, obesity was induced in rats by feeding a high-fat diet with or without 1-kestose for 19 weeks. The results showed that the genus *Bifidobacterium* levels and total gut bacteria were significantly increased in cecal contents of rats fed the 0.3% 1-kestose diet. The results using type 2 diabetes rats showed that supplementation with 1-kestose suppressed the development of diabetes, i.e., later onset of insulin resistance and hyperglycemia. The cecal contents of the rats fed 1-kestose were high in butyrate and harbored a higher proportion of the butyrate-producing genus *Anaerostipes* compared to rats fed a control diet. The results using obese rats showed that 1-kestose reduced fasting plasma insulin concentrations. This amelioration was accompanied by changes in mRNA expression of inflammatory cytokines in adipose tissues, and microbial compositions and short-chain fatty acid concentrations in cecal contents.

These results suggest prebiotic effects of 1-kestose as follows; first, for stimulation of beneficial bacteria, the minimum dose of dietary 1-kestose to induce significant bifidogenic activity in rats is presumably as low as 0.3% by weight in the diet. Second, the alteration of short-chain fatty acids, specifically butyrate, in the ceca may be responsible for a suppressive effect on glucose intolerance in type 2 diabetes rats. Thirdly, 1-kestose may increase insulin sensitivity in obese rats with normalizing short-chain fatty acid concentrations in the ceca. Both type 2 diabetes and obese rates may be deeply associated with the gut microbial community's modulation, i.e., increases in butyrate-producing bacteria. On this basis, modulation of the gut microbiota should be taken into account when regaining health from sick associated with gut microbial dysbiosis.

Apart from these studies mentioned above, this dissertation aims to propose

a new therapeutic approach that integrates gut microbial interventions with conventional therapy. The resilience of the gut microbiota is a feature of healthy gut microbiota. Since associations between diseases and the gut microbiota have been increasingly recognized in humans, besides lifestyle interventions, microbial interventions to increase the resilience of the gut microbiota, including probiotics, prebiotics, and fecal microbial transplantations, have been utilized clinically. The last part of the dissertation explores the idea of "co-resilience," which emphasizes the importance of both gut microbiota and host fitness by outlining the current evidence showing that gut microbial interventions greatly influence host fitness by building the resilience of the gut microbiota.

The dissertation contributes to our understanding of the prebiotic effect of 1-kestose and the question of how host and gut microbiota symbiotically affect diseases and fitness. The findings from the experiments using T2D and diet-induced obese rats indicate that parameters observed in the gut environment can be used to predict the likelihood that insulin resistance develops and an actual assessment of the incidence.

The dissertation practically contributes to the framework shift to understand how we regain our health upon physical illness. The application of "co-resilience" helps enhance our health by taking care of our body and gut microbiota. We still know very few host-microbiota interactions. Therefore, based on the "co-resilience" proposal, future study is needed to determine the inter-related effects of medication and 1-kestose using pathological rodent models and humans. This notion will be necessary for better understanding our symbiotic body and help create and sustain our health.

There is a great demand for preventing and treating lifestyle-related diseases because of the global severe disease burden. Application of 1-kestose to clinical practice with appropriate strategies may reduce the disease burden of a wide range of populations.