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学 位 論 文 要 旨
Dissertation Abstract

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学位論文題目：
Title of Dissertation

Effects of Anti-insulin Resistance Food Materials and Endurance Exercise on Skeletal Muscular Fat Metabolism in Rats
（インスリン抵抗性改善剤および持久性運動が骨格筋脂質代謝に及ぼす影響）

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Excess fat accumulation in muscles has been known to contribute to the development of insulin resistance (IR) and type-2 diabetes (T2DB), but the regulatory mechanisms has not perfectly clarified and controversial topics are left to be unsolved. Uptake and accumulation from the endogenous and exogenous fat in muscles are regulated by some enzymes, such as lipoprotein lipase (LPL), stearoyl-CoA desaturase (SCD), and diacylglycerol transferase (DGAT). In particular, regulation of the SCD activity and triacylglycerol (TAG) accumulation in muscles by dietary nutrients were focused. SCD is a rate-limiting enzyme for TAG synthesis and responsible for the conversion of saturated fatty acid to their respective unsaturated fatty acids. Decrease in the SCD activity is reported to inhibit TAG synthesis and fat accumulation in the liver, muscles, and total body, which can lead to improvement of IR and T2DB. A lot of food materials have been reported to suppress the SCD activity and TAG accumulation in the liver and adipose tissues, but these effects have not been well-clarified in muscles.

Dietary proteins are also not only body protein sources but also functional food factors to have an anti-IR and T2DB effects. Dietary proteins can affect IR and T2DB differently via various mechanisms, but to the present, anti-IR and T2DB effects of egg white (EW) or egg white hydroltsate (EWH) have not yet evaluated from the aspect of the muscular fat metabolism. Therefore, I firstly evaluated the suppressive effects of EWH on TAG accumulation and SCD activity index of muscles in rats with T2DB, and revealed that the higher TAG accumulation and SCD indices in the muscles were decreased by dietary EWH in parallel with improving insulin sensitivity (Experiment 1). Next, I evaluated the suppressive effects of dietary EW and EWH on fat accumulation in muscles of rats free-fed and pair-fed with a high-fat and high-sucrose diet (HFSD) (Experiments 2 and 3). As results, dietary EW and EWH significantly or slightly suppressed TAG accumulation in muscles, liver, and total body by inhibiting food intake, fat absorption, and SCD indices in the muscles and liver (Experiment 2). In case of pair-feeding, these suppressive effects of EW and EWH on fat absorption and TAG accumulation were observed especially in the liver (Experiment 3). In Experiment 4, I investigated the effects of EW and EWH on lipids-induced hypertriglycemia and small intestinal transit in ddY mice in order to investigate the mechanisms for decreases in body fat accumulation. As results, single administration of EW and EWH was not effective to

suppress the lipids-induced hypertriglycemia and to delay the rate of small intestinal transit in mice. Experiments 1~4 concluded that dietary EW and EWH can be effective materials to protect from muscular TAG accumulation, IR, and T2DB in rats, but not effective for lipids-induced hypertriglycemia in mice.

Thiazolidinediones (TZDs) is well-known as a kind of medications used in the treatment of T2DB and IR. TZDs are known to stimulate peroxisome proliferator receptor gamma (PPAR-γ) and facilitate the differentiation of adipocytes and generate small adipocytes, resulting in the improvement of adiponectin secretion and insulin sensitivity. Unlike anti-obesity materials such as EW and EWH described above, TZDs are well-known to facilitate TAG accumulation and induce obesity in parallel with improving insulin sensitivity. As excess body fat accumulation had closely associated to the development of IR and T2DB, this has been controversial and the regulatory mechanisms in muscles need to be clarified. Therefore, I evaluated the effects of repeated administration of pioglitazone (PIO), a kind of TZDs, on IR and TAG accumulation in muscles in rats (Experiment 5). As results, administration of PIO improved glucose tolerance and increased TAG accumulation and SCD indices in muscles. I also partially revealed their regulatory mechanism that the increase in TAG accumulation induced by PIO was closely correlated with LPL activity in adipose tissues, but not correlated with LPL activity in the muscles (Experiment 5).

It has also been reported that endurance athletes exhibit excess TAG accumulation in muscles despite preserved high insulin sensitivity in the same case as PIO administration. The regulatory mechanisms about excess TAG accumulation and impaired insulin sensitivity have not yet fully clarified, but swimming-endurance exercise (Ex) in combination with dietary PPAR-γ agonists can much more improve IR and T2DB.

In the next experiments, I focused on *Kaempferia parviflora* (black ginger, BG) and resveratrol (RES) as PPAR-γ agonists, and evaluated the anti-IR and T2DB effects. In the Experiment 6, I investigated about the PPAR-γ ligand-binding activities of BG and other food materials in in vitro assay. As results, BG crude and BG extracts from methyl alcohol, ethyl alcohol, acetone, and ethyl acetate, but not water and hot water, had PPAR-γ ligand-binding activities in dose-dependent manners. The short-term dietary intake of BG and RES improved the glucose metabolism in rats adiponectin-dependently or adiponectin-independently (Experiment 7). The lomg-term dietary intake of BG improved the serum glucose metabolic parameters, but did not remarkably increase the SCD indices and TAG accumulation in muscles, which did not mean that dietary BG, but not RES, improved IR by regulating muscular fat metabolism. On the other hand, Ex with or without BG or RES dramatically improved IR, but decreased TAG accumulation in muscles contrary to my expectations (Experiment 8).

In conclusion, dietary EW and EWH improved IR and T2DB by suppressing fat accumulation, SCD activity indices and TAG accumulation in muscles. On the other hand, PIO improved IR by increasing SCD index and TAG accumulation in muscles. Dietary BG improved IR, but their regulatory mechanisms were not clarified in my study.