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学位論文内容の要旨

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Novel functions of flazin against lipid metabolic disorder and mitochondrial dysfunction

(脂質代謝異常およびミトコンドリア機能不全に対するフラジンの新たな機能に関する研究)

Flazin is a β -carboline alkaloid firstly and mainly found in Japanese fermented foods, such as soy sauce, sake, and rice vinegar. It has been reported that flazin has various health beneficial effects, such as anti-HIV, quinone reductase inducing, immunomodulatory, xanthine oxidase inhibiting, and protein glycation inhibiting activities.

Recent studies have suggested that dyslipidemia and oxidative stress are considered novel therapeutic targets for several diseases, including diabetic nephropathy (DN). DN, a serious complication of diabetes mellitus, is the primary cause of end-stage kidney disease, associated with a high rate of morbidity and mortality. Development of effective therapeutic strategies for treating and preventing DN is urgently needed. β -carboline alkaloid has been reported to have anti-adipogenic and antioxidant activities. However, the effect of flazin on dyslipidemia and oxidative stress remains unknown. Therefore, this study aims to clarify the effect of flazin on lipid metabolism and oxidative stress, exploring its potential in treatment and prevention of DN.

First, the lipid metabolism-regulatory effect of flazin was investigated using human proximal tubular HK-2 cells. Flazin was found to improve viabilities of HK-2 cells under

lipid overloading, while also reducing cellular triglyceride levels and enhancing cellular lipid profiles. Additionally, flazin regulated lipid droplet dynamics, including its size and membrane properties. The potential mechanism was proved to be the inhibition of lipogenic genes expression and the promotion of lipolytic gene expression.

Second, the antioxidative effect of flazin was also investigated in HK-2 cells. Flazin reduced reactive oxygen species (ROS) levels in cells and enhanced viabilities of cells under oxidative stress. Since the generation of energy in the mitochondria results in the production of ROS as byproducts., mitochondria play critical roles on oxidative stress. Flazin also improved mitochondrial morphology and enhanced profile of cardiolipin, a distinct phospholipid located in the inner membrane of mitochondria that regulates mitochondrial functions. All of these beneficial effects suggesting that flazin alleviated oxidative stress and improved mitochondrial dynamics under oxidative stress. Mechanistically, flazin decreased expression of mitochondrial-dependent apoptotic genes and increased expression of antioxidant genes, fusion-related genes, and cardiolipin biogenesis genes.

Considering the beneficial effect of flazin, the quantitation method is worth developing. A liquid chromatography/mass spectrometry based quantitation method of flazin was established, optimized, and validated.

To conclude, the lipid metabolism-regulatory and antioxidant activity of flazin indicated the potential of flazin as a novel therapeutic strategy contributing to the treatment and prevention of DN.