Prevention and Reversal of Lipotoxicity-Induced Hepatic Insulin Resistance and Steatohepatitis in Mice by an Antioxidant Carotenoid, β-Cryptoxanthin

Paper　Outline（論文要約）

The title of the main paper(主論文題名)
Prevention and Reversal of Lipotoxicity-Induced Hepatic Insulin Resistance and Steatohepatitis in Mice by an Antioxidant Carotenoid, β-Cryptoxanthin

Department(専攻部門・研究分野)　Division of Environmental Science
Name(氏名)　Ni Yinhua (倪　銀華)
(The head of a department(主任教員)　Prof. Kaneko Shuichi)

Background & Aims: Excessive hepatic lipid accumulation promotes the activation of macrophages/Kupffer cells, resulting in exacerbation of insulin resistance and progression of non-alcoholic steatohepatitis (NASH). However, few promising treatment modalities target lipotoxicity-mediated hepatic activation/polarization of macrophages for NASH. Recent epidemiological surveys showed that serum β-cryptoxanthin, an antioxidant carotenoid, was inversely associated with the risks of insulin resistance and liver dysfunction. Here, we first examined the effect of β-cryptoxanthin on hepatic steatosis. Next, we investigated the preventative and therapeutic effects of β-cryptoxanthin using a lipotoxic model of NASH: mice fed a high-cholesterol and high-fat diet (“CL diet”). **Methods**: C57BL/6 mice were fed a CL or CL diet with 0.003% of β-cryptoxanthin for 12 weeks. The liver histology, insulin sensitivity, and hepatic gene expression profile were examined. Next, we quantified intrahepatic immune cells by flow cytometry. **Results**: β-Cryptoxanthin administration ameliorated hepatic steatosis in high-fat diet-induced obese mice. After 12 weeks of CL diet feeding, β-cryptoxanthin administration attenuated insulin resistance and excessive hepatic lipid accumulation and peroxidation, with increases in M1-type macrophages/Kupffer cells and activated stellate cells, and fibrosis in CL diet-induced NASH. Comprehensive gene expression analysis showed that β-cryptoxanthin downregulated macrophage activation signal-related genes significantly without affecting most lipid metabolism-related genes in the liver. Importantly, flow cytometry analysis revealed that, on a CL diet, β-cryptoxanthin caused a predominance of M2 over M1 macrophage populations, in addition to reducing total hepatic macrophage and T cell contents. In parallel, β-cryptoxanthin decreased lipopolysaccharide-induced M1 marker mRNA expression in peritoneal macrophages, whereas it augmented IL-4-induced M2 marker mRNA expression, in a dose-dependent manner. Moreover, β-cryptoxanthin reversed steatosis, inflammation, and fibrosis progression in pre-existing NASH in mice. **Conclusions**: β-cryptoxanthin prevents and reverses insulin resistance and steatohepatitis, at least in part, through an M2-dominant shift in macrophages/Kupffer cells in a lipotoxic model of NASH. β-Cryptoxanthin could be a potential preventative or therapeutic agent for NASH.