論 文 の 内 容 の 要 旨

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論　文　題　目

PPARα protects against *trans*-fatty-acid-containing diet-induced steatohepatitis
（PPARα はトランス脂肪酸含有食誘発性脂肪性肝炎に対し保護的に作用する）

【Background and Aim】

Trans-fatty acids (TFA), unsaturated fatty acids (FA) containing *trans* double bonds, are reported to be more harmful to humans compared with other FA. Peroxisome proliferator-activated receptor α (PPARα) is a ligand-activated nuclear receptor that regulates lipid homeostasis, inflammation, and immune responses, but the role of PPARα in TFA-induced liver abnormalities remains unclear. The present study investigated the contribution of PPARα to liver damage induced by TFA.

【Methods】

We gave two diets, a purified control diet and an isocaloric TFA-containing diet, to wild-type and *Ppara*-null mice for two months. After the treatment, the mice were killed and serum and liver tissues were collected for biochemical analysis, histological analysis, quantitative polymerase chain reaction analysis, and immunoblot analysis. Statistical analysis was performed using two-way ANOVA with Bonferroni's correction.

【Results】

Ppara-null mice fed a TFA-containing diet showed more severe hepatosteatosis and liver damage compared with similarly-treated wild-type mice, as revealed by increased hepatic triglyceride (TG) contents and serum alanine aminotransferase activities. While the TFA diet increased hepatic expression of enzymes involved in *de novo* FA synthesis and decreased TG-hydrolyzing enzymes in both genotypes, the expression of FA-catabolizing enzymes were decreased in *Ppara*-null mice only. Additionally, the expression levels of key contributors to inflammation, such as osteopontin, were increased, and nuclear factor-kappa B was activated in TFA-containing diet-fed *Ppara*-null mice. Enhanced inflammatory signaling in these mice was presumably mediated by toll-like receptor 2, but not inflammasome activation.

【Conclusion】

PPARα deficiency is more sensitive to TFA-induced steatohepatitis, indicating that PPARα plays a protective role for dietary TFA-induced liver abnormalities.