論 文 審 査 の 結 果 の 要 旨

報 告 番 号	甲 第 1315 号	氏 名	ZHANG ZHE
論 文 審 査 担 当 者	主 査　　竹下　敏一 副 査　　梅村　武司　・　森　政之　・　本多　彰		

（論文審査の結果の要旨）

　Pemafibrate (PEM) is a novel lipid-lowering drug classified as a selective peroxisome proliferator-activated receptor α (PPARα) modulator whose binding efficiency to PPARα is superior to that of conventional fibrates. This agent is also useful for non-alcoholic fatty liver disease and primary biliary cholangitis with dyslipidemia. However, it remains unclear on how PEM exerts lipid-lowering action in the clinical setting.

　PEM at a clinically relevant dose (0.1 mg/kg/day) or relatively high dose (0.3 mg/kg/day) was administered to male C57BL/6J mice for 14 days. In this study, histopathological analysis of several organs such as liver, heart, kidney and adipose tissue, biochemical analysis, quantitative polymerase chain reaction, Western blot, and enzyme-linked immunosorbent assay were conducted.

　「ZHANG ZHE」 obtained the following conclusions.

1.　Clinical dose of PEM efficiently lowered circulating triglyceride (TG) levels without apparent hepatotoxicity in mice, likely due to hepatic PPARα stimulation and enhanced fatty acid uptake and β-oxidation in the liver.

2.　Hepatic microsomal triglyceride transfer protein was increased by clinical dose of PEM.

3.　PEM activated PPARα only in the liver, but not in the heart, kidney, or adipose tissue.

4.　Clinical dose of PEM increased serum/hepatic levels of fibroblast growth factor 21 (FGF21) without enhancing hepatic lipid peroxide 4-hydroxynonenal or inflammatory signaling.

A clinically relevant dose of PEM could efficiently and safely reduce serum TG and increase FGF21 targeting of hepatic PPARα in mice. These findings may help explain the precise mechanism of how PEM attenuates circulating TG in humans.

　主査、副査は一致して本論文を学位論文として価値があるものと認めた。