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Inhibition of Endoplasmic reticulum stress by 4 phenyl butyric acid reduced lipotoxicity and lipid accumulation through induction of autophagy in human hepatoma cells

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ABSTRACT

Defective autophagy has been linked to lipotoxicity in several cellular models. The aim of the study was to investigate autophagy in lipid stimulated hepatocytes and tested whether 4-Phenyl butyric acid (4PBA) has beneficial role in hepatic fat accumulation and lipotoxicity. This study shows that long term (24h) exposure of hepatocytes to palmitate block autophagic flux that leads to lipid accumulation and cell death. Western blotting analysis showed increased accumulation of SQSTM1/P62 and LC3II, decreased expression of Beclin1 and Atg7 in palmitate treated hepatocytes. Induction of autophagy by 4PBA reduced lipid accumulation and cell death. Autophagy inhibition by 3-methyladenine (3-MA) in palmitate treated cells neither increased SQSTMI/p62 accumulation nor cell death, thus suggesting complete blockade of autophagy by palmitate. Moreover, 4PBA failed to reduce the lipid accumulation in presence of autophagy inhibitors 3-MA and chloroquine, suggesting that 4PBA mediates its lipid lowering effect via autophagy. Apoptotic parameters including altered Bcl2/Bax ratio and PARP1 cleavage induced by palmitate were improved by 4PBA. Our results indicate that palmitate impairs autophagy and increases LD formation in hepatocytes and 4PBA activates autophagy and might play protective role in fatty acid induced lipid accumulation and lipotoxicity.

Key words: Autophagy, Lipid droplet, cell death, chemical chaperone, 4-phenyl butyric acid, Lipotoxicity