Pyrazinamide-induced hepatotoxicity is alleviated by 4-PBA via inhibition of the PERK-eIF2α-ATF4-CHOP pathway.

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Abstract
Pyrazinamide (PZA)-induced serious liver injury, but the exact mechanism of PZA-induced hepatotoxicity remains controversial. Endoplasmic reticulum (ER) stress-caused cell apoptosis plays a critical role in the development of drug-induced liver injury (DILI). However, the direct connection between PZA toxicity and ER stress is unknown. In this study, we describe the role of ER stress in PZA induced hepatotoxicity in vivo and in vitro. We found that PZA induces apoptosis in HepG2 cells, and causes liver damage in rats, characterized by increased serum ALT, AST and TBA levels. PZA impairs antioxidant defenses, although this effect did not play an important role in resulting liver injury. The ER stress related proteins GRP78, p-PERK, p-eIF2α, ATF4, CHOP and caspase12 were activated after PZA exposure both in vivo and in vitro. Furthermore, as an ER stress inhibitor, sodium 4-phenylbutyrate (4-PBA) could ameliorate PZA toxicity in HepG2 cells and rat liver. These results have potential implications for the pathogenesis of PZA-induced hepatotoxicity in which ER stress especially PERK-eIF2α-ATF4-CHOP pathway participates in hepatocellular injury.

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KEYWORDS: Endoplasmic reticulum (ER) stress; Hepatotoxicity; PERK-eIF2α-ATF4-CHOP pathway; Pyrazinamide; Sodium 4-phenylbutyrate

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