

# The effects of Insulin Pre-Administration in Mice Exposed to Ethanol: Alleviating Hepatic Oxidative Injury through Anti-Oxidative, Anti-Apoptotic Activities and Deteriorating Hepatic Steatosis through SRBEP-1c Activation

Jiangzheng Liu1, Xin Wang1, Zhengwu Peng2, Tao Zhang1, Hao Wu1, Weihua Yu1, Deqing Kong1, Ying Liu1, Hua Bai1, Rui Liu1, Xiaodi Zhang1, Chunxu Hai1?

1. Department of Toxicology, the Ministry of Education Key Lab of Hazard Assessment and Control in Special Operational Environment, Shaanxi Provincial Key Lab of Free radical biology and medicine, School of Public Health, The Fourth Military Medical University, Xi'an, 710032, P. R. China; 2. Department of Psychiatry, Xijing Hospital, The Fourth Military Medical University, Xi'an, 710032, P. R. China. ? Corresponding author: Department of Toxicology, the Ministry of Education Key Lab of Hazard Assessment and Control in Special Operational Environment, Shaanxi Provincial Key Lab of Free radical biology and medicine, School of Public Health, The Fourth Military Medical University, Xi'an, 710032, Shaanxi, P. R. China. Tel: +86 02983374879. Fax: +86 02984774879. Email: cx-hai@fmmu.edu.cn.

### Abstract :

Alcoholic liver disease (ALD) has become an important liver disease hazard to public and personal health. Oxidative stress is believed to be responsible for the pathological changes in ALD. Previous studies have showed that insulin, a classic regulator of glucose metabolism, has significant anti-oxidative function and plays an important role in maintaining the redox balance. For addressing the effects and mechanisms of insulin pre-administration on ethanol-induced liver oxidative injury, we investigated histopathology, inflammatory factors, apoptosis, mitochondrial dysfunction, oxidative stress, antioxidant defense system, ethanol metabolic enzymes and lipid disorder in liver of ethanol-exposed mice pretreatment with insulin or not. There are several novel findings in our study. First, we found insulin pre-administration alleviated acute ethanol exposure-induced liver injury and inflammation reflected by the decrease of serum AST and ALT activities, the improvement of pathological alteration and the inhibition of TNF- $\alpha$  and IL-6 expressions. Second, insulin pre-administration could significantly reduce apoptosis and ameliorate mitochondrial dysfunction in liver of mice exposed to ethanol, supporting by decreasing caspases-3 activities and the ratio of Bax/Bcl-2, increasing mitochondrial viability and mitochondrial oxygen consumption, inhibition of the decline of ATP levels and mitochondrial ROS accumulation. Third, insulin pre-administration prevented ethanol-mediated oxidative stress and enhance antioxidant defense system, which is evaluated by the decline of MDA levels and the rise of GSH/GSSG, the up-regulations of antioxidant enzymes CAT, SOD, GR through Nrf-2 dependent pathway. Fourth, the modification of ethanol metabolism pathway such as the inhibition of CYP2E1, the activation of ALDH might be involved in the anti-oxidative and protective effects exerted by insulin pre-administration against acute ethanol exposure in mice. Finally, insulin pre-administration deteriorated hepatic steatosis in mice exposed to ethanol might be through SRBEP-1c activation. In summary, these results indicated that insulin pre-administration effectively alleviated liver oxidative injury through anti-inflammatory, anti-oxidative and anti-apoptotic activities but also deteriorated hepatic steatosis through SRBEP-1c activation in mice exposed to ethanol. Our study provided novel insight about the effects and mechanisms of insulin on ethanol-induced liver injury

### Key Word :

Insulin; Alcoholic liver disease; Oxidative injury; Nrf-2; Ethanol metabolism; Inflammatory