Abstract

Introduction: Liver diseases represent a significant cause of morbidity and mortality worldwide. Previous experimental studies have shown that polyphenolic compound, resveratrol, as a less specific activator of sirtuin 1 (SIRT1) and AMP-activated protein kinase (AMPK) can effectively attenuate acute liver injury. Although SIRT1 and AMPK have been widely studied for many years, further evidence for a mutual SIRT1/AMPK signaling mechanism and how it is modulated by drugs of small molecules had not been fully clarified at start of our experimental work.

Goal: The main objective of the presented research was to investigate the relationship of SIRT1 and AMPK in process of hepatotoxicity/hepatoprotection in *in vivo* and *in vitro* animal model of acute drug-induced liver injury.

Methods: Male Wistar rats were used for both *in vivo* and *in vitro* studies. Hepatotoxicity was induced by a single dose of D-Galactosamine (GalN)/lipopolysaccharide (LPS) or acetaminophen (APAP). Some rats and cultured hepatocytes were treated by resveratrol, synthetic selective activator or inhibitor of SIRT1 and AMPK. Biochemical markers of liver injury (aminotransaminases, total bilirubin), oxidative stress (nitrites) and lipid peroxidation (conjugated dienes, TBARS) were measured in the plasma, medium or liver homogenate. Liver histology, hepatocyte viability, SIRT1 and AMPK activity and protein expression were also assessed.

Results: Our findings demonstrate that the harmful effects of D-GalN/LPS and APAP were associated with decreased activity and/or protein expression of SIRT1 and AMPK alongside enhanced oxidative stress in hepatocytes which can be significantly attenuated by the administration of the SIRT1 activator. In addition, our results from *in vitro* experiments originally suggest that hepatoprotective effects of SIRT1 against APAP toxicity could be at least partially independent of AMPK activity.

Conclusion: The differentiated modulation of SIRT1 and AMPK activity, especially by their specific synthetic activators, could provide an interesting and novel therapeutic option for hepatocyte injury in the future.

Keywords: acetaminophen; adenosine monophosphate protein kinase (AMPK); AICAR; CAY10591; Compound C; D-Galactosamine (GalN)/lipopolysaccharide (LPS); enzyme activation; EX-527; hepatocyte protection; hepatotoxicity; sirtuin 1 (SIRT1).