Molecular and Metabolic Signatures Associated with Acute Paracetamol Multiple Doses Toxicity in Mice

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Abstract

Paracetamol (APAP), also known as acetaminophen, is the most extensively used antipyretic and pain-reliever drug. It has been indicated by World Health Organization to treat all stages of pain intensity. APAP overdosing leads to liver toxicity worldwide. Although APAP is described as non-toxic under therapeutic doses, toxicity can occur when taken in a single overdose or repeated sub-toxic doses. Liver fibrosis induced by repeated toxic APAP doses is not well studied, particularly, dynamics of the liver toxicity. Therefore, adult fastened Balb/C mice were exposed to two doses of 300mg/kg APAP with 72h interval. Subsequently, blood and livers were harvested at 24h and 72hours after APAP administration. Macroscopically only at 24h after first dose, APAP induced white spots was recorded.

Moreover, liver transaminases, ALT and AST level revealed that fulminant liver damage in a good correlation with HE necrotic areas. Further, picrosirius red staining analysis indicated that accumulation of extracellular matrix after second dose only in agreement with consistent upregulation of fibrogenic signatures. Unfocused liver tissue metabolic profiling indicated that most dramatic alterations occurred at 24h after first dose of APAP. However, the level of most metabolites recovers- to some extent- to basal levels in time. We can conclude that there is a different liver response to APAP toxic doses, if liver exposed once or more than one. Necroinflammatory process followed by liver regeneration is reported after first APAP hit. However, fibrogenesis through accumulation of extracellular matrix was observed after second challenges. Therefore, further studies are required to mechanistically understand what so called "liver memory".