Second exposure to acetaminophen overdose is associated with liver fibrosis in mice

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Abstract

Repeated administration of hepatotoxicants is usually accompanied by liver fibrosis. However, the difference in response as a result of repeated exposures of acetaminophen (APAP) compared to a single dose is not well-studied. Therefore, in the current study, the liver response after a second dose of APAP was investigated. Adult fasted Balb/C mice were exposed to two toxic doses of 300 mg/kg APAP, which were administered 72 h apart from each other. Subsequently, blood and liver from the treated mice were collected 24 h and 72 h after both APAP administrations. Liver transaminase, i.e. alanine amino transferase (ALT) and aspartate amino transferase (AST) levels revealed that the fulminant liver damage was reduced after the second APAP administration compared to that observed at the same time point after the first treatment. These results correlated with the necrotic areas as indicated by histological analyses. Surprisingly, Picro Sirius Red (PSR) staining showed that the accumulation of extracellular matrix after the second dose coincides with the upregulation of some fibrogenic signatures, e.g., alpha smooth muscle actin. Non-targeted liver tissue metabolic profiling indicates that most alterations occur 24 h after the first dose of APAP. However, the levels of most metabolites recover to basal values over time. This organ adaptation process is also confirmed by the upregulation of antioxidative systems like e.g. superoxide dismutase and catalase. From the results, it can be concluded that there is a different response of the liver to APAP toxic doses, if the liver has already been exposed to APAP. A necroinflammatory process followed by a liver regeneration was observed after the first APAP exposure. However, fibrogenesis through the accumulation of extracellular matrix is observed after a second challenge. Therefore, further studies are required to mechanistically understand the so called “liver memory”.

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