Increased acetaminophen hepatotoxicity in the Nas1 and Sat1 sulfate transporter null mice

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Sulfate is required for detoxification of xenobiotics such as acetaminophen (APAP), a leading cause of liver failure in humans. The NaS1 and Sat1 sulfate transporters are involved in maintaining blood sulfate levels sufficiently high for sulfonation reactions to work effectively for drug detoxification. The aims of this study were to determine the physiological consequences of APAP treatment in hyposulfataemic Nas1-/- and Sat1-/- mice. Male Nas1-/-, Sat1-/- and wild-type mice aged 1-4 months (n=5-7), were injected ip with APAP (250 mg/kg body weight). The animals were sacrificed at various times: 0, 2, and 12 hours after APAP administration. Serum alanine aminotransferase (ALT) levels were measured as an indicator of APAP-induced liver injury. ALT levels were 3-fold higher in Nas1-/- mice and 1.5- fold higher in Sat1-/- mice, when compared to wild-type mice, at 12 hours after APAP treatment (250 mg/kg). This supports our histological findings of increased cellular damage in Nas1-/- and Sat1-/- mice. Analysis of urinary APAP metabolites, using LC-MS-MS with multiple reaction monitoring (MRM), revealed a significantly lower ratio of APAP-sulfate to APAP-glucuronide in the Nas1-/- mice. This technique allowed accurate quantification of metabolites as it specifically detects the assigned mass of each metabolite molecule along with a specific fragment of the molecule produced by collision induced dissociation. In conclusion, this study has highlighted the significance of plasma sulfate level as a key modulator of APAP metabolism and suggests that individuals with reduced sulfate transporter function would be more sensitive to xenobiotic hepatotoxicity.