Increased acetaminophen hepatotoxicity in the NaS1 sulphate transporter null mouse
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Sulphate (SO\textsubscript{4}\textsuperscript{2-}) plays an important role in the detoxification of numerous xenobiotics, including the widely used analgesic drug, acetaminophen (APAP) (Cole & Evrovski, 2000). The Na\textsuperscript{+}-SO\textsubscript{4}\textsuperscript{2-} cotransporter, NaS1 is expressed in the kidney, where it maintains blood sulphate levels (Markovich, 2001). NaS1 knock-out (\textit{Nas1}\textsuperscript{-/-}) mice exhibit hyposulphataemia and hypersulphaturia (Dawson \textit{et al.} 2003). This project assessed the molecular, biochemical and physiological consequences of APAP challenge. Male \textit{Nas1}\textsuperscript{+/-} and \textit{Nas1}\textsuperscript{-/-} mice aged 1-4 months (\textit{n} = 5-7 mice), were injected with 125-, 250- or 500-mg/kg of APAP i.p. The animals were sacrificed at various times (0, 2, 4, 5, 6 and 12 hours) after APAP administration. Serum alanine aminotransferase (ALT) levels in \textit{Nas1}\textsuperscript{+/-} and \textit{Nas1}\textsuperscript{-/-} mice were measured as an indicator of APAP-induced liver injury. ALT levels were 3-fold higher in \textit{Nas1}\textsuperscript{-/-} mice when compared to \textit{Nas1}\textsuperscript{+/-} mice at 12 hours after APAP treatment (250-mg/kg). This supports our histological findings of increased cellular damage in \textit{Nas1}\textsuperscript{-/-} mice. Extensive haemorrhaging was observed in lobular areas of \textit{Nas1}\textsuperscript{+/-} mice (500-mg/kg APAP, \textit{t}=5 hours post-injection) but not in \textit{Nas1}\textsuperscript{+/-} mice. Hepatic glutathione (GSH) depletion was greater in \textit{Nas1}\textsuperscript{-/-} mice (87\% reduction), compared to \textit{Nas1}\textsuperscript{+/-} mice (63\% reduction) at 250-mg/kg dosage regime (\textit{t}=2 hours post-injection) whereas repletion of GSH showed no significant differences between and \textit{Nas1}\textsuperscript{+/-} and \textit{Nas1}\textsuperscript{-/-} mice. The GSTpi mRNA levels were significantly induced (2-fold) in \textit{Nas1}\textsuperscript{-/-} mice, when compared to \textit{Nas1}\textsuperscript{+/-} mice. The induction of GSTpi mRNA levels in APAP-treated \textit{Nas1}\textsuperscript{-/-} mice, could be a compensatory response to the GSH depletion. The mRNA levels of CYP3A11, which are responsible for the production of reactive metabolite, N-acetyl-p-benzoquinone imine (NAPQI) (Zhang \textit{et al.} 2002), were significantly increased (1.5-fold) in \textit{Nas1}\textsuperscript{-/-} mice when compared to \textit{Nas1}\textsuperscript{+/-} mice (250-mg/kg APAP, \textit{t}=2 hours post-injection). In summary, we have identified increased APAP-induced hepatotoxicity and more rapid GSH depletion in the hyposulphataemic \textit{Nas1}\textsuperscript{-/-} mice and this may be due to low blood sulphate levels, which limits APAP sulphonation. This study suggests the potential role of NaS1 in the modulation of APAP-induced hepatotoxicity.