Increased acetaminophen hepatotoxicity in the NaS1 sulphate transporter null mouse

S. Lee, P.A. Dawson and D. Markovich, School of Biomedical Sciences, University of Queensland, Brisbane, QLD 4072, Australia.

Sulphate (SO_4^{2-}) plays an important role in the detoxification of numerous xenobiotics, including the widely used analgesic drug, acetaminophen (APAP) (Cole & Evrovski, 2000). The Na^+-SO_4^{2-} cotransporter, NaS1 is expressed in the kidney, where it maintains blood sulphate levels (Markovich, 2001). *NaS*1 knock-out (*Nas1*$^{-/-}$) mice exhibit hyposulphataemia and hypersulphaturia (Dawson *et al*. 2003). This project assessed the molecular, biochemical and physiological consequences of APAP challenge. Male *Nas1*$^{+/+}$ and *Nas1*$^{-/-}$ mice aged 1-4 months (*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 *Nas1*$^{+/+}$ and *Nas1*$^{-/-}$ mice were measured as an indicator of APAP-induced liver injury. ALT levels were 3-fold higher in *Nas1*$^{-/-}$ mice when compared to *Nas1*$^{+/+}$ mice at 12 hours after APAP treatment (250-mg/kg). This supports our histological findings of increased cellular damage in *Nas1*$^{-/-}$ mice. Extensive haemorrhaging was observed in lobular areas of *Nas1*$^{-/-}$ mice (500-mg/kg APAP, t=5 hours post-injection) but not in *Nas1*$^{+/+}$ mice. Hepatic glutathione (GSH) depletion was greater in *Nas1*$^{-/-}$ mice (87% reduction), compared to *Nas1*$^{+/+}$ mice (63% reduction) at 250-mg/kg dosage regime (t=2 hours post-injection) whereas repletion of GSH showed no significant differences between and *Nas1*$^{+/+}$ and *Nas1*$^{-/-}$mice. The GSTpi mRNA levels were significantly induced (2-fold) in *Nas1*$^{-/-}$ mice, when compared to *Nas1*$^{+/+}$ mice. The induction of GSTpi mRNA levels in APAP-treated *Nas1*$^{-/-}$ 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 *et al.*, 2002), were significantly increased (1.5-fold) in *Nas1*$^{-/-}$ mice when compared to *Nas1*$^{+/+}$ mice (250-mg/kg APAP, t=2 hours post-injection). In summary, we have identified increased APAP-induced hepatotoxicity and more rapid GSH depletion in the hyposulphataemic *Nas1*$^{-/-}$ 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.

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