Sulphate ions in mammalian physiology: lessons from sulphate transporter knock-out mice

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Inorganic sulphate (SO_4^{2-}) is the fourth most abundant anion in mammalian plasma and is essential for numerous metabolic and cellular processes (Markovich, 2001). In humans and rodents, sulphate reabsorption is mediated by the Na^+-SO_4^{2-} cotransporter (NaS1) located at the brush border membrane, and Sat-1, a SO_4^{2-}-anion exchanger located on the basolateral membranes of proximal tubular cells. Both NaS1 null (*Nas1*$^{-/-}$) and sat-1 null (*sat-1*$^{-/-}$) mice exhibit hyposulphataemia, highlighting the importance of these transporters in maintaining SO_4^{2-} homeostasis. Since *Nas1*$^{-/-}$ mice exhibit reduced growth and liver abnormalities, including hepatomegaly (Dawson *et al*. 2003), we aimed to investigate the hepatic gene expression profile of *Nas1*$^{-/-}$ mice using oligonucleotide microarrays. The mRNA levels of 130 genes with functional roles in metabolism, cell signalling, cell defence, immune response, cell structure, transcription or protein synthesis were altered (66 induced, 64 down-regulated) in *Nas1*$^{-/-}$ mice when compared to *Nas1*$^{+/+}$ mice. The most up-regulated transcript levels in *Nas1*$^{-/-}$ mice were found for the sulphotransferase genes, *Sult3a1* (~500% increase) and *Sult2a2* (100% increase), whereas the metallothionein-1 gene, *Mt1*, was amongst the most down-regulated genes (70% decrease). Several genes involved in lipid metabolism, including *Scd1*, *Acly*, *Gpam*, *Elov16* and *Acs15*, were found to be up-regulated (≥30% increase) in *Nas1*$^{-/-}$ mice. Increased levels of hepatic lipid (~16% increase), serum cholesterol (~20% increase) and LDL (~100% increase), and reduced hepatic glycogen levels (~50% decrease), were found in *Nas1*$^{-/-}$ mice. In addition, *Nas1*$^{-/-}$ mice have an increased hepatotoxicity to acetaminophen (250-mg/kg i.p.) associated with increased serum ALT activity (>300% increase) and reduced hepatic GSH levels (>60% decrease). *Nas1*$^{-/-}$ mice live longer (~25% increase) than their *Nas1*$^{+/+}$ littermates, and have a decreased incidence (0/7 affected, $P<0.025$) of hepatic tumours, when compared to *Nas1*$^{+/+}$ mice (4/7 affected) at 2 years of age. In summary, the hyposulphataemic *Nas1*$^{-/-}$ mouse provides a previously uncharacterised animal model of increased lifespan and altered hepatic metabolism.

Dawson, P.A., Beck, L. & Markovich, D. (2003) *Proceedings of the National Academy of Science U.S.A.* **100**, 13704-13709.

Markovich, D (2001) *Physiological Reviews* **81**, 1499-1534.