

The Sat1 (Slc26a1) Anion Transporter and Calcium Oxalate Urolithiasis

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Kidney stones are a common disorder, leading to significant health care costs and morbidity. Both genetic and environmental factors are likely to be involved in the aetiology of kidney stones. Disturbed oxalate homeostasis is the most common metabolic abnormality in patients with renal stones. Oxalate is a metabolic end product derived from the liver and diet. However, the genetic contribution to the development of most calcium oxalate renal pathologies is yet unknown. We have shown the Sat1 anion exchanger mediates oxalate transport, but its precise role in the body is yet unknown. To ascertain the physiological role of Sat1, we generated a Sat1 null (Sat1^{-/-}) mouse, which develops kidney stones and has increased plasma oxalate concentrations (by ≈ 1.5 -fold) and urinary oxalate/creatinine ratios (by ≈ 2 -fold), when compared to Sat1^{+/+} (control) mice. Urinary glycollate/creatinine ratios in Sat1^{-/-} mice (0.18 ± 0.03) were not significantly different to Sat1^{+/+} mice (0.18 ± 0.02), implying that the hyperoxalaemia may not be due to increased hepatic oxalate synthesis. Stones were detected in the bladder, as well as the kidney, which were primarily composed of calcium ($11.1 \pm 0.1\%$), oxygen ($36.5 \pm 0.2\%$) and carbon ($51.5 \pm 0.1\%$), indicating a composition of calcium oxalate. Sat1^{-/-} kidneys showed infiltration of leukocytes around renal cortical vessels, a sign of obstructive uropathy and found in humans with nephrocalcinosis, which is absent in Sat1^{+/+} mice. Thus, the tubular nephrocalcinosis in the Sat1^{-/-} mice closely resembles that in humans with calcium oxalate stones, thereby providing a new model for studying kidney pathophysiology. Our study provides an important link between a membrane transporter that regulates oxalate homeostasis and thereby impacts on kidney stone pathology.
