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Identification of Cl^- Activated Uric Acid Transporter as a Risk Factor for Gout

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Summary

Urate is an end product of purine metabolism in humans and acts a natural antioxidant with neuroprotective properties. Elevated serum urate levels caused by the loss of urate oxidase ctivity provided a survival advantage because hyperuricemia helped to maintain blood pressure levels under the low salt dietary conditions that prevailed in the middle to late Miocene period. Despite its beneficial role, the elevated urate level is associated with several metabolic disorders such as gout and kidney stones in humans. It is known that about 2/3 of urate is excreted from renal proximal tubules by at least two distinct types of transporters, one of which is ABCG2, and ATP-driven ABC type transporter and unidentified Dy-driven anion transporters. Very recently, we have shown that NPT1 and NPT4, SLC17 anion transporter family members, are urate exporter. The present study aims to demonstrate that NPT3 and NPT homologues, other SLC17 members, also act as urate exporter. Using specific antibodies, we found that a human NPT homologue (hNPT homologue) is specifically expressed and present in the intestinal brush border membrane. Proteoliposomes containing the purified protein took up radiolabeled *p*-aminohippuric acid (PAH) in a Cl^--dependent manner at the expense of an electrochemical gradient of protons, especially Dy, across the membrane. The Dy- and Cl^--dependent PAH uptake was inhibited by diisothiocyanostilbene-2,2'-disulfonic acid and Evans blue, common inhibitors of SLC17 family members. *cis*-Inhibition studies revealed that various anionic compounds, such as hydrophilic non-steroidal anti-inflammatory drugs, pravastatin and urate inhibited the PAH uptake. Proteoliposomes took up radiolabeled urate, the uptake having properties similar to those of PAH uptake. These results strongly suggested that the hNPT homologue acts as a polyspecific organic anion exporter in the intestines. Since NPT1 and NPT4 are responsible for renal urate extrusion, our results reveal the possible involvement of a NPT homologue in urate extrusion from the intestinal duct.