Disorders of neutral amino acid resorption in epithelial cells

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Recent successes in the molecular cloning and identification of apical neutral amino acid transporters have shed a new light on inherited neutral amino acidurias, such as Hartnup disorder and iminoglycinuria. Hartnup disorder is caused by mutations in the neutral amino acid transporter B^0AT1 (SLC6A19) (Kleta *et al.*, 2004; Seow *et al.*, 2004). The transporter is found in kidney and intestine, where it is involved in the resorption of all neutral amino acids (Bröer *et al.*, 2004). It belongs to the SLC6 family, comprising transporters for neurotransmitters, osmolytes and creatine. B^0AT1 transports neutral amino acids together with 1 Na^+-ion but in contrast to other members of the SLC6 family is chloride independent. The SLC6 family also contains a number of 'orphan transporters' the physiological function of which has remained elusive. Identification of SLC6A19 as a Na^+-dependent amino acid transporter suggested that orphan neurotransmitter transporters might in fact be amino acid transporters. SLC6A20 turned out to be the long-sought IMINO system, a Na^+ and Cl^--dependent proline transporter (Kowalczuk *et al.*, 2005). SLC6A20 is highly expressed in the kidney and intestine and may play a role in iminoglycinuria, a disorder characterised by hypersecretion of proline and glycine in the urine. Although SLC6A20 transports proline but not glycine, it is considered a candidate for iminoglycinuria because excess of proline in the proximal tubule could compete for glycine uptake by the proline/glycine transporter PAT1 (SLC36A1). Further functional analysis of SLC6 orphan transporters demonstrated that SLC6A15 is a transporter for large neutral amino acids plus proline. The transporter is highly expressed in the brain and kidney. In the kidney it may serve as a high-affinity back-up transporter for selected amino acids in the distal parts of the proximal tubule. Functionally SLC6A15 is related to B^0AT1 and was hence named B^0AT2. It transports neutral amino acids together with 1 Na^+ and is chloride independent. In summary, a new family of Na^+-dependent amino acid transporters has been identified, the members of which are involved in the transport of amino acids in epithelial cells and the nervous system.

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