A novel digestive complex and its role in Hartnup disorder: trafficking of the neutral amino acid transporter B^0AT1 by angiotensin converting enzyme 2 (ACE2)

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In the intestine, proteins are digested by proteases and brush-border peptidases into small peptides and amino acids, which are then absorbed by peptide and amino acid transporters. Neutral amino acids are absorbed by the amino acid transporter B^0AT1. B^0AT1 is also expressed in the kidney, where it mediates reabsorption of neutral amino acids from the primary urine. Mutations in B^0AT1 cause Hartnup disorder, a defect in neutral amino acid transport resulting in neutral aminoaciduria.

In the kidney, B^0AT1 requires the auxiliary protein collectrin for trafficking to the brush-border membrane. However, collectrin is not expressed in the intestine, suggesting that a different protein facilitates B^0AT1 trafficking in this tissue. Interestingly, the closest homologue of collectrin is a brush-border carboxypeptidase, angiotensin converting enzyme 2 (ACE2).

Coexpression of B^0AT1 and ACE2 in *Xenopus laevis* oocytes* caused a dramatic increase in the surface expression of B^0AT1. Addition of a peptide containing a carboxyterminal leucine residue to these oocytes resulted in leucine transport by B^0AT1, demonstrating that B^0AT1 and ACE2 form a complex that performs two consecutive steps in protein digestion and absorption. The Hartnup disorder associated mutations B^0AT1 (D173N) and B^0AT1 (R240Q) showed reduced interaction with both ACE2 and collectrin, thereby explaining how these mutations cause Hartnup disorder.

**Xenopus laevis* oocytes were harvested by surgery of anaesthesized frogs (MS-222, 1.5g/l). The procedure was approved by the Animal Experimentation Ethics Committee of the Australian National University.