Collectrin forms a functional transport unit with SLC6 amino acid 2 transporters

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Collectrin is a type I single-pass membrane protein which acts as a molecular chaperone of two apical membrane transporters in the kidney epithelium. Its regulation has been implicated in renal aminoacidurias, hypertension, insulin exocytosis and beta-cell proliferation in the pancreas. Whilst collectrin's role as trafficking facilitator of amino acid transporters is well-established, the site, mode and full extent of these interactions remain undefined. Here we show that collectrin is essential for the catalytic activity and functional complex formation of the major kidney apical membrane neutral amino acid transporters B0AT1 and B0AT3. We also show that collectrin expression and stability is as reliant on transporter expression as functioning transporters are on collectrin. Structural considerations and mutational analysis have allowed us to identify a region and specific residues of B0AT1 and B0AT3 where heteromer formation with collectrin occurs. Collectrin residue tryptophan 143 located in the transmembrane helix, was identified as essential for catalytic interaction between collectrin and B0AT3. Further evidence from functional assays indicates that collectrin may interact with B0AT1 at a common site of heteromer formation in the SLC6 transporter family. Combined, these results demonstrate that collectrin and the amino acid transporters form an essential functional unit, with collectrin being necessary not only for trafficking but also for catalytic function of B0AT1 and B0AT3.