The role of Na^+-dependent neutral and acidic amino acid transporter family in Na^+-reabsorption in kidney

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Summary

Na^+-coupled organic solute transport plays important roles in the reabsorption of Na^+ from the proximal tubules of kidney. For the understanding of the mechanisms of the coupling of Na^+ transport to the organic solute transport and of the actual contribution of the Na^+-coupled organic solute transport to Na^+ reabsorption, it is necessary to isolate cDNA clones coding for the transporters which would be quite useful tools to investigate their transport properties and the exact location of expression. The molecular nature of Na^+-dependent amino acid transport systems has been elusive for many years; however, recent cloning studies have established a family of Na^+-dependent neutral and acidic amino acid transporters. In this family, glutamate transporter EAAC1 and neutral amino acid transporter ASCT2 are expressed in kidney.

We isolated ASCT2 cDNA from human kidney. The comparison of human ASCT2 (hASCT2) with a neutral amino acid transporter human ASCT1 (hASCT1) which we obtained from teratocarcinoma cells revealed important properties of Na^+ binding sites. The Hill coefficient of Na^+-dependence of threonine uptake was 1.8 for ASCT1, whereas that for ASCT2 was 1.1, indicating that ASCT2 couples to a single Na^+ transport, which is distinct from the other members of the family that couple to two Na^+. The Na^+ binding site of ASCT2 is capable of accepting Li^+ instead of Na^+, although the affinity for amino acid substrates becomes ~10 times lower in Li^+. In contrast, ASCT1 dose not operate in Li^+. Surprisingly, ASCT2-mediated threonine uptake exhibited a sigmoidal dependence on Li^+. This suggests that the "residual" Na^+-binding site of ASCT2 which corresponds to the 2nd Na^+ binding site in the other members of the family and dose not accept Na^+ anymore in ASCT2 probably because of replacement of amino acid residues has acquired the structure to accept Li^+.

Based on the comparison of ASCT2 with the other members of Na^+-dependent neutral and acidic amino acid transporter family, it would be feasible to design site-directed mutagenesis studies to determine the Na^+ binding sites and to understand the mechanisms of Na^+ drive in the Na^+ cotransport which is one of the important physiological roles of Na^+ in animal body.