Structure of the human carnitine transporter

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Carnitine is a zwitterionic molecule whose main physiological function is to facilitate the transport of long-chain fatty acids across the mitochondrial inner membrane for ß-oxidation and subsequent ATP formation. The carnitine transporter OCTN2 (Organic Cation Transporter Novel 2, SLC22A5) transports both carnitine and organic cations across the plasma membrane in most tissues, and is highly expressed in the kidney, heart, skeletal muscle and brain. As such, OCTN2 plays a significant role in human physiology, with mutations that disrupt function resulting in systemic primary carnitine deficiency, a severe disorder that affects the ability to transport and metabolise fatty acids. The mechanisms by which OCTN2 achieves both high affinity, sodium-coupled carnitine transport, as well as transport of organic cations are unclear. Here we present the first cryo-EM structures of OCTN2 in a carnitine- and sodium-bound outward-occluded state, and an inward-facing unliganded state. Like other related organic cation/anion transporters, OCTN2 adopts the canonical Major Facilitator Superfamily fold, and is decorated by a prominent extracellular domain. Despite its overall similarity to other SLC22A family members, OCTN2 exhibits significant structural differences in the binding cleft and interactions that gate the transporter, with the occluded state structure offering a rare glimpse into the coupling between substrate binding and gating. We identify the molecular determinants of high-affinity carnitine transport and describe an unusual Na^+ ion binding site that is allosteric to the substrate-binding site. These structural data allow us to rationalise the mutations in OCTN2 that lead to systemic primary carnitine deficiency and further aid in understanding how OCTN2 may transport cationic drug molecules throughout the body.