Structure and electromechanical coupling of a voltage-gated Na+/H+ exchanger

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Voltage-sensing domains control the activation of voltage-gated ion channels, with a few exceptions1. One such exception is the sperm-specific Na+/H+ exchanger SLC9C1, which is the only known transporter to be regulated by voltage-sensing domains2,3,4,5. After hyperpolarization of sperm flagella, SLC9C1 becomes active, causing pH alkalinization and CatSper Ca2+ channel activation, which drives chemotaxis2,6. SLC9C1 activation is further regulated by cAMP2,7, which is produced by soluble adenyl cyclase (sAC). SLC9C1 is therefore an essential component of the pH–sAC–cAMP signalling pathway in metazoa8,9, required for sperm motility and fertilization4. Despite its importance, the molecular basis of SLC9C1 voltage activation is unclear. Here we report cryo-electron microscopy (cryo-EM) structures of sea urchin SLC9C1 in detergent and nanodiscs. We show that the voltage-sensing domains are positioned in an unusual configuration, sandwiching each side of the SLC9C1 homodimer. The S4 segment is very long, 90 Å in length, and connects the voltage-sensing domains to the cytoplasmic cyclic-nucleotide-binding domains. The S4 segment is in the up configuration—the inactive state of SLC9C1. Consistently, although a negatively charged cavity is accessible for Na+ to bind to the ion-transporting domains of SLC9C1, an intracellular helix connected to S4 restricts their movement. On the basis of the differences in the cryo-EM structure of SLC9C1 in the presence of cAMP, we propose that, upon hyperpolarization, the S4 segment moves down, removing this constriction and enabling Na+/H+ exchange.