Simulations of ion selectivity in the acid-sensing ion channel ASIC1a

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Acid sensing ion channels (ASICs) are Na^+-selective, voltage independent ion channels activated by a change in extracellular pH. They are widely distributed both in the central and peripheral nervous system where they primarily participate in neuronal sensitivity to acidosis. Recently solved crystal structures for the ASIC1a channel provides us with an excellent opportunity to investigate functional mechanisms using molecular dynamics simulations. Selectivity of ASICs has been proposed to be governed by a constriction site in the middle of the pore made up of 3 Gly, Ala and Ser (GAS) residues. We instead show that the channel makes use of rings of Glu and Asp residues in the lower pore to discriminate against K^+ ions, supported by new mutagenesis and unnatural amino acid substitution experiments. Our results further suggest that the experimentally observed selectivity is better explained by a channel with narrower intracellular pore opening, such that multiple Glu and Asp side chains can form complexes with ions; not possible with the currently accepted, yet incomplete, ASIC1a open state structure. These studies provide insight into ASIC structure and function and may assist the design of therapeutics for neurological disorders including chronic pain, cerebral ischemia and seizures.