Mechanism of NH4(+) Recruitment and NH3 Transport in Rh Proteins

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In human cells, membrane proteins of the rhesus (Rh) family excrete ammonium and play a role in pH regulation. Based on high-resolution structures, Rh proteins are generally understood to act as NH3 channels. Given that cell membranes are permeable to gases like NH3, the role of such proteins remains a paradox. Using molecular and quantum mechanical calculations, we show that a crystallographically identified site in the RhCG pore actually recruits NH4(+), which is found in higher concentration and binds with higher affinity than NH3, increasing the efficiency of the transport mechanism. A proton is transferred from NH4(+) to a signature histidine (the only moiety thermodynamically likely to accept a proton) followed by the diffusion of NH3 down the pore. The excess proton is circulated back to the extracellular vestibule through a hydrogen bond network, which involves a highly conserved and functionally important aspartic acid, resulting in the net transport of NH3.

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