LETTER

Two Conflicting NHE1 Model Structures: Compatibility with Experimental Data and Implications for the Transport Mechanism[1]

Nygaard *et al.* (1) suggested a model structure of the human NHE1 exchanger, using the crystal structure of the bacterial NhaA antiporter (2) as a template. The topology and helix assignment in their model differ significantly from those of an earlier model proposed by Landau *et al.* (3) based on the same template. Nygaard *et al.* (1) carried out a single electron paramagnetic resonance measurement to support their model. This single data point is equally compatible with both structural models and does not substantiate either of them.

Since Nygaard *et al.* (1) did not analyze their model with respect to the available empirical data nor provide a detailed comparison with the Landau model, we felt compelled to reassess both models using all the empirical data, including mutagenesis, accessibility measurements, and nuclear magnetic resonance (NMR) studies, along with hydrophobicity and evolutionary conservation profiles (unpublished data; available upon request). Although neither model is in absolute agreement with all published experiments, the Landau model better recapitulates the empirical data than the Nygaard model. Most importantly, the Landau model places the charged, essential, and conserved residues in strategic locations, including the presumed ion translocation pathway and the TM4-TM11 assembly region, implicated in the transport mechanism of NhaA (2, 4, 5). The Nygaard model, in contrast, predicts that many of these highly polar residues, *e.g.* Asp^{238}, Glu^{262}, Asn^{266}, and Asp^{267}, reside in peripheral regions, even facing the hydrocarbon core of the membrane, where they are unlikely to participate in the transport mechanism. Overall, incorporating structural and experimental information, we suggest that the Landau model better captures the essence of the functional elements of NHE1 and depicts a more reliable structural scaffold.

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