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Analysis of TMC Proteins, Unknown Function Proteins in Mammals, as Novel Na^+ Sensor

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Summary

Excessive salt intake is a leading course of several cardiovascular diseases, including hypertension. Underlying salt intake is our ability to taste salt. Although molecular mechanisms of sensing sweet, sour, umami and bitter taste are relatively well defined, molecular basis of the salt taste is poorly understood. Recent evidence suggests that the tmc-1 (transmembrane channel-like protein-1) gene in *C. elegance* is a sodium sensor required for behavioral avoidance of high salt concentrations. There are eight ortholog genes in mammals (TMC1 to TMC8). TMC1 and TMC2 have a role in hair-cell mechanotransduction and mutations in these genes are associated with deafness. TMC3 is expressed specifically in neuron and TMC8 is in the thymus. The function and expression of the remaining genes (TMC4-TMC7) are poorly characterized. To address this limitation, we obtained mouse TMC4-7 cDNAs and constructed GFP-tagged fusion proteins. We also produced subtype-specific antibodies against TMC4, 5, 6 and 7 that are designed to recognize extracellular epitopes. These antibodies demonstrated that TMC 5 and 6 are expressed in the heart and brain at different developmental stages of mice. TMC4, 5 and 7 are expressed at the plasma membrane in cultured cells since they were detected in non-permeabilized cells with extracellular accessible antibodies. To determine the function of these molecules, we performed Ca^{2+}imaging analysis and examined the effects high extracellular Na^+ stimulation (300 mM NaCl-containing Tyrode solution). This intervention evoked a rise in intracellular Ca^{2+}, but only when cells were transfected with one of the TMC cDNAs. Thus, we conclude that TMC proteins sense high concentrations of Na^+ and/or a high extracellular osmolality. This result provides a strong support that TMC proteins are Na^+ sensors or mechanosensors. Further studies are required to determine the expression in the tong and whether they are ion transporters using electrophysiological techniques.