DEFECTS IN THE ATP2B2 GENE CAUSING HEREDITARY HEARING AND BALANCE LOSS IN MICE AND HUMANS: A BIOPHYSICAL STUDY OF NORMAL AND MUTATED PMCA2 PUMP FUNCTION

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Abstract Ca^{2+} acts as a fundamental signal transduction element in the inner ear, delivering information about sound acceleration and gravity through a small number of mechano-transduction channels in the hair cell stereocilia as far as to the ribbon synapse, where it drives neurotransmission. The genetic approach is proving fundamental in unravelling the molecular basis of these important biological functions. In particular, ablation or missense mutations of the PMCA2 Ca^{2+}-pump of stereocilia cause deafness and loss of balance. To investigate the physiological significance of these genetic defects, we used a combination of confocal fluorescence microscopy and cytosolic Ca^{2+} photo-liberation. The study of Ca^{2+}-extrusion in hair cells from neonatal mice inner ear permitted us to show that Ca^{2+} extrusion was compromised by various degrees in PMCA2 knockout mice as well as in the mutant *deafwaddler* and *Oblivion* mice. We suggest that the consequent reduced endolymphatic Ca^{2+} concentration can trouble the finely tuned control mechanisms of signal transduction, eventually resulting in hair cell death.

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