

Oral presentation

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## Physiological roles of cGMP-gated channels: lessons from mouse models and human channelopathies

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### Background

Cyclic nucleotide-gated (CNG) channels are members of the superfamily of pore loop cation channels that are activated by the binding of cGMP or cAMP. The channels are important cellular switches which transduce changes in intracellular levels of cyclic nucleotides into changes of the membrane potential and the Ca<sup>2+</sup> concentration. CNG channels play a central role in the signal transduction pathways of vision and olfaction. We have studied the physiological significance of a particular member of the CNG channel family, CNGB1. The two splicing variants of CNGB1, termed CNGB1a and CNGB1b, assemble with CNGA1 and CNGA2/4 to form the native tetrameric CNG channels of rod photoreceptors and olfactory neurons, respectively.

### Results

Using gene knockout in mice we have analyzed the specific physiological roles of the two splicing variants of CNGB1 in vision and olfaction. We find that CNGB1 is not only modulating the biophysical properties of the CNG channel but that it is also crucially required for normal CNG channel targeting to outer segments and olfactory cilia. In the retina, impairment of CNG channel targeting induces a degenerative process that is reminiscent of human retinitis pigmentosa. A few years ago, a mutation in the cGMP-binding domain of CNGB1 (CNGB1aG993V) was detected in a family suffering from

retinitis pigmentosa [1]. Using a combination of electrophysiological measurements, biochemistry and studies in mouse models we have analyzed the pathology of this channelopathy.

### Conclusion

Our findings provide new insights into the functional role of distinct CNGB1 channel domains.

### References

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