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# Signal Transduction by Neurotransmitters in Brain and Heart in Health and Disease

## Position

Professor of Physiology, Sackler Faculty of Medicine

## Research

Electrical activity of excitable cells is their most important feature, which allows the performance of fundamental functions of brain, heart and muscle. We are addressing a key issue in modern cardiology and neurobiology: how neurotransmitters regulate cardiac cells and neurons by acting on ion channels – proteins that underlie the electrical activity in these cells; and how errors in these processes cause disease. Main projects in the lab:

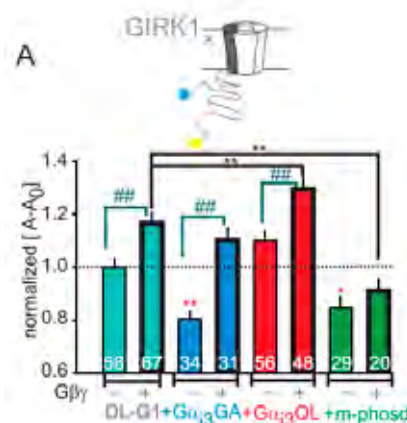
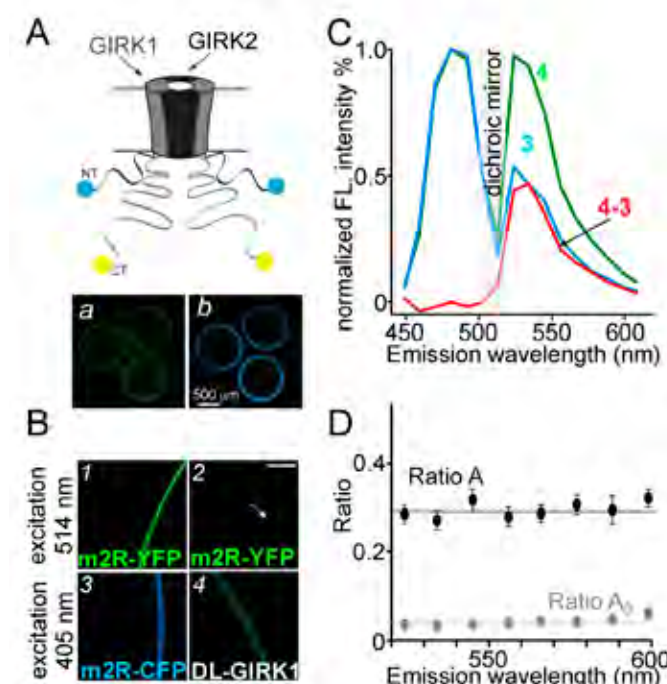
Function and regulation of receptors, G proteins,  $Ca^{2+}$  and  $K^+$  channels in health and disease; Ion channel-related hereditary cardiac and neurological disorders (channelopathies); Mechanisms of coupling of G protein-coupled receptors with effectors; Molecular mechanisms of bipolar disorder.

**Research methods:** Electrophysiology, Neurophysiology, Heterologous Expression, Protein Biochemistry, Fluorescence Resonance Energy Transfer (FRET), Molecular biology, Mathematical and Kinetic Modeling and Simulation, Immunocytochemistry

## Publications

Babai N, Kanevsky N, **Dascal N**, Rozanski GJ, Singh DP, Fatma N & Thoreson WB (2010). Anion sensitive regions of L-type  $Ca_v1.2$  calcium channels expressed in HEK293 cells. *PLoS One*, 5, e8602.

Berlin S, Keren-Raifman T, Castel R, Rubinstein M, Dessauer CW, Ivanina T & **Dascal N** (2010).  $G\alpha_i$  and  $G\beta\gamma$  jointly regulate the conformations of a  $G\beta\gamma$  effector, the neuronal G-protein activated  $K^+$  channel (GIRK). *J Biol Chem*, 285, 6179-6185.



**Studying GIRK channels expressed in a heterologous system (*Xenopus oocytes*).** Intramolecular fluorescence resonance energy transfer (i-FRET) shows interactions of cytosolic N- and C-termini of the channel. **A**, GIRK channel labeled with two fluorescent proteins. **B**, Imaging the expressed fluorescent proteins with a confocal microscope. **C**, **D**, Example of use of FRET analysis to study conformational changes in the channel caused by neurotransmitter, G proteins or drugs. **E**,  $G\alpha_i$  and  $G\beta\gamma$  synergistically alter the conformation of GIRK1 subunit.

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- Laish-Farkash A, Brass D, Marek-Yagel D, Pras E, **Dascal N**, Antzelevitch C, Nof E, Reznik H, Glikson M & Luria D (2010). A novel mutation in the HCN4 gene causes symptomatic sinus bradycardia in Moroccan Jews. *J Cardiovasc Electrophysiol* **21**, 1365-1372.
- Tselnicker I & **Dascal N**. (2010). Further characterization of regulation of  $\text{Ca}_v2.2$  by stargazin. *Channels* **4**, 351-354.
- Oz S, Tsemakhovich V, Christel CJ, Lee A & **Dascal N**. (2011). CaBP1 regulates voltage dependent inactivation and activation of  $\text{Ca}_v1.2$  (L-type) calcium channels. *J Biol Chem* **286**, 13945-13953.
- Edelheit O, Hanukoglu I, **Dascal N** & Hanukoglu A. (2011) Identification of the roles of conserved charged residues in the extracellular domain of an epithelial sodium channel (ENaC) subunit by alanine mutagenesis. *Am J Physiol Renal Physiol* **300**, F887-897.
- Berlin S, Tsemakhovich VA, Castel R, Ivanina T, Dessauer CW, Keren-Raifman T & **Dascal N**. (2011) Two distinct aspects of coupling between  $\text{G}\alpha_i$  and G protein-activated  $\text{K}^+$  channel (GIRK) revealed by fluorescently-labeled  $\text{G}\alpha_{i3}$  subunits. *J Biol Chem* **287**, 19537-19549.
- Almagor L, Chomsky-Hecht O, Ben-Mocha A, Hendin-Barak D, **Dascal N** & Hirsch JA. (2012). The role of a voltage-dependent  $\text{Ca}^{2+}$  channel intracellular linker: a structure-function analysis. *J Neurosci* **32**, 7602-7613.
- Pankonien I, Otto A, **Dascal N**, Morano I & Haase H. (2012). Ahnak1 interaction is affected by phosphorylation of Ser-296 on  $\text{Ca}_v\beta2$ . *Biochem Biophys Res Commun* **421**, 184-189.
- Weiss S, Keren-Raifman T, Oz S, Ben Mocha A, Haase H & **Dascal N**. (2012). Modulation of distinct isoforms of L-type calcium channels by  $\text{G}_q$ -coupled receptors in *Xenopus* oocytes: Antagonistic effects of  $\text{G}\beta\gamma$  and protein kinase C. *Channels* **6**, 426-437.
- Almagor L, Chomsky-Hecht O, Ben Mocha A, Hendin-Barak D, **Dascal N** & Hirsch JA. (2012).  $\text{Ca}_v1.2$  I-II linker structure and Timothy syndrome. *Channels* **6**, 468-472.
- Edvardson S, Oz S, Abulhijaa FA, Taher FB, Shaag A, Zenvirt S, **Dascal N** & Elpeleg O. (2013). Early infantile epileptic encephalopathy associated with a high voltage-gated calcium channelopathy. *J Med Genet* **50**, 118-123
- Treiber F, Rosker C, Keren-Raifman T, Steinecker B, Gorischek A, **Dascal N** & Schreiber W. (2013) Molecular basis of the facilitation of the heterooligomeric GIRK1/GIRK4 complex by cAMP dependent protein kinase. *Biochim Biophys Acta* **1828**, 1214-1221.
- Oz S, Benmocha A, Sasson Y, Sachyani D, Almagor L, Lee A, Hirsch JA & **Dascal N**. (2013). Competitive and non-competitive regulation of calcium-dependent inactivation in  $\text{Ca}_v1.2$  L-type  $\text{Ca}^{2+}$  channels by calmodulin and  $\text{Ca}^{2+}$ -binding protein 1. *J Biol Chem*. **288**, 12680-12691.
- Weisbrod, D., Peretz, A., Ziskind, A., Menaker, N., Oz, S., Barad, L., Eliyahu, S., Itskovitz-Eldor, J., **Dascal, N.**, Khananshvili, D., Binah, O., and Attali, B. (2013) SK4  $\text{Ca}^{2+}$  activated  $\text{K}^+$  channel is a critical player in cardiac pacemaker derived from human embryonic stem cells. *Proc Natl Acad Sci USA* **110**, E1685-1694.
- Weiss S, Oz S, Benmocha A, **Dascal N**. (2013) Regulation of cardiac L-type  $\text{Ca}^{2+}$  channel  $\text{Ca}_v1.2$  via the  $\beta$ -adrenergic-cAMP-protein kinase A pathway: old dogmas, advances, and new uncertainties. *Circ Res* **2013**, 113:617-31.
- Farhy Tselnicker I, Tsemakhovich V, Rishal I, Kahanovitch U, Dessauer CW & **Dascal N**. (2014). Dual regulation of G proteins and the G-protein-activated  $\text{K}^+$  channels by lithium. *Proc Natl Acad Sci USA* **111**, 5018-5023.
- Edelheit O, Ben-Shahar R, **Dascal N**, Hanukoglu A & Hanukoglu I. (2014). Conserved charged residues at the surface and interface of epithelial sodium channel (ENaC) subunits: roles in cell surface expression and  $\text{Na}^+$  self-inhibition response. *FEBS J*. **281**:2097-111.

## Grants

- 2013-2016 Mechanisms of isoform-specific regulation of L-type  $\text{Ca}^{2+}$  channels by protein kinases. German-Israel Foundation (GIF), With S. Weiss and E. Klusmann.