

Overall research theme:

Cardiac potassium channels: molecular function, pharmacology and role in disease

Latest update:

August 11th 2002

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Characteristics of the research group:

The research group focuses on the molecular function of cardiac ion channels and the pathological consequences of channel dysfunction primarily in cardiac arrhythmia. The main topic of research is the two delayed rectifier channels being responsible for the repolarization of the cardiac action potential. The molecular constituents of these currents are called the hERG and KCNQ1 (=KvLQT1) channels. We work on the cloned channels expressed in mammalian cell lines or in *Xenopus* oocytes and address their function by site directed mutagenesis, use of pharmacological tools and selective toxins, functional electrophysiological studies and immunolocalisation in the heart and vasculature. There are currently 12 people in the group and the laboratory is composed of a molecular biological lab, an electrophysiological lab and an imaging lab equipped with state of the art techniques.

Running projects: Titles and abstracts:

Localisation of KCNE potassium channel subunits in the heart

We have localised the hERG1 channel and the KCNQ1 channel to the transverse tubular system in the heart using immunohistochemistry and confocal imaging (Rasmussen et al 2002). These pore forming alpha subunits may interact with accessory proteins, so-called beta subunits, which modulate their function. This is well described in heterologous expression systems, but it is much less clear whether these subunits have a chance to get together in situ. We are thus in the process of elucidating the distribution of different KCNE beta subunits and their interaction with the alpha subunits using immunohistochemistry and immunoprecipitation.

Regulation of hERG current by beta1 receptors

The shortening of the cardiac action potential during tachycardia and increased sympathetic tone must involve an increased repolarising K current and we are characterising the interaction between the beta1 receptor and the hERG current in the heart

Volume regulation of KCNQ1 current

We have found that the KCNQ1 current is strongly volume sensitive and the current is increased during cell swelling. The significance of this mechanism during relative cardiac ischemia is being characterised.

Recent publications related to the projects described above:

Grunnet, M., Jensen, B.S., Olesen, S.-P. & Klærke, D. Apamin interacts with all subtypes of cloned small-conductance Ca²⁺-activated K⁺ channels. *Pflügers Arch.* 441, 544-550, 2001.

Søgaard, R., Ljungstrøm, T., Pedersen, K.A., Olesen, S.-P. & Jensen, B.S. KCNQ4 channels expressed in mammalian cells: Functional characteristics and pharmacology. *Am.J.Physiol., Cell Physiol.* 280 (4), C859-C866, 2001.

Korolkova Y.V., Kozlov S.A., Lipkin A.V., Pluzhnikov K.A., Hadley J.K., Filippov A.K., Brown D.A., Angelo K., Strøbak D., Jespersen T., Olesen S.-P., Jensen B.S., Grishin, E.V. An ERG channel inhibitor from the scorpion *Buthus eupeus*. *J. Biol. Chem.* 276 (13), 9868-76, 2001.

Schrøder, R.L., Strøbak, D., Christophersen, P., Jensen, B.S. & Olesen, S.-P. KCNQ4 channel activation by BMS204352 and retigabine. *Neuropharmacology* 40, 888-898, 2001.

Jensen, B.S., Strøbak, D., Olesen, S.-P. & Christophersen, P. The Ca²⁺-activated K⁺ channel of intermediate-conductance: A molecular target for novel treatments? *Current Drug Targets* 2, 401-422, 2001

Korsgaard, M. G., Christophersen, P., Ahring, P.K. & Olesen, S.-P. Identification of a novel voltage-gated Na⁺ channel rNa_v1.5a in the rat hippocampal progenitor stem cell line HiB5. *Pflügers Arch.* 443, 18-30, 2001

Jesperen, T., Grunnet, M., Angelo, K., Klaerke, D.A. & Olesen, S.-P. Dual-function vector for protein expression in both mammalian cells and *Xenopus laevis* Oocytes. *Biotechniques* 32 (3), 1-5, 2002

Dupuis, D.S., Schrøder, R.L., Jespersen, T., Christensen, J.K., Christophersen, P., Jensen, B.S. & Olesen, S.-P. BMS-204352 activates KCNQ5 channels expressed in HEK293 cells. *Pflügers Arch* 437, 129-137, 2002

Grunnet, M., MacAulay, N., Jensen, B.S., Olesen, S.P., Klaerke, D.A. 2000. Regulation of cloned, Ca²⁺-activated K⁺ channels by volume changes. *Pflügers Arch* 444, 167-77, 2002

Grunnet, M., Jespersen, T., Rasmussen, H.B., Ljungstrøm, T., Jørgensen, N.K., Olesen, S.-P. & Klaerke, D. KCNE4 is an inhibitory subunit to the KCNQ1 channel. *J. Physiol.* 542 (1), 119-130, 2002.

Angelo K, Jespersen T, Grunnet M, Nielsen M, Klaerke DA & Olesen S-P. KCNE5 controls the activity of KCNQ1. *Biophys J* (in press)

Korolkova YV, Bocharov EV, Angelo K, Maslennikov IV, Grinenko OV, Lipkin AV, Nosireva ED, Pluzhnikov KA, Olesen S-P, Arseniev AS, & Grishin EV. Unique binding site on the molecular scaffold of scorpion toxin BeKm-1 provides selectivity for HERG potassium channels. *J Biol Chem* (in press)

Schrøder RL, Strøbak D, Olesen S.-P. & Christophersen P. Voltage-independent KCNQ4 currents induced by BMS-204352, *Pflügers Arch* (in press)

Grunnet M, MacAulay N, Jespersen T, Jørgensen NK, Pongs O, Olesen S-P & Klaerke DA. KCNQ1 channels as volume sensors. (submitted)

Jørgensen NK, Pedersen SF, Rasmussen HB, Grunnet M, Klaerke DA & Olesen S-P. Cell swelling activates cloned Ca²⁺-activated K⁺ channels: A role for the F-actin cytoskeleton. (submitted)

Grunnet M, Rasmussen HB, Hay-Schmidt A, Rosenstjerne M, Klaerke DA, Olesen S-P & Jespersen T. KCNE4 is an inhibitory subunit to Kv1.1 and Kv1.3 potassium channels (submitted)

Rasmussen HB, Møller M, Knaus HG, Jensen BS, Olesen S-P, & Jørgensen NK. Subcellular localization of the delayed rectifier potassium channels KCNQ1 and ERG1 in rat heart (submitted)

