The Doctoral Program
ION CHANNELS AND TRANSPORTERS AS MOLECULAR DRUG TARGETS („MolTag“)
is pleased to invite you to the following lecture

“Subunit-dependent variations in stoichiometry and function in G protein-GIRK signaling complexes”

by Prof.Dr. Nathan DASCAL

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on: on: Thursday, March 30th 2017, 05:00 pm (17:00 Uhr)
at: UZA II, Althanstraße 14, Lecture Hall 6 (Pharma and Food Lecture Series)

Abstract: G protein-gated K+ channels (GIRK; Kir3) are activated by Gβγ subunits derived from Gi/o proteins following activation by neurotransmitters or hormones. GIRKs regulate heartbeat and neuronal excitability and plasticity, and are involved in drug addiction and cardiac, neurologic and psychiatric disorders. In different tissues and brain structures, the full GIRK channels are composed of different combinations of the four homologous subunits (GIRK1-4), encoded by 4 separate genes. We have found profound differences between GIRK channels formed by different subunit combinations abundant in different tissues or brain structures. To unveil the underlying mechanisms, we conducted mutagenesis-based structure-function analyses, measured plasma membrane densities, whole-cell and single channel properties of these channels, and have developed quantitative models of GIRK function. We present experimental data and mathematical modeling results suggesting different extents of association of GIRK with Gβγ and Gα subunits, which in some cases lead to unequal, non-canonical stoichiometries of Gα and Gβγ, resulting in channels acting either sensitive bidirectional servo-type detectors of changes in GPCR/G protein signaling states (the hippocampal GIRK1/2), or channels acting as simple binary on-off Gβγ detectors (the mesolimbic GIRK2). Our results suggest that variation in GIRK subunit combination has profound physiological consequences and may allow for developing of differential, specific pharmaceutical or genetic interventions.

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