SFB 35 Colloquia in Membrane Transport

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"Ion channels as drug targets"

The present talk will be divided into 3 parts: 1) A brief introduction to the biotech company NeuroSearch specialized in performing research and development of compounds targeting membrane proteins. This introduction will include drugs that targets transporters. 2) A general introduction to ion channels and 3) A detailed description of a research project aiming at developing new principles for the treatment of cardiac arrhythmias. A more elaborated introduction to point 3) is as follows: The cardiac action potential is the result of an orchestrated function of a number of different ion channels. Action potential repolarisation in humans relies on three current components named IKr, IKs and IK1 with party overlapping functions. The ion channel α-subunits conducting these currents are hERG1 (Kv11.1), KCNQ1 (Kv7.1) and Kir2.1 (KCNJ2). Loss of function in any of these currents can result in long QT syndrome. Long QT is a pro-arrhythmic disease with increased risk of developing lethal ventricular arrhythmias such as Torsade de Pointes and ventricular fibrillation. In addition to congenital long QT, acquired long QT can also constitute a safety risk. Especially unintended inhibition of the hERG1 channel constitutes a major concern in the development of new drugs. Based on this knowledge is has been speculated whether activation of the hERG1 channel could be anti-arrhythmic and thereby constitute a new a principle in treatment of cardiac arrhythmogenic disorders. The first hERG1 channel agonist was reported 4 years ago and a limit number of this new compound class is now available. The present talk will illustrate how a research program aiming at developing a new principle for anti-arrhythmic treatment can be accomplished. Results will include data from in vitro to in vivo. The biophysical mode of action for hERG1 channel activators will be revealed by different electrophysiological experiments after heterologous expression in both Xenopus laevis oocytes and mammalian cells. Patch clamp experiments will further be included in characterization of hERG1 channel activators using native cardiomyocytes. Finally, the physiological and anti-arrhythmic properties of hERG1 channel activators will be demonstrated in isolated hearts and in different in vivo models.