COLLOQUIA IN PHYSIOLOGY AND VASCULAR BIOLOGY

Venue: Medical University Vienna, Center for Physiology and Pharmacology, Institute of Pharmacology, Waehringerstrasse 13a, 1090 Vienna, "**Leseraum**"

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Friday 27.03.2015 10.00 s.t. **Nicole Schmitt** (host: Jae-Won Yang)

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"Kv7.1 surface expression; a regulatory mechanism for insulin secretion"

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The potassium channel $K_V7.1$ is probably best known for its role in the heart, where it contributes to the repolarizing current of the cardiac action potential. Yet, in recent years both genetic and physiological evidence has emerged indicating an additional and important role in the pancreas. Specifically, $K_V7.1$ was reported to contribute to the membrane potential in β-cells, and channel block led to increased insulin secretion.

The aim of our study was to identify signaling pathways that may link $K_V7.1$ expression to the reported changes in insulin secretion. Acetylcholine is released by intra-pancreatic vagal nerve endings during nutrient intake and activates muscarinic acetylcholine receptor M3 (M3R) on pancreatic β-cells, which results in a potentiation of insulin secretion. Employing confocal and live-cell imaging, and electrophysiology, we here demonstrate that membrane expression of $K_V7.1$ in the pancreatic cell lines such as INS-1 or MIN6 can be regulated by activation of the M3R. We show that activation of M3R results in activation of protein kinase C (PKC) which initiates endocytosis of $K_V7.1$ channels. We further provide evidence that this endocytosis is mediated by the ubiquitin ligase Nedd4-2.

In conclusion, removal of the channels by activation of the identified M3R-PKC-Nedd4-2 pathway might play an important physiological role in fine-tuning the amount of secreted insulin during a meal.