A new drug target in human heart – the calcium-sensing receptor

Dr. Ziegelhöffer, Barbara , Dr. Pfannmüller, Bettina , Prof. Dr. Kostelka, Martin , Prof. Dr. Mohr, Friedrich W. , Prof. Dr. Dhein, Stefan. University Leipzig, Heart Centre Leipzig Clinic for Cardiac Surgery, Strümpellstr. 39, 04289 Leipzig, Germany.

As previously shown, extracellular calcium (Ca^{2+}_e) plays a regulatory role in some of the processes related to development of sustained arrhythmias. This regulation by Ca^{2+}_e-level is independent of the Ca^{2+}-channels as it is not abolished by Verapamil.
In various tissues Ca^{2+}_e exerts direct action on cells via its own Ca^{2+}_e-sensing receptors (CaSR). Thus Ca^{2+}_e participates in the regulation of cell differentiation, cell migration, hormone secretion etc. We investigated the possibility of expression of CaSR in the human heart.

Methods: The presence of CaSR mRNA in left and right atrial tissue was investigated via reverse-transcription (RT)-PCR as well as with single cell RT-PCR. The CaSR protein was detected in Western blot as a specific band with the apparent size of 150 kD as well as by immunohistochemistry. The function of CaSR was investigated by stimulation of atrial tissue with the specific activator calcium (4 $mmol.l^{-1}$) in the absence and presence of Ca^{2+}-channel blocker Verapamil (100 $nmol.l^{-1}$) and CaSR-antagonist Calhex231 (1 $\mu mol.l^{-1}$). Subsequently, downstream signaling pathway of CaSR has been examined.

Results: CaSR mRNA is expressed in atrial tissue and particularly in the cardiomyocytes. The immunohistochemistry revealed a strong positive staining for CaSR in cardiomyocytes, weak staining in non-myocytes and endothelial cells and no staining in fat cells. Western blot confirmed activation of down-stream signaling pathway as shown by increased phosphorylation of ERK 1/2. On the transcriptional level CaSR influences the DNA binding activity of some transcription factors (thyroid hormone receptors 3.17 ± 1.08 fold of change, HNF-4/COUP-TF receptors 3.89 ± 1.14 fold of change and retinoic acid receptors 2.49 ± 0.88 fold of change).

Conclusion: We demonstrate for the first time the presence and function of CaSR in the human atria. These findings could after some further investigation offer a new target for modulation of cardiac function.