

## Editorial: Calcium as a First Messenger

Calcium is well known as a trigger for many cellular effects such as contractility and signal transduction. Thus, calcium can be considered as a second messenger. Its intracellular concentration can be changed by modifying the open probability of calcium channels or formation of inositol-3-phosphate (IP<sub>3</sub>). However, not only intracellular calcium but also extracellular calcium concentration is strictly regulated and as a consequence its concentration in the plasma and in the extracellular compartment of tissues quite stable. Extracellular calcium concentration is regulated by the cells of the parathyroidea. *Via* a so-called calcium-sensing receptor these cells measure extracellular calcium concentrations and *via* their release of parathyroid hormone (PTH) calcium concentration can be regulated. However, most recently it is getting obvious that a drop of ionized plasma calcium is commonly observed in patients with heart failure. This led to the question how plasma ionized calcium is linked to cardiac physiology and pathophysiology.

In this Mini Spot-Light of The Open Heart Failure Journal authors focus on various aspects of calcium regulation and heart failure. Smajilovic *et al.* from the group of Tfelt-Hansen will discuss a new and growing topic in cardiac physiology, namely the role of calcium-sensing receptors in cardiac cells [1]. Noteworthy, the calcium-sensing receptor is not unique for cells of the parathyroidea. Many cells of the cardiovascular system express this receptor and interestingly enough the receptor initiates signal cascades known to influence growth and differentiation of cardiac cells. These findings make clear that calcium can also act as a first messenger because it represents a natural agonist of calcium-sensing receptors. As a consequence of this regulation of plasma ionized calcium concentration is getting more important. Schreckenber *et al.* will discuss how hormones such as PTH and the locally formed and endothelial dependent sister peptide, PTHrP, are involved in the progression of heart failure and how this is linked to the control of plasma ionized calcium in patients with heart failure [2]. Of note, the regulation of the release of these peptides and expression of the corresponding receptors is part of more general regulation loops that are well known to be deregulated in the context of heart failure, namely the renin-angiotensin-aldosterone system and the sympathetic nervous systems. However, cardiac physiology is a complex topic and as so it may not be surprising that the situation concerning calcium sensing and calcium regulation in cardiac physiology is further complicated by the fact that calcium-sensing receptors have a relative low affinity to calcium but a high affinity to other polycationic molecules. The polyamine metabolism forms not only polyamines like putrescine, spermine, and spermidine with different positive charges. Noteworthy, the molecules are released by cardiac cells and compete with calcium to the activation of calcium-sensing receptors and also modify important intracellular events such as hypertrophic growth. Giordano *et al.*, will focus in his review on the activation and relevance of polyamine metabolism in cardiac physiology [3].

Not all aspects of calcium sensing and plasma ionized calcium regulation in cardiac and vascular physiology could be addressed in this issue. Calcium-sensing receptors seem to play a role in the secretion of PTHrP [4]. Due to the role of this peptide in the regulation of growth and apoptosis of endothelial cells it will be of interest to study this relationship in the future. Vascular biology will definitively be getting a topic in the next future when considering the relevance of calcium-sensing in the cardiovascular context. Weston *et al.* from the group of Gillian Edwards have highlighted the role of calcium-sensing receptors in hyperpolarization of smooth muscle cells [5]. Another important issue is the question whether calcimimetics can be used as a new therapeutic target in heart failure and whether cardiac site effects can be expected from such drugs if they are used in the treatment of osteoporosis [6]. Although these topics are not discussed in this issue the articles published here will give the reader a new and important look on key questions of calcium acting as a first messenger in the context of heart failure.

## REFERENCES

- [1] Smajilovic S, Chattopadhyay N, Tfelt-Hansen J. Calcium sensing receptor in cardiac physiology. *Open Heart Fail J* 2010; 3: 11-15.
- [2] Schreckenber R, Wenzel S, Schlüter K-D. Role of extracellular calcium control, calcium sensing, and regulation of calcium regulating hormones in heart failure. *Open Heart Fail J* 2010; 3: 16-24.
- [3] Giordano E, Flamigni F, Guarnieri C, *et al.* Polyamines in cardiac physiology and disease. *Open Heart Fail J* 2010; 3: 25-30.
- [4] Chattopadhyay N. Effects of calcium-sensing receptor on the secretion of PTHrP and its impact on humoral hypercalcemia of malignancy. *Am J Physiol Endocrinol Metab* 2006; 290: E761-70.
- [5] Weston AH, Absi M, Ward DT, *et al.* Evidence in favor of a calcium-sensing receptor in arterial endothelial cells. *Circ Res* 2005; 97: 391-8.
- [6] Hebert SC. Therapeutic use of calcimetics. *Annu Rev Med* 2006; 57: 349-64.

**Klaus-Dieter Schlüter**

Physiologisches Institut  
Justus-Liebig Universität Giessen  
Aulweg 129  
D-35392 Giessen  
Germany

Tel: +49 641 99-47212

Fax: +49 641 99-47219

E-mail: Klaus-Dieter.Schluerer@physiologie.med.uni-giessen.de

© Klaus-Dieter Schlüter; Licensee *Bentham Open*.

This is an open access article licensed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted, non-commercial use, distribution and reproduction in any medium, provided the work is properly cited.