

Overall research theme:

Ion transport and associated signalling in vascular and epithelial function

Latest update:

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Characteristics of the research group:

The research group combines competences in physiological and molecular biological techniques. These techniques include ion imaging, electrophysiology (membrane potentials, patch clamp), myography, perfused tubules, cloning and generation of knock-out mice. The overall focus is to understand the role of ion transport and associated intracellular signalling events in the control of vascular, renal and intestinal function. In particular we have expertise in 1) calcium signalling in vascular smooth muscle, vascular nerves and epithelia, 2) the role of transmembrane transport of acid equivalents in the control of intracellular and intestinal pH, 3) the function of purinergic receptors.

Running projects: Titles and abstracts:

The mechanism of vasomotion

Vasomotion is the slow (<1 Hz) oscillation in vascular tone seen in all vascular beds, most pronounced in the smallest arteries. We investigate how this coordinated smooth muscle activity is accomplished in smooth muscle cells which have no action potential like activity. We use isolated mesenteric resistance arteries from rat. We have recently suggested a model for the synchronization of smooth muscle cell activity and are now investigating how the individual elements of this synchronizing mechanism (which include release and uptake of Ca²⁺ from the sarcoplasmic reticulum, a cGMP dependent, Ca²⁺ activated chloride channel and gap junctions) are modified by drugs and via the interaction with the sympathetic nervous system.

Vasomotor nerves

Confocal fluorescence microscopy allows the measurement of calcium dynamics, not only in the smooth muscle cells, but also in nerve fibres of the vascular wall. We are studying the relation between intraneural calcium, transmitter release, and smooth muscle response during neural activation. This is to further our understanding of the excitation-release coupling in the peripheral sympathetic nervous system of the vasculature.

Bicarbonate transport

Transport of acid and base equivalents across the cell membrane is of central importance for the excretion from the body of the daily net ingestion of acids or bases. Furthermore, the control of pH in the cells of the heart and the vascular wall is crucial for the normal integrated function of these tissues. Recently we cloned a novel sodium coupled bicarbonate transporter (NBCn1) from rat arteries. This transporter is expressed in many tissues including the kidney, the heart and blood vessels. We are currently investigating 1) the role of this transporter in regulation of acid base balance in the body by studying expression at RNA, protein and functional level in different conditions with perturbed acid base balance; this question is further addressed through the production of knock-out mice for this transporter and related transporters, 2) the mechanisms which are responsible for regulation of expression and 3) the mechanisms which are involved in acute hormonal regulation of this transporter.

The function of purinergic (P2) receptors

All cellular functions are controlled via systemic or local hormonal agonists. One novel class of local agonists are extracellular nucleotides like ATP or UTP. These nucleotides are found in the interstitial space and bind to the large family of P2 receptors ("ATP receptors"). Almost all organs and cellular systems display extensive expression of P2 receptors and a myriad of different cellular event are controlled or modified by extracellular

nucleotides. In epithelial organs like the kidney, the lung or the intestine and in the cardiovascular system extracellular nucleotides regulate ion transport and are thought to be involved in functions like organ development, repair and differentiation. The goal of this project area is to extend our understanding of P2 receptors function in epithelial biology. This comprises also the use different disease model (acute renal failure, chronic inflammatory bowel disease, knock-out animals).

Recent publications related to the projects described above:

- Aalkjær C, Hughes A: Chloride and bicarbonate transport in rat resistance arteries. *Journal of Physiology* 1991,436:57-73.
- Peng HL, Jensen PE, Nilsson H, Aalkjær C: Effect of acidosis on tension and $[Ca^{2+}]_i$ in rat cerebral arteries - is there a role for the membrane potential. *American Journal of Physiology*. 1998,274:H655-H662.
- Aalkjær C, Mortensen FV, Jensen PE, Nielsen H: The role of $[Ca^{2+}]_i$, membrane potential and pH_i for the relaxation of rat mesenteric arteries to hyperosmolar acetate. *Pflügers Archives, European Journal of Physiology* 1998,436:705-711.
- Buus CL, Aalkjær C, Nilsson H, Juul B Møller JV, Mulvany MJ: Mechanisms of Ca^{2+} sensitization of force production by noradrenaline in rat mesenteric small arteries. *Journal of Physiology* 1998,510:577-590.
- Choi I, Aalkjær C, Boulpaep EL, Boron WF: An electroneutral sodium/bicarbonate cotransporter NBCn1 and associated sodium channel. *Nature* 2000,405:571-575.
- Vorum H, Kwon T-H, Fulton C, Simonsen B, Choi I, Boron WF, Maunsbach AB, Nielsen S, Aalkjær C: Immunolocalization of electroneutral Na/HCO_3 -cotransporter cotransporter in rat kidney. *American Journal of Physiology*. 2000 279:F901_F909.
- Maunsbach A, Vorum H, Kwon T-K, Nielsen S, Simonsen B, Choi I, Schmitt BM, Boron WF, Aalkjær C: Immunoelectron microscopical localization of the electrogenic Na/HCO_3 -cotransporter in rat and ambystoma kidney. *Journal of the American Society of Nephrology*. 2000,11:2179-2189.
- Pratorius J, Hager H, Aalkjær C, Nielsen S, Friis UG, Ainsworth MA, Johansen T: Molecular and functional evidence for electrogenic and electroneutral $Na^+HCO_3^-$ cotransporters in the murine duodenum. *American Journal of Physiology*. 2001,280:G332_G343.
- Peng Hl, Matchkov V, Ivarsen A, Aalkjær C, Nilsson H. Hypothesis for the initiation of vasomotion. *Circulation Research*. 2001,88:810-815.
- Sandmann S, Yu M, Kaschina E, Blume A, Bouzinova E, Aalkjær C, Unger T. Differential effects of angiotensin AT_1 and AT_2 receptors on the expression, translation and function of the Na^+H^+ exchanger and $Na^+HCO_3^-$ symporter in the rat heart after myocardial infarction. *Journal of American College of Cardiology*. 2001,37:2154-2165.
- T._H. Kwon, T-H, Fulton C, Wang W, Kurtz I, Frøkiær J, Aalkjær C, Nielsen S. Chronic metabolic acidosis upregulates rat kidney Na/HCO_3 cotransporters NBCn1 and NBC3 but not NBC1. *American Journal of Physiology* 2002,282:F34 -