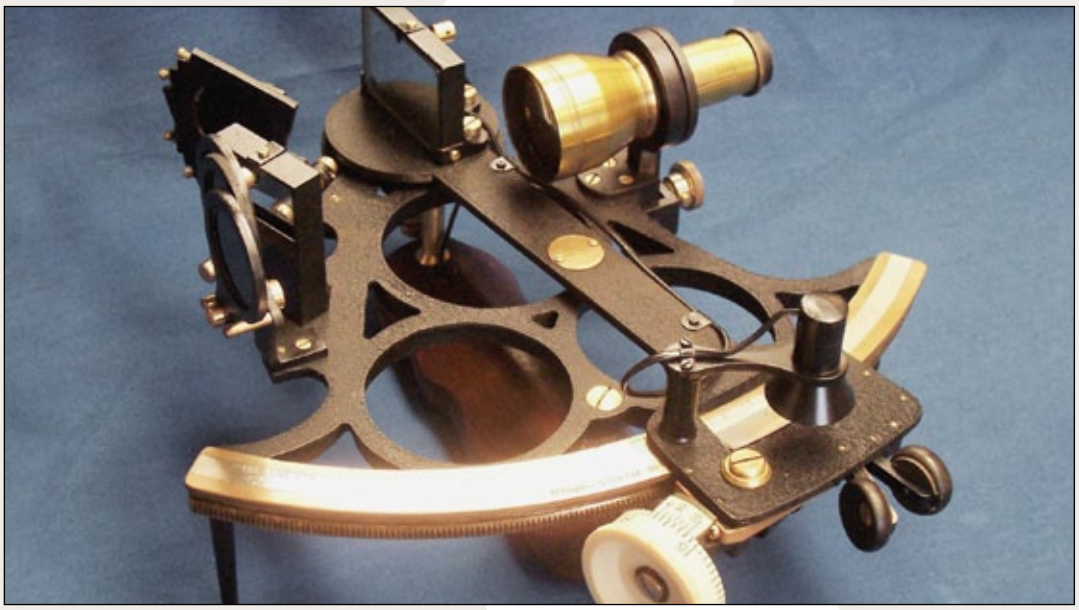
SWISS NATIONAL CENTRE OF COMPETENCE IN RESEARCH

KIDNEY
CONTROL OF HOMEOSTASIS

NEWSLETTER ::: NO. 2 ::: APRIL 2011

DO WE SENSE PHOSPHATE?



Phosphate plays important functions in many biological processes. Therefore, the regulation of phosphate homeostasis is of high importance for our well-being.

Phosphate (HPO_4^{2-}/ $H_2PO_4^-$) is a key element in many biological processes. It is essential for the polymeric structure of the genome, is an important constituent of phospholipids forming biological membranes, a major component of bones, is involved in a plethora of cellular signaling cascades and finally, phosphate is essential for the production of ATP and thus powers life. It therefore appears needless to state that proper control of extracellular concentration of phosphate is necessary for normal structural and functional life. The extracellular concentration of phosphate is balanced by renal excretion of extracellular phosphate that is determined by small intestinal intake of dietary phosphate and phosphate metabolism of skeletal muscles and bones (see figure 1: Phosphate Homeostasis).

CENTRAL ROLE OF THE KIDNEY

The kidneys represent the major control site for whole body homeostasis of phosphate. After filtration in the glomeruli, approximately 80% of phosphate is reabsorbed from primary urine along the proximal tubules. This process involves several sodium-dependent phosphate Na/P_i-cotransporters that are localized at the luminal membrane. Control of proximal tubular reabsorption of phosphate occurs by regulation of the amount of Na/P_i-cotransporters residing in the luminal membrane. This is achieved by intracellular mechanisms activated by several hormones such as parathyroid hormone (PTH) and fibroblast growth factor (FGF-23) and various metabolic factors. These inputs involved in the regulation of reabsorption of phosphate in the proximal tubule are integrated in regulatory networks that include the parathyroid glands, bones, small intestine and the kidney itself.

Circumstantial evidence has accumulated suggesting that phosphate per se could regulate phosphate homeostasis. In fact, extracellular phosphate directly or indirectly can modulate the levels of PTH and FGF-23 via regulation of synthesis and/or secretion of PTH (in parathyroid glands) and FGF-23 (in osteocytes). Although these observations suggest that phosphate sensing mechanisms are located both in parathyroid glands and bone cells, the onset of these mechanisms

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FNSNF
Swiss National Science Foundation

EDITORIAL

Jan Loffing

The concept of homeostasis was defined in 1929 by W. B. Cannon as "the coordinated physiological reactions which maintain most of the steady states in the body." Since then, we've learned a lot about hormones, receptors, signal transduction pathways, transport and channel proteins involved in maintaining homeostasis. However, we still know very little about the initial events that trigger all these "physiological reactions". In fact, control of homeostasis first and foremost depends on an effective sensing system that detects or even anticipates changes to the homeostatic balance. For example, each meal is a major challenge for homeostasis as our body has to cope with extra loads of fluids, nutrients and ions as soon as they are taken up by the intestine. Wouldn't it be good to have a system that senses the composition of our food already in the gut and primes the kidney and other homeostatic organs to adapt their function even before significant changes to the body steady states occur? In fact, there is increasing evidence for anticipatory sensing and control systems. In the cover story of this Newsletter, you will read more about one of our NCCR projects in which physiologists, clinicians and industrial partners cooperate to elucidate sensing systems for extracellular phosphate, a molecule important for numerous biochemical processes including bone calcification. Although still speculative, the project promises to provide exciting novel insights into the integrative mechanisms of this homeostasis control.

Jan Loffing

are slower than changes in urinary phosphate excretion. These therefore do not appear to represent phosphate sensing mechanisms in the sense of responding to altered extracellular phosphate concentrations within the time frame of minutes. A putative phosphate sensing mechanism in this sense should occur via receptors or metabolic pathways that sense changes of extracellular phosphate concentration and transmit this information into cellular responses.

EVIDENCE FOR PHOSPHATE SENSING

A fundamental observation related to phosphate homeostasis is that intake of diets containing different amounts of phosphate alters renal excretion of phosphate. Within approximately one hour, renal phosphate reabsorption is adjusted to a diet of different phosphate content by an alteration of the abundances of sodium-dependent phosphate cotransporters. Importantly, these immediate effects are independent of PTH and other factors such as the vitamin D endocrine system, suggesting that this phenomenon is intrinsic to the kidney or could originate from the small intestine. Thus, phosphate sensing as a result to dietary phosphate load could be localized either in kidney or small intestine.

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PORTRAIT

1947: REUBI MEETS HOMER SMITH

The kidney is a mysterious organ. Therefore, it is not surprising that the general population has a rather hazy knowledge of renal function. This was clearly demonstrated by a survey of the Journal Science in the eighties, where they asked high school graduates: "Does the liver make urine?" One third answered "yes", one third "no" and one third "I don't know". The study was repeated in England with the same result.

Physicians know that the kidney makes urine. However, when it comes to explain important concepts such as renal clearance, fractional excretion or hemodynamics, the answer is often limited. The reason why these parameters were and still are so important lies in the anatomical location of the kidneys. Hidden in the back of the trunk of our body, they are not easily accessible for direct functional investigation, which was a real problem in the early days of nephrology. Finally, in the 1940s, the clearance concept was developed by Van Slyke and Homer Smith, who thereby introduced a technique that would revolutionize nephrology. The so-called clearance technique provided a tool for quantitative measurement of renal function and it is still in use today.

François Reubi, an internist from Neuchâtel and later chairman of the "Medical Polyclinic" at the University of Berne, was the first Swiss physician realizing that the clearance concept might be of great clinical relevance. So, he went to St. Louis to visit Homer Smith, returned to Switzerland armed with the new technique and then made fundamental contributions with respect to clearance and renal hemodynamics. He also was the first to describe that renal perfusion remains virtually normal during acute tubular necrosis, when no urine is produced.

Reubi was a practical and far sighted person. Realizing the central importance and great potential of renal replacement therapies, he sent his best co-workers abroad to learn: F. Blumberg went to Scribner in Seattle and brought back professional dialysis treatment and A. Montandon returned from Cleveland with an effective immunosuppressive treatment for kidney transplantation.

But this was not all: Reubi also realized early on that the kidneys play a central role for maintaining body homeostasis, after he observed that renal failure affects many organ systems leading for instance to bone disease, hypertension or anaemia. To improve adequate treatment of these complications, he established a chair in hypertension and his strong commitment to clinical treatment of renal disorders led to Switzerland being the first country to have erythropoietin available on the market.

After Reubi retired, the Department of Nephrology and Hypertension at the University Hospital Berne was created to maintain the long-standing tradition of integrative nephrology. Today the Department covers a broad variety of research topics (see box for more details) ranging from non-invasive diagnostics to investigation of various molecular mechanisms involved in renal pathophysiology and of genetic analysis in hypertension.

The NCCR Kidney – Control of Homeostasis with the ultimate goal to develop an integrative view of renal function is thus a welcome framework to integrate the various specific research topics addressed at the Department of Nephrology and Hypertension in Berne.

RESEARCH FOCUS AT BERNE'S DEPARTMENT OF NEPHROLOGY AND HYPERTENSION

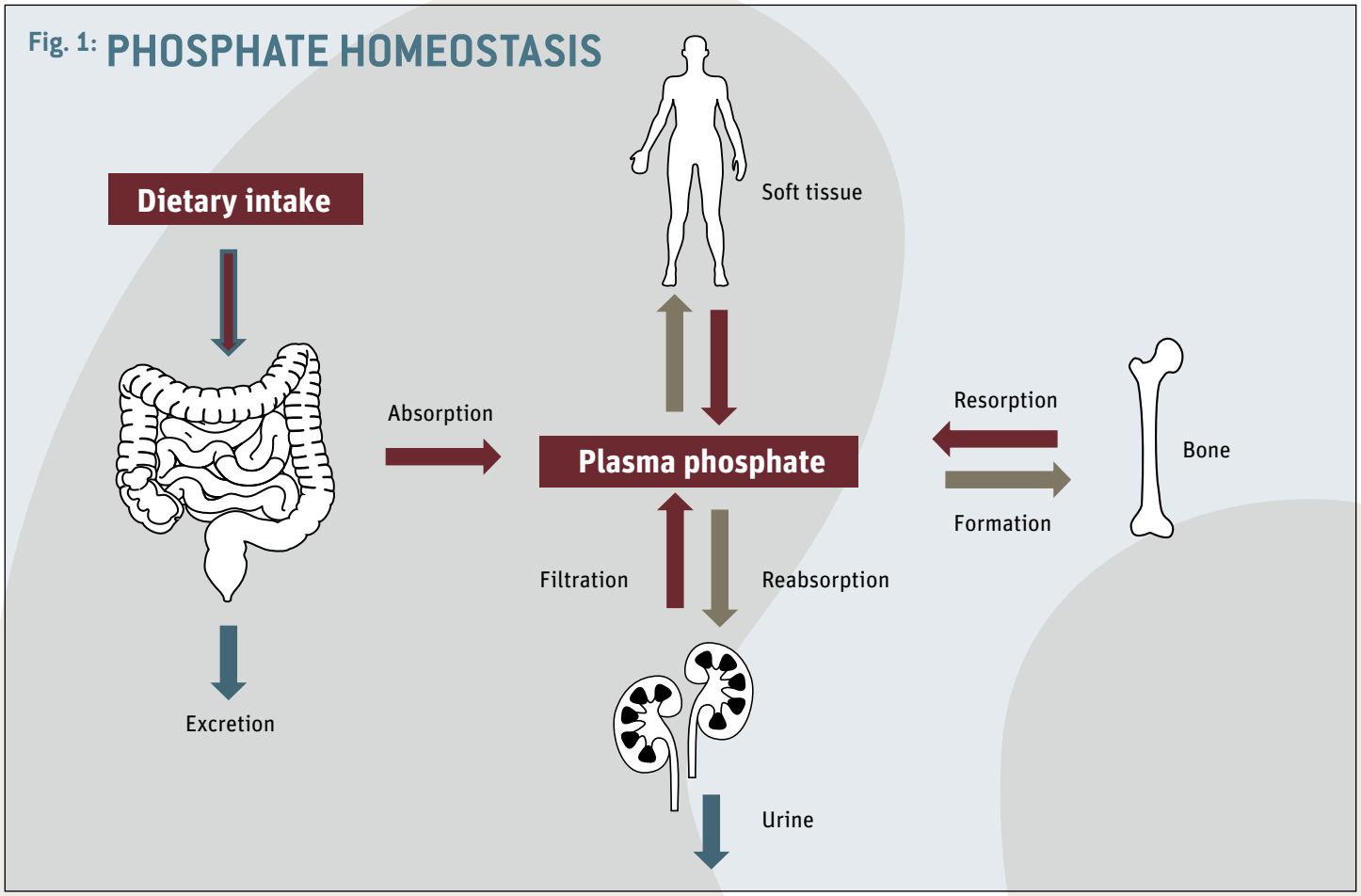
RENAL FAILURE AND REPLACEMENT THERAPIES:
Non-invasive diagnostics for renal hemodynamics, impact of sodium-thiosulfate on calcifications in uraemia and kinetic analysis of different dialysis techniques
U. Eisenberger; S. Farese; D. Uehlinger; J. Czerwinska; A. Kruse

MOLECULAR APPROACHES IN PATHOPHYSIOLOGY:
Investigating the role of specific molecules/enzymes such as metalloproteinases, 11β-hydroxysteroid dihydrogenase 1 and 2, ephrin receptor, aldosterone and NHA2 exchanger
F. Frey; B. Frey; H-P. Marti; U. Huynh-Do; D. Fuster; M. Mohaupt; A. Pasch

GENETICS:
Investigation of healthy families to identify genetic factors for hypertension
D. Ackermann

Felix Frey is professor at the University of Berne and Director of the Department of Nephrology and Hypertension

Fig. 1: PHOSPHATE HOMEOSTASIS



MODULE 3: ACID & MINERALS

Project 3.1: Sensors of Phosphate, Acid and Mineral Homeostasis

The research network combines researchers from basic and clinical science.

JUERG BIBER
University of Zurich
Acute adaptive responses to phosphate

OLIVIER BONNY
University Hospital Lausanne
Regulation of bone mineral homeostasis in mice and PTH secretion in humans

DANIEL FUSTER
University Hospital Berne
Characterization of acid, calcium and phosphate transport systems in osteoclasts

RETO KRAPF
State Hospital Basel
Acute and chronic phosphate loads in normal human subjects

KLAUS SEUWEN
Novartis AG
Role of G protein-coupled receptors in phosphate homeostasis

CARSTEN WAGNER
University of Zurich
Candidate sensors for phosphate and minerals

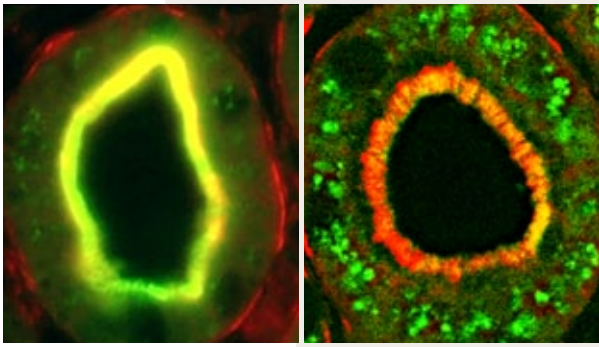
SENSING IN THE KIDNEYS

Evidence that phosphate may be sensed in the kidney comes from various phosphate loading studies performed with animals (injection of phosphate directly into the blood system), cultured renal cells and isolated perfused proximal tubules. In all these studies, altered extracellular phosphate concentration provoked changes of the amount of renal sodium-dependent phosphate cotransporters through as yet uncharacterised mechanisms.

SENSING IN SMALL INTESTINE

Direct placement of phosphate into the duodenum of rats increases renal excretion of phosphate within minutes independent of several hormones and changes in extracellular phosphate concentration. To explain this phenomenon, a gut-derived phosphaturic factor was postulated that is released depending on the amount of dietary phosphate. If so, the release of such a new intestinal hormone would require a phosphate sensing mechanism located in the small intestinal mucosa.

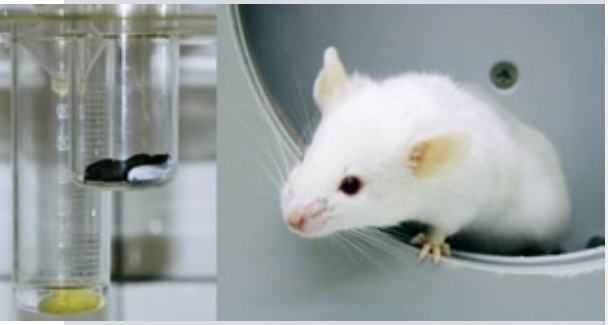
Thus, there is good evidence for the existence of phosphate sensing mechanisms in kidney, gut and perhaps other organ systems. However, the molecular identity of this phosphate sensing mechanism remains unknown. Is it a simple, single receptor protein like the previously described calcium receptor or is it a more complex sensor? Is it localized to specialized cells or is it ubiquitously expressed? What signals are evoked by the sensor and how are the signals linked to the homeostatic systems that control extracellular phosphate? Within our NCCR module Acid & Minerals, a team of researchers from basic and clinical science aims to get answers to these questions by using an integrated physiological approach that combines studies on renal and gut epithelial cell lines in vitro as well as in vivo studies on rodent models and humans. In collaboration with Novartis, candidate sensors for phosphate will be tested through experimental approaches that include screening of a G-protein-coupled receptor library. Besides addressing fundamental questions of the physiology of phosphate homeostasis, answering these questions may also help to resolve clinical problems in patients with chronic kidney disease where phosphate balance is offset and causes an increase in secondary cardiovascular problems such as arteriosclerosis, stroke or myocardial infarctions.



Left: Renal phosphate transporter NaP_iIIa is localized in the apical brush border membrane of the proximal tubule (yellow).
Right: After phosphate load NaP_iIIa is internalized within minutes from the brush border membrane (red) into cytoplasmic vesicles (green).

By Juerg Biber

NCCR KIDNEY.CH SUPPORTS THE CORE FACILITY FOR RODENT PHYSIOLOGY



The Core Facility for Rodent Physiology of the Zurich Center for Integrative Human Physiology (ZIHP) offers the basis for advanced analyses of rodent physiology with a focus on renal, metabolic, cardio-vascular and respiratory functions.
Besides a housing facility for small rodents (mice, rats) a variety of equipment and services is provided. The equipment can be used independently or in collaboration with a technician. Services range from single interventions up to the complete realization of studies. Additionally, the Core Facility offers veterinary and technical support to establish and run experiments. A list of equipment and services is available on the Core Facility's homepage.

New Services

This year the Core Facility will further expand and introduce several innovations:

- Individually ventilated cage systems (IVC) for mice and rats
- Internet-based booking tool for the reservation of equipment and information about free capacities
- A laboratory for comprehensive analysis of small blood and urine samples, which will be established in close collaboration with Olivier Devuyst and the support of Kidney.CH.

Additionally, an infrastructure for preclinical imaging including optical imaging and micro CT systems is currently in the planning phase.
Please visit the Core Facility's homepage to see our progress and feel free to contact us for additional information. www.zihp.uzh.ch

Dr. Petra Seebeck is managing the ZIHP Core Facility for Rodent Physiology since August 2010. She is a veterinarian with an expertise in bone and cartilage biology and holds a specialist degree in laboratory animal science.
contact: corefacility@zihp.uzh.ch

STUDENT'S DAY

More than 60 people from all over Switzerland participated in our 1st Kidney.CH Student's Day on March 10, 2011. Excellent talks were followed by intensive discussions, which made this day very lively and a full success. We are already looking forward to next year's Student's Day, which will then for the first time be organized by the students themselves.

"...It would not be too much to say that the first student's days was a success..." C. Kessara, PhD student

"...the idea of having only PhD students and Post-Docs with two moderators but without our PIs or other Professors is really good. This way I really felt much more relaxed to ask questions, without being afraid whether my question is really a good one or not..."
F. Storti, PhD student

"...I was impressed to see so many young people attending this day on integrative renal physiology. This turned me confident for the future seeing this new generation of basic and translational kidney researchers..." Prof. Dr. A. Kurtz, Speaker

"...the students did a very good job and I enjoyed seeing them discussing and interacting so well already at this first meeting... the student's day will certainly become an important platform for exchange between our students..." Prof. Dr. J. Loffing, Moderator

EVENTS

1ST INTERNATIONAL NCCR SYMPOSIUM ON KIDNEY - CONTROL OF HOMEOSTASIS: KIDNEY, EPO AND IRON
June 17, 2011
Zurich, Switzerland

Invited Speakers:
David R. Mole
University of Oxford
Wolfgang Jelkmann
University of Lübeck
Carole Peysonnaux
INSERM, Paris
Kai-Uwe Eckardt
University of Erlangen
Felix Frey
University Hospital Bern
Andrew T McKie
Kings College London
Lukas Kühn
EPFL Lausanne
Roland Wenger, Carsten Lundby, François Verrey
University of Zurich

FOREFRONTS 2011 SYMPOSIUM PROTEINURIA: FROM GLOMERULAR FILTRATION TO TUBULAR HANDLING
September 22-25, 2011,
Aarhus, Denmark

ASN KIDNEY WEEK 2011
November 8 – 13, 2011,
Philadelphia, USA

43RD ANNUAL MEETING OF THE SWISS SOCIETY OF NEPHROLOGY
November 30 – December 2, 2011, Montreux, Switzerland

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