THE SODIUM-HYDROGEN EXCHANGER

*From Molecule to its Role in Disease*
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From Molecule to its Role in Disease

edited by

Morris Karmazyn
University of Western Ontario
London, Ontario, Canada

Metin Avkiran
King's College London
United Kingdom

Larry Fliegel
University of Alberta
Edmonton, Alberta, Canada

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List of Contributors
(email address provided for corresponding authors)

Metin Avkiran  
Centre for Cardiovascular Biology and Medicine  
King’s College London  
The Rayne Institute  
St Thomas’ Hospital  
London SE1 7EH  
United Kingdom  
metin.avkiran@kcl.ac.uk

Henry J Binder  
Departments of Internal Medicine  
Cellular and Molecular Physiology and Surgery  
Yale University  
New Haven, Connecticut 06520  
USA  
henry.binder@yale.edu

Iyad M Ayoub  
Department of Medicine  
Finch University of Health Sciences  
The Chicago Medical School  
North Chicago VA Medical Center  
3001 Green Bay Road  
North Chicago, Illinois 60064  
USA

María C Camilión de Hurtado  
Centro de Investigaciones Cardiovasculares  
Facultad de Ciencias Médicas  
60 y 120 (1900) La Plata  
Argentina

Jay M Baltz  
Ottawa Health Research Institute  
Loeb Building  
725 Parkdale Ave  
Ottawa, Ontario K1Y 4E9  
Canada  
jbaltz@ohri.ca

Horacio E Cingolani  
Centro de Investigaciones Cardiovasculares  
Facultad de Ciencias Médicas  
60 y 120 (1900) La Plata  
Argentina  
cicmes@infovia.com.ar

Norbert Beier  
Diab & Compl Res DA  
Merck KGaA  
Frankfurter Str 250  
D-64271 Darmstadt  
Germany

Rodney J Dilley  
Morphology Laboratory  
Baker Medical Research Institute  
Melbourne, Vic 8008  
Australia

Irene L. Ennis  
Centro de Investigaciones Cardiovasculares  
Facultad de Ciencias Médicas  
60 y 120 (1900) La Plata  
Argentina
Takashi Hisamitsu  
Department of Molecular Physiology  
National Cardiovascular Research Institute  
Fujishirodai 5-7-1, Suita  
Osaka 565-8565  
Japan

Morris Karmazyn  
Department of Physiology and Pharmacology  
University of Western Ontario  
Medical Sciences Building  
London, ON N6A 5C1  
Canada  
Morris.Karmazyn@fmd.uwo.ca

Hans Jochen Lang  
Aventis Pharma Deutschland GmbH  
Building G878  
65926 Frankfurt am Main  
Germany  
HansJochen.Lang@aventis.com

Peter J Little  
Cell Biology of Diabetes Laboratory  
Baker Medical Research Institute  
St. Kilda Road Central  
PO Box 6492  
Melbourne, Vic 8008  
Australia  
Peter.Little@baker.edu.au

Marcus Müller  
Division of Microbial and Molecular Ecology  
Institute of Life Sciences  
The Hebrew University of Jerusalem  
91904 Jerusalem  
Israel

M Lee Myers  
Division of Cardiovascular Surgery  
London Health Sciences Centre-Victoria  
University of Western Ontario  
London, Ontario N6A 4G5  
Canada  
Ml.Myers@lhsc.on.ca

John Orlowski  
Department of Physiology  
McGill University  
Montreal, Quebec H3G 1Y6  
Canada  
john.orlowski@mcgill.ca

Michael H O'Regan  
Biomedical Sciences School of Dentistry  
University of Detroit Mercy  
8200 W. Outer Drive  
Detroit, Michigan 48219  
USA

Etana Padan  
Division of Microbial and Molecular Ecology  
Institute of Life Sciences  
The Hebrew University of Jerusalem  
91904 Jerusalem  
Israel  
etana@vms.huji.ac.il

Tianxiang Pang  
Department of Molecular Physiology  
National Cardiovascular Research Institute  
Fujishirodai 5-7-1, Suita  
Osaka 565-8565  
Japan
Néstor G. Pérez  
Centro de Investigaciones Cardiovasculares  
Facultad de Ciencias Médicas  
60 y 120 (1900) La Plata  
Argentina

John W Phillis  
Department of Physiology  
School of Medicine  
Wayne State University  
540 E. Canfield Ave  
Detroit, Michigan 48201  
USA  
jphillis@med.wayne.edu

Julie G Pilitsis  
Department of Neurological Surgery  
School of Medicine  
Wayne State University  
4201 St. Antoine  
Detroit, Michigan 48201  
USA

Vazhaikkurichi M Rajendran  
Departments of Internal Medicine  
Cellular and Molecular Physiology and Surgery  
Yale University  
New Haven, Connecticut 06520  
USA

Abraham Rimon  
Division of Microbial and Molecular Ecology  
Institute of Life Sciences  
The Hebrew University of Jerusalem  
91904 Jerusalem  
Israel

Wolfgang Scholz  
Diab & Compl Res DA  
Merck KGaA  
Frankfurter Str 250  
D-64271 Darmstadt  
Germany  
Wolfgang.Scholz@merck.de

Munekazu Shigekawa  
Department of Molecular Physiology  
National Cardiovascular Research Institute  
Fujishirodai 5-7-1, Suita Osaka 565-8565  
Japan

Kenneth W Spitzer  
Nora Eccles Harrison Cardiovascular Research and Training Institute  
University of Utah  
Salt Lake City, Utah 84112  
USA  
spitzer@cvrti.utah.edu

Tzvi Tzubery  
Division of Microbial and Molecular Ecology  
Institute of Life Sciences  
The Hebrew University of Jerusalem  
91904 Jerusalem  
Israel

Richard D Vaughan-Jones  
Burdon Sanderson Cardiac Science Centre  
University Laboratory of Physiology  
Parks Road  
Oxford, OX13PT  
United Kingdom
Shigeo Wakabayashi
Department of Molecular Physiology
National Cardiovascular Research Institute
Fujishirodai 5-7-1, Suita
Osaka 565-8565
Japan
wak@ri.ncvc.go.jp
Foreword

I am extremely honored and pleased to have the opportunity to write a few introductory words for this timely volume on Na⁺/H⁺ exchange. This is a field of investigation that I entered into by challenge and necessity, embraced with passion and finally left in my quest for new discoveries in growth control.

Ten years, one third of my scientific life, has been devoted to uncovering the mysteries of intracellular pH (pHi) regulation with respect to growth factor action. I got started on this new topic in 1980, when I heard a rather provocative hypothesis presented by Enrique Rozengurt at an ICN-UCLA Keystone meeting on "Cell Surface and Malignancy". He showed that all mitogens induced amiloride-sensitive Na⁺ entry into resting cells and proposed that, if a compound stimulates Na⁺ influx, it could be a mitogen. In support of his proposal Enrique reported that the amphipathic polypeptide, mellitin, which induced Na⁺ influx, was indeed mitogenic for 3T3 cells. This was only correlation at this stage. However, I was fascinated by this talk. I immediately approached Enrique to inform him of my skepticism about this beautiful story, and to indicate that I would only be convinced when I succeeded in isolating mutant fibroblasts lacking the amiloride-sensitive Na⁺ transporter. "Good luck!" was his response.

I took Enrique's "good luck" wish to mean that he was not going to compete with us on genetics, which was great! At the same Keystone meeting, I had presented the properties of a glycolysis-deficient fibroblast mutant (phosphoglucose isomerase'), demonstrating that both increased aerobic glycolysis and glucose transport were not essential for the transformed phenotype. Mutant fibroblasts impaired in aerobic glycolysis developed tumors in nude mice with the same incidence as wild type cells. This simple genetic approach killed the Warburg hypothesis. I was therefore confident that somatic cell genetics could be an efficient approach in dissecting growth control mechanisms. Although I knew the risk and the price (at least one to two years of work), I was eager and convinced that it was the right time to attack another important issue in growth control. My goal was to evaluate the role of this mitogen-induced Na⁺ flux mechanism and the associated pHi alkalization in both growth factor action and cell cycle progression.

At that time the "Yale School of Physiology", with the pioneering work of Peter Aronson, Walter Boron and others, illuminated the field of transport and pHi regulation in higher eukaryotes. Their advances greatly facilitated the progress of Sonia Paris and Gilles L'Allemain, working in my group, in understanding the biochemistry and functionality of the amiloride-sensitive Na⁺/H⁺ antipporter. This step was a prerequisite for establishing a genetic screen. The reversibility, ion selectivity and
allosteric activation of the antiporter by intracellular H⁺ provided the basis for my inspiration for “H⁺ suicide selection”. With this killing method and specific genetic screen in hand, it was a simple delight to isolate mammalian cells lacking a functional Na⁺/H⁺ exchanger and to show that pHi, regulated via the growth factor-activatable NHE1, truly did control cell cycle progression. The next step was to get the sequence and structure of this molecule, and it took the time of Claude Sardet’s PhD thesis to complete the relevant work. Functional complementation with human genomic DNA of a mouse cell line lacking the antiporter led to the identification of the first human molecule, NHE1.

This book is entitled "The Sodium-Hydrogen Exchanger: From Molecule to its Role in Disease". I am glad to have, with my group, contributed to the identification of the Molecule and I am particularly pleased to see how this field has expanded beautifully since we left it.

Jacques Pouyssegur
Director of the Institute of Signaling
Developmental Biology and Cancer Research
Nice, France
Preface

The concept of a mammalian sodium-hydrogen exchanger was first proposed in 1961 when Peter Mitchell, a British biochemist and Nobel Laureate (Chemistry, 1978), postulated its existence to explain his chemiosmotic hypothesis. Six years later, Mitchell demonstrated the presence of a sodium-hydrogen exchanger in liver mitochondria. In 1976, Heini Murer and colleagues reported the first identification of a sodium-hydrogen exchanger in cell membranes from mammalian intestine and kidney. As we now know, the sodium-hydrogen exchanger, or NHE (Na-H Exchanger) as it is commonly referred to, is not one protein but consists of a large and growing family of isoforms. These isoforms are derived from distinct genes and play a multiplicity of roles in regulating cellular and organ function in health and disease. To date, eight NHE isoforms, termed NHE-1 to NHE-8, have been cloned. While most NHE isoforms demonstrate substantial tissue specificity, NHE-1 is ubiquitously expressed in virtually all tissues and has been generally referred to as the housekeeping isoform. Other unique sodium-hydrogen exchangers have also been described, such as the newly identified colonic chloride-dependent NHE or the NhaA of E. coli and other species.

This volume brings together international authorities to review major advances in distinct areas of NHE research. These state-of-the-art reviews address a broad range of complementary topics, progressing from the structure and regulation of NHEs to targeting NHE as a therapeutic modality for the treatment of pathological conditions. Indeed, the past two decades have seen startling and rapid advances in our understanding of the regulation of the activity of many NHE isoforms, as well as in the identification and cloning of novel isoforms. NHE has been directly implicated in several pathologies, most notably in the damage that occurs to the myocardium during ischemia and reperfusion and in cardiac hypertrophy and failure. In the area of therapeutics, chemical synthesis of isoform-selective NHE inhibitors has led to the initiation of a number of clinical trials, particularly in the area of cardiovascular disease. Emerging evidence indicates that targeting NHE may also hold promise for other conditions, as discussed in this volume.

The chapters that comprise this volume address the basic structure, function and regulation of NHE proteins, their roles in various diseases, and the development, characterization and clinical evaluation of NHE inhibitors. By covering such a broad range of complementary topics, from molecular biology to clinical therapeutics, this unique volume provides an opportunity for students, basic scientists and clinicians to learn the newest developments in this rapidly evolving field.
We thank all those who helped bring this book to fruition, in particular Pamela Burgess for her outstanding word processing skills. Ultimate thanks go to all contributors without whom this book would not have been possible.

Morris Karmazyn (London, Ontario, Canada)
Metin Avkiran (London, United Kingdom)
Larry Fliegel (Edmonton, Alberta, Canada)