Advances in Experimental Medicine and Biology 961

Lucio Annunziato *Editor*

# Sodium Calcium Exchange: A Growing Spectrum of Pathophysiological Implications

## Proceedings of the 6th International Conference on Sodium Calcium Exchange

Springer

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ISBN 978-1-4614-4755-9 ISBN 978-1-4614-4756-6 (eBook)
DOI 10.1007/978-1-4614-4756-6
Springer New York Heidelberg Dordrecht London

Library of Congress Control Number: 2012951339



Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

*This book is dedicated to Mordecai Blaunstein and Kenneth Philipson as a tribute to their outstanding scientific carreers: most of the current knowledge on NCX is due to their passionate work over the last 45 years and this conference would not have been possible without their memorable contribution.*

# Preface

From October 1 to October 5, 2011 more than 100 scientists from 21 countries of all the continents conveyed in the nice, little village of Lacco Ameno in the Island of Ischia in the Gulf of Naples, Italy, to take part to the 6th International Conference on Sodium Calcium Exchange. This book reports the text of the lectures of the Conference and the state-of-art of the topic discussed and it intends to represent a long lasting memory of the magic atmosphere of the meeting where science and friendship perfectly matched in a lovely natural setting.

The 6th International Conference on Sodium Calcium Exchange is the last of a series that begun with the meeting held in Stowe 1987, England and, thereafter, every 4–5 years each time in a different location. Nowadays, 35 years after this first meeting, the International Conference on Sodium Calcium Exchange is an highly expected appointment for the NCX community where new data are presented and fruitful discussions take place. The last 30 years experienced big changes in the field of NCX that, at the very beginning was a partially characterized protein object of the interest of few highly focused scientists and nowadays is a protein characterized even in its three dimensional structure with an ever growing spectrum of pathophysiological implications. Two lectures, given at the 6th International Conference on Sodium Calcium Exchange and reported in the present volume, gave an enthusiastic overview of the tremendous progress in the knowledge on the exchanger with the words of two leaders in the field, Mordecai Blaunstein and Kenneth Philipson to whom we intend to dedicate this book as a tribute to their outstanding scientific careers.

Looking back to the volumes of the Proceedings of the previous conferences it can be easily realized that all the milestones in the field have been documented in these books which, therefore, represent an important part of the literature on the exchanger. We are confident that the same will also happen for the present book that uncovers the most striking new findings on NCX that emerged since the previous Conference on Sodium Calcium Exchange, such as the structural dissection of the molecular determinants of $Ca^{2+}$ sensitivity of the exchanger, the epigenetic regulation of *ncx1* gene, the molecular identification of the mitochondrial Sodium Exchanger, and the discovery of NCX in unexpected anatomical locations such as the female reproductive tract.

As a final remark we would like to emphasize that many of the participants to the Conference were young scientists under 35 years: it looks like that

besides the outstanding past of the fathers of NCX we should also celebrate the birth of a new generation of NCX proselytes that we hope will keep high the tradition of the NCX Conferences also in the future.

We would like to express our gratitude for their precious help in the organization of the meeting to all the members of the International (Luis Beaugé, Lorella MT Canzoniero, Ernesto Carafoli, Gianfranco Di Renzo, David Eisner, André Herchuelz, Takahiro Iwamoto, Lung-Sen Kao, Daniel Khananshvili, Jonathan Lytton, Kenneth D Philipson, Hannah Rahamimoff, John Reeves, Paul Schnetkamp, Karin R Sipido, Dandan Sun, Bruno Trimarco, Jin Zhang) and Local (Lorella MT Canzoniero, Mauro Cataldi, Gianfranco Di Renzo, Pasquale Molinaro, Anna Pannaccione, Giuseppe Pignataro, Antonella Scorziello, Agnese Secondo, Maurizio Taglialatela) Organizing Committees. Special thanks also to Mauro Cataldi for helping in the revision of the chapters and in the organization of the book, to Springer for taking care of the publication of the book, and to Studio Grafico Ciotola, Naples, Italy, for preparing all the illustrations of the book.

Lucio Annunziato, M.D.
Chairman of the Conference

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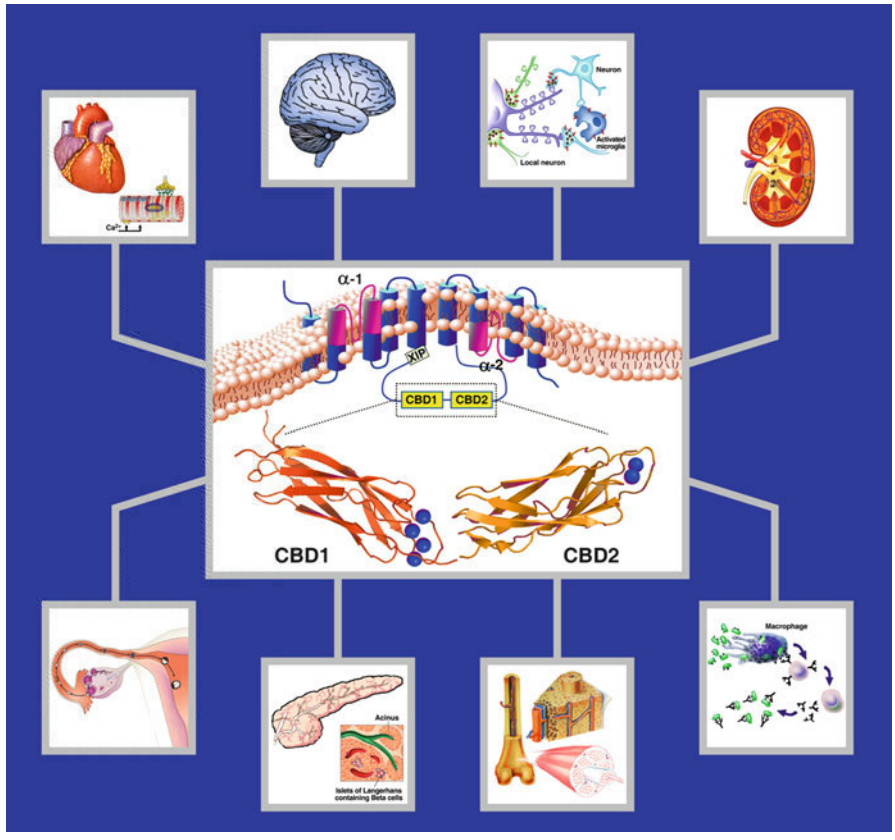
**Participants to the 6th Conference on Sodium Calcium Exchange, Lacco Ameno, Ischia, Naples, Italy, October 1–5, 2011**



# Part I

# Historical Perspective

# Livin' with NCX and Lovin' It: A 45 Year Romance

1

Mordecai P. Blaustein

*Sit down before fact as a little child, be prepared to give up every conceived notion, follow humbly wherever, whatever abysses nature leads, or you will learn nothing.*

Thomas H. Huxley,
letter to C. Kingsley, September 20, 1863

**Abstract**

This conference commemorates, almost to the day, the 45th anniversary of the discovery of the $Na^+/Ca^{2+}$ exchanger (NCX). The discovery was serendipitous, as is so often the case with scientific breakthroughs. Indeed, that is what is so fascinating and romantic about scientific research. I will describe the discovery of NCX, but will begin by explaining how I got there, and will then discuss how the discovery influenced my career path.

**Keywords**

Cardiotonic steroids • Hypertension • PLasmERosomes • Synaptosomes • Vascular smooth muscle

## 1.1 For the Love of Physiology

I was introduced to cell physiology by Howard Schneiderman, a distinguished insect physiologist and developmental biologist, during my undergraduate days at Cornell University. I was interested in neurophysiology and the mind-brain problem but came under the spell of Daniel Tosteson when I was a medical student at Washington University in St. Louis. Dan convinced me to work on the $Na^+,K^+$-ATPase ("sodium pump"), which had just been discovered (Skou 1957).

I spent a year and a half in Dan's lab studying the red blood cell cardiotonic steroid-sensitive $Na^+$ pump. In 1963, after completing medical school and an internship at Boston City Hospital, I was offered a naval commission to work at the US Naval Medical Research Institute in Bethesda, MD (much better than a tour in Vietnam!).

Thus, I returned to neurophysiology, and under David Goldman (of the Goldman-Hodgkin-Katz

In memory of Peter F. Baker, David E. Goldman, Alan L. Hodgkin, Howard A. Schneiderman, Daniel C. Tosteson, and Mani Matter.

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L. Annunziato (ed.), *Sodium Calcium Exchange: A Growing Spectrum of Pathophysiological Implications*, Advances in Experimental Medicine and Biology 961, DOI 10.1007/978-1-4614-4756-6_1,

equation), I studied the effects of divalent cations and anesthetics on lobster nerve conduction (Blaustein and Goldman 1966; Blaustein 1968). I also was fortunate to spend a few weeks at Woods Hole with John Moore and Toshio Narahashi working on tetrodotoxin's action on squid axons (Moore et al. 1967).

I was planning to continue my career in cellular neurophysiology and arranged for a position in Alan Hodgkin's laboratory in Cambridge, England, with a special fellowship from the NIH. My family and I arrived in Cambridge in late August of 1966. After a family trip to Vienna for the International Congress of Biophysics, I left my wife Ellen and our two children (ages 3 and 5) in Cambridge and headed off to the Laboratory of the Marine Biological Association in Plymouth, England, for the fall squid season.

## 1.2 All Hands to the Pump

My expectation was to study squid axon electrophysiology, but Peter Baker, Alan's junior associate, a lecturer at Emmanuel College, Cambridge, took a mini-sabbatical that fall, and he wanted all Plymouth squid researchers to work on the $Na^+$ pump. I was paired up with Rick Steinhardt, Richard Keynes' postdoctoral fellow, and we were tasked with studying the activation of the $Na^+$ pump by external cations. Richard came to Plymouth at the end of September; he showed us how to dissect squid axons (not knowing of my prior experience) and how to measure $^{22}Na^+$ efflux after injecting the giant axons (0.8–1.2-mm diameter) with a microsyringe that he and Alan designed (Hodgkin and Keynes 1956). Richard then went off to Homburg (Saar), Germany, to teach in a course on membrane biophysics organized by Hermann Passow and Robert Stampfli (more about this later).

Rick and I began our $^{22}Na^+$ efflux experiments on squid axons, and we rapidly identified a component that depended on external $K^+$ and was blocked by ouabain, i.e., the $Na^+$ pump component. When we removed external $Na^+$ and $K^+$ ($Na_o$ and $K_o$, respectively), preparatory to adding back one monovalent cation at a time, we exposed a very large $^{22}Na^+$ efflux that did not depend upon $K_o$ and was not blocked by ouabain (Fig. 1.1).

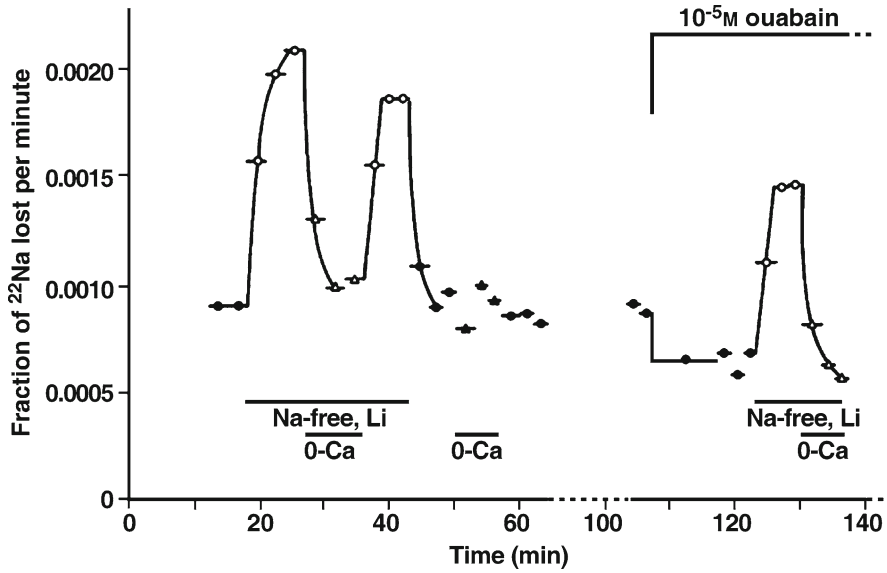


**Fig. 1.1** *Reduction of $[Na^+]_o$ activates a large $Ca_o$-dependent, ouabain-resistant $^{22}Na^+$ efflux in squid axons with high $[Na^+]_i$.* Replacement of 460 mM NaCl in the artificial seawater (ASW) by LiCl greatly increased $^{22}Na^+$ efflux, measured as the fraction of $^{22}Na^+$ lost per minute. The increment was abolished by removal of the 11 mM $CaCl_2$ in the ASW ($MgCl_2$ was increased from 55 to 66 mM). This is evidence of "$Na_o$-$Ca_o$ antagonism" and indirect evidence for $Na^+/Ca^{2+}$ exchange. Ouabain ($10^{-5}$ M; added at 107 min) reduced the $^{22}Na^+$ efflux in control Na ASW (i.e., it inhibited the $Na^+$ pump), but it had no effect on the large $Ca_o$-dependent $^{22}Na^+$ efflux in Li ASW) (Reprinted from Baker et al. (1969), with permission)

This efflux persisted when the external NaCl and KCl were replaced by sucrose, LiCl, or choline $Cl^-$. We consulted with Peter Baker, who agreed that internal $Na^+$ could be exiting with an anion or exchanging for a cation. It was easiest to remove the other external cations, $Ca^{2+}$ and $Mg^{2+}$, so we first removed the $Ca^{2+}$ – et voila! The large $Na^+$ efflux was reversibly abolished, i.e., the $Na^+$ efflux was external $Ca^{2+}$-dependent (Fig. 1.1). Removal of external $Mg^{2+}$ had negligible effect on the $Na^+$ efflux, so we had our answer: Na/Ca exchange! This was just the first month of my fellowship!

Peter had read Ralph Niedergerke's articles on $Na^+$-$Ca^{2+}$ interactions in frog cardiac muscle, and he suggested that they might be of interest. There was no time to read, however, we were working 14–16-h days during October because I feared that a gale would interrupt our daily squid supply; the large squid did not survive in the relatively small holding tanks. In fact, the squid usually were injured in the nets and would die before the collection boat docked. Therefore, as soon as squid were caught, the fishermen removed the head and internal organs and placed the mantle (containing the giant axons) in a thermos of iced seawater. With the $Na^+$ pumps thus turned off, the axons slowly gained $Na^+$; the axons did not last overnight. As we shall see, this rise in the intracellular $Na^+$ concentration, $[Na^+]_i$, was fortuitous for the $Ca^{2+}$ influx experiments.

In the meantime, we ordered some $^{45}Ca^{2+}$ to test the $Na^+/Ca^{2+}$ exchange idea directly. The $^{45}Ca^{2+}$ arrived the first week in November, but just before that, we had a gale. Finally, I had a chance to catch my breath. It was a miserable, stormy afternoon, and the laboratory building was deserted; I completed my data analysis for the last experiments and sauntered down the hall to the library. As soon as I started to read the description (Luttgau and Niedergerke 1958) of extracellular $Na^+$-$Ca^{2+}$ ($[Na^+]_o$-$[Ca^{2+}]_o$) antagonism and its influence on frog cardiac contraction (reduced $[Na^+]_o$ induces cardiac contraction), I got very excited. I immediately recognized that NCX must be widely distributed in both tissues and species, including vertebrate heart. Therefore, since NCX apparently functions in the heart, it is the missing link to the puzzle that had stumped me ever since my first studies on the $Na^+$ pump and, as an intern, my use of digitalis to treat patients with heart failure: How does $Na^+$ pump inhibition by cardiotonic steroids increase the force of contraction of the heart? Because of both my clinical and research experiences, I frequently thought about this enigma.

Here was the answer: raising $[Na^+]_i$ promotes net $Ca^{2+}$ gain by NCX and thereby enhances cardiac contraction. That "Eureka! moment" was even more thrilling than the discovery of NCX itself. I was, for a brief time, the only one in the world who understood how cardiotonic steroids enhance cardiac contraction! I was so exhilarated that I went off, alone, to the nearby Green Lantern restaurant, for a fine celebratory dinner with a bottle of claret. Then, slightly inebriated, I returned to the lab to reread Luttgau-Niedergerke, to be sure I was not delusional. It was a great day!

## 1.3 $^{45}Ca^{2+}$ Flux Studies: Verification of $Na^+/Ca^{2+}$ Exchange

The following Monday afternoon, Alan Hodgkin came down to Plymouth to see how I was getting on. After we dissected a few axons for the evening's $^{22}Na^+$ efflux experiments, he and I went to dinner with Trevor Shaw, another Plymouth squidder. We talked about the NCX, including my explanation of how $Na^+$ pump inhibitors exert their cardiotonic effect. Alan asked a few questions but was, otherwise, impassive. I was crestfallen. How could he fail to be enthused by the story? Two days later, however, Alan asked me if I would mind if he remained in Plymouth to perform the $^{45}Ca^{2+}$ flux experiments with me. Would I mind? I was ecstatic! We had won him over.

Alan and I performed the first influx experiments the next Monday. Axons were incubated for 1 h in artificial seawater (ASW, the external fluid) containing either NaCl or LiCl as the predominant salt and labeled with $^{45}Ca^{2+}$. The axons were then washed in tracer-free solution, and the axoplasm