CRC

SODIUM: ITS BIOLOGIC SIGNIFICANCE

Solomon Papper

CRC PRESS

Sodium: Its Biologic Significance

Editor

Solomon Papper, M.D.
Distinguished Professor and Head
Department of Medicine
University of Oklahoma College of Medicine, and
Staff Physician
Veterans Administration Medical Center
Oklahoma City, Oklahoma

Editor-in-Chief

Jerry K. Aikawa
CRC Series on
Cations of Biologic Significance

CRC Press, Inc.
Boca Raton, Florida

Library of Congress Cataloging in Publication Data

Sodium, its biologic significance.

(Cations of biologic significance, ISSN 8493-5870)
Bibliography: p.
Includes index.
Contents: The normal state: Sodium transport and metabolism/Sidney Solomon and William R. Galey. Renal regulation of sodium excretion/Mark H. Gardenswartz and Robert R. Schrier — Sodium excess. An introductory overview/Solomon Papper.
1. Sodium metabolism disorders. 2. Sodium in the body. 3. Sodium metabolism disorders—Complications and sequelae. I. Papper, Solomon, 1922- . II. Series: Cations of biologic significance.
[DNLM: 1. Sodium—Physiology. 2. Sodium—Adverse effects. 3. Hyponatremia. 4. Hypernatremia. QV 275 S679]
RC632.S6S66 616.3'99 81-3804
ISBN 0-8493-5873-6 AACR2

This book represents information obtained from authentic and highly regarded sources. Reprinted material is quoted with permission, and sources are indicated. A wide variety of references are listed. Every reasonable effort has been made to give reliable data and information, but the author and the publisher cannot assume responsibility for the validity of all materials or for the consequences of their use.

All rights reserved. This book, or any parts thereof, may not be reproduced in any form without written consent from the publisher.

Direct all inquiries to CRC Press, Inc., 2000 N.W. 24th Street, Boca Raton, Florida 33431.

© 1982 by CRC Press, Inc.

International Standard Book Number 0-8493-5873-6

Library of Congress Card Number 81-3804
Printed in the United States

EDITOR-IN-CHIEF

Dr. Jerry K. Aikawa is Professor of Medicine and Biometrics and Acting Head of the Division of Laboratory Medicine and Clinical Pathology at the University of Colorado School of Medicine. He is Director of Laboratory Services at the University of Colorado Health Sciences Center in Denver, Colorado.

Dr. Aikawa received his M.D. degree from the Bowman Gray School of Medicine of Wake Forest University. His graduate medical education includes completion of residency in internal medicine followed by research fellowships sponsored by the National Research Council, the U.S. Atomic Energy Commission, and the American Heart Association. He is author of numerous scientific articles and five books on myxedema, Rocky Mountain spotted fever, clinical data processing, and magnesium. Dr. Aikawa began his research in magnesium in the late 1950s when the U.S. Atomic Energy Commission was encouraging the application of radioactive isotopes to biomedical research, and has maintained his interest in this subject ever since.

THE EDITOR

Solomon Papper, M.D. is a Distinguished Professor and Head of the Department of Medicine at the University of Oklahoma at Oklahoma City Health Sciences Center. He is also a staff physician at the Oklahoma City Veterans Administration Medical Center.

Dr. Papper received his A.B. from Columbia College and his M.D. at New York University in 1944. After completing his internship and residency and a stint in the Army Medical Corps, Dr. Papper became a fellow at Thorndike Memorial Laboratory and Harvard Medical School where he began his research on the regulation of sodium excretion and the kidney in liver disease. He is especially known for his work on the Hepatorenal Syndrome.

In 1962 he became Professor and Chairman of a newly created Department of Medicine at the new medical school of the University of New Mexico. In 1968 he moved to the University of Miami, where he was Professor and Co-Chairman of the Department of Medicine. Before moving to the University of Oklahoma in March 1973, Dr. Papper was Professor of Medicine and Chairman of the Department of Medicine at General Rose Memorial Hospital at the University of Colorado. In April 1974, the Veterans Administration selected him for the designation "Distinguished Physician". He relinquished that title when he accepted the position of Head of the University of Oklahoma Department of Medicine in July 1977.

Dr. Papper has written or co-authored more than 100 published articles in addition to writing a book, *Clinical Nephrology,* whose second edition was published in 1978. He edited *The Kidney,* a publication of the National Kidney Foundation, for ten years. In addition, he has served on the editorial boards of *Journal of Laboratory and Clinical Medicine, Clinical Nephrology,* and *The Forum on Medicine,* and is currently an associate editor of *American Journal of Nephrology.* Dr. Papper is a member of the Association of American Physicians, the American Society for Clinical Investigation, and the American Federation for Clinical Research. He is a Fellow of the American College of Physicians, and at present is Governor of the Oklahoma Region of the American College of Physicians.

PREFACE

Sodium is concerned with the physiology, pathophysiology, and clinical consequences of altered physiology involving the sodium ion.

The first section focuses on the presence and handling of sodium in the normal state. In chapter one, Drs. Solomon and Galey deal with the fundamentals of transport and energy metabolism as they relate to sodium. This is followed by a chapter in which Drs. Gardenswartz and Schrier consider in detail the normal body economy of sodium, and especially the factors (particularly extracellular fluid volume) that regulate the renal handling of sodium and the responses of the various portions of the nephron to these influences.

The rest of the book emphasizes departures from normal physiology. For convenience we have divided these into three broad categories: sodium excess, sodium deficit, and alterations in serum sodium concentration.

The section on sodium excess includes edematous conditions and hypertensive disorders. In the former, Drs. Bernard and Alexander, Epstein, Czerwinski and Llach, and Kem delineate the mechanisms of enhanced renal reabsorption of sodium in the common edematous states. That sodium excess is somehow involved in the causation of some hypertensive states is a fascinating and still incomplete story. Drs. Frohlich and Messerli explore the evidence for the role of sodium and consider the mechanisms whereby excess sodium may be a causative and preventive mechanism in the genesis of hypertension. Finally, diuretic agents are considered by Drs. Whitsett and Chrysant primarily from the pharmacological viewpoint.

Sodium deficit, i.e., extracellular fluid volume deficit, is presented by Dr. Vaamonde in systematic fashion.

The book ends with detailed discourses on hypo- and hypernatremia by Drs. Llach and Czerwinski, and Finberg, respectively.

In all sections there is a commitment to expounding the knowns and exploring the unknowns, and the two are distinguished from each other carefully. There is repetition in the book. Our efforts to maintain each section and chapter as a discrete entity led in several instances to the judgment that repeating material found elsewhere made for a more complete free-standing story.

I thank each author for sharing with skill his knowledge and expertise. As editor I deeply valued and appreciated their cooperative and good natured spirit. Ms. Beverly Clarke's editorial assistance is gratefully acknowledged.

S.P.

此为试读,需要完整PDF请访问: www.ertongbook.com

CONTRIBUTORS

Edward A. Alexander, M.D.
Professor of Medicine and Professor of Physiology
Boston University School of Medicine
Chief, Renal Section and Associate Director of Medicine
Boston City Hospital
Boston, Massachusetts

David B. Bernard, M.D.
Assistant Professor of Medicine
Boston University School of Medicine
Director, Clinical Nephrology
Evans Memorial Department of Clinical Research
University Hospital
Boston, Massachusetts

Steven G. Chrysant, M.D.
Associate Professor of Medicine
University of Oklahoma College of Medicine
Oklahoma City, Oklahoma

Anthony W. Czerwinski, M.D.
Professor of Medicine
University of Oklahoma College of Medicine
Associate Chief, Nephrology Section
Oklahoma City Veterans Administration Medical Center
Oklahoma City, Oklahoma

Murray Epstein, M.D.
Professor of Medicine
University of Miami School of Medicine
Miami Veterans Administration Medical Center
Miami, Florida

Laurence Finberg, M.D.
Professor
Department of Pediatrics
Montefiore Hospital and Medical Center
Albert Einstein College of Medicine
Yeshiva University
New York, New York

Edward D. Frohlich, M.D.
Vice President, Education and Research
Alton Ochsner Medical Foundation and Division of Hypertensive Diseases
Ochsner Clinic
New Orleans, Louisiana

William R. Galey, Ph.D.
Associate Professor of Physiology
Department of Physiology
University of New Mexico School of Medicine
Albuquerque, New Mexico

Mark H. Gardenswartz, M.D.
Assistant Chief of Nephrology
Lenox Hill Hospital
New York, New York

David C. Kem, M.D.
Professor of Medicine
Chief, Endocrinology, Metabolism and Hypertension Section
Department of Medicine
University of Oklahoma College of Medicine
Oklahoma City, Oklahoma

Francisco Llach, M.D.
Associate Professor of Medicine
Chief, Nephrology Section
Department of Medicine
University of Oklahoma College of Medicine
Oklahoma City Veterans Administration Medical Center
Oklahoma City, Oklahoma

Franz H. Messerli, M.D.
Staff Member
Division of Hypertensive Diseases
Ochsner Clinic and
Division of Research
Alton Ochsner Medical Foundation
New Orleans, Louisiana

Robert W. Schrier, M.D.
Professor and Chairman
Department of Medicine
University of Colorado Health Sciences Center
Denver, Colorado

Sidney Solomon, Ph.D.
Professor of Physiology
University of New Mexico School of Medicine
Albuquerque, New Mexico

Carlos A. Vaamonde, M.D.
Professor of Medicine
University of Miami School of Medicine
Chief, Nephrology Section
Miami Veterans Administration Medical Center
Miami, Florida

Thomas L. Whitsett, M.D.
Professor of Medicine
Chief, Clinical Pharmacology Section
Department of Medicine
University of Oklahoma College of Medicine
Oklahoma City Veterans Administration Medical Center
Oklahoma City, Oklahoma

TABLE OF CONTENTS

The Normal State

Chapter 1

SODIUM TRANSPORT AND METABOLISM

Sidney Solomon and William R. Galey

TABLE OF CONTENTS

此为试读,需要完整PDF请访问: www.ertongbook.com

I. INTRODUCTION

During the evolutionary development of cells, one of the early manifestations of these biological units appears to have been the establishment of ionic gradients. Cellular accumulation of potassium and extrusion of sodium became established. The basis of biological actions depending on ionic gradients, i.e., action potential generation, was thereby created. With the evolution of metazoan species, changes in marine environments, invasion of fresh water, and adaptation to a semiarid environment (land), new problems had to be solved to allow for development and diversification of species. A variety of adaptive measures developed. Most species excluded the external environment and maintained the old surrounding for cells—the "internal environment" of Claude Bernard. The most common solution to the homeostasis problem was accomplished through transport of electrolytes, and in particular, sodium. Sodium transport systems serve to maintain ionic balance and cellular transmembrane ionic gradients. On the other hand, some species responded by providing for osmotic equilibration through either the intracellular accumulation of amino acids,[1] or by accumulating extracellular urea[2] or trimethyl amine.[3] In order to maintain functional integrity, however, it remained necessary to keep ionic gradients and this need still persists.

Whenever compartments exist with differing ionic activities or capability for exchange of materials, energy has to be expended to maintain these gradients. Such is the case, whether one is interested in single cells, metazoan cells in contact with the internal environment, or in the interaction of the internal environment of metazoan organisms with the external environment. Current evidence would indicate that transport of sodium is one of the most ubiquitous mechanisms used for maintenance of ionic gradients. As a result, the link between cellular metabolism as a source of energy and sodium transport is an extremely intriguing question. Another consequence of the maintenance of the sodium gradient is that the potential energy of the gradients can be utilized for providing the driving force for movement of organic substrates. The energetic events involved in establishing the sodium gradient, as well as the utilization of the energy the gradient provides, form the basis of this chapter.

II. IONIC MOVEMENTS AND THE NEED FOR ENERGY

Simple passive permeation across membranes is a movement down an electrochemical gradient for the solute being considered and requires no cellular energy. The electrochemical gradient across a membrane has been defined by investigators[4,5] and is given formally by:

$$\mu = RT\,n \cdot C_1/C_2 + ZFE \qquad (1)$$

where R and T have their usual definitions of gas constant and absolute temperatures; C_1 and C_2 are the concentrations of the solute under consideration on the two sides of the membrane; Z is the valence of the ion in question (which in the case of sodium has a value of one); F is the Faraday constant; and E is the potential difference between the two compartments which the membrane separates. A simple expression relating potential to concentration gradient is given by the Nernst equation:

$$E = \frac{RT}{ZF}\,1n\,\frac{C_2}{C_1} \qquad (2)$$

It is easily seen that Equation 2 can be derived from Equation 1, when μ is set equal to zero.

When solutes permeate a membrane, there is movement in both directions. It was shown by Ussing[6] that the relationships of passive fluxes (M) in each direction are given by the following equation:

$$\frac{M_{1\rightarrow 2}}{M_{2\rightarrow 1}} = \frac{C_1}{C_2}\, e^{\frac{ZFE}{RT}} \qquad (3)$$

where e is the base of the natural logarithms and all other symbols have the same meanings as given. One can define a passive movement of a solute as one where the ratio of fluxes $M_{1\rightarrow 2}/M_{2\rightarrow 1}$ is predicted by Equation 3. If such a relationship is not found, as a first assumption, active transport can be postulated. Active transport, however, is not always required. A movement has been described wherein one ion exchanges for another with no net permeation. This form of membrane transfer has been called exchange diffusion.[7] If exchange diffusion is appreciable, the mathematical ratio will not be observed and although the flux of the solute is not active, an error of interpretation will be made by considering Equation 3 only.

From these considerations it becomes clear that additional criteria are needed for definition when a solute is actively transported. Many current hypotheses hold that for a solute to be transported actively, there must be combination of the solute with a carrier. Metabolic energy is transformed to a mechanical energy so that the carrier either moves or undergoes a conformational change, with the result that the solute is carried to the opposite side of the membrane and then released. Hypothesized models* of the transport process are shown in Figure 1.

Obviously, if the living cell is to maintain ionic disequilibrium between the environment and its internal milieu, energy must be expended. Hence, cells must utilize some of their metabolic energy to accomplish the thermodynamically unfavorable "uphill" transport of the ions against their electrochemical gradients. This, then, is one of the two requirements for showing that the transport of a molecular species is "active". Specifically, the cell must use directly cellular metabolic energy to accomplish the transport of the actively transported solute. As is well known, this energy source is in the form adenosine triphosphate (ATP). The second requirement for active transport has already been alluded to but not directly stated. The process for active transport of a solute must be capable of moving the solute up its electrochemical gradient. These two requirements,

1. The direct expenditure of cellular metabolic energy, and
2. The capability of moving the solute against its electrochemical gradient,

are the necessary and sufficient prerequisites for stating that the solute in question is actively transported. This transport has been called "primary active transport" for reasons that will be discussed later.

The fact that the movement of a solute, be it an electrolyte or nonelectrolyte, is against its electrochemical gradient is not sufficient evidence to prove that it is actively transported. It may be that a solute is being transported at the expense of the ionic gradient that exists across the cell membrane as a result of a previous active transport process. In this case cellular metabolic energy is not being used directly to accomplish the transport and thus should not be considered "active" transport.

The frog skin has been extensively used for studies of sodium transport. In fact, it

* Some investigators do not believe that any cellular accumulation or extrusion of ions requires an active process such as the one to be described (see Ling,[8] for example).

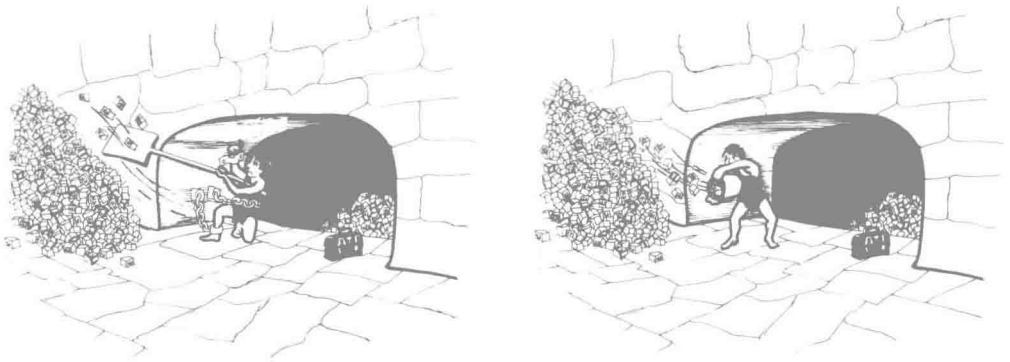

FIGURE 1. Models of a conformational and mobile transport carrier. In the conformational system, the carrier is fixed in place and transports sodium uphill only through a change in shape of the transporting molecule (left panel). In the case of a mobile carrier, the transporting molecule becomes associated with sodium on the side of low concentration, moves across the membrane, and then becomes dissociated from the sodium (right panel). In both models ATP provides energy for doing the transport work.

was Huf who first coined the term "active transport" from an investigation on this tissue.[9] He was first to show that the skin moved sodium chloride against a concentration and that the movement of the sodium ion was also against an electrical gradient. He and others further established that these movements were suppressed by inhibitors of both aerobic and anaerobic metabolism.[10,11] Ussing and Zerahn carried out their first "short circuit" studies on this tissue and were able to establish that sodium was the ionic species being actively moved.[12] Subsequent work involved studies of the quantitative relationship between metabolism (i.e., oxygen consumption) and active sodium transport.[13] Experiments with this tissue have been extensively used as a prototype for investigation of sodium transport in other tissues.

Energy may be put directly into a system involved directly in the movement of a solute — primary active transport — or a solute may be moved, even uphill, in conjunction with the flow of another solute or of solvent. The movement of one solute can be coupled to the flow of another solute either by having the solutes move in opposite directions (exchange processes or antiport) or by the flux of solutes being in the same direction (symport). An example of exchange is the movement of K^+ into a cell secondary to the active extrusion of the Na^+ out of the cell. These types of exchange reactions are very common, occurring in cells (red cells[14] and muscle[15]) and epithelial sheets of cells (kidney[16] and intestine[17]). Another common form of antiport is that of hydrogen exchanging for sodium.[18,19]

Within the past decade or so, the significance of symport has been increasingly recognized as a mechanism for moving solutes. At a much earlier date, however, the basis of the symport phenomenon was established when it was found that Na was required for optimal transport of glucose by the intestine and that the presence of glucose also increased the transport of sodium.[20] Current evidence indicates a linkage between sodium movement and that of a variety of organic solutes. This evidence will be reviewed later in this chapter to indicate that energy is put into the system to create a sodium gradient and that energy for transport of the organic solute is derived in whole or in part through dissipation of this gradient.

In consideration of cell transport, it becomes important to define the localization of the energetic steps. Two problems are encountered: the first is the question of what transport process is involved in maintaining electrolyte gradients between a cell and its environment. Since all cells maintain such gradients, it is likely that this process is relatively primitive and ubiquitous. The second problem relates to cell sheets and

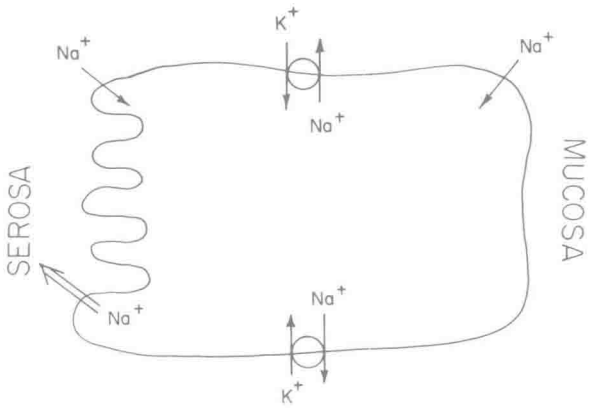

FIGURE 2. Schematic diagram of different paths for sodium movement. Inward passive diffusion of extracellular sodium is indicated by the arrows pointing downward at the upper corners of the cell. Na—K exchange is represented by the loop showing the movement of these two ions in opposite directions. Both of these pathways may undergo membrane-localized changes in density, but probably exist on all cell surfaces. The outward active transport step for sodium is indicated by the double arrow pointing upward and located in the serosal side of the cell.

glands wherein unidirectional transport processes occur. The question is one of how unidirectional transport across an epithelium can be accomplished. It seems likely that the unidirectional processes arose as a modification of the mechanism responsible for maintaining the cellular electrolyte gradients.

Figure 2 shows an idealized cell which illustrates both kinds of transport. It has been shown for a variety of single cells (e.g., nerve,[21] muscle,[22] and kidney[23]) that sodium enters the cell by passive permeation, i.e., down its electrical and chemical gradient. A membrane-localized process then actively extrudes sodium from the cell. Evidence has accumulated that the extrusion of sodium can also be accompanied by the entrance of potassium. When such an exchange process occurs, i.e., one ion of K replacing one ion of Na, no net electrical charge is moved, and the process is considered to be nonelectrogenic. Consequently, only concentrative work is required to move the ions up their concentration gradients. No electrical work is done. However, in most systems, the ratio is not a one-for-one exchange (e.g., 3 Na for 2 K in the red cell[24]). Additional electrical energy is required for the fraction of sodium moving against the electrical gradient, unaccompanied by another ion of like sign moving in the opposite direction.

Transcellular transport involves the same steps, i.e., a passive leak of Na into the cell followed by active extrusion. If, as seems to be the case, the same processes involved in vectorial transport are involved in maintaining cellular electrolyte balance, the question arises as to how directionality is achieved. Two mechanisms which have been suggested are:

1. Infoldings of the membrane on the side to which the solute (usually Na) is to be moved (usually the serosal side of cell sheets, the peritubular side of the renal tubules) could provide for more transport sites on this side.
2. More ATP for energy may be made available on the serosal side through localization of mitochondria, the major ATP source. This kind of localization is well demonstrated by the nephron.[25]

Another possibility which should be investigated is simply that there are more transport sites on the serosal or peritubular membrane independent of membrane area. Finally, the basic assumption may be incorrect and a separate pathway may exist for vectorial transport unrelated to maintenance of the ionic balance of cells.

III. THE ROLE OF METABOLISM IN ACTIVE TRANSPORT

There are several ways by which cellular metabolism may affect the transport of ions across cell membranes. Primarily, cellular metabolism is necessary to provide energy for the active transport of the solute. Often, however, it is simply assumed that if the transmembrane movement of a solute is dependent upon metabolism, that movement of the solute must be active. Although the direct utilization of cellular energy is a necessary condition, it is in itself not sufficient evidence for active transport. There are other ways by which metabolism can influence solute movement without implicating active transport. The fact that the passive movement of ions down their electrochemical gradients requires specific structures within the cell membrane, whether they be hydrophilic conductive channels or specific carriers, demands that such structures must by necessity be produced and maintained functional through processes which utilize energy.[26] Thus, although metabolism is a requisite for the transport of these solutes, it merely plays a facilitory role in providing the appropriate structure for transport and is not directly involved in the translocation of the solute itself.

Another way by which metabolism may effect transmembrane solute movement is through the active transport of some species other than the solute of interest. The other species provides a concentration gradient (i.e., potential energy) for the carrier mediated but passive transport of the solute of interest. Although cellular metabolic energy is being utilized, it does not directly participate in the translocation of the solute. This process is generally not thought of as being active transport. In some cases it is called "secondary active transport" since the movement of the solute is secondary to the active transport of the driving solute which provides the energy gradient for the "uphill transport".

Although one must be cautious not to couple nonactive transport processes erroneously with cellular metabolism, the necessary coupling between metabolism and active transport has proven to be useful in understanding the energetics of the active transport of Na^+ and K^+.[27-29]

In cells such as erythrocytes, which utilize glycolysis as their main metabolic source of energy, numerous authors[27,30-32] have shown that glucose utilization and lactate production are coupled to active transport of sodium and potassium. Furthermore, as early as 1928, Lund[33] perceived the dependence of action transport on oxygen consumption by frog skin. Since that time there have been numerous studies of the role and stoichiometry of oxygen consumption with active ion transport.[13,34,35] Clearly, for several tissues it has been shown that the rate of oxygen consumption is related to the rate of active sodium transport.[29,34,36] When care is taken to eliminate the contributions of bacterial contamination to oxygen consumption, as well as the required "basal metabolism" of cells, studies have shown not only that oxygen consumption by the various tissues parallels active transport, but also that there is an extremely tight coupling stoichiometry between the utilization of oxygen and the amount of sodium transported across the tissue.[37,38] While studies of the stoichiometry of catabolic metabolism to active transport have been useful and have led to several unique and potentially useful tools for studying active transport,[37,39] their success is the direct result of the tight coupling of both anaerobic and aerobic metabolism to the production of adenosine triphosphate (ATP).

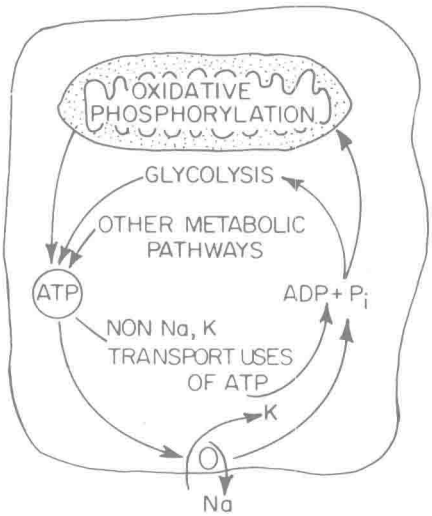

FIGURE 3. Schematic representation of pathways for generation of ATP and for its utilization in providing energy for sodium transport.

IV. THE ROLE OF ATP

As is seen in Figure 3, whether the main metabolic source of energy is glycolysis, oxidative phosphorylation, or even another less important metabolic pathway,[40] the currency for energy is ATP. This ubiquitous molecule is found in virtually every mammalian cell which transports sodium and potassium. Clearly the transport machinery of the cell cannot tell where the ATP it will utilize to bring about the translocation of the ionic species came from. Thus, the production of ATP by whatever cellular metabolic process and its hydrolysis by the ionic transporting mechanism are of paramount importance in understanding the nature of active transport.

V. THE MOLECULAR BASIS FOR ACTIVE TRANSPORT — Na-K-ATPase

It is clear that transport of sodium out of cells and the simultaneous transport of potassium into cells is an active transport process. Not only are both ions moved against their electrochemical gradients but also these movements require cellular energy in the form of ATP.

Within the last 20 years numerous studies have provided overwhelming evidence that the active transport of Na^+ and K^+ are associated with the K^+- Na^+-, Mg^{++}-dependent ATPase enzyme commonly called Na-K-ATPase (see Glynn and Karlish[41] for a review of this subject). From the earliest work of Skou[42] on this subject to the most recent papers,[41,43] parallels have been established between active Na^+ and K^+ transport and this enzyme system. Not only are both the enzyme system and the active transport "pump" associated with cell membranes, but also both require the same substrates, Na^+, K^+, Mg^{++}, and ATP,[44] and they are both poisoned by the same agents, ouabain,[45] and Ca^{++},[46] as well as others.[47] Furthermore, both systems have high activities in cells and tissues[48] where the active Na and K transport is high.

In a recent excellent review, Glynn and Karlish[41] survey much of the evidence for the association of the sodium pump to Na-K-ATPase and discuss the mechanism by

此为试读,需要完整PDF请访问: www.ertongbook.com