J. exp. Biol. ***196****, 1–4 (1994)*
Printed in Great Britain © The Company of Biologists Limited 1994

COUPLING AS A WAY OF LIFE

WILLIAM R. HARVEY

Department of Biology, Temple University, Philadelphia, PA 19122, USA

AND CLIFFORD L. SLAYMAN

Department of Cellular and Molecular Physiology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510, USA

Rationale for *Transporter* volume

More than three decades years ago, Aharon Katchalsky and Ora Kedem (1958, 1962) pointed out that the essence of biological transport is *coupling*. This insight was not so much a deduction as a concise summary of observations. At an elementary level, movement of a solute in the simplest aqueous solution implies movement of a hydration shell, and therefore movement of water, thence coupling of water movement to solute movement. In biological systems, for our present purposes specifically in biomembranes, more complex coupling mechanisms were clearly perceived, *albeit* largely without mechanistic understanding. The necessary response of these and other physically oriented biologists was to seek an understanding of coupling processes, along with formal descriptions, in the familiar language of thermodynamics. Their effort produced an elegant systematic statement of transport coupling, in the so-called Kedem equation (Kedem, 1961; see Gerencser and Stevens, 1994):

$$J_S = (1/R_S)(\Delta\mu_S + z_S F\Delta\Psi + R_{SW}J_W + R_{SA}J_A + R_{SB}J_B + R_{SR}J_R)\,,$$

stating that any species (S) of ion or molecule capable of flow (J) across a biological membrane may do so under the influence of several categories of driving force: that due to thermal agitation acting on a concentration difference $\Delta\mu_S$, that due to an electric field ($\Delta\Psi$), that due to water flow (J_W) and drag, that due to chemical/physical interaction with other transiting ions or molecules (J_A, J_B, ...) and that due to chemical coupling with metabolic reactions (J_R). This formalism neatly solved a major conceptual problem of the time, i.e. how to define (primary) *active transport* in an unequivocal and still useful way: as endergonic transport due to coupling with J_R alone, where the coupled exergonic reaction would provide the driving energy. [In this version of the Kedem equation, R_s is the resistance to movement of the solute, S; and R_{SW}, R_{SA}, R_{SB}..., are the operational resistances of the membrane to the coupled flows.] A logical spin-off of this exercise was another useful definition, that of *secondary active transport*: i.e. transport of S coupled to J_W, J_A, J_B, etc.), wherein S moves up its electrochemical gradient (usually concentrated into cytoplasm) at the expense of downhill movement of W, A, B, etc. Passive transport was taken by default as being due to $\Delta\mu_S$, or $\Delta\Psi$, with both of these resultant flows being exergonic and requiring no other input of energy.

Key words: transporters, facilitated diffusion–uniport, cotransport–symport, exchange diffusion–antiport.

We have progressed a very long way in the past 35 years, to the point where we know that all of these processes are mediated rather specifically by proteins, and where we know the primary structures (amino acid sequences) of tens to hundreds of proteins in each category. One of the major generalities that has emerged during this progress is that the great functional diversity of active transport processes existing among living systems is based mainly on mechanisms in the fourth category: protein-mediated coupling between different species of transiting ions and molecules. That is the central subject of this volume, which has been assembled to provide a comprehensive, contemporary review of coupled transport and the responsible transporter proteins.

The volume is directed to scientists working in membrane transport and related areas, to graduate students and advanced undergraduate students seeking a broad purview of the subject, and to other investigators and would-be investigators seeking a view across the new frontier of Molecular Physiology. Contributers were chosen by the Editorial Board of the *Journal of Experimental Biology* and were selected for their accomplishments in the field, for their clarity of presentation and for their breadth of coverage in ensemble. The articles are arranged into seven chapters, each with a short introduction to put the chapter topics into a general perspective; moreover, most of the articles themselves begin with cogent background to their specific material. All of the articles were written in the period January–June, 1994.

Terms and definitions

A major difficulty in reading the literature of transport coupling proteins, particularly on first appproach, is a somewhat skeltered and redundant terminology, which arose as the field grew up among two quite separated groups of investigators. First, medically oriented researchers – exploiting such traditional model systems as the frog skin or toad bladder, and clinically related tissues such as red blood cells, kidney, gut and brain – adopted ‘exchange diffusion’ (Ussing, 1947), ‘ion exchange’ and later the term ‘countertransport’ for coupling in which the separate ionic (or molecular) species move in *opposite* directions through the biomembrane; they used the term ‘cotransport’ (Crane, 1965) for coupled movement of two species in the *same* direction. Later, bioenergeticists and microbial physiologists – inspired by Peter Mitchell’s insightful work on mitochondria and chloroplasts (e.g. Mitchell, 1972) and by the rapid development of molecular studies on bacterial transporters, particularly the lactose permease (Kaback, 1974; Newman and Wilson, 1980) – adopted the more compact terms ‘*antiport*’ and ‘*symport’* for countertransport and cotransport; and adopted the related term ‘*uniport*’ (in favor of ‘facilitated diffusion’) for protein-mediated transfer of a single species of ion or molecule.

Multiple terminologies have likewise been used in reference to membrane electrical variables: for example, ‘P.D.’, ‘membrane potential’, ‘membrane voltage’, V_m, E_m, and $\Delta\Psi$, for the transmembrane difference of electrical potential. Since most coupled transporters move ionic charges through biological membranes and therefore must interact with the membrane’s electric field, this multiplicity too is cumbersome.

Table 1. *Transport terminology*‡

Primary transport processes

1. *Primary solute translocation.* A vectorial enzymatic reaction catalyzing transmembrane solute transfer up an electrochemical gradient, but without chemical alteration of the solute. This process is traditional *active transport*. Examples include transport carried out by the Na^+/K^+-ATPase, the Ca^{2+}-ATPase of sarcoplasmic reticulum and various proton-translocating P-, F- and V-ATPases.

2. *Group translocation.* An enzymatic reaction which catalyzes transfer of a solute across a membrane and *simultaneous* chemical transformation of the solute to another species of molecule. Examples include accumulation of various sugar phosphates in bacteria growing upon simple sugars, due to the action of phosphotransferases.

3. *Electron translocation.* Electron transport occurring between redox enzyme couples arrayed across a biological membrane. Examples include oxidation of cytochrome *c* by cytochrome *a* in the inner membrane of mitochondria.

Secondary transport processes

1. *Symport**. Coupled transport of two solutes in the same direction across a membrane, mediated by a single type of protein molecule; also called '*cotransport*'. Examples include Na^+-linked uptake of neurotransmitters, sugars and amino acids by animal cells, and H^+-linked uptake of sugars, amino acids and nucleosides by plants, fungi and bacteria.

2. *Antiport**. Coupled transport of two solutes as above but in opposite directions across the membrane; also called '*exchange*' or sometimes 'exchange diffusion'. Examples include Na^+/H^+ exchange in bacteria and many animal tissues, nigericin-mediated K^+/H^+ exchange.

3. *Uniport*†. Transmembrane transfer of solute, with kinetic characteristics similar to symport and antiport, but involving only a single species moving predominantly in one direction, not coupled either to metabolic energy or to other solute gradients. Uniport can mediate net transfer only down the solute's electrochemical gradient; also called '*facilitated diffusion*'. Examples include glucose uptake by erythrocytes and valinomycin-mediated K^+ transport.

*Symport and antiport together correspond to traditional *secondary active transport* when one of the paired solutes moves up its electrochemical gradient.

†For simplicity, we specifically exclude from this definition the functions of membrane pores or channels.

‡Modified from Harold (1986).

Table 2. *Nomenclature for elementary electrical variables*

Primary quantities

$\boldsymbol{R}$	gas constant, $Jmol^{-1}$; K^{-1}
F	Faraday constant; $Cmol^{-1}$
T	temperature
z_k	valence of ionic species k
$\Delta\Psi$	measured transmembrane voltage taken as side 2 minus side 1, also E_m, V_m; V
c_{k1}	concentration of ionic species k on side 1 of a membrane also $[k]_1$; $mol\,l^{-1}$

Calculated quantities

$\Delta\bar{\mu}_k = \boldsymbol{R}T[\ln(c_{k1}/c_{k2})] + z_kF\Delta\Psi$; $Jmol^{-1}$; the transmembrane difference of electrochemical potential for a monovalent cation, k

$\Delta k = \Delta\bar{\mu}_k/z_kF$; volts; the so-called ion-motive force for a monovalent cation, k (Mitchell, 1961)
$E_k = (\boldsymbol{R}T/z_kF)[\ln(c_{k1}/c_{k2})]$; volts; the Nernst potential or equilibrium potential difference for a monovalent cation, k, at two different concentrations on two sides of a membrane. Electrical equivalent of the concentration ratio for k.

In order to minimize the reader's confusion due to these and other purely semantic problems, we have set down a list of preferred terms in Tables 1 and 2 and have asked contributing authors to adhere to them as closely as possible and, when variant terms are deemed necessary, to indicate the corresponding form in the table upon first use of each particular variant. A table of these terms has been compiled previously (Harold, 1986) and they are discussed more fully in Wolfersberger (1994).

References

CRANE, R. K. (1965). Na^+-dependent transport in the intestine and other animal tissues. *Fedn Proc. Fedn Am. Socs exp. Biol.* **24**, 1000–1006.

GERENCSER, G. A. AND STEVENS, B. R. (1994). Thermodynamics of symport and antiport catalysed by cloned or native transporters. *J. exp. Biol.* **196**, 59–75.

HAROLD, F. M. (1986). *The Vital Force: A Study of Bioenergetics*. 577pp. New York: W. H. Freeman and Co.

KABACK, H. R.(1974). Transport studies in bacterial membrane vesicles. *Science* **186**, 882–892.

KATCHALSKY, A. AND KEDEM, O. (1962). Thermodynamics of flow processes in biological systems. *Biophys. J.* **2** (Suppl.), 53–78.

KEDEM, O. (1961). Criteria of active transport. In *Membrane Transport and Metabolism* (ed A. Kleinzeller and A. Kotyk), pp. 87–93. Prague: Academia Publishing House.

KEDEM, O. AND KATCHALSKY, A. (1958). Thermodynamic analysis of the permeability of biological membranes to non-electrolytes. *Biochim. biophys. Acta* **27**, 229–246.

MITCHELL, P.(1961). Coupling of phosphorylation to electron and hydrogen transfer by a chemi-osmotic type of mechanism. *Nature* **191**, 144–148.

MITCHELL, P. (1972). Performance and conservation of osmotic work by proton-coupled solute porter systems. *Bioenergetics* **4**, 265–293.

NEWMAN, M. J. AND WILSON, T. H. (1980). Solubilization and reconstitution of the lactose transport system from *Escherichia coli*. *J. biol. Chem.* **255**, 10583–10586.

USSING, H.(1947). Interpretation of the exchange of radio-sodium in isolated muscle. *Nature* **160**, 262.

WOLFERSBERGER, M. G.(1994). Uniporters, symporters and antiporters. *J. exp. Biol.* **196**, 5–6.