AD-A188 725 MOLECULAR AND ELECTRONIC MECHANISM IN THE CONTROL OF NA(+) AND (K+) PERME..(U) PENNSYLVANIA HOSPITAL PHILADELPHIA DEPT OF MOLECULAR BIOLOGY.. G N LING

UNCLASSIFIED 12 NOV 87 N00014-85-K-0573 F/G 6/1 NL

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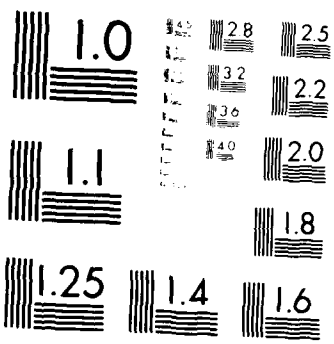

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REPORT DOCUMENTATION PAGE

1 AD-A188 725	1b RESTRICTIVE MARKINGS: NA
2 NA	3 DISTRIBUTION/AVAILABILITY OF REPORT: Distribution Unlimited
4 PERFORMING ORGANIZATION REPORT NUMBER(S): NA	5 MONITORING ORGANIZATION REPORT NUMBER(S): NA
6a NAME OF PERFORMING ORGANIZATION: Pennsylvania Hospital; 6b OFFICE SYMBOL (If applicable): NA	7a NAME OF MONITORING ORGANIZATION: Office of Naval Research
6c ADDRESS (City, State, and ZIP Code): Molecular Biology Department, Pennsylvania Hospital, Eighth & Spruce Sts., Phila., PA 19107	7b ADDRESS (City, State, and ZIP Code): 800 N. Quincy Street, Arlington, VA 22217-5000
8a NAME OF FUNDING/SPONSORING ORGANIZATION: Office of Naval Research; 8b OFFICE SYMBOL (If applicable): ONR	9 PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER: N00014-85-K-0573
8c ADDRESS (City, State, and ZIP Code): 800 N. Quincy Street, Arlington, VA 22217-5000	10 SOURCE OF FUNDING NUMBERS: PROGRAM ELEMENT NO: 61153N; PROJECT NO: RR04108; TASK NO: ; WORK UNIT ACCESSION NO:

11 TITLE (Include Security Classification)

(U) Annual Report - Molecular and Electronic Mechanism in the Control of Na^+ and K^+ Permeability of Excitable Cell Membrane by Ligand Binding on Receptor Sites

12 PERSONAL AUTHOR(S): Gilbert N. Ling, Ph.D.

13a TYPE OF REPORT	13b TIME COVERED	14 DATE OF REPORT (Year, Month, Day)	15 PAGE COUNT
Annual	FROM 7/1/86 TO 10/31/87	November 12, 1987	4

16 SUPPLEMENTARY NOTATION

17 COSATI CODES			18 SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	Permeability, Drugs, Electronic Theory, Na, K
08			

19 ABSTRACT (Continue on reverse if necessary and identify by block number)

Our objective is to investigate the control of cell membrane permeability to Na^+, K^+, and other ions by transmitters, drugs, and other biologically potent ligands: to extend and test a general electronic theory of the control of physiological activities.

20 DISTRIBUTION/AVAILABILITY OF ABSTRACT	21 ABSTRACT SECURITY CLASSIFICATION
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Dr. J. A. Majde	202/696-4055	ONR

DD FORM 1473, 84 MAR — 83 APR edition may be used until exhausted. All other editions are obsolete.

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Principal Investigator: Gilbert N. Ling, Ph.D.

Contractor: Pennsylvania Hospital

Contract Title: " Molecular and Electronic Mechanism in the Control of Na^+ and K^+ Permeability of Excitable Cell Membrane by Ligand Binding on Receptor Sites"

Start Date: 1 July 1985

Research Objective:

To investigate the control of cell membrane permeability to Na^+, K^+, and other ions by transmitters, drugs, and other biologically potent ligands: to extend and test a general electronic theory of the control of physiological activities.

Progress:

(Year 1 and 2): In 1962, a new theory of cell physiology called the association-induction (AI) hypothesis was published. As its title indicates, this theory can be roughly divided into two parts: " association" which describes, in time-space coordinates, the relationships among the three major components of the living matter: proteins, water, and ions; " induction" which describes in electronic terms the all-or-none shifts between resting and active physiological states brought on by controlling agents including transmitters, drugs, hormones, ATP, Ca^{++}, etc. Uninterrupted support of ONR (and NIH) for the last 25 years had made possible the verification of the essence of the association aspect of the new paradigm. The new ONR interest in the excitable " membrane physiology", guided by Dr. Martin Blank, gave impetus to new efforts to study the control mechanisms (which contributes to hopes that one day mankind may eventually through the development of rational drug therapy conquer the ever-mutating and ever-evolving lethal viruses like AIDS).

In the last two years we have made progress in two directions:

(1) To establish that electronic polarization or induction - which underlies the behaviors of all small organic molecules - also plays key roles in the behaviors of proteins and hence all living cells which are made of proteins (water and ions). More specifically, the secondary structures of proteins (i.e., the specific ways of folding) are predetermined by its primary structure (i.e., the nature and sequential order of the amino acid residues in the protein chain) - a fact known, but essentially unexplained - is now found explicable in terms of the inductive effect (see Publ. #1 - Ling, Physiol. Chem. Phys. and Med. NMR 18:3 (1986)).

(2) The key postulates of the theory of (the resting and) action potential which was first introduced in 1960, have been confirmed (though both the theory and its confirmation have been little known). These postulates include:

(i) that during the initial phase of the action potential, the cell surface β- and γ-carboxyl groups undergo an increase of electron density or " c-value" (and a rise of pK_a values); and

(ii) that such c-value changes occur in the same β- and γ-carboxyl groups. Using the multiple ion probe method, Ling and Fu have now obtained additional evidence that the cell surface β- and γ-groups of two types of living cells (frog skeletal muscle and frog ovarian

eggs) do indeed increase their c-value in response to interaction with a cardinal adsorbent, the drug, ouabain. Furthermore, ouabain consistently acts as an " electron donating cardinal adsorbent" EDC) in its control of the cytoplasmic β- and γ-carboxyl groups (responsible for the bulk phase accumulation of alkali-metal ions); the cell surface β- and γ-carboxyl groups (that give rise to the resting potential); as well as the cell surface β- and γ-carboxyl groups (that mediate the traffic of K^+, Na^+, and other alkali-metal ions in and out of living cells) (Ms. #2).

Work Plan:

(Year 3): The success of the multiple ion probe method (Ms. #1 and 2) in detecting and in measuring both the direction and magnitude of the c-value changes of β- and γ-carboxyl groups in response to the binding of drugs or other ligands has opened the door toward further testing the hypothesis that alkaloids like veratridine and aconitine that can emulate the theoretical " gating particle" and generate a sustained cell membrane depolarization and activation like that seen transiently during an action potential is distinguished from effects of other non-activating EDC's (e.g., ouabain) in consequence of a much larger c-value increase created and the hypothesis that " channel blockers" (e.g., tetradotoxin) may act by virture of this opposing electronic effect on the β- and γ-carboxyl group as that giving rise to the rapid initial surge of inward Na^+ current; in other words, tetradotoxin may act as an electron-withdrawing cardinal adsorbent (EWC). We also plan to see if we can study the effects of enough numbers of drugs, transmitters, and other cardinal adsorbents on the membrane permeability (and other related physiological manifestations) to test the hypothesis that all effective drugs, transmitters, and other cardinal adsorbents can be classified in two categories: EDC and EWC and that each cardinal adsorbent can produce a characteristic quantitatively similar c-value change on different parts of the living cell as our study of the cardiac glycoside has already demonstrated.

Publications:

Multiple supports from different grant-agencies have been vital to our operation. Our continued research and publications on cell water related subjects (after ONR support for work on cell water had ceased) was because 75% of our total current financial support is from the National Cancer Institute, under the title, " What Distinguishes Water in Normal and Cancer Cells?"

* A. Book: " A Revolution in Physiology of the Living Cell: and Beyond" is a landmark volume chronicling work performed under both previous and present ONR contracts. It is in this volume (but not yet in the large volume, In Search of the Physical Basis of Life) that the completion of a revolution in cell physiology is fully described.

B. Publications in Print:

* Publ. #1 - Ling, G. N., " The Role of Inductive Effect in the Determination of Protein Structure", Physiol. Chem. Phys. and Med. NMR 18:3 (1986)

Publ. #2 - Heidorn, D. B., Rorschach, H. E., Hazlewood, C. F., Ling, G. N., and Nicklow, R. M., " Neutron Scattering Studies of Water in Frog Muscle", Biophys. J. 49:92A (1986)

Publ. #3 - Ling, G. N., and Ochsenfeld, M. M., " Membrane Lipid Layer vs.

* Polarized Water Dominated by Fixed Ions: A Comparative Study of the

Effects of Three Macrocyclic Ionophores on the K^+ Permeability of Frog Skeletal Muscle, Frog Ovarian Eggs, and Human Erythrocytes", Physiol. Chem. Phys. and Med. NMR 18:109 (1986)

* Publ. #4 - Ling, G. N., "Cooperative Interaction Among Surface β- and γ-carboxyl Groups Mediating the Permeation of Ions Into Frog Muscle Cells", Physiol. Chem. Phys. and Med. NMR 18:125 (1986)

Publ. #5 - Ling, G. N., Reid, C., and Murphy, R. C., "Are the Proteins in Malignant Cancer Cells of Diverse Origin Similar or Different?" Physiol. Chem. Phys. and Med. NMR 18:147 (1986)

Publ. #6 - Ling, G. N., "A Theory of the Water Contents of Living Cells in Solutions Containing Different Concentrations of Permeant Solutes" (short note) Physiol. Chem. Phys. and Med. NMR 18:131 (1986)

Publ. #7 - Ling, G. N., "The Origin of Cellular Electrical Potentials" in: Modern Bioelectrochemistry, eds. F. Gutman and H. Keyzer, Plenum Press, New York, 1985

Publ. #8 - Ling, G. N., "Experimental Confirmation of the Polarized Multilayer Theory of Cell Water Including Data That Lead to an Improved Definition of Colloids" in: Water and Ions in Biological Systems, eds. A. Pullman, V. Vasilescu, and L. Packer, Plenum Press, New York and London, 1985

Publ. #9 - Ling, G. N., "In Search of the Physical Basis of Life" in: Advances in Physiological Research, eds. H. McLennan, J. R. Ledsome, C. H. S. Mc Intosh, and D. R. Jones, Plenum Press, New York, p. 469-492 (1986)

C. Manuscripts in Various Stages of Publication But Not Yet in Print:

* Ms. #1 - Ling, G. N., and Fu, Y., "An Electronic Mechanism in the Action of Drugs, and Other Cardinal Adsorbents. I. Effect of the Cardiac Glycoside, Ouabain, on the Relative Affinities of the Frog Muscle Cell Surface β- and γ-carboxyl Groups for K^+, Na^+, and Other Ions" (in press), Physiol. Chem. Phys. and Med. NMR

* Ms. #2 - Ling, G. N., and Fu, Y., "An Electronic Mechanism in the Action of Drugs, and Other Cardinal Adsorbents. II. Effect of Ouabain on the Relative Affinities for Li^+, Na^+, K^+, and Rb^+ of Surface Anionic Sites that Mediate the Entry of Cs^+ into Frog Ovarian Eggs" (accepted for publication), Physiol. Chem. Phys. and Med. NMR

Ms. #3 - Ling, G. N., "Cell Volumes and Water Contents of Frog Muscles in Solutions of Permeant Sugars and Sugar Alcohols" (in press), Physiol. Chem. Phys. and Med NMR

* Ms. #4 - Ling, G. N., "On the Large Error Introduced in the Estimate of the Density of Membrane Pores from Permeability Measurements when Diffusion in 'Unstirred Layer' within the Cells is Disregarded" (in press), Physiol. Chem. Phys. and Med. NMR

Ms. #5 - Ling, G. N., and Ochsenfeld, M. M., "Studies on the Physical State of Water in Living Cells and Model Systems. VI. Concentration-dependent Sustained Volume Changes of Dialysis Sacs Containing Aqueous Solution of

* These publications or manuscripts are primarily supported by ONR contract and/or are of direct relevance to the ONR-supported program.

Native and Denatured Protein, Gelatin, and Oxygen-containing Polymers Immersed in Solutions of Na Salt and of Sugar and Sugar Alcohol" (in press) Physiol. Chem. Phys. and Med. NMR

Ms. #6 - Ling, G. N., " Studies on the Physical State of Water in Living Cells and Model Systems. VII. Exclusion of Sugars and Sugar Alcohols from the Water in Sulfonate Ion Exchange Resins: The 'Size Rule'" (in press) Physiol. Chem. Phys. and Med. NMR

Ms. #7 - Ling, G. N., and Hu, W. X., " Studies on the Physical State of Water in Living Cells and Model Systems. VIII. Water Vapor Sorption on Proteins and Oxygen-containing Polymers at Physiological Vapor Pressures: Presenting a New Method for the Study of Vapor Sorption at Close To and Including Saturation" (in press) Physiol. Chem. Phys. and Med. NMR

Ms. #8 - Ling, G. N., " Do We Need a New View of the Living Cell" The Physical Aspect of the Living Cell, Eugene Ernst Memorial Symposium, July 3-5, 1986, Pecs, Hungary (accepted for publication)

Ms. #9 - Ling, G. N., " The Association-Induction Hypothesis and Life" Second European Congress on Cell Biology, July 6-11, 1986, Budapest, Hungary (accepted for publication)

Ms. #10 - Ling, G. N., " A Physical Theory of the Living State: Application to Water and Solute Distribution, SEM Conf., May 4-5, 1987, Hamilton, Ontario (accepted for publication)

Ms. #11 - Ling, G. N., " Solute Exclusion by Polymer and Protein-Dominated Water: Correlation with Results of NMR and Calorimetric Studies and Their Significance Toward the Understanding of the Physical State of Water in Living Cells" (accepted for publication)

Training Activities

Sharyn Horowitz, a highly motivated honor student, worked this summer at the laboratory on a volunteer basis.

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