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Milton Zaitlin

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Cornell University
Ithaca, NY 14853

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13. ABSTRACT (Maximum 200 words)

Graduate student fellowships in the area of Protein Structure and Function, with subcategories of Enzymes and Receptors, were awarded annually on a competitive basis. Research activities of fellows were aimed at providing a fundamental understanding of the interactions between ligands and receptors. Areas of emphasis included protein folding, thermal stability and assembly, controlled-release neuroagents and detection systems. This research continues to provide the fundamental science and knowledge base required for the ultimate production of "designer" receptors and ligands engineered for biosensors, environmental decontamination, and for chemical/biological blocking agents.

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Twenty-three individual graduate fellows were supported for a total of 49.75 person years. Fifteen ARO fellows completed their PhD thesis research and were granted degrees, one student left graduate school for medical reasons and six fellows are completing their PhD degree in 1992 with their final years support from the ARO Center of Excellence Research program.

ARO 24631.29-LS-UIF

CENTER OF EXCELLENCE IN BIOTECHNOLOGY (FELLOWSHIPS)

FINAL REPORT

Dr. Milton Zaitlin
Biotechnology Program
Cornell University

12 December 1991

U. S. Army Research Office

Proposal No. 24631-LS-UIF
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Office of Sponsored Programs
120 Day Hall
Cornell University
Ithaca, New York 14853

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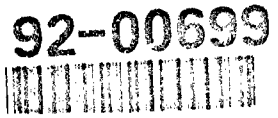

Center of Excellence in Biotechnology
Graduate Fellowship Program
Grant No. DAALO3-86-G-0204
1 October 1986 - 30 September 1991
Final Report

Forward

ARO Center of Excellence Fellows have received broad-based, interdisciplinary research training in the laboratories of outstanding faculty at Cornell University. In addition, they have been exposed to both Army and industrial scientists and their research and the employment opportunities available outside the university setting. The Biotechnology Program and the ARO fellows commend the Army Office of Research for their insight in establishing and funding this fellowship program. The number of fellows supported each year formed a cohesive group, involved in both formal and informal seminars and symposia, presenting a viable presence on Campus. We are disappointed this excellent program will not continue.

2. No table of contents is provided.

3. Appendixes: Abstracts of publications not previously reported.
Special ARO Symposia Programs

4.A. Graduate student fellowships in the area of Protein Structure and Function, with subcategories of Enzymes and Receptors, were awarded annually on a competitive basis. Research activities of fellows were aimed at providing a fundamental understanding of the interactions between ligands and receptors. Areas of emphasis included protein folding, thermal stability and assembly, controlled-release neuroagents and detection systems. This research continues to provide the fundamental science and knowledge base required for the ultimate production of "designer" receptors and ligands engineered for biosensors, environmental decontamination, and for chemical/biological blocking agents.

4.B. Twenty-three individual graduate fellows were supported for a total of 49.75 person years. Fifteen ARO fellows completed their PhD thesis research and were granted degrees, one student left graduate school for medical reasons and six fellows are completing their PhD degree in 1992 with their final years support from the ARO Center of Excellence Research program. A complete list of ARO fellows, including current positions of those students who

have completed degree requirements, appears in Section 4.D; thesis titles and degree dates are shown in that Section also.

Fellows were selected following campus-wide competition announcements. Applicants submitted a three-page research proposal along with the usual transcripts and letters of recommendation. Students were eligible to apply after completing two years of graduate study, at which time they were generally finished with all formal course work and were concentrating on their thesis research. Ad hoc faculty committees representing a number of scientific specialty areas judged and ranked the applications. The Program's Scientific Administrative Board was responsible for the final selection of Army Center Fellows.

ARO fellows, thus selected, represented eight different Fields of Study at Cornell: Biochemistry, Chemistry, Chemical Engineering, Pharmacology, Genetics, Vet Microbiology, Animal Science and Animal Health. They were involved in interdisciplinary projects covering the areas of (1) cell surface receptors, (2) protein structure and function, (3) molecular biology, and (4) bioprocess engineering.

In addition to individual research projects, all Biotechnology Fellows (including ARO fellows) participated in a number of symposia, seminars, and numerous industrial, state and federal progress site visits. The annual Biotechnology Program Symposium included poster presentations by each student. Special ARO symposia were held, (see Appendix) consisting of oral presentations from students and/or participation of scientists from various Army units (Natick Army Research Center, Walter Reed Institute of Research and the Chemical Research, Development and Engineering Center at Aberdeen). In addition, two students visited Army laboratories at Natick, five students visited Walter Reed and two students went to Aberdeen, in order to familiarize themselves with the work and facilities available at these installations. Of this group, two ARO fellows have indicated an interest in pursuing postdoctoral work at Aberdeen when they complete their PhD degrees in 1993.

One of the ARO fellows, Renee Reijo, participated in the development and testing of a DNA laboratory protocol for use at the pre-college level. During the past two summers, she has also taken part in teaching this laboratory to high school students during a three day in residence extension program. This has proven to be a highly successful hands-on laboratory experience for teenagers and will be repeated again this summer. The teenagers were impressed with the fact that this accomplished young woman was an Army fellow.

Student interaction with Army scientists has been detailed in progress reports submitted during the tenure of this grant. ARO fellow, Linda Tempelman and Dr. Daniel Hammer, continue their communications with Dr. Sheila Wood-Helie and Dr. James Valdes from the Aberdeen Proving Ground involving work on the receptor-mediated cell adhesion project as well as pathogen detection. Ms. Tempelman will complete her thesis research during the summer of 1992. She is currently considering a postdoctoral position at the Aberdeen Proving Ground.

4.C.

ARO Fellows Publication List

(Publications not previously reported are *)

Abstracts:

Braaten, B.A., **Platko, J.**, vanWoude, M., deGraaf, F.K., Calvo, J., and Low, D.A.
* (1991) "Leucine Responsive Regulatory Protein (Lrp) Controls the Expression of Both the Pap and Fan Pili Operons in *Escherichia coli*", Submitted to Proc. National Academy of Science, USA.

Ward, Michael D. and Hammer, Daniel A. (1991) "The Effects of Receptor and
* Glycocalyx Redistribution and Cytoskeletal Reorganization on the Morphology and Strength of Attachment of Cells to Ligand-Coated Surfaces", Submitted to Annual Meeting of the American Institute of Chemical Engineers.

Ward, Michael D. and Hammer, Daniel A. (1991) "The Influence of Cell-Surface
* Events and Cytoskeletal Reorganization on the Strength of Receptor-Mediated Cell Adhesion", Submitted to the 1991 An Biomed Engineering Soc Meeting.

Denton, M. E. and Scherage, H. A. (1988) The Folding of Hen Egg White Lysozyme: An Immunochemical and Spectroscopic Study. Presented at the Immunology of Lysozyme Workshop, NIH, June.

Holowka, D., Narashimhan, V., **Labrecque, G.**, Fewtrell, C. and Baird, B. (1988) Mechanisms of IgE Receptor-Mediated Activation of Ion Movements During Stimulus-Secretion Coupling in a Mast Cell Line. Soc of Gen Physiologists, September.

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Wilcox, B. D., Ignotz, G. G. and Currie, W. B. (1988) Effects of Ovariectomy, Steroid Replacement, and Parturition on Creatine Kinase Content and Activity in the Myometrium and Endometrium of Pregnant Rabbits. Society for the Study of Fertility, March.

Wilcox, B. D., Ignotz, G. G. and Currie, W. B. (1988) "Effects of Ovariectomy, Steroid Replacement, and Partuition on Creatine Kinase Content and Activity in the Myometrium and Endometrium of Pregnant Rabbits", J. Reprod. Fert. Abstract Series No. 1, 62.

Baird, B. and **Labrecque, G.** (1987) "Characterization of an Increased K+ Permeability Associated with the Stimulation of the Receptor for Immunoglobulin E (IgE) on Rat Basophilic Leukemia (RBL) Cells", 32nd Meeting of the Biophysical Society.

Manuscripts:

Ziegra, C.J., Willard, J.M. and Oswald, R.E. (1991) "Copurification of a Kainate Receptor from Goldfish Brain with a Functionally Coupled Pertussis Toxin-Sensitive G Protein". Submitted to J. Biol. Chem.

Carraway, K.L., III, and Cerione, R.A. (1991) "Comparison of Epidermal Growth Factor (EGF)Receptor-Receptor Interactions in Intact A431 Cells and Isolated Plasma Membranes. Large Scale Receptor Micro-Aggregation is Not Detected During EGF-Stimulated Early Events". J. Biol. Chem. 266, 8899-8906.

Carraway, K.L., III, and Cerione, R.A. (1991) "An Antibody to the Epidermal Growth Factor Receptor Inhibits Receptor-Receptor Interactions But Not EGF-Stimulated Tyrosine Kinase Activity". In Revision for Science.

Shapiro, A.B., Huber, A.H., and McCarty, R.E. (1991) "Four Tight Nucleotide Binding Sites of Chloroplast Coupling Factor 1". J. Biol. Chem., 266, 4194-4200. Willins, D.A., Ryan, C.W., **Platko, J.V.,** and Calvo, J.M. (1991) "Characterization of Lrp, an Escherichia coli Regulatory Protein that Mediates a Global Response to Leucine". J. Biol. Chem., 266, 10768-10774.

Denton, M.E., and Scheraga, H.A. (1991) "Spectroscopic, Immunochemical, and
* Thermodynamic Properties of Carboxymethyl(Cys^{6},Cys^{127})-Hen Egg White Lysozyme", J. Protein Chemistry, 10, 213-232.

Labrecque, G., Holowka, D., and Baird, B. (1991) "Characterization of Increased
* K+ Permeability Associated with the Stimulation of Receptors for Immunoglobulin E on Rat Basophilic Cells", J. Immunology, in press.

Wang, Ding-ji, Huang, Ning-na, **Gonzalez, Fernando** and Heppel, Leon A.
* (1991) "Multiple Signal Transduction Pathways Lead to Extracellular ATP-stimulated Mitogenesis in Mammalian Cells. II. A Pathway Involving Arachidonic Acid Release, Prostagiandin Synthesis and Cyclic AMP Accumulation", J. Cell Physiology, in press.

Huang, Ning-na, Wang, Ding-ji, **Gonzalez, Fernando** and Heppel, Leon A.
* (1991) "Multiple Signal Transduction Pathways Lead to Extracellular ATP-stimulated Mitogenesis in Mammalian Cells. I. Involvement of Protein Kinase C-dependent and Independent Pathways", J. Cell Physiology, in press.

Shapiro, A.B., Gibson, K.D., Scheraga, H.A., and McCarty, R.E. (1991) "Fluorescence Resonance Energy Transfer Mapping of the Fourth of Six Nucleotide Binding Sites of Chloroplast Coupling Factor 1", Submitted to J. Biol. Chem.

Yaney, G.C., **Stafford, G.A.,** Henstenberg, J.D., Sharp, G.W.G. and Weiland, G.A.
* (1991) "Binding of the Dihydropyridine Calcium Channel Blocker [^{3}H]PN200-110 to RINm5F Membranes and Cells: Characterization and Functional Significance", Submitted to J. Pharmacology and Experimental Therapeutics.

Witmer, M.R., Falcomer, C.M., Weiner, M.P., Kay, M.S., Begley, T.P., Ganem,
* B. and Scheraga, H.A. (1991) "U-3'-BCIP: A New Chromogenic Substrate for the Detection of RNase A", Submitted to J. Organic Chem.

Witmer, M.R., Weiner, M.P., Falcomer, C.M., Begley, T.P., Ganem, B. and
* Scheraga, H.A. (1991) "A New Chromogenic Substrate for Assaying Ribonuclease A Activity", Submitted to Nucleic Acid Research.

Walker, F., Nice, E., Fabri, L., Ray, P., Wu, R., **Moy, Franklin,** Scheraga, H.A., and Burgess, A.W. (1990) "Reduction in Receptor Mediated Degradation of a Marine Epidermal Growth Factor Analogue (Val47-EGF) Potentiates Mitogenic Activity. In preparation.

Platko, Jill V., Willins, Debra Aker and Calvo, Joseph M. (1990) "The *ilvIH* Operon of *Escherichia coli* is Positively Regulated". J. Bacteriology, In Press.

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Walker, F., Nice, E., Fabri, L., **Moy, Franklin,** Liu, Jin-Fu, Wu, R., Scheraga, H.A., and Burgess, A.W. (1990) "Resistance to Receptor-Mediated Degradation of a Marine Epidermal Growth Factor Analogue (EGF-Val-47) Potentiates Its Mitogenic Activity". Biochemistry, 29, 10635-10640.

Ziegra, Cynthia J., Oswald, Robert E. and Bass, Andrew H. (1990) "[3H]Kainate Localization in Goldfish Brain: Receptor Autoradiography and Membrane Binding". Brain Research, 527, 308-317.

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Gonzalez, F. A., Ahmed, A. H., Lustig, K. D., Erb, L. and Weisman, G. A. (1989) "Permeabilization of Transformed Mouse Fibroblasts by 3'-O-(4-Benzoyl)benzoyl Adenosine 5'-Triphosphate and the Desensitization of the Process", J. Cell. Physiol., 139, 109-115.

Gonzalez, F. A., Rozengurt, E., and Heppel, L. A. (1989) "Extracellular ATP Induces the Release of Calcium from Intracellular Stores in Swiss 3T6 Mouse Fibroblasts Without the Activation of Protein Kinase C", Proc. Natl. Acad. Sci. USA, 86, 4530-4534.

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Leipold, H. R., Burton-Wurster, N., Peery, M. S., and Lust, G. (1989) "Fibronectin and Keratan Sulfate Synthesis by Canine Articular Chondrocytes in Culture is Modulated by Dibutyryl Cyclic AMP", J. Orthop. Res, in press.

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Gonzalez, Fernando A., Alfonzo, Ramona G., Toro, Jorge R., and Heppel, Leon A. (1989) "Receptor Specific for Certain Nucleotides Stimulates Inositol Phosphate Metabolism and Ca^{2+} Fluxes in A431 Cells". J. Cellular Physiology, 141, 606-617.

Gonzalez, Fernando A., Bonapace, Eugene, Belzer, Ilana, Friedberg, Ilan and Heppel, Leon A. (1989) "Two Distinct Receptors for ATP Can be Distinguished in Swiss 3T6 Mouse Fibroblasts by Their Desensitization". Biochem. Biophys. Res. Commun., 164, 706-713.

Moy, Franklin, Scheraga, Harold A., Liu, Jin-Fu, Wu, Ray and Montelione, Gaetano, T. (1989) "Conformational Characterization of a Single-site Mutant of Murine Epidermal Growth Factor (EGF) by 'HNMR Provides Evidence That Leucine-47 is Involved in the Interactions with the EGF Receptor. PNAS 86, 9836-9840.

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Nowak, L. M. and **Christiansen, J. L.** (1988). Pharmacological Characterization of Non-NMDA Receptor-Channels in Mammalian Central Neurons. Neurochemistry International 12, Sup. 1, 5.

Burton-Webster, Nancy, **Leipold, Harry R.** and Lust, George (1988) "Dibutyryl Cyclic AMP Decreases Expression of Ed-A Fibronectin by Canine Chondrocytes", Biochem. Biophys. Res. Commun., 154 , 3, 1088-1093.

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McCarty, Richard E., **Shapiro, Adam B.**, and Feng, Yu (1988) "Regulation and Mechanism of the Chloroplast ATP Synthase in Relation to Function" In Light Energy Transduction in Photosynthesis: Higher Plant and Bacterial Models (S. E. Stevens, Jr. and D. A. Bryant, Eds.) The American Society of Plant Physiologists, pp. 290-304.

4.C. Technical Reports Submitted

Progress Reports Submitted:	Period Covered:
July 1987	January 1987 - June 1987
January 1988	July 1987 - December 1987
July 1988	January 1988 - June 1988
January 1989	July 1988 - December 1988
July 1989	January 1989 - June 1989
January 1990	July 1989 - December 1989
July 1990	January 1990 - June 1990
January 1991	July 1990 - December 1990
July 1991	January 1991 - July 1991

4.D. ARO Fellowship Awardees - 1986-1991

Student Name	Field of Study	Faculty Adviser	Appointment Period	Degree Earned	Current Position
Labrecque, Gary	Chemistry	Baird, Barbara	10/1/86-9/30/88	PhD 1989	Postdoctoral with G. Feigenson, Biochemistry, Cornell University
Papke, Roger	Pharmacology	Oswald, Robert	10/1/86-12/31/86	PhD 1987	Postdoctoral with Steve Heinemann, Salk Institute
Denton, Mary	Chemistry	Scheraga, Harold	10/1/86-6/30/89	PhD 1989	Postdoctoral with A. Stern, Hoffmann-LaRoche
Schultz, Bruce	Pharmacology	Sharp, Geoffrey	10/1/86-6/30/89	PhD 1990	Postdoctoral with Dr. Frizzell, University of Alabama
Zagotta, Michelle	Biochemistry	Wilson, David	10/1/86-10/30/88	PhD 1988	Postdoctoral with D. Ry Meeks-Wagner,University of Oregon
Gonzalez, Fernando	Biochemistry	Heppel, Leon	12/1/86-6/30/89	PhD 1989	Postdoctoral with Rober Davis, U of Mass Med Center
Witmer, Mark	Chemistry	Begley, Tadhg	7/1/87-6/30/90	PhD 1990	Postdoctoral, Pennsylvania State University
Wilcox, Brian	Animal Science	Currie, W. Bruce	7/1/87-6/30/90	PhD 1990	Research Assoc., Albany Medical College
Leipold, Harry	Animal Health	Lust, George	7/1/87-6/30/89	PhD 1989	Postdoctoral Assoc., CIBA-GEIGY
Davis, Mary Beth	Genetics	MacIntyre, Ross	7/1/87-6/30/89	PhD 1989	Postdoctoral with Charles Emerson, University of Virginia
Christianson, Janet	Pharmacology	Nowak, Linda	7/1/87-1/11/89	Med Leave	Medical Technician, Southern Calif Hospital
Glaser, Amy	Vet Microbiol	Seeger, Christoph	7/1/87-6/30/89		Continuing as Vet Asst., Diagnostic Labs, Cornell Vet School
Platko, Jill Verbeck	Biochemistry	Calvo, Joseph	7/1/88-6/30/91	PhD 1991	Postdoctoral with Richard Cerione, Cornell University
Carroway, Kermit	Biochemistry	Cerione, Richard	7/1/88-6/30/91	PhD 1991	Temp Postdoctoral with Richard Cerione, Cornell University
Champlin, David	Biochemistry	Lis, John	7/1/88-6/30/91	PhD 1991	Postdoctoral, University of Washington
Shapiro, Adam	Biochemistry	McCarty, Richard	7/1/88-6/30/91	PhD 1991	Posudoctoral, Ontario Cancer Institute
Ziegra, Cynthia	Pharmacology	Oswald, Robert	7/1/88-6/30/91	PhD 1991	Postdoctoral with Maja Suter, Vet Pathology, Cornell University
Tempelman, Linda	Chemical Engr	Hammer, Daniel	7/1/89-6/30/91		Continuing Fellow on ARO Research Funds
Yarnell, William	Biochemistry	Roberts, Jeffrey	7/1/89-6/30/91		Continuing Fellow on ARO Research Funds
Moy, Franklin	Chemistry	Scheraga, Harold	7/1/89-6/30/91		Continuing Fellow on ARO Research Funds
Stafford, Grace	Pharmacology	Weiland, Gregory	7/1/89-6/30/91		Continuing Fellow on ARO Research Funds
Ward, Michael	Chemical Engr	Hammer, Daniel	7/1/90-6/30/91		Continuing Fellow on ARO Research Funds
Reijo, Renee	Biochemistry	Huffaker, Timothy	7/1/90-6/30/91		Continuing Fellow on ARO Research Funds

Papke, Roger	PhD 1987	"Single Channel Currents of the Nicotinic Acetylcholine Receptor from the BC3H-1 Cells:..."
Zagotta, Michelle	PhD 1988	"Characterization of the Lambda S Protein using Antibiotics"
Labrecque, Gary	PhD 1989	"Studies on the Mechanism of Activation of Potassium Efflux and Receptor-Cytoskeleton Association by Aggregated Immunoglobulin E-Receptor Complexes on Rat Basophilic Leukemia Cells"
Denton, Mary	PhD 1989	"The Folding of Hen Egg-White Lysozyme"
Davis, Mary Beth	PhD 1989	"A Genetic and Molecular Analysis of alpha Glycerophosphate Oxidase Locus in Drosophila Melanogaster"
Leipold, Harry	PhD 1989	"Articular Chondrocyte Metabolism and Osteoarthritis"
Gonzalez, Fernando	PhD 1989	"Receptors for Extracellular Adenosine 5'-Triphosphate on the Plasma Membrane of Mammalian Cells"
Schultz, Bruce	PhD 1990	"Effect of Serotonin and Serotonergic Agents on Intestinal Ion Transport"
Witmer, Mark	PhD 1990	"Mechanistic Investigations of DNA Photolyase from E. Coli"
Wilcox, Brian	PhD 1990	"Steroid Modulation of Creatine Kinase and Other Induced Proteins in the Rabbit Uterus..."
Platko, Jill Verbeck	PhD 1991	"Genetic Analysis of lrp, a Leucine-responsive Regulatory Protein of E. Coli"
Carroway, Kermit	PhD 1991	"Role of EGF-Receptor Aggregation in Mitogenic Signaling"
Champlin, David	PhD 1991	"Chromatin Distribution and Molecular Characterization of the Drosophila B52 Protein"
Shapiro, Adam	PhD 1991	"Nucleotide Binding and the Catalytic Mechanism of Chloroplast Coupling Factor 1"
Ziegra, Cynthia	PhD 1991	"Characterization of the Kainate Receptor from Goldfish Brain"

For Biochemistry

Spectroscopic, Immunochemical, and Thermodynamic Properties of Carboxymethyl(Cys^{6}, Cys^{127})-Hen Egg White Lysozyme†

Mary E. Denton‡ and Harold A. Scheraga*

Baker Laboratory of Chemistry
Cornell University
Ithaca, New York 14853-1301

†This work was supported by research grants from the National Institue of General Medical Sciences of the National Institutes of Health (GM-14312) and the Cornell Biotechnology Center.

‡Cornell Biotechnology Army Research Office Predoctoral Fellow, 1986-1989.

*To whom requests for reprints should be addressed.

Running Title: Characterization of Carboxymethyl(Cys^{6}, Cys^{127})-Lysozyme

Abstract

A three-disulfide form of hen egg white lysozyme with Cys^{6} and Cys^{127} blocked by carboxymethyl groups was prepared, purified, and characterized for eventual use in protein folding experiments. Trypsin digestion followed by proline-specific endopeptidase digestion facilitated the unambiguous assignment of the disulfide bond pairings and the modified residues in this derivative. The pH dependence of the enzymatic activity demonstrated that, at the pH optimum for 3SS-lysozyme, pH 5.5, this derivative had nearly full enzymatic activity. The 3SS-lysozyme derivative and unmodified lysozyme were shown to be identical by CD spectroscopy at pH 3.6, whereas the spectrum of CM-lysozyme (completely reduced and blocked lysozyme) showed appreciably less structure. Immunochemical binding assays demonstrated that the conformation of lysozyme was perturbed predominantly only locally by breaking and blocking the disulfide bond between Cys^{6} and Cys^{127}. The 3SS-lysozyme derivative competed unsuccessfully against ^{125}I-labeled lysozyme, [^{125}I]L, for monoclonal antibodies known to bind to the N-terminal region of lysozyme, but competed nearly as well as unmodified lysozyme for antibodies known to bind to lysozyme in other distinct and separate regions. Both 3SS-lysozyme and unmodified lysozyme exhibited reversible thermally-induced transitions at pH 2.0, but the T_m of 3SS-lysozyme, 18.9 °C, was found to be 34° lower than that of native lysozyme under the same conditions. The conformational chemical potential of the denatured form of

unmodified lysozyme was determined from the transition curves to be 6.6 kcal/mol higher than that of the denatured form of 3SS-lysozyme, at pH 2.0 and 35°C, if the conformational chemical potential for the folded forms of *both* 3SS-lysozyme and unmodified lysozyme is arbitrarily assumed to be 0.0 kcal/mol. A calculation of the increase in the theoretical loop entropy of denatured 3SS-lysozyme resulting from the cleavage of the Cys^{6}-Cys^{127} disulfide bond, however, yielded a value of only 5.4 kcal/mol for the difference in conformational chemical potential. This suggests that, in addition to the entropic component, there is also an enthalpic contribution to the difference in the conformational chemical potential corresponding to approximately 1.2 kcal/mol. Thus, it is concluded that the reduction and blocking of the disulfide bond between Cys^{6} and Cys^{127} destabilizes 3SS-lysozyme relative to unmodified lysozyme predominantly by stabilizing the denatured conformation by increasing its chain entropy. In addition, there is an enthalpic component corresponding either to the relative stabilization of the denatured conformation of 3SS-lysozyme or, more likely, to the destabilization of the native conformation of the 3SS-lysozyme relative to the native conformation of unmodified lysozyme, presumably by electrostatic repulsion and steric interference effects.

BINDING OF THE DIHYDROPYRIDINE CALCIUM CHANNEL BLOCKER [^{3}H]PN200-110 TO RINm^5F MEMBRANES AND CELLS: CHARACTERIZATION AND FUNCTIONAL SIGNIFICANCE[1]

G.C. Yaney[2], G.A. Stafford, J.D. Henstenberg,

G.W.G. Sharp and G.A. Weiland[3]

Department of Pharmacology
N.Y.S. College of Veterinary Medicine
Cornell University
Ithaca, NY 14853

ABSTRACT

This report provides direct evidence for a dihydropyridine receptor/calcium channel in the insulin-secreting β-cell line RINm5F. The receptor/channel can modulate the intracellular Ca^{2+} concentration and the resultant insulin secretion by regulating the influx of extracellular Ca^{2+} through dihydropyridine-sensitive voltage-dependent L-type calcium channels. Elevated extracellular K^+ or the dihydropyridine Ca^{2+} channel agonist, BAY k 8644, stimulated the uptake of $^{45}Ca^{2+}$, raised $[Ca^{2+}]_i$, and increased insulin secretion in a concentration-dependent manner. These actions were inhibited by L-type Ca^{2+} channel blockers including nitrendipine, verapamil and diltiazem. (+)[^{3}H]PN200-110 bound specifically with high affinity to RINm5F cell membranes (K_d ~200 pM). Specific binding was competitively inhibited by dihydropyridines while phenylalkylamines incompletely inhibited [^{3}H]PN200-110 binding, consistent with an allosteric interaction. The benzothiazepine diltiazem had no effect on [^{3}H]PN200-110 binding in the presence of Ca^{2+}, but allosterically increased binding in the absence of Ca^{2+} (in the presence of EGTA). Maximal [^{3}H]PN200-110 binding required divalent cations and Mg^{2+}, Mn^{2+}, and Ba^{2+} were equally as effective as Ca^{2+} in reversing the effects of EGTA, while binding was not supported by Cd^{2+} or La^{3+}. Specific high affinity [^{3}H]PN200-110 binding was also demonstrated in intact RINm5F cells and shown to be modulated by membrane potential. Depolarization of the cells by raising extracellular K^+ from 5 to 80 mM increased the affinity of [^{3}H]PN200-110 four- to five-fold (decreased K_d) with no significant effect on the number of binding sites (B_{max}).

for J Cell Physiol

Multiple signal transduction pathways lead to extracellular ATP-stimulated mitogenesis in mammalian cells.

II. A pathway involving arachidonic acid release, prostaglandin synthesis and cyclic AMP accumulation.

Ning-na Huang, Ding-ji Wang, Fernando Gonzalez†

and Leon A. Heppel*

Section of Biochemistry, Molecular and Cell Biology,

Cornell University, Ithaca, New York 14853

This work was supported by grants from the National Institutes of Health (DK-11789), the American Cancer Society (BC-501A), the National Institute of Aging (AG-07429), and the Cornell Biotechnology Program, which is sponsored by the New York State Science and Technology Foundation, a consortium of industries, the U.S. Army Research Office, and the National Science Foundation.

†Dr. Fernando A. Gonzalez is now at Howard Hughes Medical Institute and Program in Molecular Biology and Department of Biochemistry, University of Massachusetts Medical Center, Worcester, MA 01605.

*To whom correspondence should be addressed.

Running Title: ATP-induced mitogenesis and arachidonates

Key words: Extracellular ATP, Mitogenesis, Cyclic AMP, Arachidonic Acid, Prostaglandin E_2

Total number of figures: 10

Total number of tables: 3

ABSTRACT

We have previously shown that extracellular ATP acts as a mitogen via protein kinase C (PKC)–dependent and independent pathways (Wang et al: *Journal of Cellular Physiology*, accompanying paper, 1990). The present aim was to determine if metabolism of arachidonic acid, resulting in prostaglandin E_2 (PGE_2) synthesis and elevation of cAMP levels, plays a role in mitogenesis mediated by extracellular ATP. Addition of ATP caused a marked enhancement of cyclic AMP accumulation in 3T3, 3T3 and A431 cells. Aminophylline, an antagonist of the adenosine A_2 receptor, had no effect on the accumulation of cyclic AMP elicited by ATP, while it inhibited the action of adenosine. The accumulation of cyclic AMP was concentration dependent, which corresponds to the stimulation of DNA synthesis by ATP. The maximal accumulation was achieved after 45 min with an initial delay period of about 15 min. That the activation of arachidonic acid metabolism contributed to cyclic AMP accumulation and mitogenesis stimulated by ATP in 3T3, 3T6 and A431 cells was supported by the following observations: (a) Extracellular ATP stimulated the release of [^{3}H]arachidonic acid and PGE_2 into the medium; (b) Inhibition of arachidonic acid release by inhibitors of phospholipase A_2 blocked PGE_2 production, cyclic AMP accumulation and DNA synthesis activated by ATP, and this inhibition could be reversed by adding exogenous arachidonic acid; (c) Cyclooxygenase inhibitors, such as indomethacin and aspirin, diminished the release of PGE_2 and blocked cyclic AMP accumulation as well as [^{3}H]thymidine incorporation in response to ATP; (d) PGE_2 was able to restore [^{3}H]thymidine incorporation when added together with ATP in the presence of cyclooxygenase inhibitors; (e) Pertussis toxin inhibited ATP–stimulated DNA synthesis in a time and dose dependent fashion as well as arachidonic acid release and PGE_2 formation. Other evidence for involvement of a pertussis toxin–sensitive G protein(s) in ATP–stimulated DNA synthesis as well as arachidonic acid release is presented. In A431 cells, the enhancement of arachidonic acid and cyclic AMP accumulation by ATP was partially blocked by PKC down–regulation, implying that the activation of PKC may represent an additional pathway in ATP–stimulated

metabolism of arachidonic acid. In all of those studies, ADP and AMP–PNP, but not adenosine, were as active as ATP. In summary, the data support a role for arachidonic acid metabolism in ATP–dependent DNA synthesis in 3T3, 3T6 and A431 cells.

for J Cell Physiol

Multiple signal transduction pathways lead to extracellular ATP-stimulated mitogenesis in mammalian cells.

I. Involvement of protein kinase C-dependent and independent pathways.

Ding-ji Wang, Ning-na Huang, Fernando A. Gonzalez† and Leon A. Heppel*

Section of Biochemistry, Molecular and Cell Biology, Cornell University, Ithaca, New York 14853

This work was supported by grants from the National Institutes of Health (DK-11789), the American Cancer Society (BC-501A), the National Institute of Aging (AG-07429), and the Cornell Biotechnology Program, which is sponsored by the New York State Science and Technology Foundation, a consortium of industries, the U.S. Army Research Office, and the National Science Foundation.

†Dr. Fernando A. Gonzalez is now at Howard Hughes Medical Institute and Program in Molecular Medicine & Department of Biochemistry, University of Massachusetts Medical Center, Worcester MA 01605.

*To whom correspondence should be addressed.

Running Title: ATP-induced mitogenesis and protein kinase C

Key words: Protein kinase C, Extracellular ATP, Mitogenesis, Diacylglycerol, Phosphatidylcholine

Total number of figures: 10

Total number of tables: 2

ABSTRACT

We recently reported that extracellular ATP was mitogenic for Swiss 3T3, 3T6 and A431 cells (Huang et al: *Proc. Natl. Acad. Sci. USA* 86: 7904–7908, 1989). Here we examined the possible involvement of activation of the protein kinase C (PKC) signal transduction pathway in the mechanism of action of extracellular ATP. A potent synergistic stimulation of DNA synthesis in quiescent cultures of 3T3 and 3T6 cells was observed when ATP was presented in combination with growth factors that activate PKC, such as bombesin, vasopressin or tumor-promoting phorbol esters. This finding suggests that ATP and these mitogens do not act through a common mechanism. In contrast, ATP was unable to show synergism with phorbol esters in A431 cells. We discovered striking differences when we examined the kinetics of formation of diacylglycerol (DAG) stimulated by ATP among these cell lines. Thus, ATP stimulated a sustained biphasic increase of DAG in A431 cells, but only a rapid transient increase of DAG formation was observed in 3T3 and 3T6 cells. The breakdown of phosphatidylcholine was stimulated by ATP in A431 cells; however, a significantly reduced effect was displayed in 3T6 cells. Furthermore, we found that the diacylglycerol-kinase inhibitor, 1-monooleoylglycerol, greatly potentiated ATP-stimulated DNA synthesis in A431 cells. Finally, down-regulation of PKC by long-term exposure to phorbol dibutyrate (PDBu) prevented stimulation of DNA synthesis induced by bombesin, vasopressin or phorbol esters in 3T3 or 3T6 cells, while it had no such effect on ATP-stimulated mitogenesis in the presence of insulin or epidermal growth factor. On the other hand, PDBu-mediated down-regulation of PKC partially inhibited [^{3}H]thymidine incorporation stimulated by ATP in A431 cells. Taken together, we conclude that a protein kinase C-dependent pathway is partially involved in ATP-stimulated DNA synthesis in A431 cells, but a protein kinase C-independent pathway exists in 3T3 and 3T6 cells. Pertussis toxin (PTX) inhibited the sustained phase of DAG formation and the breakdown of phosphatidylcholine stimulated by ATP in A431 cells. This suggests involvement of a PTX-sensitive G protein.

A New Chromogenic Substrate for Assaying Ribonuclease A Activity.

(Differential Staining, ELISA, nucleotide chemistry, recombinant DNA, RNase A)

Mark R. Witmer[1], Michael P. Weiner[2], Caterina M. Falcomer, Tadhg P. Begley, Bruce Ganem and Harold A. Scheraga*

Baker Laboratory of Chemistry
Cornell University
Ithaca, New York 14853-1301

[1]Cornell Biotechnology Program Predoctoral Fellow, 1987-1990.
[2]N.I.H. Postdoctoral Fellow, 1988-1990.

Address correspondence to: Harold A. Scheraga.
Telephone: (607) 255-4034

We have synthesized a new chromogenic substrate for ribonuclease A (RNase A, EC. 3.1.27.5). This substrate, uridine-3'-(5-bromo-4-chloroindol-3-yl)-phosphate (U-3'-BCIP, Figure 1), incorporates a substituted indole moiety which is liberated by the phosphodiesterase activity of RNase A to give an indol–3–ol that undergoes rapid aerobic oxidation to the insoluble blue 5,5'-dibromo-4,4'-dichloroindigo (1; λmax= 660 nm). Figure 2 shows a composite time-dependent UV-Visible spectrum demonstrating the utility of this compound when tested with purified RNase A. We are now testing this compound for use in *in vivo* assays for differentiating bacterial clones expressing active RNase A, and in ELISA-type analysis using RNase A-linked antibodies.

Synthesis of the uridine phosphodiester was achieved by phosphorylation (2) of 5'-DMTr-2'-TBDMS-Uridine (3) with the corresponding N-acetylindol-3-yl phosphorodichloridate (4). The DMTr, acetyl and TBDMS groups were removed in that order using standard conditions (4,5). The product was purified as the tetra-n-butyl ammonium salt by preparative TLC and characterized by NMR spectroscopy and high resolution FAB mass spectrometry.

Acknowledgement: This research was supported by a grant from the Cornell Biotechnology Program, which is sponsored by the New York State Science and Technology Foundation, a consortium of industries, the U. S. Army Research Office and the National Science Foundation, and by grants GM–14312 and GM–40498-01A1 from the National Institute of General Medical Sciences, and HL–30616 from the National Heart, Lung and Blood Institute.

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Figure 1. U-3'-BCIP.

Figure 2. Composite time-dependent UV-Visible spectrum. Obtained in 50mM Tris, pH 7.5, containing RNase A (approx. 0.05 Kunitz units, Sigma) and U-3'-BCIP (150 µg) in a 1.0 cm cell (1.00 mL). Scans were recorded over a period of 4 hours at room temperature.

U-3'-BCIP: a New Chromogenic Substrate for the Detection of RNase A

Mark R. Witmer, Caterina M. Falcomer, Michael P. Weiner, Michael S. Kay
Tadhg P. Begley, Bruce Ganem and Harold A. Scheraga*

Nucleic Acid Research, 19, pages 1-4, 1991.

Abstract

The synthesis of the Ribonuclease A (RNase A, EC 3.1.27.5, from bovine pancreas) chromogenic substrate uridine-3'-(5-bromo-4-chloroindol-3-yl)-phosphate (U-3'-BCIP) is described. The pyrimidine-specific RNase A hydrolysis of U-3'-BCIP releases a halogenated indol-3-ol that undergoes rapid aerobic oxidation to the insoluble dark blue 5,5'-dibromo-4,4'-dichloroindigo. Preliminary kinetic studies indicate that this compound may have practical use for assaying RNase A activity both *in vitro* and *in vivo*.

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October 12-14, 1991
Charlottesville, VA

THE INFLUENCE OF CELL-SURFACE EVENTS AND CYTOSKELETAL REORGANIZATION ON THE STRENGTH OF RECEPTOR-MEDIATED CELL ADHESION

M. D. Ward and D. A. Hammer
School of Chemical Engineering, Cornell University, Ithaca, New York 14853

After initial adhesion to a ligand-coated substrate, many cells reorganize their cell-surface receptors and cytoskeletal proteins in order to concentrate these molecules in localized adhesive regions known as focal contacts. Centrifugation assays have determined that focal contact formation can increase the force required to detach a cell from the substrate by several orders of magnitude. We report results from mathematical analyses which examine how focal contact formation affects the morphology and strength of attachment of cells to ligand-coated surfaces. We utilize a one-dimensional tape-peeling model of the cell membrane and model receptor-ligand bonds as springs and the glycocalyx as an assemblage of freely diffusible repeller molecules. Cytoskeletal architecture is accounted for by the presence of cytoplasmic nucleation centers which interact with the cytoplasmic portion of adhesive receptors. We report how the attachment strength, represented by the critical tension to peel the membrane, varies with ligand density in the absence of receptor-cytoskeleton binding. Cytoskeletal involvement leads to increased cross-linking of receptors and a concomitant enhancement of adhesiveness. The dependence of attachment strength on nucleation center concentration and receptor-cytoskeleton affinity will be discussed. These results suggest mechanisms for cellular regulation of adhesive behavior through modulation of cell-surface events such as upregulation of receptors, or intracellular changes such as the expression of different levels of cytoskeletal molecules. In addition, the consequences for the adhesive behavior of cells with defective cytoskeletal-receptor interactions (eg. tumorigenic cells, and cells transfected with dysfunctional cell adhesion receptors) will be discussed.

The Effects of Receptor and Glycocalyx Redistribution and Cytoskeletal Reorganization on the Morphology and Strength of Attachment of Cells to Ligand-Coated Surfaces

It is well known that certain aspects of cell physiology, including proliferation, motility, and differentiation are influenced by the composition of the surface to which a cell adheres. Many of these effects are related to cell shape and attachment strength, which in turn are regulated by cell surface and cytoskeletal events.

We report results from mathematical analyses which explain how receptor-ligand binding, steric stabilization forces, and cytoskeletal involvement alter the morphology and strength of attachment of cells to a ligand-coated surface. Using a one-dimensional tape-peeling model, we quantify how these factors modify the critical tension necessary to peel the membrane. The dependence of adhesive strength on ligand density is investigated, and analytical expressions are derived in the limits of high and low ligand density. Redistribution of receptor and glycocalyx molecules, as well as the presence of cytoplasmic nucleation centers, enhances the accumulation of receptors into localized regions on the cell surface and modulates the morphology of the cell-substrate interface. The clustering of receptors into focal contacts significantly increases the required detachment force in agreement with experimental evidence.

Using these results, we discuss the possibilities of cell regulation of adhesive behavior and contemplate the consequences of defective cytoskeletal-receptor interactons (eg. tumorigenic cells, or cells transfected with alternative forms of integrin receptors with defective cytoplasmic tails).

Michael D. Ward and Daniel A. Hammer
School of Chemical Engineering
Cornell University
Ithaca, NY 14853

Accepted to the 1991 Annual Meeting of the American Institute of Chemical Engineers, November 17-22, Los Angeles, CA.

SECOND ANNUAL MEETING OF BIOTECHNOLOGY PROGRAM PREDOCTORAL FELLOWS
NOVEMBER 10, 1990
BIOTECHNOLOGY BUILDING ROOM G-01

9:20 - 9:30	Opening Remarks, Dr. Milton Zaitlin
9:30 - 9:45	"Mapping the Nucleotide Binding Sites of Chloroplast Ccupling Factor 1: Implications for the Catalytic Mechanism", Adam Shapiro Advisor: R. McCarty
9:45 - 10:00	"Characterization of a Transcription Anti-termination Complex In Vitro", William Yarnell Advisor: J. Roberts
10:00 - 10:30	"Biotechnology Applications for Polymers and Materials", Dr. David Kaplan, U.S. Army Natick RD&E Center
10:30 - 10:45	"Lrp: A Leucine Responsive Regulatory Protein", Jill Platko Advisor: J. Calvo
10:45 - 11:00	"Regulation of L-Type Voltage-Gated Calcium Channels in AtT-20 Cells", Grace Stafford Advisor: G. Weiland
11:00 - 11:15	"Large-Scale EGF Receptor Micro-Aggregation Is Not Prerequisite for Transmembrane Signalling", Kermit Carraway Advisor: R. Cerione
11:15 - 11:30	"Molecular and Genetic Properties of an Extragenic Suppressor of a Cold-Sensitive β-Tubulin Mutation", Renee Reijo Advisor: T. Huffaker
11:30 - 12:00	"Biotechnology Applications for Biosensors", Dr. James Valdes, U.S. Army CRDEC
12:00 - 1:15	Lunch
1:15 - 1:45	"Research Opportunities in Basic Biomedical Science at the Walter Reed Army Institute of Research", Dr. Judith Nyquist, Walter Reed Army Institute of Research
1:45 - 2:00	"Quantifying Receptor-Mediated Cell Adhesion Under Flow Using a Model Cell Line", Linda Tempelman Advisor: D. Hammer
2:00 - 2:15	"The Characterization of the Kainate Receptor from Goldfish Brain", Cynthia Ziegra Advisor: R. Oswald

Cornell University

Biotechnology Program
130 Biotechnology Building
Ithaca, NY 14853-2703 USA
(607) 255-2300

FIRST ANNUAL MEETING OF BIOTECHNOLOGY PROGRAM PREDOCTORAL FELLOWS
NOVEMBER 4, 1989
BIOTECHNOLOGY BUILDING ROOM G-01

8:30 - 8:45	Opening Remarks, Dr. Richard McCarty
8:45 - 9:00	"Molecular Mechanics of Catalyses by Chloroplast Coupling Factor 1", Adam Shapiro Advisor: R. McCarty
9:00 - 9:15	"Isolation of an Efficient Promoter for Monocot Transformation", David McElroy Advisor: R. Wu
9:15 - 9:30	"Characterization of a Protein Associated with Heat Shock Puffs", David Champlin Advisor: J. Lis
9:30 - 9:45	"Characterization of a Transcription Antitermination Complex *In Vitro*", Bill Yarnell Advisor: J. Roberts
9:45 - 10:00	"Mechanistic Studies on DNA Photolyase", Mark Witmer Advisor: T. Begley
10:00 - 10:15	"A Positively-Acting Gene that Regulates the *ilvIH* Operon of *E. coli*", Jill Platko Advisor: J. Calvo
10:15 - 10:30	BREAK
10:30 - 10:45	"EGF Receptor Aggregation and Its Role in Mitogenic Signalling", Kermit Carraway Advisor: R. Cerione
10:45 - 11:00	"Steroid Modulation of Myometrial Protein Synthesis During Late Pregnancy and Parturition", Brian Wilcox Advisor: B. Currie
11:00 - 11:15	"Structure-Function Studies of Murine Epidermal Growth Factor", Franklin Moy Advisor: H. Scheraga
11:15 - 11:30	"Conformational Studies of Immunoglobulin E Bound to Mast Cell Membrane FcE Receptors", Yi Zheng Advisor: B. Baird
11:30 - 11:45	"Quantifying Receptor-Mediated Cell Adhesion Using the Rat Basophilic Leukemia Cell Line as a Model System", Linda A. Tempelman Advisor: D. Hammer
11:45 - 12:00	"Neural Control of Degradation Rate of the Nicotinic Acetylcholine Receptors in Mammalian Skeletal Muscle", Show-Ling Shyng Advisor: M. Salpeter
12:00 - 1:00	LUNCH - Biotechnology Building Conference Room