Biochemical Actions of Hormones

Edited by GERALD LITWACK

VOLUME VI

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Fels Research Institute and Department of Biochemistry
Temple University, School of Medicine
Philadelphia, Pennsylvania

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Preface

There seems to be no need for rationalizing the increased frequency of appearance of new volumes in this series. With the continued progress in molecular biology and molecular genetics, research in endocrinology continues at a blistering pace.

In this volume there are up-to-date critical summaries of the regulation of protein kinases and phosphoprotein phosphatases. There is emphasis on the relationship of the endocrines to cancer. In particular, an extensive review on the precise structures of steroid hormones and carcinogens is presented by a crystallographer and some conclusions have been drawn from this analysis which bear on steroid receptors. Other reports cover hormonal regulation of chemical carcinogenesis, the question of the importance of steroid hormones as growth factors for mammary tumors, the effects of steroid hormones in the central nervous system, and properties of the purified estrogen receptor. A contribution summarizes recent work on the biochemical actions of neurohypophysial hormones and neurophysin. Plant hormone action is represented by a report on the biochemistry and physiology of cytokinins. Multihormonal systems are exemplified by control of the α_{2u} globulin produced in the liver.

As in previous volumes, this treatise is organized by presenting articles of general interest first and then to proceed to more specialized subject matter, although when topics have similar subjects they are grouped together in preference to the aforementioned organization.

GERALD LITWACK

List of Contributors

Numbers in parentheses indicate the pages on which the authors' contributions begin.

Francesco Bresciani* (461), Department of Pathology, University of Toronto, Toronto, Ontario, Canada

Ronald H. Cooper (1), Department of Biological Chemistry, School of Medicine, University of California, Davis, California 95616

Randall T. Curnow (77), Departments of Internal Medicine and Pharmacology, University of Virginia School of Medicine, Charlottesville, Virginia 22901

Jenny P. Glusker (121), The Institute for Cancer Research, The Fox Chase Cancer Center, Philadelphia, Pennsylvania 19111

Russell Hilf (205), Department of Biochemistry and University of Rochester Cancer Center, University of Rochester, Rochester, New York 14642

R. J. B. King (247), Hormone Biochemistry Department, Imperial Cancer Research Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England

Joseph Larner (77), Department of Pharmacology, University of Virginia School of Medicine, Charlottesville, Virginia 22901

Ivan Lieberburg (415), The Rockefeller University, New York, New York 10021

Bruce S. McEwen (415), The Rockefeller University, New York, New York 10021

*Present Address: Istituto Patologia Generale, I Facoltà di Medicina e Chirurgia, Università degli Studi di Napoli, Napoli, Italy.

A. Frances Pearlmutter (265), Department of Biochemistry, Medical College of Ohio, Toledo, Ohio 43699

Arun K. Roy (481), Department of Biological Sciences, Oakland University, Rochester, Michigan 48063

Ruth Y. Schmitz (335), Institute of Plant Development and Department of Botany, Birge Hall, University of Wisconsin, Madison, Wisconsin 53706

Vincenzo Sica* (461), Department of Pathology, University of Toronto, Toronto, Ontario, Canada

Folke Skoog (335), Institute of Plant Development and Department of Botany, Birge Hall, University of Wisconsin, Madison, Wisconsin 53706

Melvyn S. Soloff (265), Department of Biochemistry, Medical College of Ohio, Toledo, Ohio 43699

Donal A. Walsh (1), Department of Biological Chemistry, School of Medicine, University of California, Davis, California 95616

Alessandro Weisz† (461), Department of Pathology, University of Toronto, Toronto, Ontario, Canada

*Present Address: Istituto Patologia Generale, I Facoltà di Medicina e Chirurgia, Università degli Studi di Napoli, Napoli, Italy.

†Present Address: Istituto Patologia Generale, I Facoltà di Medicina e Chirurgia, Università degli Studi di Napoli, Napoli, Italy.

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CHAPTER 1

The Physiological Regulation and Function of cAMP-Dependent Protein Kinases

Donal A. Walsh and Ronald H. Cooper

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I. INTRODUCTION

The elegant second messenger hypothesis of cAMP action proposed by Sutherland and Rall (1960) has served as a cornerstone upon which has been built our understanding of the mechanism of hormonal action. Since that time, it has been shown that a wide range of polypeptide hormones, the catecholamines, and a number of other cellular stimuli elicit the formation of cAMP, and that cAMP promotes all, or some, of the physiological events characteristic of the particular response. The elegance of this hypothesis is not compromised by recognition of the facts that (a) not all hormonal effects are mediated by this mechanism and (b) not all physiological responses initiated by the hormone are necessarily promoted through the elevation of cAMP concentration. For the latter, two primary examples are the independent regulation of K^+ release and amylase secretion from the parotid (Selinger *et al.*, 1973) and the regulation of hepatic glycogenolysis (Cherrington *et al.*, 1976).

The regulation of hepatic glycogenolysis by catecholamines provided the experimental framework on which the cAMP second messenger hypothesis was founded. These studies had in their turn been built on the earlier extensive investigations from the Coris's laboratory which provided not only our first understanding of the regulation of enzyme activity by covalent modification (Cori, 1956) but the training ground for a substantial number of the leading investigators in this area. Studies by E. G. Krebs, who received his training from the Coris, concentrated on the molecular mechanisms of skeletal muscle glycogenolysis and resulted in the identification of phosphorylase kinase, the enzyme which catalyzes the phosphorylation and activation of phosphorylase (Krebs *et al.*, 1958), and subsequently of the cAMP-dependent protein kinase, the enzyme which catalyzes the phosphorylation and activation of phosphorylase kinase (Walsh *et al.*, 1968). These enzymes are fundamental components of the glycogenolytic cascade (Fig. 1); we now know that many additional complexities are imposed on this system, and a discussion in greater depth is presented as the conclusion of this review.

The initial study of the cAMP-dependent protein kinase (Walsh *et al.*, 1968) demonstrated that this enzyme catalyzed the phosphorylation of other proteins in addition to phosphorylase kinase, that the enzyme was activated by cAMP within the concentration range that was physiologically appropriate ($K_a = 2 \sim 10 \times 10^{-8}$ *M*), and that a stoichiometric binding of cAMP to the protein occurred (Fig. 2). Thus the cAMP-dependent protein kinase was recognized as a primary site of action of the cyclic nucleotide. Kuo and Greengard (1969) extended this concept by identifying this enzyme in both a wide range of mammalian tissues and at least nine animal phyla, and they