Biochemical Actions of Hormones

Edited by GERALD LITWACK

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Preface

This volume emphasizes aspects of molecular biology with respect to hormone action. The first part of the book contains a number of chapters dealing with gene expression, transcription, RNA stabilization, and protein synthesis. E. Herbert and collaborators describe the opioid peptides. Prolactin gene expression is a system described from the point of view of gene regulation by G. H. Murdoch, R. M. Evans, and M. G. Rosenfeld, and also by C. Bancroft *et al.* The control by estrogen is detailed in a chapter by P. S. Dannies. Gene regulation by glucocorticoids is the subject of work by K. E. Mayo and R. D. Palmiter with the metallothionein gene and by D. K. Granner and E. G. Beale with tyrosine aminotransferase and phosphoenolpyruvate carboxykinase expression. D. J. Shapiro and M. L. Brock report on the roles of estrogen in the transcription and stabilization of vitellogenin mRNA. P. F. Blackmore and J. H. Exton describe mechanisms involved in the actions of calcium-dependent hormones. M. R. Banerjee and M. Antoniou narrate the multiple hormonal controls of milk-protein gene expression. S. Bourgeois and J. C. Gasson describe the genetic basis of glucocorticoid resistance in cell cultures. The remainder of the volume is dedicated to the description of various receptors: J. H. Clark's laboratory reports on estrogen and antiestrogen binding sites; D. Marver describes the mineralocorticoid receptor; G. L. Johnson's laboratory summarizes its findings regarding the nerve growth factor receptor; and L. D. Kohn's laboratory describes the thyrotropin receptor. This volume, then, stresses modern molecular biology as it pertains to hormone action as well as basic work with hormone receptors. Consequently, it should appeal both to endocrinologists and to workers in the field of molecular biology.

Gerald Litwack

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CHAPTER 1

Generation of Diversity of Opioid Peptides

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BIOCHEMICAL ACTIONS OF HORMONES, VOL. XII

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I. INTRODUCTION

During the past two decades, a great variety of small peptides that mediate specific physiological responses in animals have been discovered. These peptides, called *neuroendocrine peptides*, are the messenger molecules that convert neural signals into physiological responses and may serve both as neurotransmitters or neuromodulators in the nervous system and as hormones in the circulatory system. It is, therefore, not surprising to find them in a side variety of tissues. For example, the adrenocorticotropin (ACTH) endorphin family of peptides is found in the anterior and neurointermediate lobes of the pituitary, in several sites in the brain, and in the intestine, the placenta, and the immune system.

The structures of neuroendocrine peptides have been determined largely by classic amino acid sequencing techniques. However, their mode of synthesis could not be studied in detail until recombinant DNA techniques were developed. As a result, it was shown that the small neuroendocrine peptides are synthesized in the form of large polypeptide precursors. Determination of amino acid sequences of these precursors culminated in the discovery of an important new class of proteins, called polyproteins (or polyfunctional proteins) because they serve as precursors to more than one biologically active peptide. Indeed, one of these precursors, proenkephalin, is the source of as many as eight different bioactive peptides that must be excised from the precursors to become active. These peptides then may act in concert to coordinate complex behavioral responses.

The domains of the biologically active peptides in the precursors are usually flanked by pairs of basic amino acid residues, indicating that trypsinlike enzymes and carboxypeptidases are involved in producing bioactive peptides from precursors, as in the case of conversion of proinsulin to insulin (Steiner *et al.*, 1980). The proteolytic cleavages are often not the only events necessary to obtain a bioactive peptide from a precursor; specific amino acid residue modifications are also involved. For example, the precursors contain sequences that can specify attachment of oligosaccharides. Other forms of modification may include phosphorylation, amidation, acetylation, sulfation, and methylation of particular amino acids.

Hence, polyproteins can give rise to the variety of peptides necessary to mediate complex behavioral responses. However, this is not the only mechanism used to create diversity in the production of bioactive peptides. All steps that mediate the expression of a gene coding for a polyprotein can be involved in generating this type of diversity. Expression of a polyprotein gene can be regulated differently in different tissues. For example, glucocorticoids affect pro-opiomelanocortin (POMC) gene expression in the anterior but not in the neurointermediate lobe of the pituitary. Tissue-specific expression of neuroendocrine peptide genes can result from alternate modes of splicing of a pre-mRNA copied from a single gene. This diversity-generating mechanism leads to the formation of different mRNAs and, therefore, of different precursors in different tissues, as in the case of expression of the calcitonin gene (Amara *et al.*, 1982). Also, regulation of a complex behavior can be controlled by a family of genes producing related sets of bioactive peptides. These genes may be expressed selectively in different cells involved in the behavior pattern such as occurs in egg-laying behavior in the marine invertebrate *Aplysia californica* (Scheller *et al.*, 1983). In some instances it is the polypeptide precursor itself that is processed to different bioactive products in different tissues. This type of tissue-specific processing appears to be related to different sets of processing enzymes in each tissue. Finally, diversity of expression also occurs during the last step in the production of bioactive peptides, their secretion into the extracellular space. The secretion of bioactive peptides may be controlled by neural signals in one tissue and by hormones in another tissue, as in the secretion of POMC peptides from the anterior and neurointermediate lobes of the pituitary. Thus, diversity in the production of neuroendocrine peptides can occur at almost all levels of gene expression.

Diversification of neuroendocrine peptides is perhaps best illustrated by the opioid peptide family. More than 16 different endogenous peptides have been identified that exhibit opioid ativity in various bioassays. The first of these peptides to be isolated were the pentapeptides Met- and Leu-enkephalin (Hughes *et al.*, 1975). The other opioid peptides are C-terminal extensions of either Met- or Leu-enkephalin as shown in Fig. 1. β-Endorphin, for example, is a C-terminal extension of Met-enkaphalin, whereas dynorphin and the neo-endorphin are C-terminal extensions of Leu-enkephalin.

During the past 4 years it has been shown through the use of recombinant DNA technology and protein chemistry that all of the known opioid peptides are derived from three different precursor proteins (Fig. 2). The first opioid precursor protein to be characterized was pro-opiomelanocortin (POMC), which gives rise to the opioid, β-endorphin, and a variety of other peptides