Biochemical Actions of Hormones

Edited by GERALD LITWACK

VOLUME V

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VOLUME V

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Preface

Fundamental endocrinology seems to be expanding rapidly on three major fronts: newer understanding of the actions of well-known hormones made possible by progress in biochemistry and molecular biology, the discovery of new hormones, and the nature of interaction of multiple hormones in regulating specific phenotypes. The contributions to Volume V of "Biochemical Actions of Hormones" exemplify these categories. Topics in the first category involve modifications of chromatin structure by hormones by E. M. Johnson and V. Allfrey; regulation of exocytosis by F. Butcher; ontogeny of estrogen receptors by A. M. Kaye; hormonal regulation of cells of the seminiferous tubule by I. B. Fritz; advances on the progesterone receptor by W. V. Vedeckis, W. T. Schrader, and B. O'Malley; the role of glucocorticoids in the integration of mammary tumor virus genes by K. R. Yamamoto, R. K. Ivarie, J. Ring, G. M. Ringold, and M. R. Stallcup; and a model system for estrogen action by J. R. Tata. Under the category of phenomenology of newer hormones there are contributions from J. J. Van Wyk and L. E. Underwood on somatomedins and their actions, from G. Carpenter and S. Cohen on epidermal growth factors, and from A. W. Norman on the specific mode of action of 1,25-dihydroxyvitamin D. Finally, under the nature of interaction of multiple hormones regulating specific phenotypes, there is a contribution from D. T. Kurtz and P. Feigelson on multihormone control of mRNA for a specific hepatic protein.

The expansion of basic endocrinology must be as unlimited as the potential progress of molecular biology, an evident conclusion which will guarantee future volumes in this treatise.

This is an appropriate place in which to thank the contributors to this volume and Academic Press for their continued fine cooperation in the publication of this treatise.

GERALD LITWACK

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CHAPTER 1

Postsynthetic Modifications of Histone Primary Structure: Phosphorylation and Acetylation as Related to Chromatin Conformation and Function

Edward M. Johnson and Vincent G. Allfrey

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I. INTRODUCTION

It is now well known that individual histones are subject to several distinct biochemical modifications which occur following histone synthesis and which alter the primary structure and, consequently, the physical and chemical properties of the histone molecules. The different types of postsynthetic modifications confer a structural variability which contrasts with the conservation of amino acid sequences of most histones throughout various eukaryotic tissues and species. Changes in postsynthetic modifications of histones, occurring under cellular regulation, may represent a mechanism for altering structural and functional properties of histones in the chromatin. Little is presently known regarding possible biological functions of histone modification, and, for most modifications, possible hormonal influences have not been detailed. In certain instances histone modifications have been correlated with events occurring during hormonal stimulation or in the processes of cell differentiation or proliferation. Numerous studies have been conducted concerning the enzymes regulating histone modification. Amino acid sequences of several histones are known, and examination of modification sites has provided information regarding interactions of specific histone regions with DNA and other chromatin proteins. Such studies are relevant to an eventual assessment of the effect of modifications on histone participation in chromosomal structure and activities.

Since the earliest reports on modification of histones (Phillips, 1963; Allfrey *et al.*, 1964; Murray, 1964; Kleinsmith *et al.*, 1966a,b; Ord and Stocken, 1966), several different reactions involving alterations of histone amino acid residues have been described. These reactions include methylation resulting in modified amino acids ϵ-*N*-methyllysine in mono-, di-, or trimethyl forms, ω-*N*-methylarginine, and 3-methylhistidine (Murray, 1964; Paik and Kim, 1967; Gershey *et al.*, 1968; DeLange *et al.*, 1969; Allfrey, 1971). Histones may also be acetylated, resulting in modified amino acids *N*-acetylserine and *N*-acetyllysine (for reviews of histone acetylation, see Allfrey, 1971, 1977; Louie *et al.*, 1973; Ruiz-Carrillo *et al.*, 1975). Histone phosphorylation may result in modified amino acids *O*-phosphoserine, *O*-phosphothereonine, *N*-phospholysine, and *N*-phosphohistidine (for reviews on histone phosphorylation, see Dixon *et al.*, 1975; Bradbury, 1975; Langan and Hohmann, 1975; Johnson, 1977). Recent reports suggest that

histones may also incorporate poly(ADP-ribose) (Smith and Stocken, 1973; Dietrich *et al.*, 1973; Ueda *et al.*, 1975; Dixon, 1976), although sites of histone amino acid residues modified by ADP ribosylation have not been identified with the precision seen in localization of acetyl or methyl groups on particular amino acid residues. The present review concerns primarily the phosphorylation and acetylation of histones, the mechanisms through which these modifications are controlled, and the evidence for hormonal intervention in the dynamics of histone side-chain modification.

II. HISTONE PHOSPHORYLATION

Following initial reports on the incorporation of phosphate into lysine-rich histones (Kleinsmith, *et al.*, 1966a; Ord and Stocken, 1966; Langan and Smith, 1967), considerable progress has been made concerning both structural and regulatory aspects of histone phosphorylation. At this time amino acid sequences comprising several histone phosphorylation sites are known, and distinct protein kinases which catalyze phosphorylation of specific sites have been isolated. In at least one case, that involving phosphorylation catalyzed by cyclic AMP-dependent protein kinase, the mechanisms exist whereby hormonal modulation of histone phosphorylation may be implemented. Several reviews and recent papers have dealt with various aspects of histone phosphorylation, including technical aspects of measuring phosphorylation (Hnilica, 1972), histone phosphorylation and chromosome condensation (Bradbury, 1975; Matthews *et al.*, 1975), and the processing of newly synthesized histone molecules (Louie *et al.*, 1973; Dixon *et al.*, 1975; Ruiz-Carrillo *et al.*, 1975). Several recent reports concern biological correlates of histone phosphorylation and may be relevant to an assessment of the possible involvement of such phosphorylation in processes concerned with alterations in chromatin structure and with gene expression and replication.

A. Phosphorylation of H1

Histone H1 has been the most thoroughly characterized of the individual histones with respect to sites of phosphorylation as well as to mechanisms regulating phosphate incorporation and turnover. Many of the properties of this lysine-rich histone differ from those of the other histones. H1 is the largest of the five major histone classes, possessing a molecular weight of about 21,000, corresponding to 210–220 amino acids. Unlike the other major histones, H1 displays considerable tissue and species heterogeneity, there being three to five subfractions of H1 in all mammalian sources examined. In