

Monographs on Endocrinology

Volume 15

Edited by

F. Gross, Heidelberg · M.M. Grumbach, San Francisco

A. Labhart, Zürich · M.B. Lipsett, Bethesda

T. Mann, Cambridge · L.T. Samuels (†), Salt Lake City

J. Zander, München

A.T. Cowie
Isabel A. Forsyth
I.C. Hart

Hormonal Control of Lactation

With 64 Figures



Springer-Verlag
Berlin Heidelberg New York 1980

Alfred T. Cowie
Isabel A. Forsyth
Ian C. Hart

National Institute for Research in Dairying
University of Reading
Shinfield
Reading RG2 9AT, England

ISBN-13:978-3-642-81391-7 e-ISBN-13:978-3-642-81389-4
DOI: 10.1007/978-3-642-81389-4

Library of Congress Cataloging in Publication Data.

Cowie, Alfred T. Hormonal control of lactation. (Monographs on endocrinology; v. 15) Bibliography: p. Includes bibliographies and index. 1. Mammary glands-Growth. 2. Lactation-Regulation. 3. Lactogenic hormones. 4. Physiology, Comparative. I. Forsyth, Isabel A., 1936--joint author. II. Hart, Ian Christopher, 1946--joint author. III. Title. IV. Series [DNLN: 1. Lactation. 2. Hormones - Physiology. W1 MO57 v. 15 / WP825 C874h] QP188.M3C68 599.01'6 80-10109

This work is subject to copyright. All rights are reserved, whether the whole or part of the material is concerned, specifically those of translation, reprinting, re-use of illustrations, broadcasting, reproduction by photocopying machine or similar means, and storage in data banks. Under § 54 of the German Copyright Law where copies are made for other than private use, a fee is payable to the publisher, the amount of the fee to be determined by agreement with the publisher.

© Springer-Verlag Berlin, Heidelberg 1980

Softcover reprint of the hardcover 1st edition 1980

The use of registered names, trademarks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

Preface

Research on the hormonal control of lactation – the subject of this monograph – has long been the major interest of this laboratory. Studies were initiated in the mid 1930s by the late Professor S.J. Folley, FRS, who directed the work with immense enthusiasm and devotion until his untimely death in 1970. This fruitful area of basic and applied research has, in recent years, attracted widespread attention; there have been many exciting events and developments with a dramatic increase in the number of publications. These events are diverse and include the identification, isolation and sequencing of human prolactin; the identification and isolation of placental lactogens in several ruminant species with recognition of their importance in mammary growth and differentiation; the introduction of highly sensitive bioassay, radioimmuno- and radioreceptor-assay techniques for mammatrophic hormones; the growing clinical appreciation of the immunological and nutritional importance of colostrum and milk to the newborn; the intensification of studies on normal mammary development to establish a sound basis for studies on mammary cancer; and the exploitation of the mammary gland, with its characteristic differentiation patterns and multiple synthetic abilities, as a valuable tissue for the investigation of basic mechanisms involved in the synthesis under hormonal control of enzymes and secretory proteins; and for the study of hormone – receptor interactions.

The invitation from Springer-Verlag to contribute to their series 'Monographs on Endocrinology' is a great privilege, but in providing us with an opportunity to review endocrine aspects of mammary development and lactation we have also been given a challenge, for a monograph is defined as a 'scholarly treatise on a single subject'. The wealth of recent material, even with three authors, provided a task greater than anticipated. We have paid much attention to comparative aspects and quantitative results. Selection of material has been highly subjective – undue attention may have been given to aspects which are our particular interests – we hope, however, that we have not been unduly self-citatory! While current concepts are emphasized we have at times delved into older studies to provide some historical perspective being mindful of the recent comment by Greep (1978) [Rec. Prog. Horm. Res. 34, 1] concerning research on reproductive endocrinology that 'there is the distressingly high incidence of re-invention of the wheel'. In sum, we have tried to produce a helpful guide and reference source to aid further studies in this important and complex field.

We thank Springer-Verlag for their patience and meticulous help. We are most grateful to our colleagues Dr J.S. Tindal, Dr G.S. Pope, Dr E.A. Jones and Dr T.J. Hayden for their assistance and critical comments. Our task has been much facilitated by Miss Joan Swinburne and by Mrs Carolyn Watson who, with untiring effort, keep the department's reference and reprint collection up-to-date and who, in

preparing the typescript, deciphered with skill and patience three near-illegible styles of handwriting. Mr B. F. Bone, the librarian of this Institute, prepared the Subject Index and was of great help in tracing and obtaining references. Finally we thank all who gave us permission to reproduce material; their help is individually acknowledged in the appropriate legends.

Reading, February 1980

A.T. Cowie
Isabel A. Forsyth
I.C. Hart

Contents

Chapter 1. Introduction	1
A. Importance of Milk	1
I. Milk and the Nurture of the Young	1
II. Milk as an Item of the Post-weaning Diet	3
1. Development of Dairying	3
2. Value of Milk in the Diet	5
B. Lactation: Physiological Requirements and Demands	6
I. Mammary Growth	6
II. Milk Secretion	6
III. Milk Removal	7
IV. Behavioural Adaptations	10
V. Metabolic Adaptations	10
VI. Lactation in Prototherian and Metatherian Mammals	11
VII. Duration of Lactation	13
C. Lactation and Reproductive Cycle	14
References.	16
Chapter 2. Properties and Regulatory Mechanisms of the Mammatrophic Hormones of the Anterior Pituitary and Placenta	20
A. Isolation and Properties of Growth Hormone and Prolactin	21
B. Isolation of Placental Lactogens	21
C. Biological Effects	22
D. Immunology	24
E. Structure-Activity Relationships.	25
I. Basic Considerations	25
II. Enzymic Digestion and Investigation of Active Peptide Fragments	25
III. Chemical Modification	28
1. Disulphide Bonds	28
2. Tryptophan.	29
3. Tyrosine	29
4. Methionine	30
5. Conclusions	30

F. Peptide Hormone Heterogeneity	30
G. Biosynthesis	32
H. Regulatory Mechanisms	35
I. Prolactin	35
1. Afferent Pathways and Neurotransmitters Involved in the Release of Prolactin	35
2. Prolactin-Releasing Factor	36
3. Role of Endogenous Opioid Peptides in Prolactin Secretion	37
4. Prolactin-Inhibiting Factor	39
5. Effect of Endogenous Hormones on Prolactin Secretion	40
II. Growth Hormone	40
1. Extrahypothalamic Brain Areas and Neurotransmitters Involved in GH Secretion	40
2. Growth Hormone-Releasing Factor	41
3. Growth Hormone Release-Inhibiting Hormone (Somatostatin)	41
4. Mode of Action of the Hypothalamic Regulatory Hormones	42
5. Effect of Endogenous Hormones on GH Secretion	42
III. Placental Lactogen	43
1. Relation Between Placental Lactogen Production and Placental Weight in Sheep, Goats and Monkeys	43
2. Acute Changes in Placental Lactogen Levels	43
3. Placental Lactogen and Circulating Levels of Metabolites	44
4. Placental Lactogen and Catecholamines	45
5. Other Factors Investigated	45
References.	45
Chapter 3. Growth and Development of the Mammary Gland	58
A. Mammary Development in the Embryo and Fetus	58
I. Stages of Development	58
II. Experimental Analysis of Fetal Mammary Gland Development	61
1. Mammary Gland Morphogenesis In Vitro	61
2. Epithelial–Mesenchymal Interactions in Mammary Gland Development	61
3. The Role of Mesenchyme and the Response of Mouse Mammary Rudiments to Testosterone	62
4. Other Effects of Steroid Administration to the Fetus and Neonate	63
5. Response of Fetal Mammary Glands to Other Hormones	63
B. Mammary Gland Development in Virgin, Pregnant and Lactating Females	64
I. Methods of Evaluating Mammary Growth	64
II. Stages of Development	65
1. Monotremes and Marsupials	66
2. Primates	66
a) Rhesus Monkey	66
b) Man	67

3. Lagomorpha	67
a) Rabbit.	67
4. Rodentia	68
a) Hamster.	68
b) Rat and Mouse.	68
c) Guinea-pig.	71
5. Carnivora	71
a) Dog.	71
6. Perissodactyla.	72
a) Horse	72
7. Artiodactyla	72
a) Pig	72
b) Cow, Sheep and Goat.	72
C. Involution	74
D. Plasma Levels of Hormones Involved in Mammogenesis:	
Steroid Hormones of the Ovary, Adrenal Gland and Fetoplacental Unit	76
I. Monotremata	77
1. Ornithorhynchidae	77
a) Platypus.	77
II. Marsupialia	78
1. Phalangeridae.	78
a) Brush-tailed Possum	78
2. Macropodidae	78
a) Tammar Wallaby.	78
III. Chiroptera	78
1. Phyllostomatidae	78
a) California Leaf-nosed Bat	78
IV. Primates	78
1. Cebidae	78
a) Squirrel Monkey.	78
2. Cercopithecidae	79
a) Rhesus Monkey	79
b) Bonnet Monkey	80
c) Japanese Monkey.	80
d) Baboon	80
3. Pongidae	80
a) Chimpanzee	80
4. Hominidae	81
a) Woman	81
V. Lagomorpha	83
1. Leporidae	83
a) European Hare.	83
b) Rabbit.	83
VI. Rodentia	84
1. Sciuridae	84
a) Grey Squirrel	84

2. Cricetidae	84
a) Golden Hamster	84
3. Muridae	85
a) Rat	85
b) Mouse.	86
4. Caviidae	86
a) Guinea-pig.	86
b) Cuis.	87
VII. Carnivora	88
1. Canidae	88
a) Dog.	88
b) Blue (Arctic) Fox	89
c) Red Fox.	89
2. Mustelidae	89
a) Ferret	89
b) Mink	89
c) Spotted Skunk (Western Form)	90
3. Felidae.	90
a) Cat	90
VIII. Pinnipedia.	90
1. Otariidae.	90
a) Alaskan Fur Seal	90
IX. Proboscidae	91
1. Elephantidae	91
a) Elephant, African and Asian	91
X. Perissodactyla	91
1. Equidae	91
a) Horse	91
XI. Artiodactyla.	92
1. Suidae	92
a) Pig	92
2. Cervidae	94
a) White-tailed Deer.	94
b) Roe Deer	94
3. Bovidae	95
a) Cow.	95
b) Goat	98
c) Sheep	99
XII. General Conclusions	101
E. Plasma Levels of Hormones Involved in Mammogenesis:	
Prolactin, Growth Hormone and Placental Lactogen	102
I. Primates	102
II. Lagomorpha	104
1. Rabbit	104
III. Rodentia	104
1. Hamster	104

Contents	XI
2. Mouse and Rat	104
IV. Carnivora	105
1. Dogs	105
V. Perissodactyla	106
1. Horse	106
VI. Artiodactyla	106
1. Pigs	106
2. Cows, Sheep, and Goats	106
F. Endocrine Control of Mammary Gland Growth	110
I. Control of Mammary Duct Growth in the Rat and Mouse	110
II. Control of Lobulo-alveolar Mammary Growth in the Rat and Mouse: Role of Placental Lactogen	111
III. Lactational Mammary Growth in the Rat and Mouse	113
IV. Mammary Gland Growth in Rabbits	113
V. Mammary Gland Growth in Ruminants	114
VI. Mammary Gland Growth in Primates	115
VII. Other Factors in Mammary Gland Growth	115
1. Metabolic Hormones	115
2. Is the Effect of Oestrogen on Mammary Tissue Direct?	116
3. Relaxin	116
4. Polyamines	117
5. Chalone	117
G. Experimental Induction of Mammary Growth and Lactation	117
I. Women	117
II. Animals	118
1. Oestrogen Treatments	118
2. Oestrogen-Progesterone Treatments	119
3. Adjunct Treatments	122
4. Levels of Hormones in the Blood	123
III. Conclusions	123
References	124
Chapter 4. Lactation	146
A. The Secretion of the Mammary Gland: Colostrum and Milk	146
I. Nature and Composition	146
II. Importance to the Neonate	147
1. Transmission of Immunity	149
2. Transmission of Hormones	153
B. Lactogenesis	153
I. Terminology	153
II. Ultrastructure and Function of Mammary Epithelial Cells	154
1. Changes in Ultrastructure at Parturition and Their Relationship to Milk Composition	154

2.	Mechanisms of Synthesis and Secretion	158
a)	Milk Proteins	158
b)	Lactose	160
c)	Milk Fat.	160
3.	Are Milk Synthesis and Secretion Controlled Independently?	161
III.	Changes in Mammary Gland Stroma	161
IV.	Hormonal Mechanisms in the Initiation of Lactation	162
1.	Effects of Hormones on Mammary Gland Ultrastructure	162
2.	Effects of Hormones on Messenger RNAs for Casein	163
3.	Plasma Levels of Hormones and the Onset of Copious Milk Secretion	164
C.	Maintenance of Lactation	165
I.	Prolactin	165
1.	Effect of Reduced Prolactin on Milk Secretion	165
2.	Effect of Milking and Suckling on Prolactin Secretion.	169
3.	Circulating Prolactin and Milk Secretion	171
4.	Increased Prolactin and Milk Secretion	174
II.	Growth Hormone	176
1.	Effect of Milking and Suckling on Growth Hormone Secretion.	176
2.	Circulating Growth Hormone and Milk Secretion	176
III.	Thyroxine.	181
1.	Effect of Thyroidectomy on Milk Secretion.	181
2.	Effect of Thyroxine and Thyroactive Compounds on Milk Secretion	181
3.	Circulating Thyroxine and Milk Secretion	182
IV.	Insulin	183
1.	General	183
2.	Circulating Insulin and Milk Secretion	184
V.	Corticosteroids	185
1.	Non-ruminants	185
2.	Ruminants	187
VI.	Oxytocin	188
D.	Milk-Ejection Reflex.	189
I.	Early Studies on the Nature of Milk Ejection	189
1.	Recognition of Milk Ejection	189
2.	Milk Secretion and Milk Ejection.	192
3.	The Neuro-endocrine Reflex	193
a)	Studies in Animals	193
b)	Studies in Women	195
II.	Recent Investigations.	196
1.	Innervation of the Mammary Gland.	196
2.	Effective Stimuli.	197
3.	Afferent Pathways.	198
4.	Humoral Pathway.	199
5.	Contractile Tissue.	202

6. Species Differences in the Importance of the Milk-Ejection Reflex	203
7. Tap Reflex	204
III. Suckling and Nursing	205
1. Mechanics of Suckling	205
2. Frequency of Suckling and Patterns of Nursing	207
3. Relationship Between Suckling-Induced Release of Oxytocin and Prolactin	207
E. Disturbances of Lactation	208
I. Factors Involved	208
1. Nutritional	208
2. Pharmacological	208
3. Emotional Stress	208
II. Mechanisms of Failure	208
III. Disturbances in Animals	208
IV. Disturbances in Women	210
References.	210
Chapter 5. Hormone Assay Techniques Used in the Study of Lactation	230
A. Methods of Bio-assay	230
I. Growth Hormone	230
II. Prolactin	231
III. Placental Lactogen	232
IV. International Standards for Bio-assay	232
B. Radio-immunoassays and Radioreceptor Assays	232
I. Iodinated Prolactin and Growth Hormone	232
II. Do RIAs and RRAs for Prolactin and GH Measure the Biologically Relevant Hormone?	234
1. Prolactin RIA	234
2. Prolactin RRA	236
3. Growth Hormone RIA	238
4. Growth Hormone RRA	240
5. Conclusions	241
C. Measurement of Prolactin in Milk by RIA	242
References.	243
Chapter 6. Hormone Receptors in Mammary Gland and the Mechanisms of Hormone Action at the Cellular Level	247
A. Methods for the Study of Hormone Binding Sites.	247
I. Cell Fractionation	247
II. Cell Isolation	248
III. Tissue Slices.	248
IV. Fluorescent Antibody Localization and Autoradiography	248

V.	Labelled Ligands	248
VI.	Specific and Non-specific Binding	249
VII.	The Coupling of Binding to Response	249
B.	Steroid Hormone Binding	249
I.	Oestrogens	250
II.	Progesterone	251
III.	Glucocorticoids	252
IV.	Androgens	253
V.	Steroid Hormone Binding and Biological Activity	253
C.	Binding of Thyroid and Polypeptide Hormones.	254
I.	Thyroid Hormone	254
II.	Insulin	254
III.	Oxytocin	255
IV.	Prolactin and Other Lactogenic Hormones	256
	1. Binding Studies	256
	2. Changes in Prolactin Receptor with Physiological State in Rats, Mice and Rabbits	258
	3. Control of Prolactin Receptors	258
	4. Relation Between Prolactin Binding and Its Mechanism of Action	263
	References.	263
	Subject Index	271