Mammalian Neuroendocrinology

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CROOM HELM
London & Canberra

Croom Helm Ltd, Provident House, Burrell Row,
Beckenham, Kent BR3 1AT

British Library Cataloguing in Publication Data

Bennett, Geoffrey W.
Mammalian neuroendocrinology.
1. Neurophysiology 2. Neuroendocrinology
I. Title
599'.0142 QP356.4

ISBN 0-7099-0638-2
ISBN 0-7099-0674-9 Pbk

Printed and bound in Great Britain
by Billing and Sons Ltd, Worcester.

PREFACE

Neuroendocrinology is no longer simply a branch of endocrinology but has become an established area of scientific endeavour which is of growing interest to physiologists, biochemists, pharmacologists and zoologists alike. This new status has arisen largely as a result of recent research advances which followed the discovery of active brain peptides and has markedly advanced our knowledge of the central control mechanisms of neural and endocrine systems. This book has been written as an introduction to mammalian neuroendocrinology and provides an overview of this highly complex field with particular emphasis on the hypothalamus and the control of pituitary functions. It is suitable for science undergraduate or clinical students and graduate or research scientists interested in broadening their interests into this rapidly expanding field.

The first chapter summarises the basic facts and principles of neuroendocrinology and provides the fundamental information relevant to the reader who is completely new to the subject. It outlines the anatomy of the hypothalamic-pituitary axis, the control mechanisms of pituitary secretions and the feedback and hormone receptor interactions which are well established and understood. The second chapter describes the main methods employed in neuroendocrine research so that the reader has some insight into both well-established (classical) and more recent techniques, which include histological, physiological, biochemical, neurochemical and pharmacological methodology. Subsequent chapters then cover various areas in greater depth and incorporate details of the neuroendocrine control of the posterior pituitary, the intermediate lobe of the pituitary and the control of hormone secretions from the anterior pituitary gland. The later chapters are concerned with aspects of particular importance or interest to neuroendocrinology and cover topics such as circadian rhythms of hormone secretion, seasonal breeding and hormones and behaviour. Also included is a specific chapter on brain neuropeptides which illustrates the large amount of information already available on the nature and distribution of this recently discovered family of messenger substances and their relevance to neuroendocrine control mechanisms. The final chapter outlines important clinical aspects which include disorders of the hypothalamic pituitary axis in humans and the emerging diagnostic and therapeutic value of hypothalamic peptide hormones and related drugs.

The book contains well over 150 references and these are listed at the end of the appropriate chapters. Generally the references quoted are recent reviews from journals and books from which the reader can obtain further information and more specific references to original papers. In addition references are given to closely related topics not covered by the present book: such subjects include hormones and neuropeptides of the gastrointestinal tract and evolution of hormones. A further list of recommended books, not listed in the text, is given before the index. The book is divided into subsections and use has been made of cross referencing within the book, so that the reader is directed to related information given in other sections or chapters.

We are deeply grateful to Nicola Barrett for drawing the diagrams presented in the book, to many of our colleagues and friends for helpful advice and criticism in the preparation of the manuscript and particularly to our respective spouses for their patience and understanding throughout.

ABBREVIATIONS

Anterior Pituitary Hormones

ACTH	Adrenocorticotrophic hormone (corticotrophin)
LPH	Lipotrophic hormone (lipotrophin)
LH	Luteinising hormone
FSH	Follicle stimulating hormone
TSH	Thyroid stimulating hormone
PRL	Prolactin
GH	Growth hormone (somatotrophin)

Intermediate Lobe Hormones

MSH	Melanocyte stimulating hormone
CLIP	Corticotrophin-like intermediate lobe peptide

Posterior Pituitary Hormones

VP	Vasopressin (antidiuretic hormone, ADH)
OXY	Oxytocin
NP	Neurophysin

Hypothalamic Hormones and Factors

CRF	Corticotrophin releasing factor
Gn-RH	Gonadotrophin releasing hormone (luteinising hormone releasing hormone, LHRH)
PIF	Prolactin release inhibiting factor
PRF	Prolactin releasing factor
TRH	Thyrotrophin releasing hormone
SOM	Somatostatin
GHRF	Growth hormone releasing factor
MSH-IF	MSH release inhibiting factor
MSH-RF	MSH releasing factor

Neurotransmitters

ACh	Acetylcholine
DA	Dopamine
NA	Noradrenaline
A	Adrenaline
5-HT	5-hydroxytryptamine
HIS	Histamine
GABA	γ-Aminobutyric Acid

Amino Acids (present in peptide hormones and neuropeptides)

Ala	Alanine
Arg	Arginine
Asn	Asparagine
Asp	Aspartic Acid
Cys	Cysteine
Glu	Glutamic Acid
Gln	Glutamine
Gly	Glycine
His	Histidine
Ile	Isoleucine
Leu	Leucine
Lys	Lysine
Met	Methionine
Phe	Phenylalanine
Pro	Proline
Ser	Serine
Thr	Threonine
Trp	Tryptophan
Tyr	Tyrosine
Val	Valine

CONTENTS

1

BASIC PRINCIPLES OF NEUROENDOCRINOLOGY

Neuroendocrinology may be defined as the study of the physiological processes involved in integrating neural and endocrine functions. This chapter will summarise our present understanding of the mammalian tissues and physiological processes which are the concern of neuroendocrinology and will introduce the ways in which cells of the nervous and endocrine systems respond to environmental changes and to each other to regulate bodily functions by the mediation of specific chemical agents.

Subsequent chapters will elaborate in more detail the complex neuroendocrine roles played by the hypothalamus and pituitary in particular, and final chapters will cover some important developments which have emerged from recent neuro-endocrine research, including some novel clinical applications for the diagnosis and treatment of neuroendocrine disorders.

1:1 Neurotransmitters, Neurohormones and Hormones

Chemical agents which are released from nerve cells (neurones) and act directly on neighbouring neurones or other cells are termed neurotransmitters, whereas chemicals released from endocrine cells directly into the blood circulation and transported to distant target cells are called hormones (Figure 1.1). As a result of histochemical studies pioneered in the 1940s it emerged that certain nerve cells are neurosecretory in that they release chemical agents into the blood.

Figure 1.1: Types of chemical communication between cells. M – chemical messenger (neurotransmitters, neurohormones or hormones).

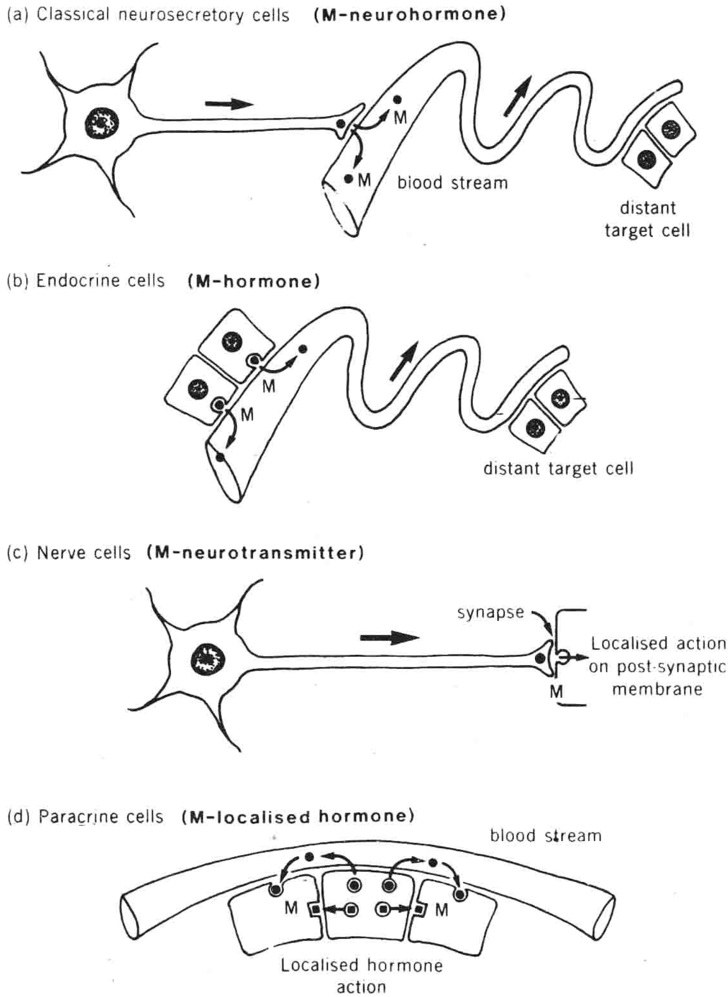


Table 1.1: Main Types of Chemical Messenger

CHEMICAL MESSENGER	SITES OF RELEASE
1. *Peptides* (Hormones, Neurohormones, Possible Neurotransmitters) Chains of amino acids of length 2 to several hundred joined by peptide bonds. These consist of any of 20 natural amino acids.	Many endocrine glands, especially Pituitary. Hypothalamus, Central and Peripheral Nervous Systems.
2. *Modified amino acids*	
(a) Thyroid hormones (Hormones) Formed from mono- and di-iodinated tyrosine (see Figure 6.1)	Thyroid gland.
(b) Catecholamines (Hormones, Neurotransmitters) Adrenaline, Noradrenaline andDopamine formed from tyrosine via L-dopa (see [10]).	Adrenal Medulla, Central and Peripheral Nervous Systems.
(c) Indoleamines (Neurotransmitters) Mainly 5-hydroxytryptamine formed from tryptophan (see [10]).	Central Nervous System.
3. *Amino acids* (Possible Neurotransmitters) Certain acidic amino acids e.g. glutamate, aspartate and γ-amino butyric acid (GABA), and glycine.	Central Nervous System.
4. *Steroids* (Hormones) Formed from cholesterol and have a characteristic planar structure of carbon atoms (see Figure 5.1)	Adrenal cortex and Gonads.
5. *Prostaglandins* (Local Hormones) Formed from arachidonic acid with characteristic structure (see [17])	Many Reproductive, Neural and Other Tissues.

Consequently the term neurohormone was introduced and the science of neuroendocrinology was born.

The wealth of neuroendocrine research which has been undertaken, particularly during the last 20 years, has shown that a minute region of the mammalian forebrain, called the hypothalamus, is an important region of neurohormone production and that the pituitary gland, situated directly beneath, acts as the principal target organ or mediator for the action of these neurohormones. More profoundly perhaps, recent research has further demonstrated previously unforeseen similarities and relationships between nervous and endocrine systems. What has become abundantly clear is that there are chemical messengers, very often small peptides in nature, which are produced and released by nerve cells in the hypothalamus and other regions of the central and peripheral nervous system that are identical with those produced by cells in the pituitary and peripheral endocrine organs. Thus the distinction between neurotransmitter, neurohormone and hormone may not always be obvious on the basis of chemical identity alone, and the same substance may possess different functions in different body tissues (Figure 1.1 and Table 1.1).

It should be mentioned in passing that a further type of localised chemical communication between cells occurs in some tissues. In this case the chemical messenger is not transported any distance in blood and only acts in a highly circumscribed area, the secretory cells are not true endocrine cells and have been termed paracrine cells (Figure 1.4 and [4]).

1:2 The Hypothalamus

The hypothalamus may be defined in either an anatomical or physiological sense. Anatomically, the hypothalamus is an area of grey matter in the basal part of the forebrain. It is divided into two symmetrical halves by the third ventricle – one of the chambers of brain filled with cerebrospinal fluid (CSF). The hypothalamus is bound rostrally (towards the nose) by the optic chiasma, caudally (towards the tail) by the mamillary bodies, laterally by the optic tracts of the eyes and dorso/laterally by the brain region called the thalamus.

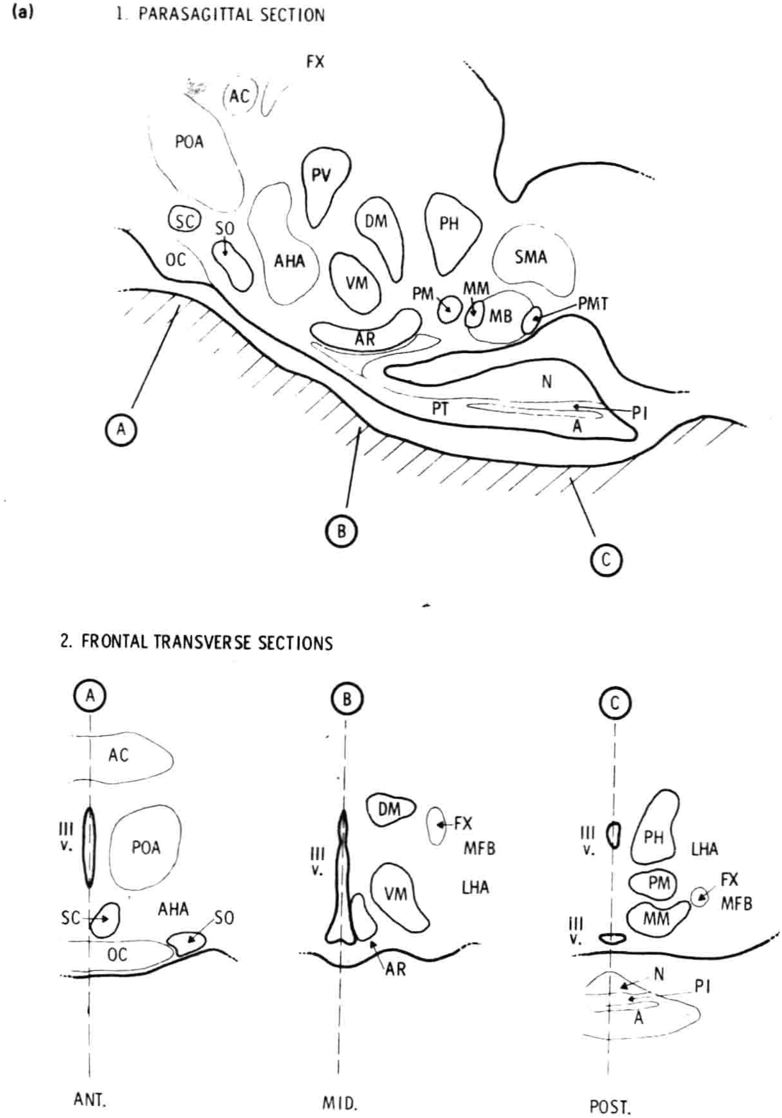
The principal nuclei (groups of nerve cell bodies) of the hypothalamus are bilaterally arranged around the third ventricle. Those concerned with pituitary regulation tend to a medial distribution, whilst those of the lateral hypothalamus are involved in other functions such as regulation of food intake. There are species differences in the presence and distribution of the hypothalamic nuclei and in the arrangement of the hypothalamic–hypophyseal tissues. This can be seen for example, by comparing the human situation with that of the most popular experimental animal, the rat (Figures 1.2a and b). It should be pointed out that these diagrams, although apparently detailed, are only a simple representation of the complexity of structures involved. For the purposes of precise experimental operations or manipulations on individual hypothalamic nuclei detailed atlases of brain nuclei for a number of species (including rat, guinea pig, cat, sheep, monkey, man) are available.

Physiologically, the hypothalamus is an important centre in the regulation of the autonomic nervous system. Visceral afferent fibres have been shown to enter the hypothalamus and efferent fibres carry impulses via subsidiary centres in the brain stem down the spinal cord

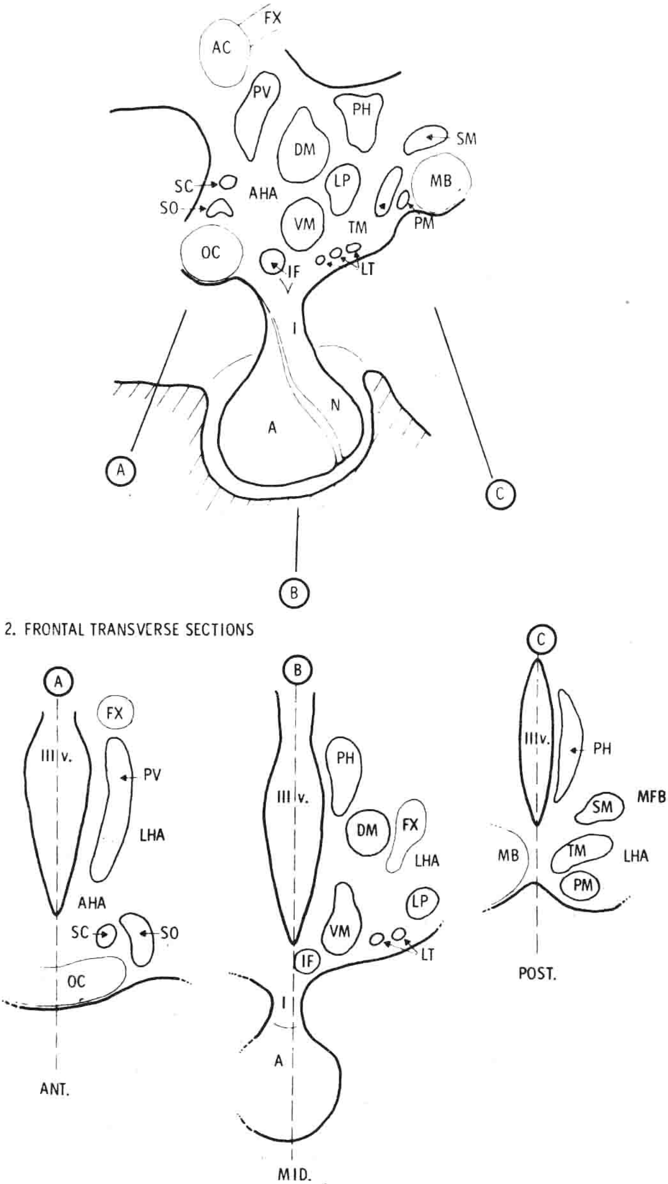
Figure 1.2: Distribution of Principal Nuclei (N) in (a) Rat and (b) Human Hypothalamus.

Abbreviations (N = nucleus)

Anterior Hypothalamus	Preoptic area	POA
	Anterior hypothalamic area (rat)	AHA
	Supraoptic N.	SO
	Suprachiasmatic N.	SC
	Paraventricular N.	PV
Mid Hypothalamus	Ventromedial N.	VM
	Dorsomedial N.	DM
	Lateral tuberal N. (human)	LT
	Lateral periventricular N. (human)	LP
	Infundibular N. (human)	IF
	Arcuate N. (rat)	ARC
Posterior Hypothalamus	Posterior hypothalamic N.	PH
	Premamillary N.	PM
	Tuberomamillary N. (human)	TM
	Supramamillary N. (human)	SM
	Supramamillary area (rat)	SMA
	Medialmamillary N. (rat)	MM
	Posteriormamillary N. (rat)	PMT
	Lateral hypothalamic area	LHA
Other landmarks	Anterior commissure	AC
	Mamillary body	MB
	Optic chiasma	OC
	Third ventricle	IIIV
	Infundibulum	I
	Fornix	FX
	Medial forebrain bundle	MFB
Pituitary	Neurohypophysis	N
	Adenohypophysis	A
	Pars intermedia	PI
	Pars tuberalis	PT


(a)
1. PARASAGITTAL SECTION
FX
AC
POA
PV
SC
SO
OC
AHA
DM
PH
SMA
VM
PM
MM
MB
PMT
AR
N
PT
PI
A
A
B
C
2. FRONTAL TRANSVERSE SECTIONS
A
AC
III v.
POA
SC
AHA
SO
OC
ANT.
B
DM
FX
MFB
III v.
VM
LHA
AR
MID.
C
III v.
PH
LHA
PM
FX
MFB
MM
III v.
N
PI
A
POST.

(b) 1. PARASAGITTAL SECTION



and along spinal nerves to the various visceral organs. In addition, there are regions of the hypothalamus which regulate complex patterns of behaviour including feeding, drinking, sexual activity, sleep and those associated with emotions such as anger, fear, joy, love and hate. Apart from the neural control of visceral and behavioural functions, the hypothalamus profoundly influences the endocrine system through regulation of pituitary function (see section 1:5). The hypothalamus is a highly vascular tissue (supplied by blood vessels from the circle of Willis) and a number of its functions are directly modulated by factors in blood. For example, osmoreceptors sensitive to sodium ion concentration are known to produce appropriate changes in the secretion of the antidiurectic hormone, vasopressin. There are also receptors sensitive to temperature and many other factors including peripheral hormones.

For further reading on the neuroendocrine aspects of the hypothalamus the reader is referred to [8, 12, 19, 20], in General Book References (p. 269).

1:3 The Pituitary Gland (Hypophysis)

The pituitary gland is formed from two embryologically distinct ectodermal tissues; an evagination of the diencephalon to form the posterior lobe and an outgrowth of the buccal cavity – 'Rathke's pouch' – to form the anterior lobe. The major subdivisions of the pituitary are shown in Figure 1.3; morphologically these vary in size and relationship in different species. The infundibulum, including the median eminence, are simple structures in the rat but more complex in other species, especially in the higher primates and man. The pars intermedia derives from the inner layer of buccal ectoderm and in some species forms a cup around the neural lobe. The pars tuberalis develops as non-secretory tissue which wraps around the infundibular stem, whilst the bulk of the adenohypophysis becomes sinusoidal tissue with developing blood vessels to form the glandular pars distalis.

The blood vessels which supply the anterior pituitary were first studied in detail in the 1930s and 1940s when it was first demonstrated that the blood flowed downwards in the hypophyseal portal vessels, contrary to the previously widely held view of flow towards the brain. The demonstration of blood flow from hypothalamus to pituitary provided a framework for the concept of a neurohumoral control of anterior pituitary function, which developed in the 1950s

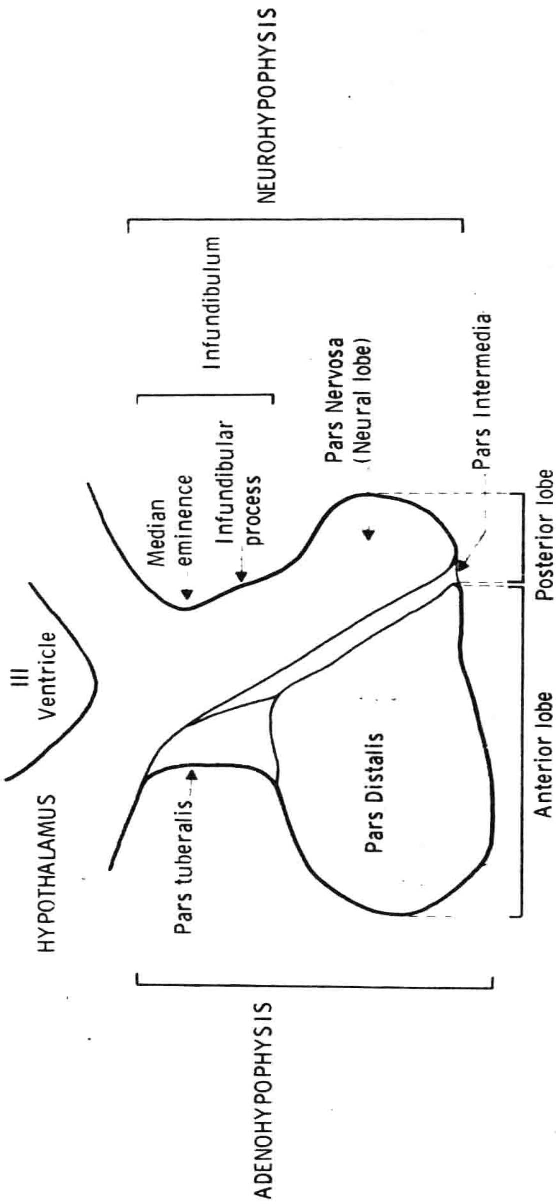


Figure 1.3: The Major Subdivisions of the Pituitary Gland.