HANDBOOK OF SEXOLOGY

Series Editors: J. MONEY and H. MUSAPH

VOLUME VI

THE PHARMACOLOGY AND ENDOCRINOLOGY OF SEXUAL FUNCTION

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J.M.A. SITSEN

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Scientific Development Group
Organon International BV
Oss, The Netherlands

1988
ELSEVIER
Amsterdam - New York - London

ISBN 0 444 90460 3

Library of Congress Cataloging-in-Publication Data
(Revised Volume/Open)

Handbook of sexology.

Includes bibliographies and indexes.
Contents: 1. History and ideology. 2. Genetics, hormones, and behavior. 3. Procreation and parenthood. [etc.] 6. The Pharmacology and endocrinology of sexual function / editor, J.M.A. Sitsen.
1. Sex (Biology)--Collected works. 2. Sex (Psychology)--Collected works. 3. Sex--Collected works. I. Money, John, 1921- . II. Musaph, Herman, 1915- . III. Sitsen, J.M.A.
QP251.H24 1978 612'.6 78-16989
ISBN 0-444-00279-0 (v. 1)

Published by:
Elsevier Science Publishers B.V.
P.O. Box 1527
1000 BM Amsterdam

Sole distributor for the USA and Canada:
Elsevier Science Publishing Co. Inc.
52 Vanderbilt Avenue
New York, NY 10017

Printed in The Netherlands

Foreword

In 1977 the *Handbook of Sexology*, edited by J. Money and H. Musaph was published, in the form of a single volume. Subsequently, it was divided and republished in five volumes with the following titles:

I History and Ideology.
II Genetics, Hormones and Behavior.
III Procreation and Parenthood.
IV Selected Personal and Social Issues.
V Selected Syndromes and Therapy.

The present 'The Pharmacology and Endocrinology of Sexual Function' is intended as the first addition to the single-volume handbook as well as to the 5-volume set. For this reason it has been numbered 'Volume VI' to provide bibliographic continuity. Further additional volumes are in preparation for future publication, among them the title 'Childhood and Adolescent Sexology'.

THE PUBLISHER

Preface

Volume VI of the *'Handbook of Sexology'* concerns itself with the effects of drugs and hormones on sexual function. The use of aphrodisiacs as sexual stimulants, as can be learned from the chapter by J. Money and his associates, has a long and fascinating tradition. But obviously the time has come for an expanded science. Thus aphrodisiology comprises only 5% of the contents of the present volume. The Editor has been successful in providing the reader with a wealth of new data. This is not the only merit of the book. The subject is treated broadly and it is clear that progress has been made in the research on drugs in relation to sexual function. It deals with the anatomical and physiological basis of sexual function. It also discusses the comparative aspects of sexual behavior from reptiles to primates, differences in male and female sexual behavior and relevant aspects of homosexual and bisexual behavior. Also the significance of social behavior and the environmental setting is taken into account. The chapters on the use of drugs which are used to facilitate or inhibit sexual function, have practical implications and more than justify the title of the book.

I recommend this volume to all those who require a broad knowledge of this field, not only sexologists but also scholars as well as physicians, psychotherapists, neurologists, psychiatrists, internists, police officers and members of the judiciary.

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J.M.A. Sitsen, editor

CHAPTER 1

Basic neuropharmacology in sexology*

M.J. RAND and M.W. NOTT

INTRODUCTION

Knowledge of the basic aspects of chemical neurotransmission and its modulation by local and circulatory hormones is necessary for a full understanding of sexual function in health and in disease, and is often crucial for interpreting the way in which drugs affect sexual activity. Both the central and the autonomic nervous systems are involved in an integrated way in all aspects of sexual function. The autonomic nervous system is controlled by brain stem centers which in turn are subject to higher neuronal systems up to the cerebral cortex. However, physiological control of the organs concerned in sexual congress is mediated by the parasympathetic and sympathetic divisions of the autonomic nervous system.

This chapter attempts to rationalize the complexity of neuronal influences on sexual function by identifying specific points at which neuronal function can be modified, these points often being common to nerves with different transmitter systems. Because noradrenergic and cholinergic transmission processes are intimately involved in autonomic function and therefore genital function, some detail will be given to their pharmacology. Because of the relatively easy access to the autonomic nervous system, details of these two neurotransmitter systems are most clear and new knowledge of ways in which neurotransmission is regulated frequently first comes to the surface after a study of one or the other of these systems. A summary of the processes involving purines will also be given. Increased complexity of neuronal control of sexual function is provided by the cotransmission process, where two or more transmitters may be released from the same nerve terminal, and

* Sexology includes basic research into mechanisms regulating sexual behavior and function. The central and peripheral nervous system and the autonomic nervous system play major roles in these mechanisms. In order to enable more clinically oriented sexologists to better understand the mechanisms of action of hormones, neurotransmitters and drugs this introductory chapter on basic pharmacology is included in this volume – Editor.

by modulation by gonadal steroids of neurotransmitter processes. Attention will be paid to these areas in this chapter. Neuropeptides are seen to be increasingly important in neurotransmission in brain and in the peripheral autonomic nervous system. An outline of their role in transmission and a brief comparison with classical transmitters will be made. Finally, the effect of gonadal steroids on transmission processes will be described.

CHEMICAL BASIS OF NEUROTRANSMISSION

The chemical transmitters are involved in carrying the signal from nerve terminals to the target cell. Direct evidence for chemical transmission was first provided by Otto Loewi in 1921 (1) for acetylcholine released from the vagus nerve terminals in the frog heart. Since then, the theory of *neurochemical transmission* has been generally accepted to account for transmission across neuroeffector junctions and nervous synapses, and many chemical transmitters have been identified. In order to establish that a substance is a neurotransmitter it must be shown that:

1. Enzymes and substrates for synthesis of the putative transmitter are present in the neuron.
2. The putative transmitter substance is present in the neuron terminals.
3. The substance applied exogenously to the target tissue mimics the effects of nerve stimulation.
4. The same mechanisms are present for the termination of action of the released transmitter and the exogenously applied substance.
5. The response to the exogenously applied substance and the response to nerve stimulation changes in the same way in the presence of drugs which affect the termination of action of the transmitter, or which block the receptors of the target cell.

Putative transmitters for which many or all of these criteria have been established, together with cotransmitters which are discussed later, are given in Table 1. The greatly increased number of substances in this list compared to lists in older literature, result largely from the recent development of immunofluorescent and immunohistochemical techniques for establishing the presence in neurons of physiologically and pharmacologically active peptides.

THE DETERMINANTS OF NEUROTRANSMITTER SYSTEMS

The nature of neurotransmission at a particular neuroeffector junction or synapse is ultimately controlled by the genetic expression of that neuron. For example, in a cholinergic neuron, the enzymes choline acetylase and acetylcholinesterase must be synthesized under the control of RNA copied from the nuclear DNA; in addition, other components of the cholinergic transmission mechanism must be made and assembled, such as the transmitter storage vesicles and receptors concerned with the modulation of transmitter release. The enzymes and other necessary components for synthesizing, storing and releasing the acetylcholine involved in cholinergic transmission are transported from the cell body along the axons to the terminals by axo-

TABLE 1 *Neurotransmitters*

	Monoamines	
1.	acetylcholine	6, 7; 25, 26; 30; 35; 43
2.	dopamine	9; 20; 35
3.	epinephrine	34; 25, 26, 34; 35
4.	histamine	
5.	norepinephrine	15; 25, 26; 34
6.	octopamine	1, 7
7.	serotonin	1, 6; 9; 20; 25, 26; 43; 43, 44; 44
	Amino acids	
8.	aspartic acid	
9.	GABA	2; 7; 20; 31; 34; 41
10.	glutamic acid	
11.	glycine	
12.	proline	
13.	taurine	
	Purines	
14.	adenosine	
15.	ATP	5
	Peptides	
16.	angiotensin	
17.	bombesin	20
18.	CGRP	
19.	carnosine	
20.	cholecystokinin	2; 7; 9; 29; 37; 41; 43
21.	corticotropin	
22.	dynorphin A	23, 26
23.	dynorphin B	22, 26
24.	β-endorphin	32, 33
25.	[met]enkephalin	1; 3, 26, 34; 5; 7; 26; 34; 41; 43; 45
26.	[leu]enkephalin	1; 3, 25, 34; 5; 7; 22, 23; 26; 34; 41; 43; 45
27.	FMRFamide	34
28.	galanin	
29.	gastrin	20; 41
30.	LHRH	1
31.	motilin-like	9
32.	α-MSH	24, 33
33.	γ-MSH	24, 32
34.	neuropeptide Y	1; 3; 3, 25, 36; 5; 9; 25; 26; 27; 41
35.	neurotensin	1; 2; 3
36.	octopamine	
37.	oxytocin	17, 20
38.	PP	
39.	peptide HI	46
40.	prolactin	
41.	somatostatin	9; 20; 25, 26; 29; 34

TABLE I *continued*

42.	substance K	43
43.	substance P	1; 7; 7, 44; 20; 25; 26; 42; 44
44.	TRH	7; 7, 43; 43
45.	vasopressin	25, 26
46.	VIP	1; 39

CGRP = calcitonin gene related peptide; FMRF = Phe-Met-Arg-Phe; LHRH = luteinizing hormone releasing hormone; MSH = melanocyte stimulating hormone; PP = pancreatic polypeptide; TRH = thyrotropin releasing hormone; VIP = vasoactive intestinal peptide.
Each transmitter has been given a number. The numbers in the righthand column refer to transmitters which have been shown to be co-released with the named transmitter. Numbers separated by a comma denote pairs of transmitters which are co-released with the named transmitter.
For references see 20, 49, 50, 63 and other papers cited in the text.

plasmic flow or by a specialized microtubular system. In a peptidergic neuron, the precursors of the peptide and the processing enzymes which cleave the propeptide to form the ultimate neuropeptide transmitter are formed under the control of the nucleus in the cell body and are transported to the axon terminals prepackaged in storage vesicles (Fig. 1).

The factors involved in the genetic expression of neurons, and hence the neurotransmitters which they release, are only beginning to be understood. They include the nature and amounts of neurotransmitters impinging on the neuron from synaptic inputs, and also chemical signals arising from the cell innervated by the axon terminals which are transported retrogradely along the axon to the nucleus in the cell body of the neuron. Furthermore, with specific reference to neurons involved in sexual function, their neurotransmitter expression may be affected by hormones, such as the steroidal sex hormones, and peptide trophic hormones.

RECEPTOR ACTIVATION AND RECEPTOR-RESPONSE COUPLING

The response of a target cell to a neurotransmitter impinging on it depends on the presence of specific receptors for recognizing the chemical stimulus, or agonist in pharmacological terms, and a transducing mechanism for coupling the agonist-receptor combination to a characteristic change in activity of the target cell.

The latent period between transmitter release and activation of the postjunctional or synaptic receptors is determined by diffusion through the junctional or synaptic cleft, a distance of 10 to 1000 μm, depending on the particular system. Then, there is a further latent period which depends on the nature of the coupling. These may be grouped in three types, according to their duration.

The shortest latent periods, of the order of milliseconds, are exhibited when the response is a change in membrane potential due to the opening of a fast ion channel. In a neuron, a decrease of membrane potential (depolarization) increases the ex-

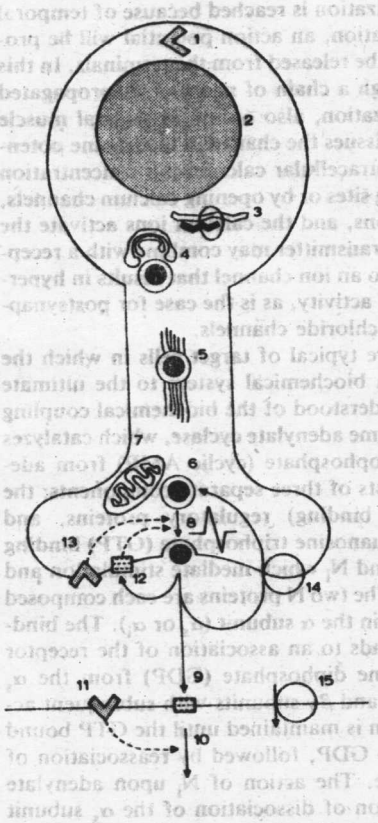

Fig. 1. Neurotransmitter processes and how they might be affected by gonadal steroids. In nonpeptidergic nerves the enzymes for synthesis of transmitter pass down the axon to the terminals. In peptidergic nerves the propeptide and associated peptidase are carried to the nerve terminal. Both systems may coexist in the neuron.

Steroids may exert a genomic effect or a direct effect. Genomic effects can occur if cytosol receptors (point 1) are present and are mediated by change in protein synthesis which may be manifested at various sites at the neuroeffector junction. Genomic effects are prevented by drugs blocking steps 2, 3 and 5. The effects of steroids described for point 6 through 15 are direct and may modify coexisting genomic actions. (1) Specific steroid receptors are required in the cytosol for a genomic effect. Effect blocked by steroid receptor antagonist. (2) DNA transcription is selectively enhanced by steroid. Blocked by dactinomycin. (3) Ribosomal synthesis of: presynaptic receptors; enzymes for formation and degradation of classical transmitter; propeptide and peptidase formation for peptidergic transmission. Blocked by cycloheximide. (4) Packaging of proteins in vesicles. (5) Axonal transport of vesicles. Blocked by colchicine. (6) Synthesis of classical transmitter within vesicle. Steroid may directly block rate limiting step. Active re-uptake into vesicle. (7) Intraneuronal metabolism. Steroid may block enzymes thereby leading to formation of false transmitters. (8) Action potential-evoked exocytosis of transmitter. Steroid may increase membrane conductance. (9) Postjunctional agonist activity of transmitter. May be mimicked or →