Monographs for Students of Medicine
Series editors: R J Harrison and A W Asscher

Control of Human Reproduction

R L Holmes
and
C A Fox

Academic Press
London New York San Francisco
A Subsidiary of Harcourt Brace Jovanovich, Publishers

MONOGRAPHS FOR STUDENTS OF MEDICINE

CONTROL OF HUMAN REPRODUCTION

R. L. HOLMES, M.Sc., M.B., Ch.B., Ph.D., D.Sc.

and

C. A. FOX, M.A., M.D., L.R.C.P., M.R.C.S., M.R.C.G.P., F.P.A.Cert.

Department of Anatomy, University of Leeds

1979

ACADEMIC PRESS

London New York San Francisco

A Subsidiary of Harcourt Brace Jovanovich, Publishers

ACADEMIC PRESS (LONDON) LTD.
24-28 Oval Road,
London, NW1

United States Edition published by
ACADEMIC PRESS INC.
111 Fifth Avenue
New York, New York 10003

Library of Congress Catalog Card Number: 78-75273
ISBN: 0-12-353450-X

PRINTED IN GREAT BRITAIN BY THE LAVENHAM PRESS LIMITED
LAVENHAM, SUFFOLK

Control of Human Reproduction

MONOGRAPHS FOR STUDENTS OF MEDICINE

SERIES EDITORS

Professor R. J. Harrison, F.R.S., M.D., D.Sc.,
School of Anatomy, University of Cambridge, Cambridge

Professor A. W. Asscher, M.D., F.R.C.P.
K.R.U.F. Institute of Renal Disease, Welsh National School of Medicine, Cardiff

AN OUTLINE OF GERIATRICS by Dr. M. Hodkinson
THE HUMAN HEART AND CIRCULATION by Dr. V. Navaratnam
GENERAL PRACTICE FOR STUDENTS OF MEDICINE by Dr. R. Harvard Davis
COMPARATIVE PLACENTATION: Essays in Structure and Function by Dr. D. Steven
SEX AND INFERTILITY by Professor R. G. Harrison and Mr. C. de Boer
THE PATHOGENESIS OF INFECTIOUS DISEASE by Professor C. A. Mims
CLINICAL EMBRYOLOGY by Professor R. G. Harrison
CONTROL OF HUMAN REPRODUCTION by Professor R. L. Holmes and Dr. C. A. Fox

Preface

The endocrinology of reproduction has many features common to all vertebrates. Most notable of these is probably the dominant part played by the pituitary gland acting as an intermediary between the central nervous and reproductive systems. Between species however, even closely related ones, there are often considerable variations in such aspects as the patterns of reproductive activity, the influences exerted by environmental factors and the relative importance of the various organs involved. Relatively few species have been subjected to extensive study; among mammals these are mainly the common laboratory animals and those of commercial importance. Extrapolation from observations on one species to others less intensely studied, even if closely related, is fallible and it is particularly unwise to assume that findings in animals can be applied directly to man, in whom "experimental" studies are necessarily largely confined to observations of normal, therapeutic and pathological aspects of reproductive processes.

A general pattern of the role played by the endocrine system in reproductive processes has emerged from the vast number of studies which have been reported; but the complexity and variability within the field of study means that inevitably generalisations introduce errors. Hence, this attempt to present a general survey, with particular reference to Man, includes statements which are not universally applicable, and which are either incorrect as regards some species, or do not accord with the views of one or other authority. It is hoped that the short list of references and suggestions for further reading, by and large restricted to reviews, may direct the reader to the greater precision (and complexity) of original studies.

The thanks of the authors are due to Professor R. J. Harrison, F.R.S. for his careful reading of the text and valuable comments; to Mr. Anthony Watkinson of Academic Press for his patience and help; and to Mrs. Barbara Whitehead for her secretarial skills.

R.L.H.
C.A.F.

Contents

1

Introduction

The various secretory tissues of the body which are commonly considered to make up the endocrine "system" have in common the essential characteristic that they secrete into the blood physiologically active substances, hormones, which exert an influence on the activity of other tissues, often situated in some other parts of the body. Endocrine glands have a rich blood supply and lack a system of ducts; but both structurally and functionally they are diverse. In general the effect of their secretions is relatively long-lasting by comparison with, for example, the action of neuro-transmitter substances, whose short-term activity is usually localized to the synaptic regions of neurons or the neuro-muscular junctions formed by motor end plates.

In so far as reproduction involves not only the reproductive organs but virtually the whole individual, the entire endocrine system is concerned in the process, but some of its components are more directly involved than others. Leading roles are played by the hypothalamus and the pituitary gland and by the gonads, the testes in the male and the ovaries in the female. The hypothalamus and pituitary together form a complex hormone-secreting control mechanism which is essential, not only for reproduction, but for the activity of other endocrine glands and for many aspects of metabolism. The gonads have dual roles, acting as endocrine glands secreting male (androgens) and female (oestrogens and progesterone) sex hormones, as well as producing the male and female germ cells, spermatozoa and ova, respectively.

The adrenal (suprarenal) glands are also of considerable importance in reproductive activity. The adrenal cortex secretes a number of steroid hormones concerned in metabolism and among these are adrenal androgens and oestrogens. Other endocrine glands influence the reproductive system to a lesser extent. The hormones of the thyroid gland are particularly involved in general metabolism, but under or over-secretion can have important effects on developmental and reproductive processes. In recent years the pineal body (or gland), whose function was uncertain for a long time, has been shown to be capable of influencing some aspects of reproductive cycles.

HORMONES

The hormones most directly concerned with reproductive processes act in several ways. In both men and women the pituitary gland secretes two gonadotropins, which act on the testes or ovaries and control not only the development of the spermatozoa and ova, but also the growth and secretion of endocrine cells lying within these organs. These produce steroids, which in turn act on the reproductive tracts, controlling their growth and the exocrine secretions of intrinsic and accessory glands, such as the endometrial glands in the lining of the uterus and the seminal vesicles which in the male contribute to the seminal fluid. The gonadal steroid hormones take part in complex feedback mechanisms which modulate the secretion of the pituitary gonadotropins (see p. 18).

Anterior Pituitary Hormones

The pituitary gland secretes at least nine distinct hormones; seven of these come from the anterior pituitary (the adenohypophysis) and two from the posterior (neurohypophysis). Six of the adenohypophysial ones are secreted by the part of the gland called the pars distalis, whose structure is described on p. 12, and three of these are of particular importance in reproduction, namely:

follicle stimulating hormone (FSH), which brings about maturation of the ovarian follicles and, in the male, influences spermatogenesis;

luteinizing hormone (LH) which with FSH effects ovulation, and subsequently growth and secretion of the corpus luteum; in the male this hormone stimulates the activity of the testicular interstitial tissue which secretes androgens (see p. 97); hence it is sometimes referred to as "interstitial cell stimulating hormone" (ICSH), but to avoid confusion the term LH is used throughout the text;

lactotropic hormone (LTH) or prolactin, which plays a part in the development and maintenance of the secretion of milk by the mammary glands.

The three other hormones of the pars distalis are particularly involved in general metabolic processes, the first two acting via the target endocrine glands. They are:

adrenocorticotropic hormone (ACTH), which controls the growth and secretory activity of the cortex of the adrenal (suprarenal) glands;

thyrotropic hormone (TSH), which controls growth and secretory activity of the thyroid gland;

somatotropic (or growth) hormone (STH) whose action is not confined to any specific target organs but has a widespread influence on metabolic processes and growth.

All these hormones are protein or peptide in nature. The gonadotropic hormones FSH and LH, and TSH are glycoproteins, that is their molecules have a carbohydrate and a protein component. This characteristic is shared by a hormone produced by the placenta, human chorionic gonadotropin (HCG) (see p. 57). Each of these four hormones is made up of two sub-units, called alpha and beta, the alpha units being homologous for all four hormones, the beta ones hormone-specific. If the original molecule of hormone is broken down to the two sub-units, each of these is found to have generally a low biological activity, but high activity is restored if the two are reunited.

The seventh hormone of the anterior pituitary is secreted by cells of the pars intermedia (see p. 13), a part of the gland which is present in most mammals, but ill-developed or, according to some, absent in man. The hormone, intermedin, can however be extracted from human pituitaries. It occurs in at least two chemical forms, and a part of the molecule is structurally common to this hormone and to ACTH, with which it shares some actions. Although many effects of intermedin have been described in man and in animals its role is unclear. In many species, particularly fish, amphibia and reptiles, intermedin acts directly on pigment cells: hence its alternative name of melanocyte or melanophore-stimulating hormone and the common abbreviation of this to MSH.

Posterior pituitary hormones

The posterior or neural part of the pituitary gland (see p. 11) of man and mammals secretes two hormones, antidiuretic hormone (ADH), which is sometimes called vasopressin, and oxytocin. These are both designated as neurosecretory hormones, since they are elaborated by neurons situated in the hypothalamus. From here they pass along nerve fibres to the posterior part of the pituitary gland where they are stored, bound to carrier substances called neurophysins. Each of these hormones is an octapeptide, containing two linked molecules of the sulphur-containing amino acid cysteine, the two usually considered as constituting one molecule of cystine. The arrangement of the amino acids in the molecule of oxytocin is shown in Fig. 1. The

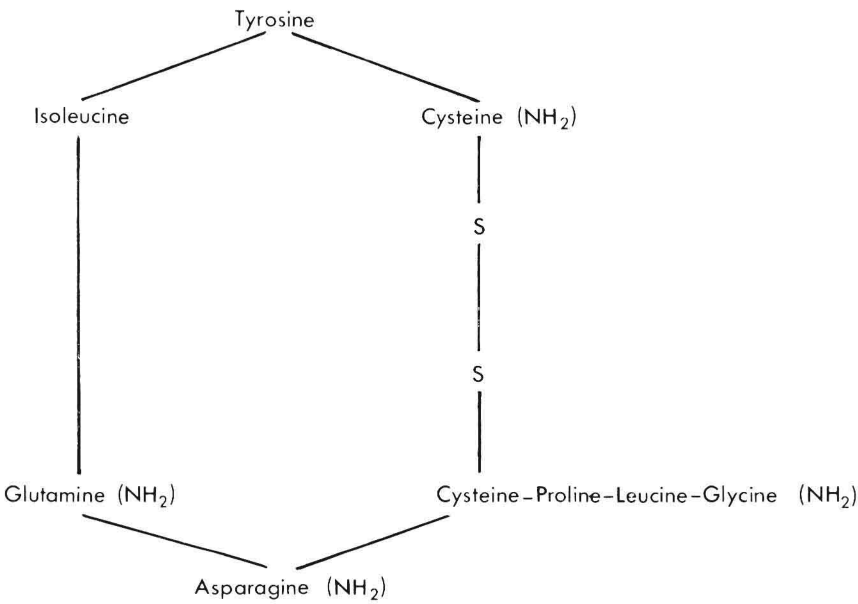

Fig. 1. Structure of a molecule of oxytocin to show the arrangement of the amino acids.

structure of ADH differs in that arginine replaces leucine in the side chain, and phenylalanine replaces isoleucine in the ring.

Oxytocin increases the contractility of smooth muscle of the reproductive tract. It is reflexly secreted during coitus and causes contractions of the uterine muscle which may aid the passage of spermatozoa through the reproductive tract and increase the likelihood of fertilisation. During labour (parturition) oxytocin stimulates uterine contractions and aids delivery of the fetus: and in the period of lactation following the birth of the infant the hormone is reflexly released during suckling and, by bringing about contraction of myoepithelial cells and smooth muscle in the mammary glands assists the outflow of milk.

ADH is not directly concerned in reproductive processes.Its main action is to increase the absorption of water from the distal renal tubules and collecting ducts, so that a concentrated urine is secreted from the kidneys. It owes its alternative name, vasopressin, to its ability to increase the blood pressure,but this effect is usually of secondary importance. The close chemical similarity of ADH and oxytocin is reflected in the finding that each can to a small extent exert the effects of the other.

Gonadal hormones

The "sex" hormones are commonly thought of as being either "male", secreted by the testes or "female", by the ovaries. The testicular hormones, androgens, include the primary hormone testosterone, while those coming from the ovaries include oestrogens and progesterone. Both male and female gonads however can synthesise both "male" and "female" hormones and, although in normal individuals the hormones of the appropriate sex predominate, both types occur in the blood of men and women and as breakdown products in their urine. Futhermore, both "male" and "female" hormones are synthesised in the adrenal cortex of each sex.

The gonadal hormones share a common basic chemical structure with others which are largely produced by the adrenal cortex and also by the liver. These are all classified as steroids. Those which are secreted by the testis and ovary influence particularly the reproductive system, as indeed do androgenic and oestrogenic steroids arising in the adrenal glands. Many of the adrenal steroids however are primarily involved in general metabolic processes in tissues not primarily concerned with reproductive activity. Some steroids of adrenal and of gonadal origin, notably androgens, exert a protein anabolic effect; that is they bring about retention of nitrogen and an increased synthesis of protein. This effect is not confined to the reproductive system, but occurs in tissues of the body such as bones, kidney and notably skeletal muscle. The increased muscular development following the administration of anabolic steroids has been made use of to increase the muscularity and performance of athletes and to increase the meat yield of cattle.

The basic structure of steroids is a nucleus of 17 carbon atoms, conventionally numbered as in Fig. 2, the valence bonds for each carbon being to adjacent carbon atoms or to hydrogen. The presence of methyl (CH3) groups or more elaborate side chains in different compounds, and the addition of oxygen to form —OH or =O at variously positioned carbon atoms of the basic nucleus, may profoundly modify the activity of a steroid. Such additional carbon atoms are also numbered, so that compounds with 18, 19 or more basic carbon atoms occur (Fig. 2).

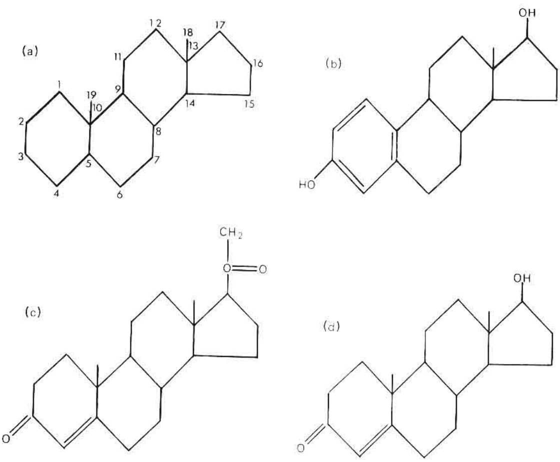

Fig. 2. Diagram to show (a) the conventional numbering of the carbon atoms in the steroid nucleus; (b) structure of oestradiol; (c) progesterone; (d) testosterone.

The precise role of any given steroid is often difficult to assess, for many of them have both specific effects exerted on particular organs and tissues and more general influences on some aspects of metabolism. Furthermore the response of a given tissue to a hormone varies and is influenced by genetic, nutritional, endocrine and other factors. Many different steroids can be isolated from tissues; and while some of these are intermediaries in the synthesis of a given end product such as testosterone, they themselves commonly have inherent endocrine activity. The lack of clear cut distinction between "male" and "female" steroid hormones is further emphasised by the fact that oestrogens and progesterone occur as intermediate products in the synthesis of androgens, and androgens are produced in the synthesis of oestrogens.

Biosynthesis and metabolism of steroids

Large amounts of steroids are synthesised by the adrenal cortex, testis and ovary, all of which have the enzymes necessary for the elaboration of the hormones from two-carbon acetate. Normally any one of these tissues produces a predominance of steroids with a particular range of actions, although each is capable of producing virtually any type. Thus the adrenal cortex usually secretes a variety of corticoids involved in general metabolic process, and some androgens; the testis secretes mainly androgens and the ovary mainly oestrogens and progesterone. But in abnormal states the secondary products may become the predominant ones.

The basic step in the synthesis of steroids by living tissues is the transformation of two-carbon acetate (CH_3COO—) into cholesterol. Not all tissues are able to utilise this two-carbon compound, and some require more complex blood-borne precursors. This applies to the placenta, which can use only small amounts of acetate for the synthesis of progesterone, and to the liver. Such tissues are in this sense incomplete endocrine organs, depending on substances formed by adrenal cortex, testis and ovary for the synthesis of their own highly active steroids; but given these "pre-hormones", which often have a relatively low activity, both liver and placenta can produce potent substances.

It is then hardly surprising that large numbers of steroids can be isolated from steroid-producing tissues and from blood. Some of these are potent substances known to be essential factors in metabolic and reproductive functions while others, formed as intermediaries in the synthetic processes, do not necessarily have such essential roles. For example, a basic pathway for the synthesis of oestrogens involves the formation of progesterone and androgens, as in the scheme.

acetate
↓
cholesterol
↓
progesterone
↓
androgens
↓
oestrogens

The most active naturally occurring oestrogen, oestradiol, can be formed by the sequence

progesterone
↓
17-hydroxyprogesterone
↓
androstenedione
↓
testosterone
↓
oestradiol

a process which involves the formation as intermediaries of the weak androgen, androstenedione, and the potent one, testosterone. An alternative sequence, giving oestrone as the end product, begins with pregnenolone

pregnenolone
↓
17-hydroxypregnenolone
↓
dehydroepiandrosterone
↓
oestrone

The metabolism of steroids takes place in the liver but also in many other tissues. Structural changes such as reduction of double bonds and oxidation results in diminution of their activity, and conjugation with sulphate or glucuronate occurs. Conjugated metabolites are excreted in the urine; metabolites of progesterone include pregnanediol and 17-hydroxyprogesterone; oestrogens are excreted as conjugated substances, and androgens as 17-ketosteroids.

Mode of Action of Sex Hormones

Testosterone, the most potent circulating androgen, is transported in the blood free or loosely bound to carrier proteins. These are beta-globulins know as sex hormone binding globulin (SHBG) and testosterone binding globulin (TeBG). Levels of these globulins are raised during pregnancy and by ingestion of oestrogens (including most oral contraceptives); increases are also seen in hyperthyroidism, hepatic cirrhosis and male hypogonadism. Androgens and oestrogens compete for binding sites on these globulins, and any increase favours the binding of androgens. This results in a fall in the level of free-circulating testosterone and a rise in the available oestrogen. Such a situation is thought to explain the gynaecomastia exhibited in the conditions mentioned.

In considering the action of steroid hormones at the cellular level it is important to understand the current nomenclature. A *target cell* is one proved by bioassay procedures to be under the regulation of a given type of steroid hormone. A *receptor* is an intracellular protein component responsible for the specific and high-affinity binding of a particular hormone and playing an integral part in its mechanism of action. An *acceptor is* a nuclear component responsible for the high affinity but limited retention of a steroid hormone-receptor complex in chromatin.

The entry of testosterone through the target cell membrane is facilitated by the action of cyclic-AMP (adenosine-3,5-cyclic monophosphate). Within the target cell it is metabolised by the enzyme 5-alpha reductase to the powerful androgen 5-alpha dihydrotestosterone which is thought to be the active androgen at the cellular level. The dihydrotestosterone-receptor protein complex is available for reaction with nuclear acceptor sites in the chromatin. At the nuclear level DNA acts as a template for the androgenic response through the accepted ribosomal RNA and messenger RNA mechanisms. The whole process is reversible so that the receptor protein-androgen complex does not form covalent bonds with the nuclear acceptor components. The antiandrogen action of oestrogens and cyproterone acetate may be considered in terms of competition for receptor binding sites at the target cell.

As already noted, the anabolic action of testosterone stimulates cell growth, increases body weight and causes nitrogen retention; additionally there is greater secretion of sebum and accelerated bone maturation. Thus, administration of anabolic steroids to children of small stature can be counter-productive by causing earlier fusion of epiphyses.

Measurement of hormones in the blood

The original bioassay methods depended on the growth of the comb in caponised cocks or increase in size of the rat ventral prostate. Analytical methods were gradually perfected so that sample size of 50 ml plasma, for example, using paper chromatography followed by enzymic conversion of the recovered testosterone to oestradiol which was measured fluorimetrically, was eventually reduced to 2 ml for competitive protein binding assays. The introduction of the radioimmunoassay has allowed the analysis of several hundred samples of less than 1 ml in a few days.

Radioimmunoassay depends on the competition between radioactively labelled hormone and unlabelled hormone for specific sites of an antibody specific to the hormone under investigation. The antibody is produced in an animal to which the antigen is foreign. The higher the blood concentration of unlabelled hormone, the less radioactive labelled hormone will be bound to antibody. It is possible to separate bound from free hormone and to measure the quantity of labelled hormone associated with bound antibody. A standard curve is prepared using known quantities of hormone and the concentration of hormone in an unknown sample may be read directly off the curve. It is assumed that antibody-bound hormone is completely separated from free hormone and that the radioactivity is measured in antibody-bound hormone. The normal values for plasma testosterone are 3-11 ng/ml in the male and 0.2-0.5 ng/ml in the female.

Oestrogens may be measured by chemical methods such as fluorimetry or gas chromatography but the preliminary purification which is so necessary for these techniques has proved tedious and time consuming. Here again, radioimmunoassay has great advantages and some centres are claiming reliable results. Plasma levels of 17-beta oestradiol vary around a mean of 50 ng/ml at mid-cycle reaching a nadir at the menstrual flow.

For the investigator, the change from large sample size taking perhaps a week for a few results to the modern situation of small volume multiple sample analysis has opened new vistas.

Pheromones

These can be considered to come under the broad heading of "hormones". They are chemical substances which typically bring about integration of activities among individuals of the same species, and their effects are particularly marked in invertebrates. Originally called ectohormones, they differ from the substances commonly classed as hormones in that the recipients respond to substances liberated by other individuals rather than to their own internal secretions. Minute amounts of pheromones are detectable by chemoreceptors. Their actions are particularly evident in invertebrates, in which they can for example initiate or inhibit complex developmental processes, or induce behaviour associated with reproductive activity. Female silkworm moths and cockroaches release substances which, as sex attractants, direct males to the females often over long distances and also trigger male sexual behaviour.

A well known example of a pheromone is "queen-bee substance". This, of known chemical structure, is secreted by mandibular glands of the queen; when ingested by the workers it inhibits development of their ovaries. Pheromones also act in some vertebrates and influence reproductive processes in some mammals (see p. 129).