Introduction to PHYSIOLOGY

VOLUME 5
CONTROL OF REPRODUCTION

HUGH DAVSON

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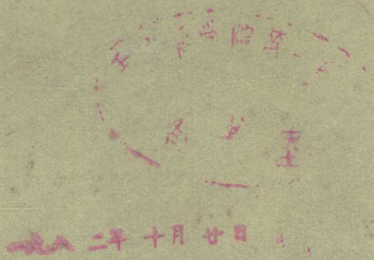

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CONTROL OF REPRODUCTION

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CHAPTER 1

Introduction

The co-ordination of the several factors concerned in the sexual reproduction of two individuals to produce one or more progeny requires control over a variety of factors; thus, mature ova and sperm must be produced at the same time, and at this time the female must be in a state to receive the sperm and the male to copulate, i.e. the female must be receptive, or on heat (in oestrus) close to the time at which she produces a new ovum. The timing of the events must be such that, at the end of gestation, there will be adequate food available for mother and offspring; and this is doubtless the basis for the breeding season in many lower animals. The fertilized ovum requires nutrition, and this is achieved by implantation of the blastocyst in the wall of the uterus; for successful implantation the uterus must be prepared—the decidual reaction—and subsequent nutrition must be achieved by formation of a placenta, whilst the mammary glands must be prepared for their later function of feeding the infant. During pregnancy the cyclically occurring events taking place in the non-pregnant female, included in the term *oestrous cycle*, or, in primates, the *menstrual cycle*, must be suppressed; and finally the relaxed state of the uterine muscle, necessary for retention of the foetus in the womb, must be succeeded by a highly active state leading to delivery.

STEROID HORMONES

Castration

The control mechanisms are mediated through the steroid hormones secreted mainly by the gonads and, if pregnancy takes place, in many species by the placenta. In the male, the primary function of its secreted androgens is to bring about a state of "maleness" in the developing foetus and young animal, and to sustain this maleness throughout adult life. Thus, castration of the young male, before puberty, prevents the development of its accessory sex organs so that the castrated male re-

tains many female features; for example, the human male voice remains unbroken, and the effects of the operation on male animals were early recognized, the castrated ox being more amenable than the bull, the capon producing more fat than the cock, and so on. These effects can be antagonized by injections of androgens, such as testosterone. Castration of the adult male has well defined effects, indicating the necessity for the continuous secretion of androgens for the maintenance of maleness. Thus, Table I from Ramirez and McCann (1965) shows the changes in weight in the seminal vesicles and ventral prostate gland of castrated rats following administration of testosterone at various doses. Castration itself causes a profound drop in weight of the

TABLE I

Changes in weight of seminal vesicles and ventral prostate gland of rats after castration and replacement therapy with testosterone propionate, Tp (Ramirez and McCann, 1965)

Type of rat	Dose of Tp μg/100g/day	Seminal vesicles (mg)	Ventral prostate (mg)
Intact	0	1025 ± 36*	341 ± 44
Castrated	0	71 ± 6	27 ± 1
Castrated	5	240 ± 2	50 ± 4
Castrated	25	397 ± 17	97 ± 13
Castrated	100	1147 ± 60	403 ± 17
Castrated	150	1416 ± 70	419 ± 26

* Mean ± S.E.

seminal vesicles, for example, from 1025 mg to 71 mg in mature animals, and from 13·9 to 5·0 mg in immature animals. This fall in weight is prevented by administration of the hormone.

Coitus

A more positive indication of the role of male steroid hormone secretion is revealed by the striking changes in blood-level of testosterone during sexual excitement and coitus. Figure 1.1 illustrates the rise in luteotrophic hormone and the subsequent rise in testosterone in a bull at sight of a cow and the ensuing copulation.*

* The relation between blood testosterone and sexual activity in the male is probably more complex than suggested by this finding in the bull; in guinea-pigs the level of blood testosterone is not related to high or low degree of sexual activity; however, animals with high activity responded with a rise in blood testosterone on exposure to an oestrous female which was large by comparison with that in animals of low activity (Harding and Feder, 1976). As we shall see, androgens can be converted in the female or male, to oestrogens, and it has frequently been argued that an effect of androgen is mediated by prior conversion to oestrogen. For example the testosterone-induced mounting behaviour of castrated male rats can be

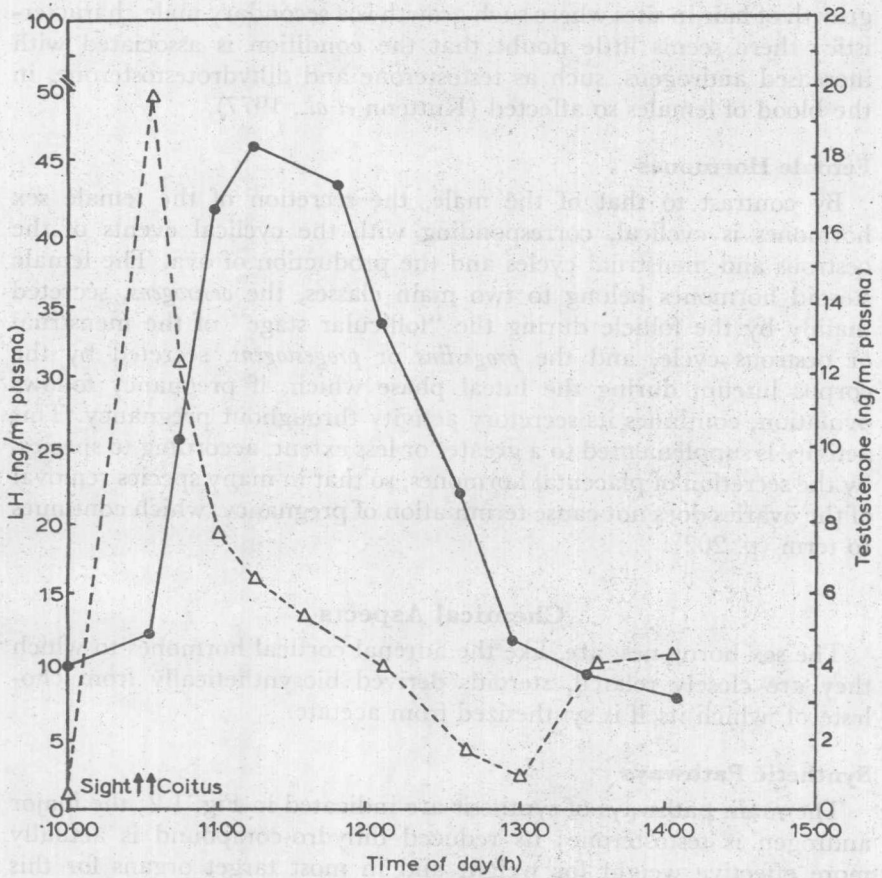

Fig. 1.1. The effect of coitus on the concentrations of luteinizing hormone (LH; △ – – – – – △) and testosterone (●————●) in the peripheral blood of a bull. (Katongole *et al.*, *J. Endocrinol.*)

Non-Reproductive Tissue

In addition to the effects on the primary and accessory sexual organs, the androgens affect many other tissues of the body; thus, the kidney, adrenal gland, liver, pancreas, thyroid, thymus, salivary glands, skin pigmentation, red blood cell formation are all affected. Their influence, moreover, is not confined to the male, except in so far as the female lacks the appropriate target organs.

This is especially obvious in the condition of hirsutism or excessive

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reduced if the testosterone is applied to the hypothalamus together with an aromatization-inhibitor, androst-1,4,6-triene-3,17-dione (ADT). It must be emphasized, however, that less than 0·1 per cent of the testosterone would be converted to oestradiol, and it may be that the much larger amounts of dihydrotestosterone formed would co-operate with oestradiol (Christensen and Clemens, 1975).

growth of hair in sites where such growth is a secondary male characteristic; there seems little doubt that the condition is associated with increased androgens, such as testosterone and dihydrotestosterone, in the blood of females so affected (Kuttenn *et al.*, 1977).

Female Hormones

By contrast to that of the male, the secretion of the female sex hormones is cyclical, corresponding with the cyclical events of the oestrous and menstrual cycles and the production of ova. The female steroid hormones belong to two main classes, the *oestrogens*, secreted mainly by the follicle during the "follicular stage" of the menstrual or oestrous cycle, and the *progestins* or *progestogens*, secreted by the corpus luteum during the luteal phase which, if pregnancy follows ovulation, continues its secretory activity throughout pregnancy. This activity is supplemented to a greater or less extent, according to species, by the secretion of placental hormones, so that in many species removal of the ovaries does not cause termination of pregnancy, which continues to term (p. 202).

Chemical Aspects

The sex hormones, are, like the adrenal cortical hormones to which they are closely related, steroids derived biosynthetically from cholesterol, which itself is synthesized from acetate.

Synthetic Pathways

The main pathways of synthesis are indicated in Fig. 1.2; the major androgen is testosterone; its reduced dihydro-compound is actually more effective weight for weight and in most target organs for this androgen there is an enzyme, 5α-testosterone dehydrogenase, that is capable of transforming testosterone rapidly to the reduced form, so that it is highly probable that it is in this form that it exerts its action on the cells of many target organs.

The human ovary secretes mainly 17-β-oestradiol (E_2), oestrone (E_1), progesterone and 17-α-hydroxyprogesterone.* It will be seen that the synthetic pathway involves the formation of both male and female sex hormones so that, in fact, the female gonad does, indeed, produce small quantities of androgens such as testosterone and the male gonad produces oestrogens; furthermore, the ovarian cells that produce the

* The main oestrogen of the goat is 17α-oestradiol. 20α-hydroxy-progesterone is formed from progesterone in peripheral metabolism; it is also secreted by the monkey ovary, especially in the later, luteal, phase of its menstrual cycle (Hayward, 1963). 17α-hydroxyprogesterone, although produced in the ovary, is relatively inactive.

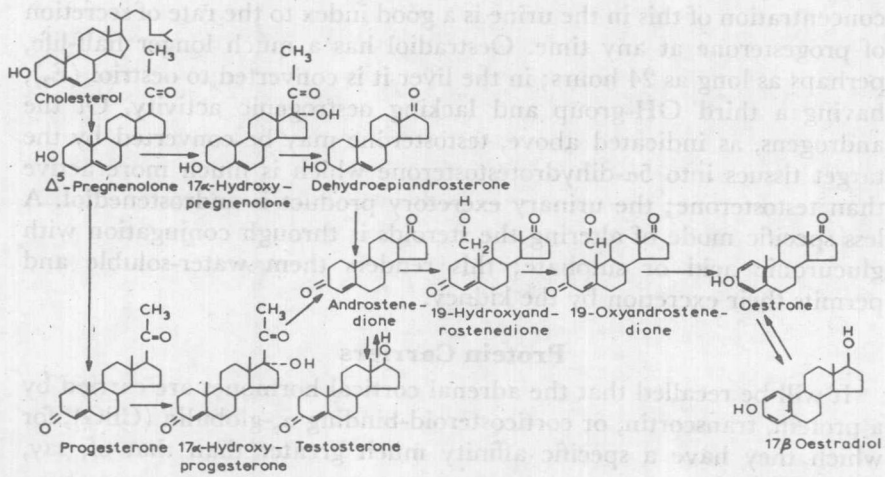

Fig. 1.2. Steroid synthetic pathways in human ovaries and testes. The major secretory product of the testis is testosterone; the ovary secretes 17β-oestradiol, progesterone and 17α-hydroxy-progesterone. (Odell and Moyer, *Physiology of Reproduction.*)

oestrogen type of hormone also produce the progesterone type, so that we must speak rather of a main product or products, of a given tissue; thus the main product of the follicular cells of the ovary is oestradiol whilst that of Leydig cells of the testes is testosterone, presumably because the enzyme compositions favour these stages in synthesis.† The similarity with the adrenal cortical hormones has already been emphasized; this extends to the use of a common synthetic pathway, so that sex hormones are, indeed, produced and secreted by the adrenal gland; this is especially true of progesterone, which is the precursor of both androgens and oestrogens as well as of corticosterone.

Metabolic Changes

When secreted into the blood the hormones may undergo chemical change so that the androgens, oestrogens, etc., isolated from urine or tissue may not be the same as the hormones originally secreted by the glands. Thus, the turnover of progesterone is quite rapid, with a half-life of about 30 minutes; it is converted into the inactive pregnandiol

† The finding of oestrogen in normal male urine could be interpreted as a metabolic conversion from testosterone, rather than release from testes; however, Kelch *et al.* (1972) cannulated the spermatic veins of 8 normal men and obtained a concentration of oestradiol of 1050 $\pm$ 57 pg/ml compared with only 20 $\pm$ 1·6 pg/ml in blood from a peripheral vein.

which appears in the urine as pregnandiol glucuronide, so that the concentration of this in the urine is a good index to the rate of secretion of progesterone at any time. Oestradiol has a much longer half-life, perhaps as long as 24 hours; in the liver it is converted to oestriol (E_3), having a third OH-group and lacking oestrogenic activity. Of the androgens, as indicated above, testosterone may be converted by the target tissues into 5α-dihydrotestosterone which is much more active than testosterone; the urinary excretory product is androstenediol. A less specific mode of altering the steroids is through conjugation with glucuronic acid or sulphate; this renders them water-soluble and permits their excretion by the kidney.

Protein Carriers

It will be recalled that the adrenal cortical hormones are carried by a protein, transcortin, or corticosteroid-binding α_2-globulin (CBG), for which they have a specific affinity much greater than that of, say, serum albumin.

SSBG and TeBP

Of the sex steroids it is known that progesterone is carried by the same protein. So far as the others are concerned, Mercier-Bodard *et al.* (1970) have reviewed the literature and described in some detail the characteristics of a "sex steroid-binding globulin" (SSBG) which is probably similar to the "testosterone-binding protein" (TeBP) of human pregnancy serum described by Gueriguian and Pearlman (1968) and by Hansson *et al.* (1974). The carrier-protein is not specific for testosterone, and binds oestradiol, the affinity constants being 1·2 and $0{\cdot}5.10^9\ M^{-1}$ for testosterone and oestradiol respectively (Mercier-Bodard *et al.*, 1970). According to Anderson (1976) if the binding by testosterone is put at 100, 5α-dihydrotestosterone (DHT) binds nearly three times as well and oestradiol about one-third as well. Δ-5 androstenediol binds as well as testosterone. Androstenedione and dehydroepiandrosterone hardly bind at all. The molecular weights of these sex steroid-binding proteins (SBP and TeBP) are higher than that of corticosterone-binding protein, being about 100,000 compared with about 66,000.

Progesterone Carrier

Of some interest is the appearance of a glycoprotein in the blood of the pregnant guinea-pig that binds specifically to progesterone; the association constant of $9.10^8\ M^{-1}$ reveals a high affinity comparing with only $1{\cdot}6.10^7\ M^{-1}$ for testosterone. This does not occur in non-pregnant

animals and cannot be induced in these by injections of oestrogens or progestins, and so it may well be synthesized in the placenta (Milgrom *et al.*, 1972).

Physiological Role

The role of the binding proteins in plasma may be simply that of carriers, as discussed in Vol. 2; as suggested by Anderson (1976), however, it is possible that variations in the quantity of a binding protein that binds androgens and oestrogens to different extents might represent a mode of controlling the dominance of oestrogenic and androgenic activity at a given target organ, since there is no doubt that the activity of a steroid is governed by the concentration of the free molecule in the neighbourhood of the target cell. An important finding in this respect is that the production of the binding protein is influenced by the concentration of steroid hormones, oestrogen tending to stimulate production whilst testosterone tends to inhibit production. Thus, the binding protein could, perhaps, act as an amplifier for testosterone action, tending to increase the amount of free androgen in the blood; it would operate in the opposite way on oestrogen action (Burke and Anderson, 1972). In this way, the virilizing in the polycystic ovary syndrome could be attributed to the low levels of SSBG in the blood.

Receptors

As we shall see, the target organs for the steroid hormones, e.g. the uterus or prostate, contain specific proteins or "receptors" with which the hormone binds on entering the cell; these "receptors" are different from the plasma carrier proteins described above, characteristically exhibiting a far greater specificity for a given steroid.

Control

In general, as indicated in Vol. 2, the steroid bound to its carrier acts as a reserve, the active form being that dissociated from the carrier at the target-site. Control over steroid activity may well be exerted, not only through alterations in secretion by the appropriate cells, but also by the amounts of carrier protein released into the blood (see, for example, Gueriguian *et al.*, 1974). In addition, control could be modified by alterations in the number and affinity of specific "receptors" with which the hormone must interact before it exerts its action within its target cell.

Binding Sites or Receptors

The results of modern studies of steroid hormone action indicate that the hormone first binds in the target cell to a protein that has a high specific affinity for it; as a result of this initial step, the hormone can now be translocated within the cell to the nucleus where it may exchange places with another—nuclear—receptor. These studies* have been based on isolation of protein material from the target cells with specific binding capacity for the hormone, and also by observation of uptake of the radioactively labelled hormone by the tissue, either by extraction or by radioautography.

Target Tissues

The "target organs" for the sex steroids are the gonads, themselves, and the secondary reproductive organs such as the prostate, uterus, mammary glands, and so on. In addition to these organs, the steroid hormones are able to influence the secretion of their trophic hormones, synthesized by the anterior pituitary, or hypophysis, and they may do this either directly by influencing the secreting cells, or indirectly by modifying the excitability of the hypothalamic neurones whose secretions, *releasing hormones*, are carried by the portal system to the anterior lobe of the pituitary. It is reasonable, therefore, to examine both the pituitary and the hypothalamus for binding sites or receptor material.

Uptake of Labelled Oestradiol

Some results of Eisenfeld and Axelrod (1966), obtained by injections of labelled oestradiol and extracting the labelled material from target organs, are shown in Fig. 1.3; uptake of oestradiol into the female target-organs, such as the uterus, was very high, but it was also high in the pituitary and the hypothalamus, regions of feedback of this hormone. It is interesting in this connection that the uptakes of this "female steroid hormone" into both male and female pituitaries and hypothalami were very similar.

Autoradiography. Stumpf has developed highly sensitive radioautographic techniques for the localization of ^{3}H-labelled steroid in the tissues; the silver grains deposited by this technique occurred over the nuclei of target tissues, such as vagina, oviduct, testis and a mammary tumour, but in the non-target tissues, such as liver and adrenal gland, there was no concentration over the nuclei. In the uterus, for example, epithelial cells, connective-tissue cells and muscle cells all showed

* The interaction of labelled steroid hormone with its target tissue, leading to the concept of the steroid receptor, was described first by Jensen and Jacobsen (1962).