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EFFECT OF HORMONES ON THE PHYSIOLOGICAL AND BEHAVIOR PROCESSES THAT INFLUENCES FERTILITY

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ABSTRACT

This chapter reviews the complex and diverse roles that hormones play in mediating the physiological and behavioral processes that influence human fertility. Much of the focus is on hormones of the reproductive axis, which mediate the physiological processes governing fertility and provide powerful modulation of sexual behavior. Secretion of these hormones changes over the life span. Reproductive hormones are secreted in surprisingly high levels in prenatal development and at this time help set the stage for later development of normal reproductive physiology and behavior in adulthood. There is then a period of childhood quiescence, when the reproductive axis is essentially "turned off", followed by a cascade of hormonal changes that occur with puberty. In males, reproductive hormone secretion is rather stable in the adult years, with a slow decline in levels occurring with aging. In contrast, much greater fluxes in hormone secretion occur throughout adulthood in women, with large changes in hormone secretion occurring over the course of each menstrual cycle, followed by a period of irregular hormone secretion during the transition to menopause and ultimately a marked decline in reproductive hormone levels in the postmenopausal period.

KEYWORDS: lead, nervous system, N-acetylcystein, biomarkers.

INTRODUCTIONS

Many lifestyle choices and life events can modulate activity of the reproductive axis and thus impact significantly on both reproductive physiology and behavior. In the modern world, pharmacological modulation of reproductive hormone levels is common. Large numbers of women take exogenous hormones in the form of contraceptives, and even greater numbers of women are given estrogen replacement therapy in the postmenopausal period. A more limited

but rapidly expanding subset of individuals consumes steroid hormones to regulate body strength and endurance, particularly individuals who participate in competitive sports. And with the more widespread consumption of foods that contain phytoestrogens, environmental exposure to hormones is becoming an issue of greater importance.

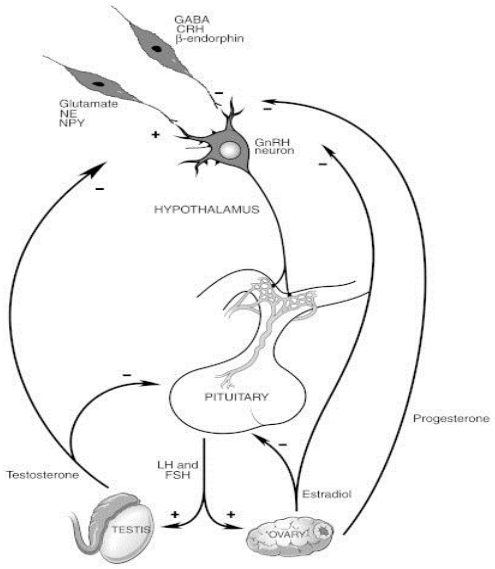
A variety of events that occur over the course of a normal life can also significantly influence activity of the reproductive axis.[1-3] Pregnancy and lactation are associated with profound changes in the functioning of the reproductive axis, fertility, sexual behavior, and maternal behavior. Common life stresses, including metabolic stresses associated with undernutrition or the increased energy expenditure of participation in chronic vigorous exercise can suppress the activity of the reproductive axis. And psychosocial stresses provide an even more common inhibition to the reproductive axis. Even if reproductive hormone secretion is maintained, these life events can markedly alter circulating levels of reproductive hormones and thus influence fertility and sexual behavior. Biodemographic studies need to track lifestyle choices and life events to allow an accurate conceptualization of factors influencing fertility outcomes in human relationships.[4-5]

Lastly, it is important to keep in mind that there are dramatic individual differences in normal circulating levels of reproductive hormones, the amount of hormone needed to maintain normal reproductive physiology and sexual behavior, and the sensitivity of individuals to the various forms of stress-induced reproductive dysfunction. We are just beginning the daunting task of elucidating the systems in the brain that underlie these individual differences. However, it is likely that the task of understanding the role that individual differences play in contributing to fertility outcomes will be even more complex.[6]

This section provides an overview of the hormones that comprise the reproductive axis, how they are regulated and secreted, and their physiological actions in the body (for more detailed information see Steiner and Cameron, 1989; and Griffin and Ojeda, 2000).[7-8] Particular attention is given to issues that influence the types of measurements made in the field of biodemography.

Although many people think of reproductive function as a bodily function governed by endocrine organs of the pelvis, testes and ovaries, specialized neurons in the brain and hormones secreted by the "master endocrine organ," the pituitary, located just beneath the brain, play critical roles in governing reproductive function (see Figure 5-1).[9] Not only do

the brain and pituitary coordinate and provide the "central drive" to the reproductive axis throughout life, the brain is also the primary site where environmental factors that modulate reproductive function act.



Schematic diagram of the hypothalamic-pituitary-gonadal axis

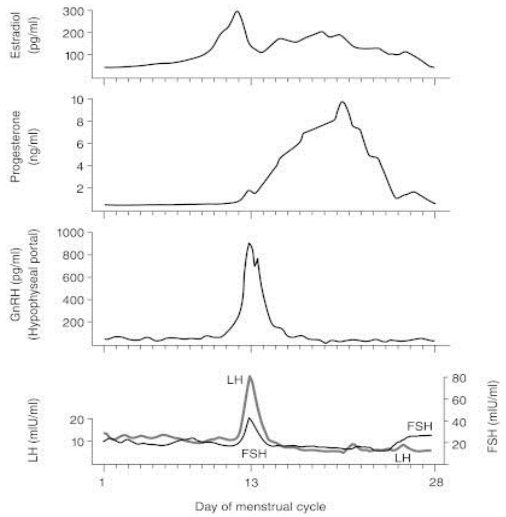
The region of the brain involved in the regulation of reproductive function as well as many of the body's other basic homeostatic functions (i.e., control of food intake, growth, response to stress, water balance, metabolic rate) is the hypothalamus. The hypothalamus sits at the base of the brain and is connected by a specialized portal blood system to the pituitary, just below. A population of specialized neurons in the hypothalamus produce the neurotransmitter, gonadotropin-releasing hormone (or GnRH, named for its ability to release the hormones in the pituitary that provide trophic support to the ovaries and testes—the gonadotropins—luteinizing hormone, LH and follicle-stimulating hormone, FSH). GnRH travels via the portal capillaries to the anterior pituitary, where it stimulates the synthesis and release of the pituitary hormones, LH and FSH.[10]

Many neurotransmitter systems from the brainstem, limbic system and other areas of the hypothalamus convey information to GnRH neurons (Kordon et al., 1994).[11-13] These afferent systems include neurons that contain neurotransmitters that are generally stimulatory to GnRH neurons, such as norepinephrine, dopamine, serotonin, glutamate, neuropeptide Y, and galanin, as well as neurotransmitters that are generally inhibitory to GnRH neurons, such as gamma aminobutyric acid (GABA), endogenous opiate peptides, and the central hypothalamic hormone that governs the adrenal axis, corticotropin-releasing hormone (CRH).

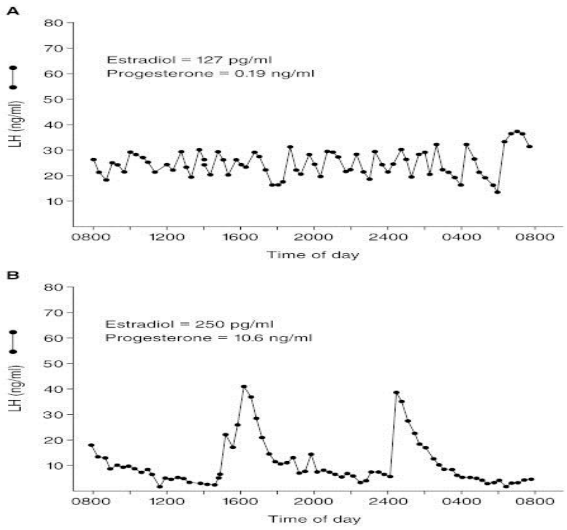
Importantly, both in normal physiological conditions and in response to environmental signals (such as changes in nutrition, exercise, and psychosocial stress) the activity of the reproductive axis is changed by modulation of the neural inputs into GnRH neurons. For example, various forms of stress can lead to a suppression of reproductive function by acting to increase inhibitory drive to GnRH neurons by increasing either ß-endorphin or CRH input into the GnRH neuronal system (Feng et al., 1991; Norman and Smith, 1992).[14-16] Decreased firing of GnRH neurons leads to less GnRH stimulation of pituitary LH and FSH release and thus less stimulation of ovarian and testicular function. It is also important to understand that changes in neuronal function in a number of neurological and psychiatric diseases can be associated with alterations in both reproductive physiology and behavior. For example, changes in both reproductive function and sexual behavior are commonly reported by patients suffering from depression, anxiety disorders, and obsessive-compulsive disorders (Clayton, 2002; Shabsigh et al., 2001).[17-18] The drugs used to treat these disorders have the potential to impact reproductive function because they can affect neural input into GnRH neurons as well as treat neurotransmitter imbalances in higher cortical areas (Clayton, 2002; Montgomery et al., 2002).[19-20]

LH and FSH are glycoprotein hormones originally named for their action at the level of the ovary in the female, but the same hormones are produced in the male and govern testicular function (Griffin and Ojeda, 2000; Steiner and Cameron, 1989).[21-23] The gonadotropins are released into the peripheral bloodstream and act at cells that have specific LH and FSH receptors, primarily at the gonads. In the male, LH binds to testicular cells (Leydig cells) and stimulates the synthesis and secretion of testosterone. FSH binds to Sertoli cells in the seminiferous tubules and along with testosterone stimulates the process of spermatogenesis. In the female, FSH acts on ovarian follicles to stimulate their growth and the production of estrogen. LH acts on the fully developed follicle to stimulate ovulation and then to support the function of the transient endocrine tissue formed during the last 2 weeks of each menstrual cycle, the corpus luteum (see Figure 5-2) for an overview of hormonal changes during the female menstrual cycle). The corpus luteum secretes both estrogen and progesterone, which play a critical role in preparing the uterine endometrium for implantation of a developing embryo should fertilization occur. Not surprisingly, in that both LH and FSH secretion are stimulated by GnRH, both hormones are released into the bloodstream in a pulsatile manner, at rates of about one pulse every 2 to 3 hours in males and at rates that vary in females from one pulse every hour to one pulse every 8-12 hours at various stages of the

menstrual cycle (Soules et al., 1984; see Figure 5-3). The pulsatile nature of LH and FSH secretion can be a confound when hormone measures are collected as part of large population studies, in that a single blood sample may be collected when hormone levels are at the peak or nadir of a pulse; thus, variation within an individual can be great, making it difficult to detect group differences or changes in hormone levels in response to environmental or social conditions.[24-25]



Diagrammatic representation of changes in plasma levels of estradiol, progesterone, LH, FSH, and portal levels of GnRH over the human menstrual cycle.



Examples of the pulsatile pattern of LH secretion in a woman during the late follicular phase (A) and midluteal phase (B) of the menstrual cycle.

The gonadal steroid hormones are produced in a common synthetic pathway, all of them derived from the same precursor, cholesterol.[26-27] Although androgens are commonly

thought of as male hormones, they are produced in both the male and the female, and likewise the female hormone, estrogen, is present in the male and the female. In males, testosterone produced by the Leydig cells of the testes can act at its target tissues by binding to testosterone receptors, or first being converted to a more potent androgen, dihydrotestosterone, by the enzyme 5 α-reductase, or by being converted to estrogen by the enzyme aromatase and acting by binding to estrogen receptors. In females the pathway for estradiol production involves an intermediate step of androgen production, and thus the ovary is a source of low levels of androgens, principally androstenedione. The body produces three forms of estrogen: estradiol, which is the principal form of estrogen produced by the ovary; estrone; and estriol, which is produced predominantly by aromatization of androgens in peripheral fat tissue. Estriol production is thus related to body fat composition and is an important source of estrogen in the postmenopausal woman, once production of estradiol by the ovaries has ceased. Steroid hormones primarily travel through the bloodstream bound to proteins (>70 percent bound). In conditions where there is a change in the concentration of binding proteins in the circulation (i.e., with long-term changes in nutritional status, changes in either the level of energy availability or the ratio of protein to carbohydrate consumed; pregnancy, liver disease), the amount of steroid hormone in the circulation and its delivery to tissues are also affected. Assay procedures are generally available to measure both free and total (free + protein bound) steroid hormone concentrations in the blood, and it is important to distinguish between these.

The gonadal steroid hormones have important actions in a number of reproductive tissues. In the male, testosterone acts to stimulate development of male secondary sexual characteristics, including enlargement of the penis and testes, increased muscle mass, deepening of the voice, and stimulation of adult hair growth patterns.[28-29] In the ovaries, estrogen acts to stimulate proliferation of follicular cells and maturation of the oocyte, preparing it for ovulation. At the uterus, estrogen acts during both the follicular and luteal phases of the menstrual cycle to stimulate development of the uterine lining and prepare it for implantation of a fertilized ovum. During the late follicular phase, rising levels of estrogen also act on the cervical mucosa to stimulate the elaboration of a thin, watery mucus that is amenable to sperm penetration. At the breast, estrogen stimulates development at puberty and further development during pregnancy and plays an important role in stimulating milk production during lactation. Estrogen receptors are also found in many other organs, including bone, pancreas, fat and blood vessels.

Progesterone is secreted in large quantities during the last 2 weeks of each menstrual cycle. Under the influence of progesterone, the uterine glands in the endometrium enter a secretory phase and produce large amounts of glycogen, which provides nutritional support for early development of an embryo. Withdrawal of progesterone at the end of the luteal phase leads to shedding of the uterine endometrium and menses, which marks the termination of one menstrual cycle and the initiation of the next cycle.[30-33] Progesterone also acts at the cervix to thicken cervical mucus, making it hostile to sperm penetration, and at the breast in late pregnancy working in concert with estrogen to prepare for lactation. All three gonadal steroid hormones also act at receptors in the brain, as will be discussed in more detail in the section below. One of the actions of these hormones in the brain is to provide feedback regulation to the hypothalamic GnRH neurons and the pituitary gonadotropin-secreting cells.

Steroid hormone secretion is relatively stable in the adult years in males, although it must be remembered that the gonadotropins and testosterone are secreted in a pulsatile fashion. However, in the female there are marked changes in the circulating concentrations of gonadotropins and gonadal steroid hormones across the menstrual cycle (Erickson, 1978; Figure 5-2).[34-37] The menstrual cycle is commonly divided into two phases, each of which is approximately 2 weeks in length. The first 2 weeks constitute the follicular phase. During this time small groups of ovarian follicles, each of which is a layer of cells surrounding an ovum, are developing and maturing and as they do so under the trophic influence of FSH and LH, they secrete increasing concentrations of estradiol. Thus, over this 2-week time span, estradiol levels are very low during the first week and then increase exponentially in the second week. The rising secretion of estradiol by a fully developed follicle provides a positive feedback signal to the brain and pituitary, resulting in a massive release of LH and FSH at midcycle, and this “surge” of gonadotropins triggers ovulation, so that the mature follicle bursts and the ovum is released into the nearby fallopian tube and can travel to the uterus. The follicular cells that surrounded the developing ovum reorganize into a transient endocrine tissue, the corpus luteum, which produces both estradiol and progesterone in the last 2 weeks of the cycle, the luteal phase. Unless pregnancy occurs, the corpus luteum spontaneously regresses after about 2 weeks and the withdrawal of progesterone support to the uterine lining leads to menstruation, which marks the beginning of a new cycle. Population studies that track reproductive hormone secretion must take these rather marked cyclic fluctuations in hormone levels into account in order to adequately

examine how changes in hormone secretion in females of reproductive age are linked to fertility outcomes, behavior, or environmental conditions.[38-41]

Measurement of reproductive hormone levels in large field studies can be a challenge. Many of these studies are conducted at some distance from medical or laboratory facilities, where collection of blood samples, centrifugation of the samples to collect plasma and immediate transfer to frozen storage to prevent deterioration of hormones is not possible. Fortunately, considerable advances have been made in the last decade in the development of techniques for measuring reproductive hormone levels in more easily obtainable body—fluids, saliva and urine (Campbell, 1994; Ellison, 1994; Lasley et al., 1994; Lasley and Shidleler, 1994).[42-47] Improvement of the sensitivity of assay methods makes it possible to detect the low levels of hormones that are present in these fluids (Clough et al., 1992; Ellison, 1988; Stanczyk et al., 1980;).[48-51] Moreover, development of collection and storage techniques that can be utilized in remote areas of the world (Lipson and Ellison, 1989; Young and Bermes, 1986)[52-55] has facilitated the study of the relationship between activity of the reproductive axis and many other parameters measured in demographic population studies. Salivary samples can reflect acute changes in plasma hormone levels, while urinary measures provide an integrated assessment of steroid hormone secretion over a number of hours. Salivary samples are useful for detection of gonadal steroid hormones. Salivary steroid hormone levels reflect the levels of free hormone present in the blood (i.e., steroid that is not bound to plasma proteins). Saliva can be easily collected at frequent intervals and can be stored at room temperature for several weeks without significant deterioration of hormones. However, it is not useful for measurement of the gonadotropins, LH and FSH, and will not provide an index of changes in plasma protein levels that may be responsible for changes in free steroid hormone concentrations. Gonadotropin metabolites, as well as steroid hormones, can be measured in urine samples. And urine is particularly useful for the early detection of human chorionic gonadotropin, a placental hormone that serves as a useful indicator of early pregnancy (Canfield and O'Connor, 1991).[56-61]

Behavioral Regulation by Reproductive Hormones

Sexual behavior can be divided into distinct aspects, in both males and females, which include attractiveness, sexual desire, arousal, orgasm and reinitiation. Here we will not focus on detailed information about how each of these sexual behaviors is influenced by hormones but rather on two broad areas—sexual desire and sexual behavior. There is evidence that

most aspects of sexual behavior, particularly in males, are influenced by gonadal steroid hormones. Steroid hormone receptors are abundant in the brain. Classical estrogen receptors (now called estrogen α-receptors) are strongly concentrated in the hypothalamus but are also found in areas of the brain with strong connections to the hypothalamus (Simerly et al., 1990).[62-65] More recently, a second form of estrogen receptor (estrogen ß-receptors) was identified and found to be present throughout the rostral-caudal extent of the brain, including the cerebral cortex (Shughrue et al., 1997).[66-67] Specific receptors for progesterone are induced by estrogen in hypothalamic regions of the brain, and there is also some evidence for constitutive expression of progesterone receptors (Bethea et al., 1992).[68-71] Androgen receptor mapping studies have shown considerable overlap in the distribution of androgen and estrogen receptors throughout the brain (Michael et al., 1995; Simerly et al., 1990).[72-73] Our discussion here will focus on the effects of gonadal steroid hormones on sexual behaviors, although there is evidence that they modulate a variety of other behaviors (Cameron, 2001).[74-75]

Recognition of an important link between sexual behavior and hormones arose originally from the finding that castration of adult males often results in diminished sexual activity and erectile difficulty (Luttge, 1971).[76] In hypogonadal or castrated men, withdrawal of testosterone has been reported to result in a rapid decrease in sexual interest and activity that is reinstated with testosterone replacement (Davidson et al., 1982; Kwan et al., 1983).[77-81] There are similar findings in nonhuman primate species, such that as the breeding season comes to an end and the annual cycle of testicular regression occurs, male sexual activity falls off sharply (Gordon et al., 1976).[82-85] However, there is also clear evidence of tremendous variability among individuals in the rate of loss of sexual activity and the degree of diminution of sexual activity with loss of testosterone. The 1959 study by Bremer followed 244 men castrated for medical reasons and found that a third of them retained sexual interest and activity for over a year, some for up to 10 years. Similarly, in male macaques castration has been associated with a gradual reduction but not an elimination of male sexual behavior (Michael and Wilson, 1974; Phoenix et al., 1973).[86-88] In normal men there is no correlation between testosterone levels and individual differences in sexual desire or behavior (Schiavi and White, 1976)[89-91] This finding supports the concept that there is a threshold for testosterone action.s on sexual behavior in males over which no further effects of testosterone are apparent (Meston and Frohlich, 2000).[92-94] Studies in macaques suggest that other social factors interact with circulating testosterone concentrations to impact on sexual

behavior. Wallen (1999) showed that suppression of testicular hormones decreased sexual activity in low-ranking male monkeys but that sexual behavior in high-ranking males was not measurably affected.[95-97]

In women the factors regulating sexual desire and activity, and the role that hormones play in this regard, are even less well understood. Studies of surgical ovariectomy generally report that these women have a decrease in sexual desire from presurgical levels (Dennerstein et al., 1977; Lieblum et al., 1983).[98-100] Both estrogen therapy and androgen therapy have been shown to have some effect on the restoration of sexual behavior after surgical ovariectomy (Lieblum et al., 1983; Sherwin et al., 1985).[101-103] Estrogen replacement in ovariectomized female monkeys has been shown to increase female initiation of sexual behavior (Zehr et al., 1998). At menopause, when there is a naturally occurring decrease in reproductive hormone levels (both estrogens and androgens), a decrease in sexual desire has been generally reported (McCoy and Davidson, 1985). There have been several reports of a general correlation between androgen levels and sexual interest in post-menopausal women (Lieblum et al., 1983; McCoy and Davidson, 1985), but these studies have not determined whether fluctuations in androgen levels in individuals correlate with changes in sexual interest. Estrogen treatment can also lead to an increase in sexual activity in postmenopausal women, but it is difficult to determine if this is an action at the level of the brain or is secondary to increased comfort with intercourse due to increased lubrication of the vagina (Sherwin, 1991). Studies looking for correlations in premenopausal females with circulating levels of androgens and estrogens have been somewhat confusing.

In macaques there is a clear increase in sexual behavior in midcycle (Goy, 1979; Wallen, 1990). Although this could be due to an increase in attractiveness of females to males as estrogen levels rise (Czaja et al., 1977), there is evidence that, when the male's mobility is limited and the female can control proximity, there is a cyclic increase in the female's approach to males (Czaja and Bielert, 1975; Pomerantz and Goy, 1983), and females will work harder on an operant task to gain access to males at midcycle (Bonsall et al., 1978). However, whether these cyclic changes in sexual interest are governed by estrogens or androgens is difficult to determine because they rise in concert, androgens being a precursor to the ovarian synthesis of estrogen. A study by Zehr et al. (1998) showing that estrogen replacement alone to ovariectomized female monkeys can stimulate female sexual initiation and earlier studies showing that in the normal menstrual cycle changes in circulating estradiol

but not androgen correlate with changes in female sexual initiation (Wallen et al., 1986) support a role for estrogen in governing female sexual behavior.

Several studies in ovariectomized, estrogen-treated monkeys have suggested that adrenal androgens may play a role in modulating female sexual behavior (Baum et al., 1977; Everitt et al., 1972), but such an effect has not been seen in ovary-intact macaques (Lovejoy and Wallen, 1990). Moreover, Wallen et al. (1986) found that ovarian suppression eliminated female sexual initiation, even though the adrenals were intact and functioning. As reviewed by Wallen (2001), hormonal influences on women's sexuality have been difficult to demonstrate and to interpret due to unwillingness of subjects to be sampled either physiologically or behaviorally and strong influences of male partners on women's sexual activity. However, there is evidence for changes in the level of female sexual desire in women with a peak at midcycle (Bancroft et al., 1983; Dennerstein et al., 1994; Stanislaw and Rice, 1988; Van Goozen et al., 1997). Thus, although hormones are not necessary for female sexual behavior, there is accumulating evidence that hormones modulate sexual desire (Meston and Frolich, 2000; Wallen, 2001).[104] Further studies are needed to understand the differential roles of estrogens and androgens in this regard. As discussed for the male, there is also evidence that social factors interact with hormonal influences with regard to sexual behavior in females. Adams et al. (1997)[105] showed that women who used less reliable contraceptives showed less pronounced midcycle increases in heterosexual initiation, but much greater midcycle increases in autosexual behavior.

Hormonal Changes throughout the life span

Early in embryonic development the components of the reproductive axis are formed and become functional. GnRH neurons, which provide the central drive to the reproductive axis, are an unusual neuronal population in that they originate from outside the central nervous system, coming originally from the epithelial tissue of the nasal placode (Schwanzel-Fukuda and Pfaff, 1989; Wray et al., 1989). During embryonic development, GnRH neurons migrate across the surface of the brain into the hypothalamus. Migration is dependent on a scaffolding of neurons and glial cells along which the GnRH neurons move, with chemical signals guiding the process (Silverman et al., 1994). Failure of GnRH neurons to properly migrate leads to a clinical condition, Kallman's syndrome, in which GnRH neuroendocrine neurons do not reach their final destination and thus do not stimulate pituitary gonadotropin secretion (Schwanzel-Fukuda et al., 1989). Patients with Kallman's syndrome do not spontaneously

enter puberty. Administration of exogenous GnRH effectively treats this form of hypothalamic hypogonadism, although, as discussed above, this requires pulsatile administration of GnRH.[106-107]

Functional activity of the reproductive axis as a whole is initiated during fetal development, and surprisingly by midgestation circulating levels of LH and FSH reach values similar to those found in adulthood (Ellinwood and Resko, 1984; Kaplan et al., 1976). Later in gestational development the gonadotropin levels decline, restrained by rising levels of circulating gonadal steroids (Kaplan et al., 1976; Resko and Ellinwood, 1985). The steroids having this effect are likely placental in origin, in that following parturition there is a rise in circulating gonadotropin levels that is apparent for the first 12 to 18 months of life (Winter et al., 1975). The decline in reproductive hormone secretion between ages one and two appears to be due to a decrease in GnRH stimulation of the reproductive axis. This decrease occurs even in agonadal individuals, and the period of elevated gonadotropin and gonadal steroid secretion can be extended by treating with administration of pulses of GnRH (Plant, 2001).

Steroid hormone secretion has effects on both primary sexual differences between males and females (i.e., differentiation of the sexual organs) and the development of secondary sexual differences (i.e., body fat distribution, muscle development, breast development, differences in hair distribution; Cooke et al., 1998; Cameron, 2001). In the case of sexual differentiation of the body, it is clear that exposure of males to various testicular secretory products, especially testosterone, during early prenatal development leads to sexual differentiation of the internal and external genitalia. Later activation of the reproductive axis at puberty, with a sustained increase in circulating testosterone then leads to the development of secondary sexual characteristics. Thus, testosterone has both “organizational” and “activational” influences on the sexual differentiation of the body. The organizational effects of gonadal hormones are conceptualized as resulting from the early influence of gonadal hormones on structural development, which do not require continued hormone exposure to maintain sexual differentiation. Activational effects are conceptualized as later stimulation of reversible influences on sexual differentiation that require continued exposure to gonadal hormones to maintain sex differences.

The concept that sex steroid hormones have important and permanent organizational effects on the developing brain was originally postulated based on experimental findings that treatment of developing mice with testosterone produced permanent effects on reproductive

capacity (Barraclough and Leathem, 1954), with early treatment with testosterone blocking later activation of ovulation by estradiol. A similar coordination of early and later influences of gonadal steroid hormones on reproductive behavior also occurs in many species studied to date (Cooke et al., 1998; MacLusky and Naftolin, 1981; Phoenix et al., 1959). In general, exposure of males to testicular hormones during prenatal and early postnatal periods leads to both masculinization of some tissues and functions (i.e., masculine changes in genital structure, copulatory behavior and other behaviors characteristic of males) and defeminization of other tissues and functions (i.e., ovulatory competence, feminine sexual behaviors like lordosis, and other behaviors characteristic of females). In rodents the critical period for steroid-hormone-mediated organization of brain regions and sexually dimorphic behaviors appears to be postnatal, with most effects occurring during the first 10 days of life. In primates, sexual differentiation of the brain occurs prenatally, over an extended period in midgestation (Phoenix et al., 1968). There is also recent evidence in male macaques that neonatal exposure to testosterone may play a role in determining the extent of adult sexual behavior (Mann et al., 1998).

Pubertal Activation of the Reproductive Axis

Pubertal reawakening of the reproductive axis occurs in late childhood and is marked by a cascade of hormonal, physical, psychological, and behavioral changes. One of the earliest signs of puberty is an elevation of gonadotropin and gonadal steroid hormone levels specifically at night (Boyar et al., 1974), although because detection of this rise requires collecting blood samples at night it is virtually never examined in demographic studies. Investigation into the mechanisms controlling the pubertal reawakening of the GnRH pulse generator has been an area of intense investigation for the past two decades (Ojeda and Bilger, 2000; Plant, 2001). Although the mechanisms are not fully understood, significant progress has been made in identifying central changes in the hypothalamus that appear to play a role in this process. There is strong evidence of both increases in stimulatory neural input into GnRH neurons and decreases in inhibitory input. Despite an increased understanding of the neural changes occurring at puberty, the question of what signals trigger the pubertal awakening of the reproductive axis is unanswered at this time. Availability of food and nutritional status have been shown to affect the timing of puberty; however, these signals appear to be only modulators of the pubertal process in that puberty can only be moderately advanced by increasing food availability (Frisch and MacArthur, 1974). Whether there is a genetic timing mechanism that regulates puberty or whether other signals from the

body are responsible for timing the reactivation of the reproductive axis awaits further research.

Changes in body habitus are the first signs of puberty detected by most individuals, although these emanate from increased levels of gonadal steroid hormones and are thus relatively late events in the reawakening of the reproductive axis. Likewise, in girls, menarche is a very late event, heralding the point where the adult cyclic interplay between the hypothalamic-pituitary-ovarian axis is initiated. As described in the section above, the increase in testosterone at puberty in males leads to development of the secondary sexual characteristics, including increased growth of facial, axillary and pubic hair; deepening of the voice; increase in muscle mass; enlargement of the testes and penis; increased incidence of erections and ejaculations; and attainment of fertility. Sexual behavior is also dramatically increased in males at puberty and there is a strong correlation at this age between plasma testosterone levels and degree of sexual desire and sexual activity (Halpern et al., 1998; Udry et al., 1985).

In females the rising tide of estrogen at puberty is the primary stimulus for development of most of the secondary sexual characteristics, including breast development, widening of the hips and increased deposition of subcutaneous body fat. The growth of axillary and pubic hair is under androgenic control and is stimulated by an increase in dehydroepiandrosterone (DHEA) from the adrenal gland. This developmental increase in DHEA is referred to as adrenarche and generally precedes puberty by several months to several years. Increases in sexual desire and sexual behavior also occur in girls at puberty. And, as in adulthood, there is controversy as to which hormones may be mediating these increases. There are correlations between androgen levels in adolescent girls and sexual interest (Udry et al., 1986) and the initiation of coitus (Halpern et al., 1997). However, the role of estrogens, which tend to covary with androgens in females, has not been adequately examined. Moreover, there is evidence that social factors can be as important as hormonal factors in determining a girl's sexual behavior (Udry et al., 1986).

Changes with Aging

In males, testosterone levels decrease slightly with aging and there is a mean decrease in sexual behavior, although again there are large individual variations (Meston and Frohlich, 2000). Although there have been a number of reports showing an improvement in libido and erectile function in older men with testosterone and dihydrotestosterone treatment (Bain, 2001; Kunelius et al., 2002; Morley, 2001; Nolten, 2000), these have been uncontrolled open

studies, with no large-scale multicenter prospective studies performed to date. Moreover, although there is fairly consistent data showing that decreases in libido and sexual activity can occur with progressive age in males (Bain, 2001; Morales and Heaton, 2001; Nolten, 2000), there is a large degree of individual variability, and within individuals who have normal testosterone levels there is no correlation between libido and testosterone levels (Rhoden et al., 2002). Most men continue to produce sperm and remain fertile well into old age. In recent years recognition that the adrenal androgen DHEA decreases with aging has led to the popular notion that DHEA treatment may increase libido and erectile function. However, several controlled double-blind studies have failed to show significant effects of DHEA supplementation on sexual function (Flynn et al., 1999; Hermann and Berger, 2001; Reiter et al., 1999).

Changes in reproductive physiology with aging are much more dramatic in females (Burger et al., 2002). The term “menopause” refers to a woman's last menstrual cycle. During the transition to ovarian quiescence at menopause, there is a gradual diminution of ovarian hormone production, with the earliest apparent decline occurring in ovarian inhibin production, which leads to a rise in FSH. With elevated FSH, estradiol production remains elevated in the early phases of menopause, but eventually there is a depletion of ovarian follicles and steroid hormone production falls below that necessary for stimulating the endometrium, and menopause occurs. The loss of ovarian cyclicity results from the gradual depletion of ovarian follicles, such that eventually there are no follicular cells to respond to elevated FSH levels. Thus, as menopause nears, plasma levels of estradiol are maintained initially or can actually be somewhat stimulated, but this is followed by a dramatic decline in circulating estrogen. The decline in estrogen levels leads to a number of other physiological changes, including a decrease in hormonal support of female secondary sexual characteristics, vasomotor instability known as hot flashes, increased loss of bone density, and loss of the protective effects of estrogen on the cardiovascular system. As discussed in the section above, a decrease in sexual desire in females after menopause has been generally reported, as well as a decrease in the frequency of sexual activity (McCoy and Davidson, 1985). Some studies have shown an increase in sexual interest in postmenopausal women taking estrogen (Dennerstein et al., 1980; Iatrakis et al., 1986; Sherwin, 1991), but other studies suggest that estrogen therapy alone has little effect on sexual behavior (Campbell and Whitehead, 1977; Furuhjelm et al., 1984; Sherwin et al., 1985). And, as in premenopausal women there are studies suggesting that androgen, not estrogen, levels correlate with sexual

interest (Bachman et al., 1985; Bachmann and Leiblum, 1991; McCoy and Davidson, 1985).[108-113]

Environmental exposure to hormones

Intentional consumption of steroids in the form of hormonal contraceptives, steroid hormones taken to increase muscle strength and fitness and hormone replacement therapy in postmenopausal women are significant, particularly in Western countries. In the case of the first two, the amount of steroids consumed can be quite significant. Although not discussed in detail here, exogenous steroids have many of the same effects as endogenous steroids on target tissues (discussed in detail above). This includes both the positive effects to stimulate secondary sexual characteristics and the inhibitory effects of providing increased negative feedback support to the hypothalamus and pituitary and thus essentially turning off or at least turning down the central drive to the reproductive axis. As a result, exogenous steroid exposure at high levels inhibits fertility. This is, in fact, the desired action in the case of contraceptives, but it is an unintended side effect of steroid hormones used to promote fitness. It is also possible for exogenous steroid hormones to influence sexual behavior; however, these effects can be complex and are poorly understood at this time. For example, for oral contraceptives one could have concern that the increased doses of estradiol and progesterone that provide increased negative feedback to the reproductive axis and thus decrease ovarian production of androgens could potentially decrease sexual drive in women. However, studies that have examined this have generally shown no effect of oral contraceptives on female sexual behavior (Meston and Frohlich, 2000). Moreover, as discussed above, there is a report by Adams et al. (1997) suggesting that sexual behavior can be increased in women using reliable contraception, most likely due to loss of fear of becoming pregnant. This reiterates a general theme discussed throughout this chapter—that hormones and many other factors interact to determine behavioral outcomes. That is, hormone exposure modulates behavior but does not determine human reproductive behavior (Wallen, 2001).[114]

In the past decade the concept that significant exposure to exogenous estrogen can come from environmental sources has gained increased attention (Golden et al., 1998). Concerns have arisen because of the theoretical potential for exogenous sources of estrogen to influence many aspects of reproductive biology and behavior, including altering reproductive physiology in females; altering reproductive behavior in both females and males, increasing reproductive pathologies in females, such as endometriosis, by providing additional

stimulation to uterine endometrial tissue; increasing the incidence of breast, testicular, and prostate cancer by providing extra trophic support to these steroid-sensitive tissues; and increasing male fertility problems by providing negative feedback to the brain and pituitary and thus leading to a decrease in endogenous testosterone production.

The two sources of environmental estrogens that have received the greatest attention are from ingestion of PCBs (polychlorinated hydroxybiphenyls), found in plastic containers that are used more and more frequently to store beverages and from consumption of phytoestrogens found in food products such as soy. Tests of estrogenic activity of a number of PCBs have shown that the most potent is 80 times less potent than estradiol in binding to estrogen receptors, and most others are at least 100 times less potent than estradiol (Korach et al., 1988).[115-119] When toxic equivalency is calculated, dietary exposure to these environmental estrogens is calculated as being no more than 0.0000025 percent of the daily intake of naturally occurring estrogenic flavonoids in the diet (Safe, 1995)[102-122] and these in turn are much less potent than endogenous estradiol. Thus, it seems unlikely that exogenous estrogen exposure from PCBs in food and drink containers has any significant impact on reproductive physiology or behavior in most human populations.

In contrast, there seems little doubt that human consumption of phytoestrogens, either due to naturalistic consumption of foodstuffs high in phytoestrogens or because women intentionally consume foods with high phytoestrogen content for their estrogenic effect, has a greater potential to have an impact on reproductive physiology. About 200 different naturally occurring phytoestrogens have been identified to date (Golden et al., 1998).[123-125] These compounds vary in structure and can act as either estrogen agonists or estrogen antagonists, with their action sometimes switching as a function of dose. Of these, coumestrol, found in soy protein, has been shown to have the greatest estrogenic potency, 0.03 to 0.2 times that of estradiol. Coumestrol binds competitively to the estrogen receptor and at low doses has an estrogenic effect, but at high doses it has an antiestrogen effect in studies examining its action in cell culture. In some cultures, such as in Japan, relatively high levels of phytoestrogen metabolites of soy protein are found in the urine (Mackey and Eden, 1998). Epidemiological studies show that the Japanese have a lower incidence of such diseases as breast, endometrial, and prostate cancer, which can be aggravated by estrogen. However, whether consumption of soy phytoestrogens plays a causal role in the lower incidences of these cancers remains to be determined (Mackey and Eden, 1998). In recent years there have been several well-controlled

intervention studies, in both women and men, examining the effects of soy intervention on reproductive function (Kurzer, 2002).[126-128] The studies in women provide evidence for very weak effects of increased soy intake on estrogen-sensitive tissues, such as the breast, and reproductive hormone levels. The studies in men have not validated the concerns of adverse effects of phytoestrogen consumption on reproductive hormone levels or sperm production.[129-131]

Life events that alter hormonal levels

Life events that impact the functioning of the reproductive axis are often those that produce various forms of stress. Many physical forms of stress, including energy restriction, increased energy expenditure with exercise, temperature stress, infection, pain and injury and psychosocial stress have been associated with suppression of reproductive hormone secretion and, if sustained, a suppression of fertility (Cameron, 1997, 1998; Lachelin and Yen, 1978; Pirke et al., 1989).[132-134] Stress-induced reproductive dysfunction can occur in both females and males. In adulthood, reproductive impairment in females is characterized by suppression of ovulation, a lengthening of the menstrual cycle, followed eventually by a loss of ovarian cyclicity and amenorrhea. As ovarian steroid production is decreased, there is also a decline in secondary sexual characteristics, including breast size and amount of subcutaneous fat. In males the reproductive impairment is characterized by a loss of libido, a decrease in testosterone secretion, and thus a decrease in spermatogenesis and hormonal support for secondary sexual characteristics. Chronic stress, occurring during the process of pubertal development, can impair the progression of puberty in both females and males, leading in some cases to a very marked delay in the pubertal development of reproductive capacity and the accompanying development of secondary sexual characteristics (Carpenter, 1994).[136-137]

The primary site of disruption of the reproductive axis, with all forms of stress studied in detail to date, appears to be at the level of the GnRH neurons, which provide the central neural drive to the reproductive axis. Using animal models of various stresses, it has been shown that for at least some stresses GnRH secretion is impaired (I'Anson et al., 2000). However, more typically, it is inferred that GnRH secretion is impaired in stress conditions, when a suppression of pituitary gonadotropin secretion is measured. This is further supported by the finding that, in all conditions of stress-induced reproductive dysfunction studied to date, administration of exogenous GnRH can stimulate the function of the reproductive axis,

indicating that stress is not acting to directly suppress pituitary or gonadal activity (Hotchkiss and Knobil, 1994). In some forms of acute stress a fall in gonadotropin secretion can be noted within minutes to hours. With more subtle stresses, impairment of gonadotropin secretion is generally noted when the stress is present on a chronic basis.

The mechanisms by which various forms of stress impair activity of the reproductive axis appear to have some common elements, but there also appear to be mechanisms specific to each type of stress. For example, many forms of stress can activate the hypothalamic-pituitary-adrenal axis (HPA) and experimental studies have shown several mechanisms by which activation of the HPA axis can impair the central neural drive to the reproductive axis. On the other hand, certain aspects of stress, such as decreased fuel availability, only occur with some forms of stress and are likely to impair the activity of the reproductive axis via relatively specific mechanisms.[138]

Summery and future prospects

It is becoming clear that to fully understand the multiplicity of factors that come together to regulate and modulate reproductive physiology and reproductive behavior will require integration of demographic and biomedical approaches to these research issues. Many aspects of reproductive biology are difficult to study from the perspective of population biology approaches because of the great variation in function within an individual over a short course of time, such as with fluctuations in hormone levels over the menstrual cycle or even the fluctuation in reproductive hormone levels on an hour-to-hour basis. Biomedical approaches of studying individuals in more detail will be able to define relationships more clearly but are limited by the low power of examining relatively few individuals. What is needed is a twofold approach, first of developing studies that nest demographic and biomedical approaches together and second of using biomedical studies to inform the design of demographic studies.

The first approach would involve performance of large demographic studies to understand the relationships between variables on a global scale, with a select subset of individuals studied in much more detail to test specific hypotheses or to differentiate between possible mechanisms underlying the general relationship. The second approach simply requires further communication between the fields of demography and biomedical sciences, such that methodologies are well understood, where possible similar measurements are made and at the least complexities understood by examining individuals are considered in the design of

demographic studies. But it is also important that the information flow go in the opposite direction, so that the field of demography can play a larger role in guiding biomedical scientists toward interesting questions for detailed study.

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