Spring 2024 – Systems Biology of Reproduction
Lecture Outline – Hypothalamus-Pituitary Development & Function
Michael K. Skinner – Biol 475/575
CUE 418, 10:35-11:50 am, Tuesday & Thursday
March 26, 2024
Week 12

Hypothalamus-Pituitary Development & Function

Cell Biology
- Structure / Lobes and Development
- Cell Populations and Hormones
- Regulators and Mutations

Hormones
- Growth Hormone / Receptors / GHRH
- Prolactin / Development
- Opiomelanocortin

Gonadotropins
- GnRH / Pulsitive Secretion
- GnRH Actions / Signaling
- LH/FSH Pulsitive Secretion/Menstrual Cycle

Regulation of Development
- Cyclisity / Estrous Cycle / Circadian Systems

Required Reading

de Kretser, et al. (2018) Hypothalamic Pituitary Testis Axis. In: Encyclopedia of Reproduction (Second Edition). Volume 1, Pages 180-183.

Padmanabhan, et al. (2018) Hypothalamus–Pituitary–Ovary Axis. In: Encyclopedia of Reproduction (Second Edition). Volume 2, Pages 121-129.

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MALE ENDOCRINOLOGY

Hypothalamic Pituitary Testis Axis

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Understanding testicular function and the pathological states that result in male infertility or androgen deprivation requires knowledge of the hormonal control of the testis. The regulation of reproduction is under the control of the hypothalamic-pituitary gonadal axis. As early as 1930, the importance of the pituitary gland in controlling reproduction as well as many other functions was recognized (Smith, 1930).

Clear evidence for the involvement of this system also emerges from the seasonal influence on reproductive processes in females and males from many species but there is less evidence for a role of season in the control of human reproduction (Popa and Fielding, 1931; Harris, 1948; Green and Harris, 1951). These observations indicate that the changing day length is detected via the eyes and result in a change in reproductive behavior. In addition, the effect of psychological stress and marked weight loss associated with anorexia are known to influence the regularity of menstrual cycles. Further, as early as 1930 the need for replacement therapy following the removal of the pituitary was recognized (Smith, 1930).

The neural pathways involved result in stimulating the hypothalamus to send signals that act to alter the secretion of hormones from the pituitary gland that influence testicular and ovarian function (Popa and Fielding, 1931; Harris, 1948; Green and Harris, 1951).

As with all endocrine glands in the body, the endocrine control of the testis is exerted via the hypothalamic-pituitary testicular axis. The pituitary gland is formed by two components, one of epithelial origin from the developing pharynx which forms the anterior pituitary or adenohypophysis and a neural down growth from the hypothalamic region of the brain that forms the neurohypophysis (**Figs. 1–4**); (Popa and Fielding, 1931). The latter is responsible for the secretion of oxytocin and vasopressin.

Those signals are transmitted by peptide hormones that utilize a portal system of blood vessels to carry them from the hypothalamus to the anterior part of the pituitary gland (**Fig. 4**). In contrast, the posterior pituitary is composed of nerve fibers arising from nerve cells which release their products into blood vessels thus entering the circulation and transporting those entities to their sites of action (Green and Harris, 1951). Harris, one of the pioneers in this field articulated the basis of our current understanding of the physiology of the hypothalamo-hypophyseal system. He used electrical stimulation to demonstrate the neural link to the pituitary gland (Green and Harris, 1951).

The mechanisms involved are the secretion of gonadotropin releasing hormone (GnRH), a decapeptide secreted by hypothalamic neurones into the hypothalmo-hypophyseal portal vascular system that conveys the secreted GnRH to stimulate the gonadotrophic hormones, follicle stimulating hormone (FSH) and luteinizing hormone (LH) secretion by the gonadotrophin secreting cells in the anterior pituitary gland (Guillemin, 1964; Gersh, 1938). In turn, FSH and LH circulate in the blood stream to stimulate spermatogenesis and testosterone secretion by the testis in the male, and ovulation and estradiol secretion by the ovary in the female.

The pulsatile nature of LH secretion clearly supports the pulsatile nature of the GnRH stimulus but the pulsatility is less evident from the pattern of FSH secretion since the longer half-life of FSH obscures the pulsatility. The pulse frequency and amplitude is set

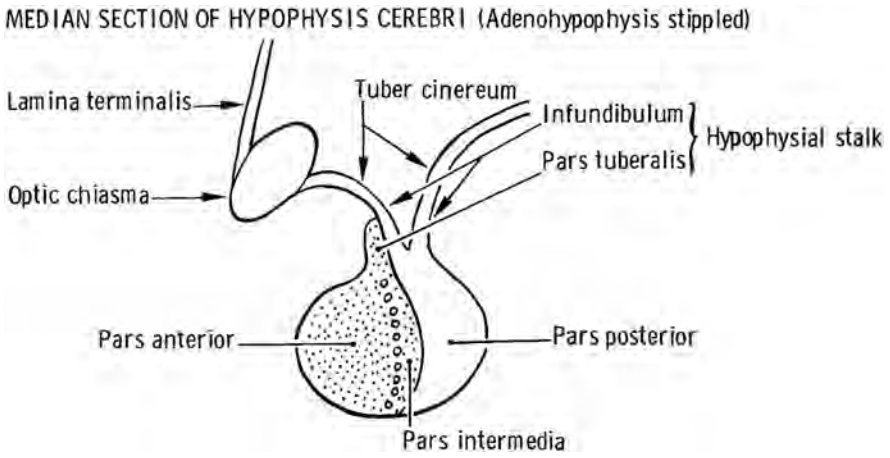

Fig. 1 A diagram of a median section of the pituitary gland.

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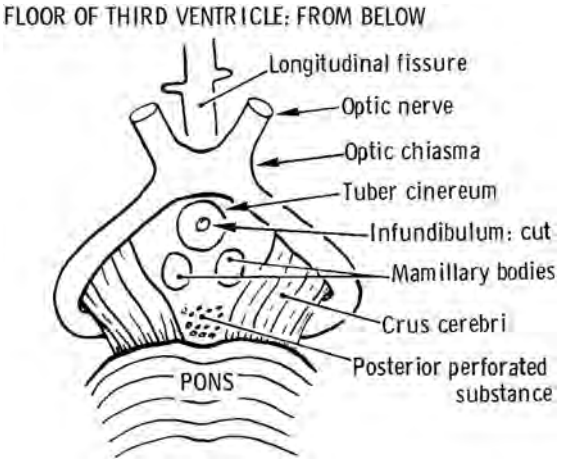

Fig. 2 A diagram of the region of the third ventricle from below.

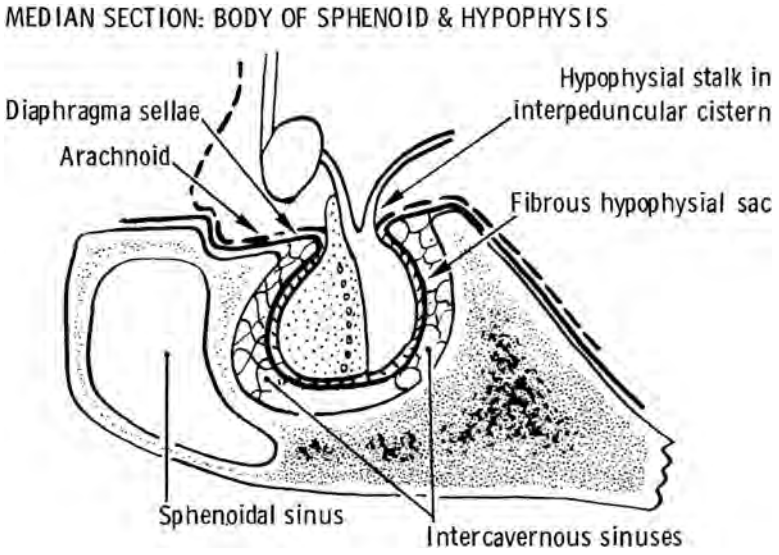

Fig. 3 A diagram of a median section through the pituitary and the body of the sphenoid bone.

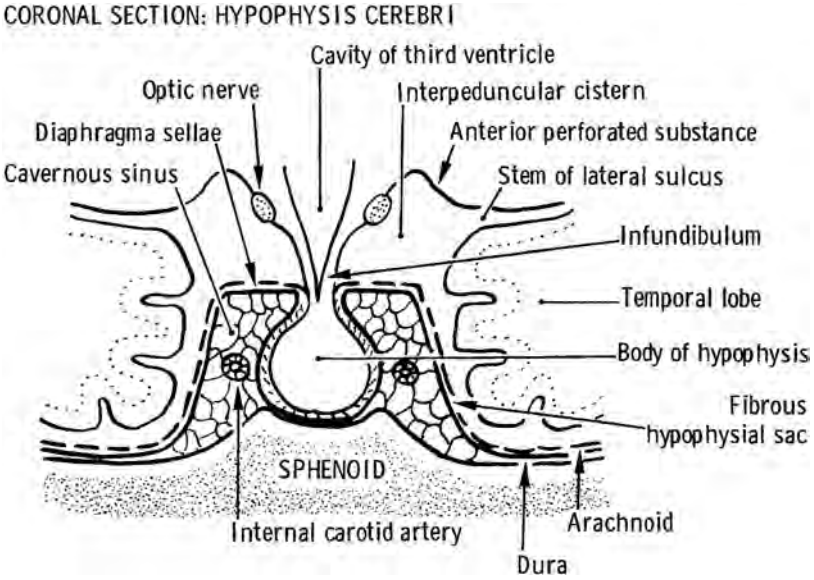

Fig. 4 A diagram of a coronal section of the pituitary gland and adjacent structures.

by signals from a collection of nerve cells in the hypothalamus called the arcuate nucleus. Thus external stimuli, such as the changes that occur due to seasonal alterations in photoperiod, are detected by the eyes and relayed to the hypothalamus. Therein, these visual stimuli are transduced into neural signals that are transmitted to pathways that affect the GnRH pulsatility. The latter, in turn, influence the secretion of FSH and LH by the pituitary. The early onset of pulsatile GnRH secretion results in precocious puberty whereas the failure to initiate pulsatile GnRH results in a delay or a failure to commence puberty in both males and females.

Modifications in the peptide structure of GnRH has resulted in some analogues having a higher affinity and high potency whereas other structural changes can result in agents that can bind to the receptor but fail to induce downstream signaling and can thus act as contraceptive agents.

As with most hormonal systems, the target tissue responds to the hormone and also sends feedback signals that modulate the bioactivity concerned. Thus the steroid hormones produced by the ovary and testis, estradiol and testosterone, exert a negative feedback action on the secretion of FSH and LH.

FSH also stimulates the ovary and the testis to secrete inhibin, a protein hormone that acts as its feedback regulator (Robertson et al., 1987). It is composed of two subunits termed α and β and specifically suppresses FSH and the DNA sequences for the encoding genes were cloned for bovine inhibin (Forage et al., 1986). A second protein that specifically suppresses FSH was also isolated (Robertson et al., 1987) and given the name FSH suppressing protein. The same protein was also isolated independently and given the name, follistatin, the name by which it is now known (Ying et al., 1987). Other agents such as neuropeptide Y enhance GnRH binding to its receptors and augment LH pulses. Immuno-neutralization of NPY attenuates the LH surge at ovulation. Similarly, the actions of estradiol on GnRH are complex, supressing the magnitude in the first 36 h of exposure and then augmenting the response after 48 h.

Since the release of GnRH by the hypothalamus is pulsatile, the subsequent FSH and LH release by the pituitary is also pulsatile. The pulsatility is more evident for LH which has a shorter half-life than FSH. Through GnRH, which enables neural inputs into the regulation of the gonadotrophins, external factors such as photoperiod, nutrition, stress, infection, and inflammation can affect their secretory patterns. The arcuate nucleus, a collection of nerve cells or neurones in the hypothalamus, is responsible for setting the pulse frequency and amplitude of GnRH secretion. Thus the early onset of pulsatile secretion initiates precocious puberty and a delay in the onset results in delayed puberty. Some mutations in the GnRH receptor can negate the pulses of GnRH from influencing FSH and LH secretion and thus acting as a cause of the failure to initiate puberty.

The pathway controlling GnRH pulse frequency involves kisspeptin acting on the GPR-54 receptor on GnRH secreting neurones. In general kisspeptin and glutamate increase GnRH release and endogenous opiod peptides inhibit GnRH secretion. The actions of estrogenic steroids such as estradiol are complex with increasing levels being initially inhibitory and later stimulatory, in part dependent on the pulse frequency. As indicated above, the onset of FSH and LH secretion determines the timing of puberty in that an early onset results in precocious puberty and a failure or delay in the onset results in delayed puberty. In some instance, mutations in the genes encoding the GnRH receptor are the cause of the failure of FSH and LH secretion or result in low levels of these gonadotrphins causing delayed puberty or infertility. Mutations in the gene encoding this receptor are known to cause hypogonadotrophic hypogonadism which presents in males and females as the failure of pubertal onset. NPY is a 36 amino acid protein member of the pancreatic polypeptide family and enhances GnRH binding to gonadotrophs in the pituitary gland and augments the LH response to GnRH. In the testis, NPY expressing nerve fibers are confined to the capsule of the testis and capsular blood vessels (Allen et al., 1989).

Given that FSH and LH are the agents that circulate via the blood to the ovary and the testis, they are critical components that regulate spermatogenesis in males and oogenesis and ovulation in females. In turn, the ovarian and testicular steroid hormones, estradiol and testosterone, act predominantly as negative regulators of FSH and LH. In addition, FSH stimulates the gonads to produce a hormone, inhibin that acts as a specific inhibitor of FSH secretion. There are two forms of inhibin which are dimers of two subunits, alpha(α) and beta(β_A) and beta (β_B). Inhibin A ($\alpha\beta_A$) and Inhibin B ($\alpha\beta_B$) both suppress FSH secretion. Castration of males or females results in a rapid decrease in the serum inhibin levels indicating that the gonads are the source of these proteins. In the male, the Sertoli cells of the testes are the site of production of inhibin. There is yet another protein that regulates FSH and that is called follistatin which is structurally unrelated to the activins and inhibins (Meinhardt et al., 1998). In contrast to inhibin, the levels of follistatin did not change after castration, indicating that it was also produced at other sites.

There are also proteins that exert a stimulatory influence on FSH levels. These are dimers of the inhibin β_A and β_B units which can form proteins called activin A ($\beta_A\beta_A$) and activin B ($\beta_B\beta_B$) and stimulate FSH secretion (Vale et al., 1986; Ling et al., 1986).

Follistatin acts by binding the activins with high affinity and in vivo, the follistatin-activin complex is targeted to a lysosomal degradation pathway. Follistatin also binds to heparin sulfate proteoglycans that form part of the basement membranes of many tissues throughout the body. In addition to binding and inactivating the activins, follistatin also binds another protein called myostatin which, as its name suggests, is a "repressor" of muscle mass. Thus mutations of myostatin in cattle, which render myostatin inactive, have very large muscles as seen in the Belgian Blue breed of cattle.

The amino acid sequence of the activins and follistatin from rodents and humans is very highly conserved such that they are virtually identical. This degree of conservation across such a wide range of animal species suggests that these proteins have important functions.

Although, the activins are involved in the control of FSH, they are also regulators of our body's response to infection. Within 30 min of a challenge using lipopolysaccharide (LPS), a component of the Salmonella bacterium, activin A increases significantly (Jones et al., 2007). Other data available suggests that activin A is a major regulator of our body's inflammatory response. For instance, the levels of serum activin A and activin B are markedly elevated in patients admitted to intensive care units with acute

respiratory failure caused by a variety of agents (de Kretser et al., 2013) Should they remain elevated, they are indicators of a very poor outcome not just in the acute phase of the infection but also for up to a year after that hospital admission.

The outcome of inflammation in many organs is fibrosis or scarring and activin is responsible for the fibrosis and follistatin can be used to attenuate the degree of fibrosis.

While this section focuses on the male, these proteins have important regulatory functions in the female, covered in another section of this Encyclopedia of Reproduction.

Acknowledgment

The figures are based on illustrations from Regional Anatomy Illustrated, Churchill Livingstone 1983, a company that does not exist any longer. It was formed from a merger of E&S Livingstone (Edinburgh, Scotland) and J&A Churchill (London). This company, originally owned by Harcourt and Pearson, is now integrated into Elsevier's Health Science Division.

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Hypothalamus–Pituitary–Ovary Axis

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Introduction

In female mammals, reproductive processes such as puberty, ovarian cyclicity and pregnancy require precise coordination of the hypothalamic–pituitary–ovarian (HPO) axis. The major components of the HPO axis include the hypothalamic gonadotropin-releasing hormone (GnRH) neurons, the pituitary gonadotropes and ovarian structures, such as follicles and the corpus luteum (Fig. 1). The gonadotropes respond to GnRH by releasing the gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which in turn stimulate folliculogenesis and steroid and peptidergic hormone secretion by the ovaries. The hypothalamic, pituitary, and ovarian hormones integrate to orchestrate the different events within the reproductive cycle so they occur in a timely manner to ensure successful reproduction (see earlier review (Beshay and Carr, 2013)). In this chapter, we present an overview of the key components and hormones of the HPO axis, discuss the complex endocrine interactions that exist between the different levels of this axis, and summarize recent findings on the main factors and mechanisms that regulate the HPO axis in the female mammals.

The Hypothalamus

The hypothalamus encompasses the lower part of the lateral wall and the floor of the third ventricle, containing several localized clusters of neurons, called nucleus, that control multiple processes such as metabolism, reproduction, and behavior. The median eminence located at the base of the hypothalamus extends to the pituitary and contains neurosecretory neurons that control hormone synthesis and secretion from the pituitary.

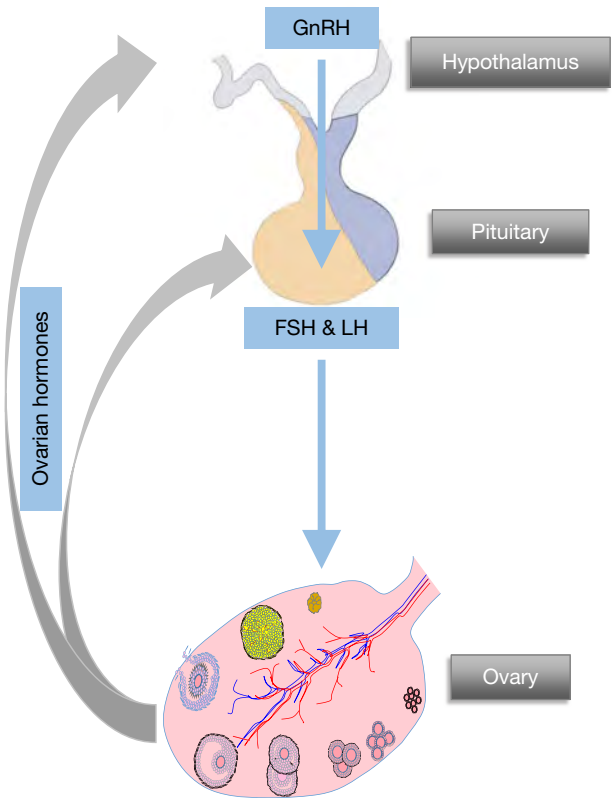

Fig. 1 Schematic showing the components of the hypothalamic–pituitary–ovarian axis.

GnRH and Its Mode of Release

The GnRH *neuron*

The decapeptide, GnRH—the primary hypothalamic regulator of reproductive function, is synthesized in specialized neurons as part of a larger precursor molecule (prohormone) containing 92 amino acids. GnRH neurons originate in the olfactory placode and migrate to the hypothalamus where several hundreds of these cells can be found diffusely distributed in the anterior portion of the hypothalamus, the preoptic area (POA), and more caudally in the medial basal hypothalamus (MBH). Most GnRH neurons have two dendritic projections, which may extend remarkable distances (2–3 mm) from the cell body. The main target of hypothalamic GnRH projections is the primary plexus of the pituitary portal system in the median eminence.

The hypothalamic–pituitary portal vasculature

Upon reaching the median eminence, GnRH axons end on capillary loops that give rise to long portal veins that descend along the pituitary stalk to terminate in the pituitary sinusoids. The portal system facilitates the rapid exchange between the hypothalamus and the pituitary, requiring only minute amounts of neurohormones to stimulate release of hormones by the pituitary. The superior hypophyseal arteries form the primary capillary plexus that supplies blood to the median eminence. From this capillary system, the blood is drained in hypophyseal portal veins to the secondary plexus, a network of fenestrated sinusoid capillaries that provide blood to the anterior portion of the pituitary. This anatomical arrangement allows rapid and undiluted transport of GnRH to the pituitary gland.

GnRH biosynthesis

To date, three isoforms of GnRH (GnRH-I, GnRH-II, and GnRH-III) have been identified in humans and many others have been detected in fish, amphibians, and protochordates. GnRH-I is the classic hypothalamic peptide responsible for regulating the synthesis and secretion of gonadotropins. GnRH-II, first reported in brain tissue and since been found in other peripheral tissues, such as the uterus and ovaries is also capable of stimulating LH release. The role of GnRH-III, first identified in the lamprey, in humans remains unclear (Schneider et al., 2006).

Upon synthesis, GnRH-I gets transported to the median eminence of the hypothalamus and then released in the portal circulation in a pulsatile manner. The lifespan of GnRH-I is very short with a half-life of 2–4 min. Because of its short half-life and rapid dilution in the peripheral circulation, GnRH-I concentrations are very difficult to measure in the peripheral circulation.

GnRH pulsatility

The cellular network that elicits the pulsatile increases in GnRH secretion is referred to as the "GnRH pulse generator" and includes the synchronously firing GnRH neurons. While there is supporting evidence that GnRH pulsatility is intrinsic to GnRH neurons themselves and that extensive intercellular mechanisms orchestrate synchrony within the network, more recent observations strongly indicate that other neurons in the MBH target the GnRH neuronal network directly to drive the pulsatile release of GnRH (Fig. 2). Kisspeptin, the most potent stimulator of GnRH secretion yet discovered, appears to be an integral component of the GnRH pulse generator. Of particular interest are the neurons in the arcuate nucleus (ARC) that co-express the neuropeptides kisspeptin, neurokinin B, and dynorphin, termed KNDy neurons. In contrast to the endogenous opioid dynorphin that has inhibitory actions on GnRH release, neurokinin B is generally stimulatory to GnRH secretion. Based on the action of these neuropeptides on GnRH release and the neuroanatomical evidences that KNDy neurons communicate with GnRH neurons (particularly at the level of the median eminence), a model for GnRH pulse generation has been established. This

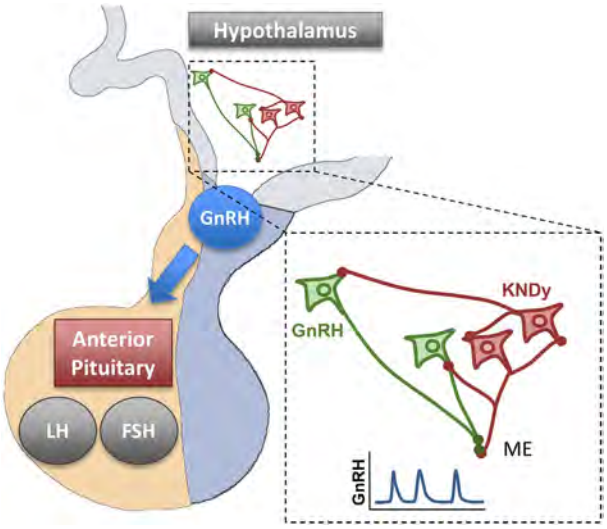

Fig. 2 Schematic depicting the control of the GnRH neurons in the hypothalamus. KNDy neurons in the arcuate nucleus project to GnRH cell bodies and axonal projections to modulate GnRH release into the median eminence (ME).

model proposes that GnRH pulse generation is initiated in the KNDy neuronal network in the ARC by a reciprocating interplay of stimulatory neurokinin B signals and inhibitory dynorphin inputs and the output of the pulse generator is relayed to GnRH neurons via the release of kisspeptin from axonal terminals originating from KNDy neurons (**Fig. 2**; Lehman et al., 2010).

The Pituitary Gland

The pituitary, also known as the master endocrine gland, is a small gland located beneath the third ventricle of the brain and above the sphenoidal sinus in a bone cavity called sella turcica. The pituitary gland contains two major lobes: anterior and posterior.

The Anterior Pituitary

Development

The anterior pituitary, also known as adenohypophysis, is a classic endocrine gland in that it is composed of secretory cells of epithelial origin supported by connective tissue rich in blood and lymphatic capillaries. The anterior pituitary is derived from the ectoderm, more specifically from the Rathke's pouch, part of the developing hard palate in the fetus. The Rathke's pouch eventually loses its connection with the pharynx, giving rise to the anterior pituitary. The pouch becomes committed to organ development several days prior to the expression of markers of individual cell types within the mature anterior pituitary gland. Between the time of organ commitment and maturation, a series of cell type-specific differentiation and proliferative events occur.

Cell types

The five cell types present in the mature anterior pituitary gland are defined based on the trophic factors that they synthesize and secrete. Corticotropes secrete adrenocorticotrophin, thyrotropes produce thyroid-stimulating hormone, somatotropes secrete growth hormone, lactotropes produce prolactin and gonadotropes secrete the gonadotropins, LH and FSH.

The Posterior Pituitary

The posterior pituitary, also known as neurohypophysis, is a grouping of axonal projections that secretes oxytocin responsible for increasing uterine contractions and vasopressin, an antidiuretic hormone.

Gonadotropes

Gonadotropes are specialized basophilic cells in the anterior pituitary that express cell surface receptors for GnRH and produce LH and FSH.

The GnRH receptor

The GnRH-I receptor is a G-protein coupled receptor that utilizes inositol triphosphate and diacylglycerol as second messenger molecules to stimulate protein kinase, release calcium ions, and cyclic adenosine monophosphate activity. While the pituitary is the classic target tissue for GnRH actions, the GnRH-I receptor is expressed in many other tissues, including ovarian follicles, pancreas, liver, heart, and the placenta. Importantly, the continuous activation of the GnRH receptor results in its desensitization thus enabling the use of GnRH agonists for treatment of reproductive disorders such as precocious puberty and endometriosis, and to prevent GnRH actions prior to ovarian stimulation cycles for in vitro fertilization. Therefore, only pulsatile GnRH administration can restore normal gonadotropin secretion in individuals lacking endogenous GnRH secretion (e.g., Kallmann syndrome).

Luteinizing hormone

LH is a glycoprotein heterodimer consisting of two subunits: α- and β-subunits. The α-subunit is common between LH, FSH, and TSH and consists of 92 amino acids. The β-subunit is distinct and hormone-specific, which allows the different biological actions of each hormone. The LH β-subunit has 120 amino acids and one to two sialic acid residues, giving it its shorter half-life of approximately 20 min. LH is secreted in a pulsatile manner except preceding ovulation when a massive release of LH (LH surge) occurs to trigger ovulation. Since LH secretion is primarily regulated by GnRH, peripheral levels of LH serve as good surrogate markers for assessing pattern of GnRH release.

Follicle-stimulating hormone

FSH is also a glycoprotein heterodimer consisting of two subunits: α- and β-subunits. The FSH β-subunit contains 118 amino acids and 5 sialic acid residues. The sialic acid content of FSH and LH is responsible for the half-life of these hormones, with greater number of sialic acid residues yielding longer half-life. FSH has a half-life of approximately 3–4 h, thus providing sustained support to facilitate growth of ovarian follicles.

Ovaries

The ovaries are the female gonads and are primarily responsible for the generation of gametes and production of hormones that regulate reproductive function. In most mammals, a pair of ovaries is present on either side of the body and is structurally

made of inner medulla and the outer cortex that is encapsulated by a connective tissue rich membrane called tunica albuginea. While the medulla contains vascular structures such as blood and lymphatic vessels, the cortex contains the follicles, which are the functional units of the ovary.

Follicular Development

An ovarian follicle contains the female gamete—oocyte, and the somatic cells, granulosa and theca cells. The number and type of somatic cells varies depending on the stage of follicular development. During the embryonic development, the primordial germ cells (PGCs) originate from the endoderm of the yolk sac and migrate into the genital ridge. These PGCs mitotically divide to form the oogonia, which later undergoes meiosis to form the oocyte. The primordial follicles are formed when the naked oocytes are surrounded by the pregranulosa cells (Fig. 3). These primordial follicles form the ovarian follicular pool or reserve and majority of these follicles remain in a quiescent state. A few follicles emerge from the reserve at specific intervals, a process termed as activation, and either undergo atresia (degeneration) or develop into primary follicles with the transformation of granulosa cells from spindle to cuboidal shaped. Follicular growth continues with granulosa cells dividing to form several layers around the oocyte leading to the development of the preantral follicle. During this developmental period, the follicle also acquires the theca cells that surround the granulosa cells. It has been suggested that follicular development up until the preantral stage occurs in a gonadotropin-independent manner, however, the role of gonadotropins cannot be ruled out because FSH receptors are present in early follicular stages.

Subsequent follicular differentiation occurs under the influence of gonadotropins with preantral follicles progressing to the antral stage with development of a fluid-filled cavity, termed the antrum. Selection of a dominant follicle from the antral follicular pool that is destined for ovulation (Fig. 3) occurs under the influence of FSH. Further maturation into Graffian or preovulatory follicle occurs predominantly under LH stimulation. Upon ovulation, the release of egg from the follicle, subsequent transformation of the follicular remnant into the endocrine structure corpus luteum is driven by LH.

Ovarian Hormones

The ovarian hormones produced under the influence of LH and FSH include steroidal and non-steroidal polypeptide hormones. Androgens and estrogens are produced by theca and granulosa cells, respectively. Under the influence of LH, theca cells take up cholesterol and convert it into 17-hydroxy-pregnenolone through the Δ^5 pathway, which is then acted on by 17-hydroxylase to synthesize the androgen androstenedione. Majority of androstenedione is aromatized into the major estrogen, estradiol, by the enzyme aromatase (CYP19) in granulosa cells, a process that occurs under the influence of FSH. In the corpus luteum, synthesis of progesterone is stimulated by LH through the Δ^4 pathway (Miller, 2008).

The non-steroidal hormones, among others, include those belonging to the transforming growth factor beta (TGFβ) family namely inhibin, activin, anti-Mullerian hormone (AMH), TGFα, bone morphogenetic proteins, and growth differentiation factors. Other factors produced by the ovary include insulin-like growth factors (IGF), kit ligand, fibroblast growth factors, epidermal growth factors, and prostaglandins.

Inhibins

Inhibins are protein hormones consisting of two subunits α and β and are secreted mainly by the granulosa cells under the influence of FSH but are also produced by the pituitary gonadotropes. Two forms of inhibin have been identified, Inhibin-A and -B. The α subunits are identical, while the β-subunit differs between both forms of inhibin (denoted as β_A and β_B, respectively). Inhibin-B is predominantly secreted during the follicular phase, while the A form is secreted during the luteal phase. Inhibins function to suppress FSH secretion by the anterior pituitary.

Activins

Activins are secreted by granulosa cells and are homo- or hetero-dimers of the inhibin β subunits, with activin A and B being the homodimer of two β_A and β_B subunits, respectively and AB being the heterodimer. Activin is also produced in the pituitary and

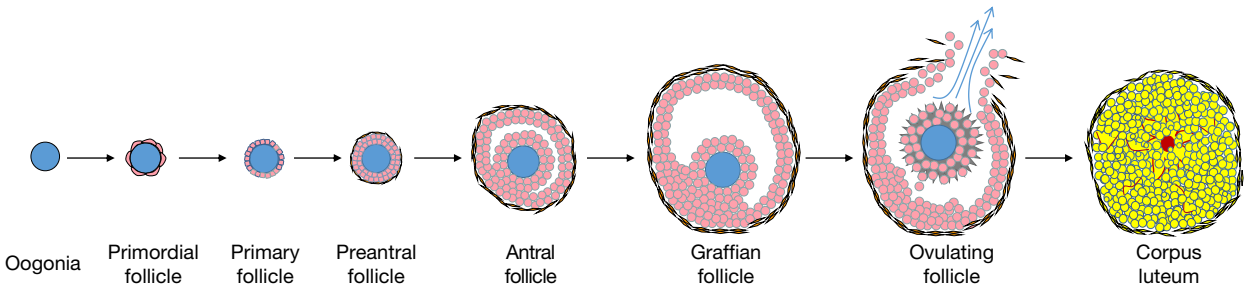

Fig. 3 Schematic representation of the different stages in the ovarian follicular development.

stimulates FSH release. Other β forms have been identified, raising the possibility of additional homo- and hetero-dimeric forms although their role in regulation of gonadotropin secretion is still being ascertained (Wijayarathna and De Kretser, 2016).

Follistatin

Follistatin is a monomeric glycoprotein produced by the ovary as well as anterior pituitary folliculostellate cells. It is a high affinity activin binding protein therefore its main role in female reproduction is to sequester activin and inhibit FSH secretion.

Anti-Mullerian hormone

AMH is produced by granulosa cells. AMH production increases from primordial to preantral follicle stage, being highest in preantral and small antral follicles but declining thereafter. AMH is implicated in inhibition of follicular recruitment from the resting pool. It acts on antral follicles to decrease FSH sensitivity, reduce aromatase activity and allow the selection of the dominant follicle (Visser and Themmen, 2014). AMH is increasingly being used as a biomarker of the relative size of the ovarian reserve (Pankhurst, 2017). Recently, receptors for AMH have also been identified in the mouse and human hypothalamic neurons suggesting a potential direct role in the neuroendocrine system (Cimino et al., 2016).

All intra-ovarian factors act in a paracrine manner to influence follicular growth and maturation (Gougeon, 2010).

Regulation of the HPO Axis

The cyclic functioning of the HPO axis involves a complex interaction between the hypothalamus, pituitary and ovary that include feed-forward, feedback and paracrine loops (Fig. 4).

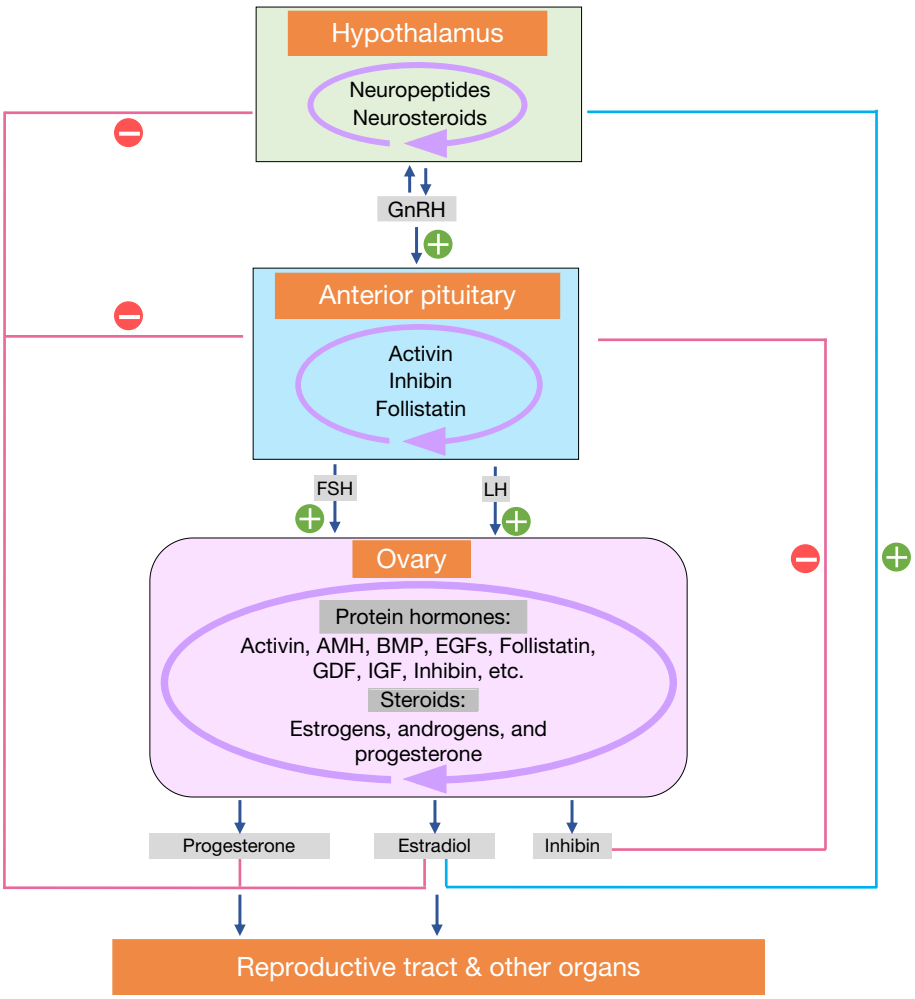

Fig. 4 Hypothalamic–pituitary–ovarian axis depicting feed-forward, feedback, and paracrine loops.

The Feed-Forward Regulation in HPO Axis

A pulsatile release of GnRH by the hypothalamic GnRH pulse generator leads to feed-forward regulation of the anterior pituitary gonadotropes that promotes synthesis, storage and secretion of gonadotropins (Fig. 4). Gonadotropin secretion depends on the frequency of pulsatile GnRH secretion with faster frequency favoring LH-β subunit gene transcription and LH release, and slower frequency favoring FSH-β gene transcription and FSH release.

The gonadotropins released under the influence of GnRH have feed-forward actions at the ovarian level (Fig. 4) where they bring about morphological and hormonal changes. These include regulation of follicular differentiation by FSH, induction of ovulation and formation of corpus luteum by the surge release of LH, stimulation of theca cell androgen production by LH, conversion of androgen to estrogen as well as synthesis of inhibin and activin by FSH, and the stimulation of progesterone production in the corpus luteum by LH.

The Feedback Regulation of the HPO Axis

The feedback regulation of HPO axis, which may be negative or positive, involves control of hormonal release from the hypothalamus, pituitary or ovary by the end products of their stimulation (Fig. 4). Such feedback ensures that follicular growth, maturation, ovulation, corpus luteum formation and preparation of the uterine lining occur in a controlled and timely manner so as to facilitate successful conception or renewal of the reproductive cycle in the event of unsuccessful conception.

Negative feedback regulation

Estradiol, progesterone, and inhibin are the main ovarian hormones that participate in the negative feedback regulation of the neuroendocrine axis to decrease gonadotropin release (Fig. 4). At the level of the hypothalamus, the exact afferent neuronal pathways and mechanisms mediating the gonadal steroid-dependent negative feedback process remain unresolved as the majority of GnRH neurons do not express receptors for gonadal steroids. Current evidence suggests that kisspeptin neurons located in the POA and ARC play a key role conveying the feedback regulatory effects of gonadal steroids on GnRH neurosecretory activity. Kisspeptin neurons located in the ARC (KNDy neurons) express receptors for gonadal steroids and have been postulated to mediate the negative feedback actions of estradiol on GnRH secretion (Lehman et al., 2010). There is considerable evidence that the inhibitory effects of progesterone on GnRH pulsatile secretion is mediated through dynorphin from KNDy neurons. This premise is supported by the observations that KNDy neurons express the progesterone receptor, local administration of an antagonist to the dynorphin receptor in the MBH increases LH pulse frequency during the luteal phase in sheep, ovariectomy decreases the expression of dynorphin in the ARC and local administration of a progesterone receptor antagonist to the ARC disrupts the negative feedback actions of progesterone on GnRH/LH secretion (Lehman et al., 2010).

The inhibitory effects of estradiol on gonadotropin secretion, apart from its action on GnRH release, also appear to be partially mediated via direct pituitary effects. This involves repression of FSH-β subunit expression by estradiol. Inhibin from the ovary also exerts negative feedback on the pituitary FSH secretion and one mechanism proposed involves competing with activin in binding to its receptors, thereby preventing activin's role in stimulating FSH secretion.

Positive feedback regulation

The ovarian hormone estradiol is the main player that exerts positive feedback action in the HPO axis (Fig. 4) and research findings suggest that there are important differences in the neuronal systems mediating its positive actions on GnRH surge release between different animal models. While in rodents it appears that the anteroventral periventricular area is the main hypothalamic area involved, in sheep and primates the estradiol positive feedback is largely mediated in the MBH. Despite these differences, in most female mammals increased expression of kisspeptin during the late follicular phase promotes a robust release of GnRH that in turn stimulates the surge release of gonadotropins. In humans, the anterior pituitary appears to be an important site of estradiol positive feedback regulation of LH secretion.

Paracrine Regulation

In addition to the positive and negative feedback regulation discussed earlier, there are several paracrine/autocrine regulatory loops at all levels of the HPO axis. For instance, GnRH has been shown to regulate its own secretion (Padmanabhan et al., 1995). Several neuropeptides produced by hypothalamic neurons, such as kisspeptin, also participate in paracrine regulation of GnRH release. More recent studies suggest neurosteroids produced within the hypothalamus may also participate in feedback regulation of GnRH release (Kenealy et al., 2013). At the pituitary level, activin, inhibin and follistatin produced by the pituitary modulate FSH synthesis through paracrine actions. Activins promote FSH secretion by increasing the number of GnRH receptors on gonadotropes (Fortin et al., 2015) while inhibin and follistatin oppose activin actions.

At the level of the ovary, there are several paracrine systems operational. Some examples of such paracrine regulation include: (1) modulation of activin action by its binding protein, follistatin, (2) promotion of theca androgen production by inhibin, (3) down-regulation of FSH receptors in antral follicles by AMH, which helps reduce FSH sensitivity thus allowing emergence of dominant follicles, (4) induction of inhibin and gonadotropin receptors by estradiol, and (5) promotion of FSH-induced estrogen production in granulosa cells and LH-induced androgen production in theca cells by inhibins. Another important example of a paracrine

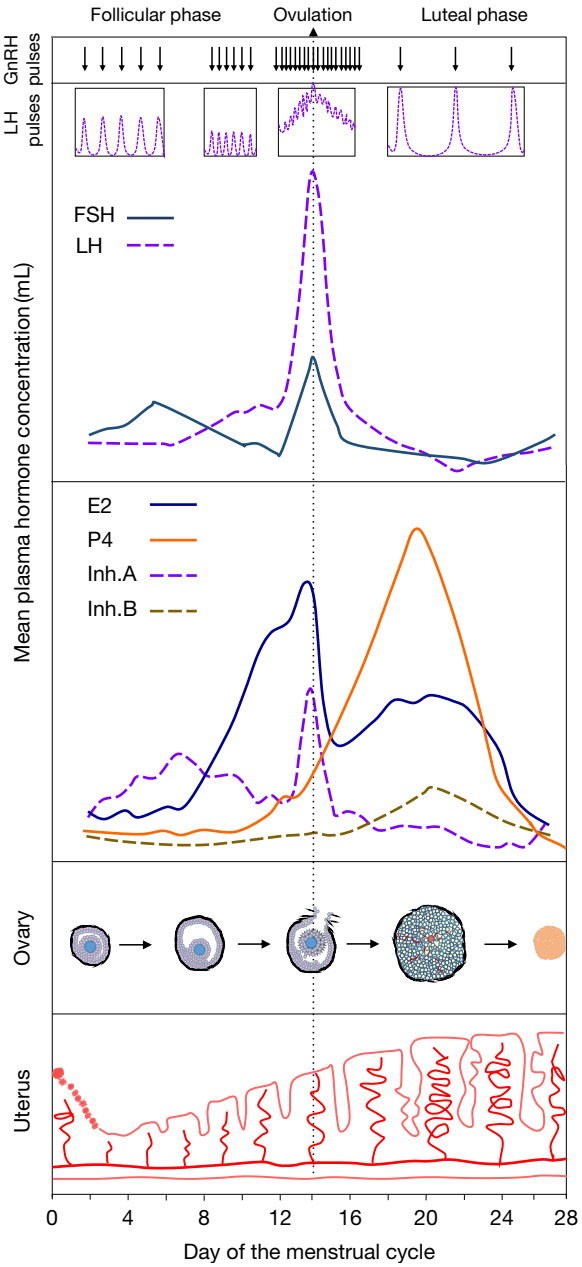

Fig. 5 Hypothalamic, pituitary, and ovarian hormonal, ovarian follicular and corpus luteum and uterine epithelial changes during the menstrual cycle. The mean concentrations of each of the hormonal changes are shown with LH pulsatile secretion shown as insets during the early and later follicular, periovulatory and luteal phases. *E2*, estradiol; *P4*, progesterone; *inh.A*, inhibin A; *inh.B*, inhibin B. Adapted with permission from Mahutte, N. G. and Ouhilal, S. (2007). In: Hurd, W. W. and Falcone, T. (eds.) *Clinical reproductive medicine and surgery*. St. Louis, MO: Elsevier.

feedback loop within the ovary involves androgen and inhibin with inhibin acting on theca cells to regulate androgen production and androgen acting back on granulosa cells to regulate inhibin production.

Other Regulators of HPO Axis

In addition to regulation of the HPO axis by its components and their secretions, nutrition, metabolic status and seasonality, among other factors, also regulate the HPO axis. Reproductive processes in female mammals can be energetically costly, thus requiring a coordinated regulation by the nutritional and metabolic systems. Therefore, the HPO axis must receive and integrate information about peripheral metabolic cues in order to regulate reproductive function. Neuropeptides and leptin are the major cues of the body's metabolic status.

Although leptin, a metabolic hormone produced primarily by adipocytes, does not affect GnRH secretion directly as its receptor is not present on GnRH neurons, the effects of leptin are mediated through intermediate neuronal pathways that encompass hypothalamic neuropeptide Y (NPY)/agouti-related protein (AgRP) neurons and proopiomelanocortin (POMC) neurons. While NPY has inhibitory action, melanocyte-stimulating hormone alpha (αMSH), one of the products of the *POMC* gene, has stimulatory effect on GnRH neurons (Evans and Anderson, 2017). Undernutrition upregulates NPY expression in the ARC reducing the GnRH pulsatility while increased leptin concentrations in circulation not only downregulates NPY but also increases αMSH increasing the GnRH/LH pulsatility (Evans and Anderson, 2017).

Photoperiod is a major factor determining annual changes in reproductive function in mammalian species that breed seasonally such as sheep (short day breeders) and mares (long day breeders). While the neuronal mechanisms involved in photoperiod control of GnRH/LH pulses remain uncertain it may involve hypothalamic dopaminergic neurons, KNDy neurons in the ARC, and neurons expressing RF-amide related peptide 3, which is also referred to gonadotropin inhibitory hormone 3 (Clarke, 2011). Another important factor modulating GnRH release in female mammals is stress. Stress influences the GnRH pulse generator reducing the frequency of GnRH/LH pulses through increased cortisol secretion (Whirledge and Cidlowski, 2010).

Apart from actions at the GnRH neurons, metabolic hormones such as insulin, leptin and adiponectin enhance gonadotropin synthesis and release via direct action on the gonadotropes. Stress in addition to reducing GnRH pulsatility also reduces pituitary responsiveness to GnRH, and amplifies the negative feedback while inhibiting the positive feedback effects of estradiol (Whirledge and Cidlowski, 2010).

At the level of the ovary, the major metabolic hormones modulating ovarian function are insulin and adiponectin. Insulin is referred to as a co-gonadotropin in the ovary as in addition to acting alone can potentiate gonadotropin action. Insulin can also activate IGF receptors in the ovary. The ovary also expresses adiponectin receptors and adiponectin promotes ovulatory and luteinization processes induced by the LH surge by increasing steroidogenesis, prostaglandin synthesis and angiogenesis (Palin et al., 2012). While glucocorticoids have an anti-inflammatory role in the ovary and aid in the formation of the corpus luteum, stress-induced increase in glucocorticoids has negative effects by suppressing the LH-induced steroidogenesis (Whirledge and Cidlowski, 2010).

Conclusions

Precise coordination of components of the HPO axis via endocrine and paracrine feedback mechanisms is essential to maintain adequate reproductive cyclic function. At the beginning of reproductive cycle, increasing levels of LH and FSH facilitate growth of multiple follicles to early antral stage (**Fig. 5**). The estradiol and inhibin B produced by the growing follicles exert negative feedback effects at the hypothalamic–pituitary level leading to a reduction in FSH secretion. The increased estradiol also promotes uterine epithelial growth to prepare for receiving the conceptus. The follicle that develops increased sensitivity to FSH in the face of reduced FSH support differentiates into the dominant follicle. The dominant follicle contributes to a further increase in estradiol secretion leading to positive feedback response at the hypothalamic–pituitary level and surge release of gonadotropins triggering ovulation. Upon release of the oocyte, the follicle remnant develops into a progesterone and inhibin A producing organ called corpus luteum. The increase in progesterone and inhibin secreted by the corpus luteum exerts negative feedback at the hypothalamic–pituitary level to reduce LH and FSH secretion. In the event of conception, luteal function is maintained by factors produced by the developing conceptus. If conception fails, the corpus luteum undergoes regression leading to a decline in progesterone and inhibin A secretion that result in removal of negative feedback effects at the hypothalamic–pituitary level leading to an increase in LH and FSH secretion and reinitiation of the cycle. All in all, the HPO axis integrates peripheral signals and via feed-forward, feedback and paracrine mechanisms it enables reproductive success to ensure the survival of the species.

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"Systems Biology of Reproduction"

Spring 2024 (Even Years) – Course Syllabus
Biol 475/575 Undergraduate/Graduate (3 Credit)
SLN: (475) – 06763, (575) – 06764
Time - Tuesday and Thursday 10:35 am-11:50 am
Course Lectures in person and recorded on Canvas/Panopto and Discussion Sessions live in person and on WSU Zoom for all campuses (Hybrid Course)
Room – CUE 418
Course Director – Michael Skinner, Abelson Hall 507, 335-1524, skinner@wsu.edu
Co-Instructor – Eric Nilsson, Abelson Hall 507, 225-1835, nilsson@wsu.edu
Learning Objective -
Current literature based course on the Systems Biology of Reproduction. Learning Systems approaches to the biology of reproduction from a molecular to physiological level of understanding.
Schedule/Lecture Outline –

January	9 & 11	Week 1	Systems Biology Introduction
	16 & 18	Week 2	Molecular/ Cellular/ Reproduction Systems
	23 & 25	Week 3	Sex Determination Systems
Jan /Feb	30 & 1	Week 4	Male Reproductive Tract Development & Function
February	6 & 8	Week 5	Female Reproductive Tract Development & Function
	13 & 15	Week 6	Gonadal Developmental Systems Biology
	20 & 22	Week 7	Testis Systems Biology
	27 & 29	Week 8	Ovary Systems Biology
March	5 & 7	Week 9	Epigenetics and Transgenerational Gonadal Disease
	11 – 15	**Week 10**	**Spring Break**
	19 & 21	Week 11	Gametogenesis/ Stem Cells/ Cloning
	26 & 28	Week 12	Hypothalamus-Pituitary Development & Function
April	2 & 4	Week 13	Reproductive Endocrinology Systems
	9 & 11	Week 14	Fertilization & Implantation Systems
	16 & 18	Week 15	Fetal Development & Birth Systems
	23 & 25	Week 16	Assisted Reproduction/Contraception
Apr/May	30 & 2	Week 17	Exam or Grant Review

Spring 2024 – Systems Biology of Reproduction
Lecture Outline – Hypothalamus-Pituitary Development & Function
Michael K. Skinner – Biol 475/575
CUE 418, 10:35-11:50 am, Tuesday & Thursday
March 26, 2024
Week 12

Hypothalamus-Pituitary Development & Function

Cell Biology
- Structure / Lobes and Development
- Cell Populations and Hormones
- Regulators and Mutations

Hormones
- Growth Hormone / Receptors / GHRH
- Prolactin / Development
- Opiomelanocortin

Gonadotropins
- GnRH / Pulsitive Secretion
- GnRH Actions / Signaling
- LH/FSH Pulsitive Secretion/Menstrual Cycle

Regulation of Development
- Cyclisity / Estrous Cycle / Circadian Systems

Required Reading

de Kretser, et al. (2018) Hypothalamic Pituitary Testis Axis. In: Encyclopedia of Reproduction (Second Edition). Volume 1, Pages 180-183.

Padmanabhan, et al. (2018) Hypothalamus–Pituitary–Ovary Axis. In: Encyclopedia of Reproduction (Second Edition). Volume 2, Pages 121-129.

Spring 2024 – Systems Biology of Reproduction
Discussion Outline – Hypothalamus-Pituitary Development & Function
Michael K. Skinner – Biol 475/575
CUE 418, 10:35-11:50 am, Tuesday & Thursday
March 28, 2024
Week 12

Hypothalamus-Pituitary Development & Function

Primary Papers:

1. Belchetz et al. (1978) Science 202:631
2. Ozaki et al. (2021) Develop Growth Differ 63:154-165
3. Bhattacharya et al. (2019) Mol Reprod Dev 86 :1505-30

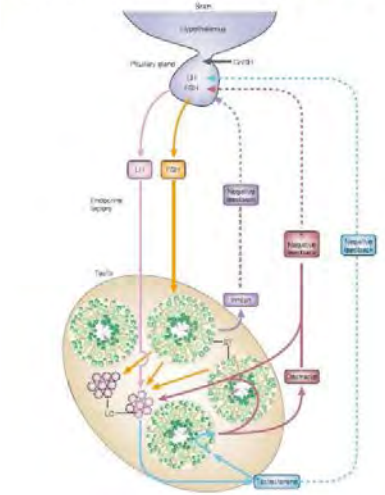
Discussion

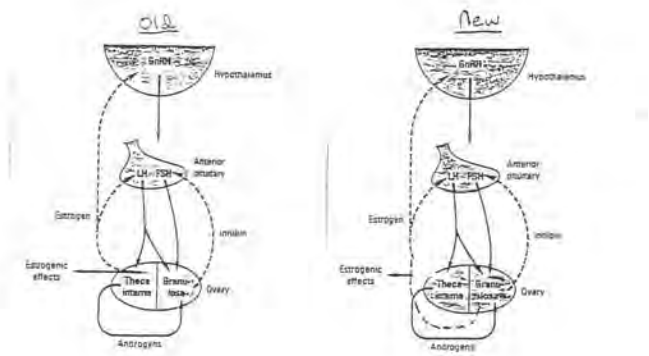
Student 6: Reference 1 above
- What unique endocrine parameter was identified in the hypothalamic regulation of pituitary function?
- What physiological advantage does this have?
- How does this information fit into the understanding of Brain-Pituitary-Gonadal axis?

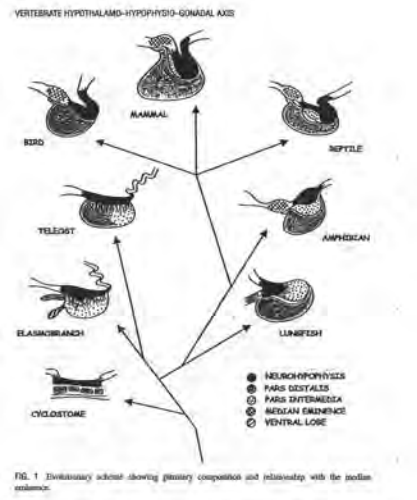
Student 7: Reference 2 above
- What was the experimental design and objectives of the study?
- How did the in vivo development maintain the organoid?
- What insights into organogenesis of the hypothalamus-pituitary were obtained?

Student 8: Reference 3 above
- How did the hypothalamus and pituitary induce puberty?
- What was the hypothalamus-pituitary and testis hormone axis established?
- What molecular mechanism in the hypothalamus and pituitary were involved?

Hypogonadal – pituitary – testis axis







Hypothalamus and Pituitary Cell Biology

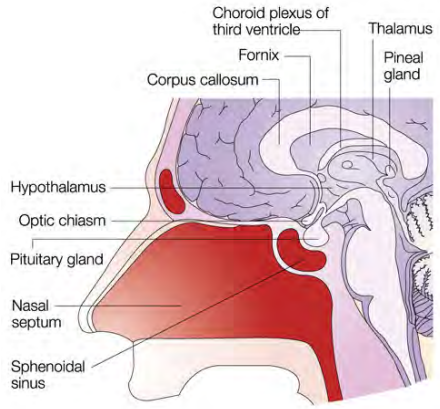


Figure 1 | **Anatomy of the pituitary gland.** Sagittal section through the midline shows the pituitary gland within the diaphragma sella (a fold that encases the pituitary), situated immediately posterior to the sphenoid sinus.

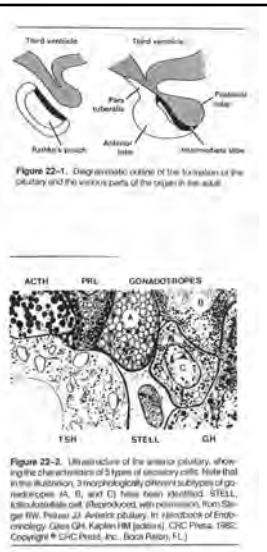


Figure 22–2. Ultrastructure of the anterior pituitary, showing the characteristics of 5 types of secretory cells. Note that in this illustration, 3 morphologically different subtypes of gonadotropes (A, B, and C) have been identified. STELL, folliculostellate cell. (Reproduced, with permission, from Sarge RW, Peluso JJ. Anterior pituitary. In: Handbook of Endocrinology. Giles GR, Kaplan HM [editors]. CRC Press, 1982. Copyright © CRC Press, Inc., Boca Raton, FL.)

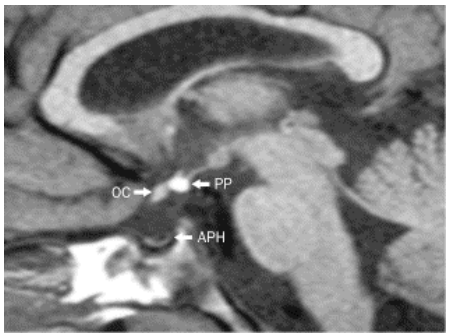


Figure 2. Sagittal MRI scan showing anterior pituitary hypoplasia. APH=anterior pituitary hypoplasia. PP=posterior pituitary, which is ectopic on this image. OC=optic chiasm., normal here. The infundibulum connecting the pituitary to the hypothalamus is not shown.

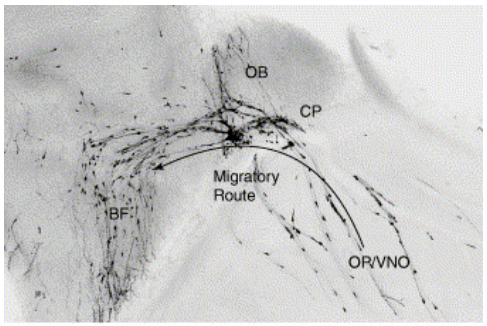


Figure 1. GnRH neuronal migration in the mouse and targeting of immortalized GnRH neuronal cell lines at specific windows across development. Immortalized NLT and Gn GnRH neuronal cells were derived from a tumor in the olfactory region to cribiform plate, whereas the GT GnRH neuronal cells were derived from a tumor in the forebrain. The photomicrograph is from E15 mouse brain stained for GnRH and peripherin, shows the normal migratory route of GnRH neurons from the olfactory placode region across the cribiform plate to the forebrain and is adapted from [1]. Abbreviations: BF, basal forebrain; CP, cribriform plate; E, embryonal day; GnRH, gonadotropin-releasing hormone; OB, olfactory bulb; OP/VNO, olfactory placode/vomeronasal organ.

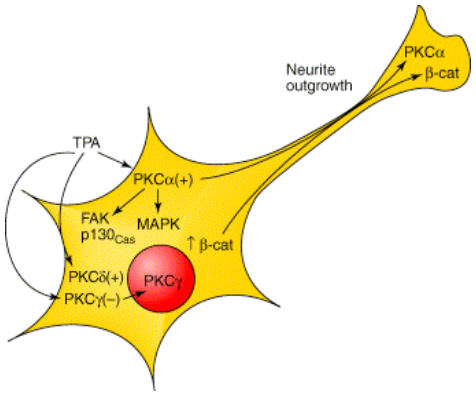
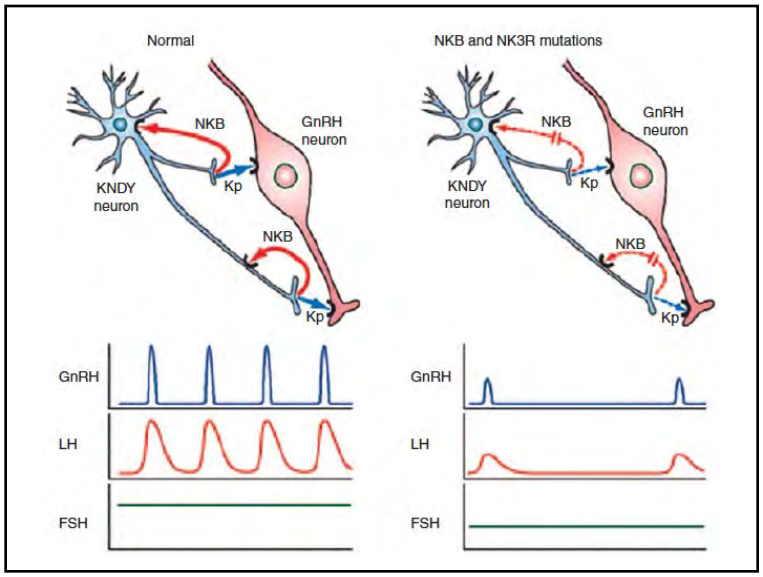
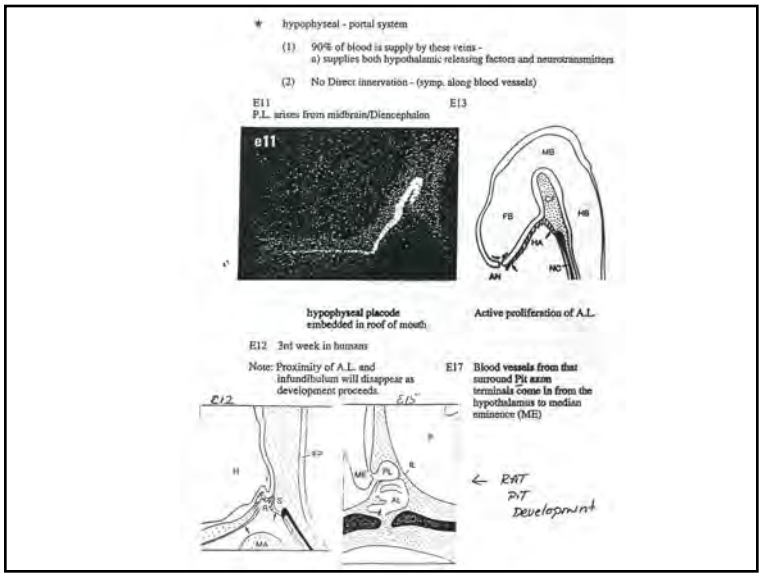
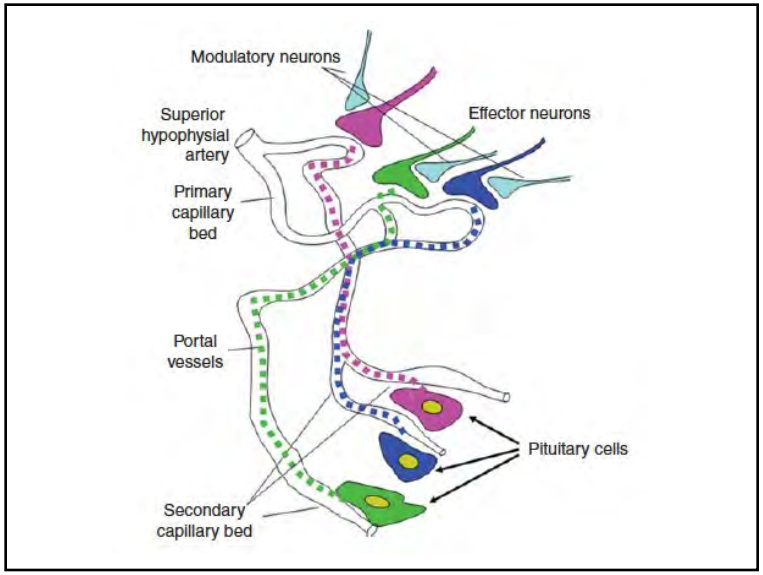


Figure 4. Phorbol ester signaling in GT1 GnRH neurons promotes neurite outgrowth. 12-O-tetradecanoylphorbol-13 acetate (TPA) signals to PKC, and in GT GnRH neurons. PKC promotes neurite outgrowth, translocates to the growth cone and activates MAPK. It also localizes to focal adhesions to stimulate FAK and p130cas phosphorylation. PKC is proposed to be another activator of neurite outgrowth. PKC, by contrast, is a negative regulator of neurite outgrowth and initially localizes to the nucleus, then to membrane ruffles. The PKC pathway also promotes neurite outgrowth through alterations in N-cadherin and translocation of -catenin to the growth cone. Based on results in [71, 72 and 73]. Abbreviations: -cat, -catenin; FAK, focal adhesion kinase; GnRH, gonadotropin-releasing hormone; MAPK, mitogen-activated protein kinase; PKC, protein kinase C; TPA, 12-O-tetradecanoylphorbol-13 acetate.


Normal
NKB and NK3R mutations
NKB
GnRH neuron
KNDY neuron
Kp
NKB
Kp
GnRH
LH
FSH


hypophyseal - portal system
(1) 90% of blood is supply by these veins -
a) supplies both hypothalamic releasing factors and neurotransmitters
(2) No Direct innervation - (symp. along blood vessels)
E11
P.L. arises from midbrain/Diencephalon
E13
e11
hypophyseal placode
embedded in roof of mouth
Active proliferation of A.L.
E12 3rd week in humans
Note: Proximity of A.L. and infundibulum will disappear as developement proceeds.
E17 Blood vessels from the surround Pit axon terminals come in from the hypothalamus to median eminence (ME)
RAT PIT Development


Modulatory neurons
Superior hypophysial artery
Effector neurons
Primary capillary bed
Portal vessels
Pituitary cells
Secondary capillary bed

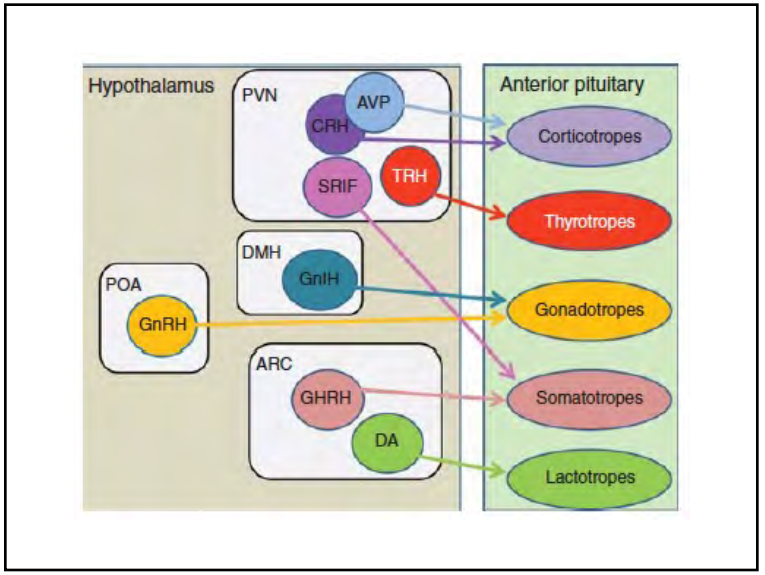

Hypothalamus
PVN
AVP
CRH
SRIF
TRH
DMH
GnIH
POA
GnRH
ARC
GHRH
DA
Anterior pituitary
Corticotropes
Thyrotropes
Gonadotropes
Somatotropes
Lactotropes

Table 22–1. Pituitary hormones in mammals.[1]

Name and Source	Principal Actions
Anterior lobe	
Thyroid-stimulating hormone (TSH, thyrotropin)	Stimulates thyroid secretion and growth of thyroid gland.
Adrenocorticotropic hormone (ACTH, corticotropin)	Stimulates secretion and growth of zona fasciculata and zona reticularis of adrenal cortex.
Growth hormone (GH, somatotropin, STH)	Accelerates body growth; stimulates secretion of IGF-I.
Follicle-stimulating hormone (FSH)	Stimulates ovarian follicle growth in female and spermatogenesis in male.
Luteinizing hormone (LH, interstitial cell-stimulating hormone, ICSH)	Stimulates ovulation and luteinization of ovarian follicles in female and testosterone secretion in male.
Prolactin (luteotropic hormone, LTH, luteotropin, lactogenic hormone, mammotropin)	Stimulates secretion of milk and maternal behavior. Maintains corpus luteum in female rodents but apparently not in other species.
β-Lipotropin (β-LPH)	?
γ-Melanocyte-stimulating hormone (γ-MSH)	May maintain adrenal sensitivity.
Intermediate lobe	
α- and β-melanocyte-stimulating hormones (α- and β-MSH, referred to collectively as melanotropin or intermedin)	Expands melanophores in fish, amphibians, and reptiles; stimulates melanin synthesis in melanocytes in humans.
γ-Lipotropin (γ-LPH), corticotropinlike intermediate lobe peptide (CLIP), other fragments of pro-opiomelanocortin	?
Posterior lobe	
Vasopressin (antidiuretic hormone, ADH)	Promotes water retention.
Oxytocin	Causes milk ejection.

[1] In addition, a variety of gastrointestinal and other polypeptides are found in one or more lobes of the pituitary gland. These include CCK, gastrin, renin, angiotensin II, and calcitonin-gene-related peptide (CGRP).

TABLE 1. Anterior pituitary cell types and hormone regulation

Somatotropes	Lactotropes	Thyrotropes	Corticotropes	Gonadotropes
Hormone product				
Growth hormone (GH)	Prolactin (PRL)	Thyroid-stimulating hormone (TSH)	Adrenocorticotropic hormone (ACTH)	Gonadotropins: luteinizing hormone (LH) and follicle-stimulating hormone (FSH)
Site of action				
Liver, kidney, most tissues	Mammary	Thyroid	Adrenal	Ovary, testis
Positive regulator				
Growth-hormone-releasing hormone	Estrogen, thyrotropin-releasing hormone	Thyrotropin-releasing hormone	Corticotropin-releasing hormone	Gonadotropin-releasing hormone
Negative regulator				
Somatostatin, insulin-like growth factor	Dopamine	Thyroid hormone	Corticosteroids	Gonad steroids, inhibins
Hypopituitarism phenotype				
Dwarfism	Failure to lactate	Thyroid hypoplasia, dwarfism, cretinism, hypothyroidism	Adrenal hypoplasia	Sexual immaturity
Hyperpituitarism phenotype				
Gigantism, acromegaly	Galactorrhea, infertility	Thyroid hyperplasia, hyperthyroidism	Cushing disease	Precocious puberty

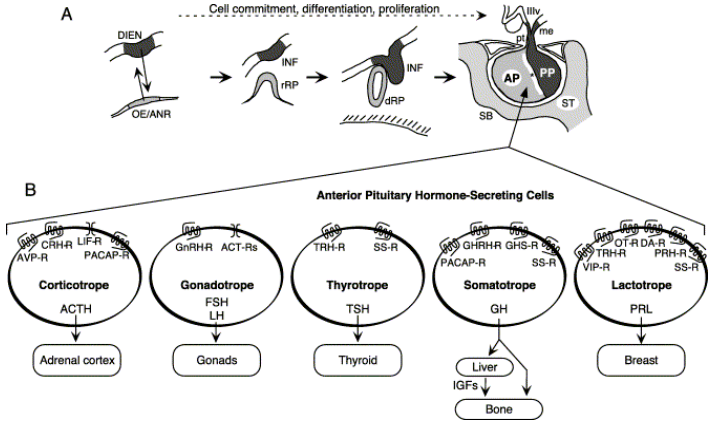


Fig. 1. Development of the mammalian anterior pituitary gland. (A) Inductive signaling between and within the ventral diencephalon (DIEN) of the brain and oral ectoderm/anterior neural ridge (OE/ANR) promotes the formation of a rudimentary Rathke's pouch (rRP), and the infundibulum (INF), the respective primordia of the adenohypophysis and neurohypophysis. Later, a definitive Rathke's pouch (dRP) forms, which then separates from the oral cavity. The mature pituitary gland is encased by the sella turcica (ST) of the sphenoid bone (SB). AP=anterior pituitary lobe, ASTERISK=intermediate pituitary lobe, IIIv=third ventricle of the brain, ME=median eminence, PP=posterior pituitary, PT=pars tuberalis. (B) The five anterior pituitary hormone-secreting cell types, their hormone products, and the target organs of the hormones are shown. In addition, the receptors that allow regulation of pituitary hormone secretion by hypothalamic and other regulatory hormones are depicted. ACT=activin, AVP=arginine vasopressin, CRH=corticotropin-releasing hormone, DA=dopamine, GHRH=growth hormone releasing hormone, GHS=growth hormone secretagogue/ghrelin, GnRH=gonadotropin-releasing hormone, LIF=leukemia inhibitory factor, OT=oxytocin, PACAP=pituitary adenylate cyclase-activating polypeptide, PRH=prolactin releasing hormone, SS=somatostatin, TRH=thyrotropin-releasing hormone, VIP=vasoactive intestinal peptide.

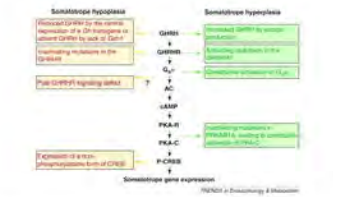


Fig. 1. Spontaneous and experimental alterations in the GHRH signaling pathway that result in either somatotrope hypoplasia or hyperplasia. Abbreviations: AC, adenylyl cyclase; cAMP, cyclic adenosine monophosphate; GHRH, growth hormone-releasing hormone; GHRH-R, GHRH receptor; Gsα, α subunit of the receptor associated G protein complex; gsh1, genetic screen homeobox protein 1; P-CREB, phosphorylated cAMP response element-binding protein; PKA-C, catalytic subunit of protein kinase A; PKA-R, regulatory subunits of protein kinase A; PRKAR1A, protein kinase cAMP-dependent regulatory type 1-α (a specific PKA-R).

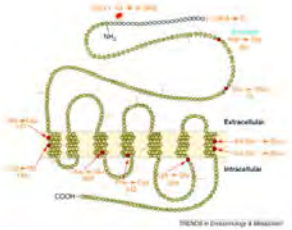


Fig. 2. Sequence of the human GHRH-R, demonstrating the amino acid changes resulting from the reported loss-of-function mutations associated with GH deficiency and somatotrope hypoplasia. The exon splice sites are shown by straight lines. The mouse Ghrhr mutation (lit) is shown in the position corresponding to the mouse GHRH-R sequence. Abbreviations: Del, deletion; GH, growth hormone; GHRH-R, growth-hormone-releasing hormone receptor; IVS1, intervening sequence (intron) 1; Stop, stop codon.

Hypothalamus and Pituitary Development

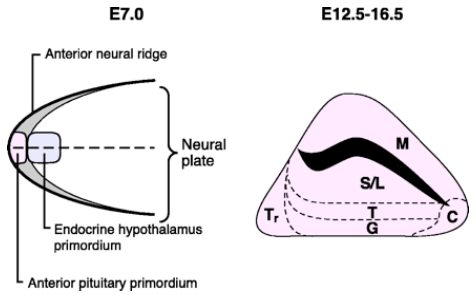
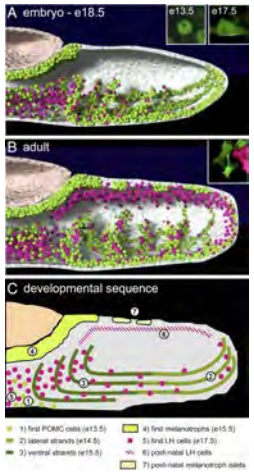
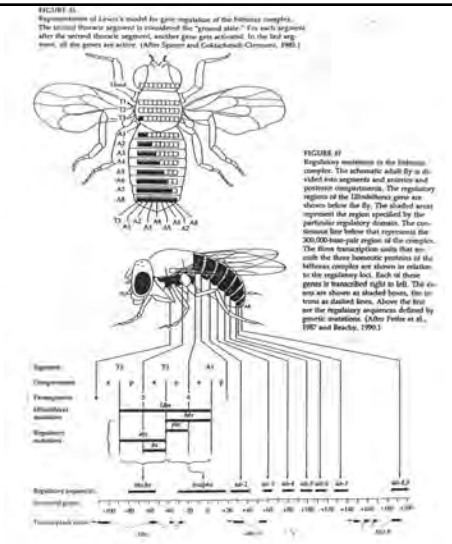


Fig. 1. Development of the hypothalamic-pituitary axis. The midline embryological primordia of the pituitary in the anterior neural ridge and of the endocrine hypothalamus in the neural plate are indicated. Cell types later arise in a temporally and spatially specific fashion: E12.5 corticotrope (C), E12.5 rostral tip thyrotropes (Tr), and subsequently, from E15.5 to E17.5, from somatotropes (S), lactotropes (L), thyrotropes (T), gonadotropes (G), and melanotropes (M).

Related pituitary cell lineages develop into interdigitated 3D cell networks.
Budry L, et al. (2011) Proc Natl Acad Sci U S A. 26;108(30):12515-20.





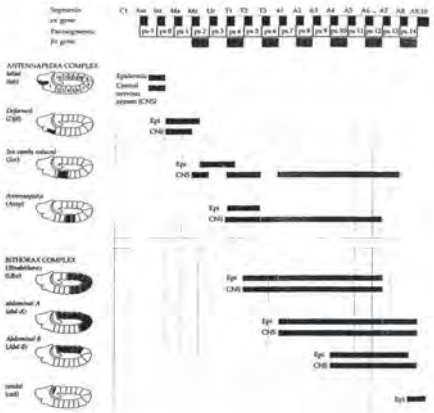


FIGURE 30
Region of homeotic gene expression (both mRNA and protein) in the blastoderm of the *Drosophila* embryo and (a few hours later) in its central nervous system. The darker shaded areas are those segments or parasegments with the most product. The diagram beside the chart represents gene expression within the parasegmental boundaries. (After Kaufman et al., 1990.)

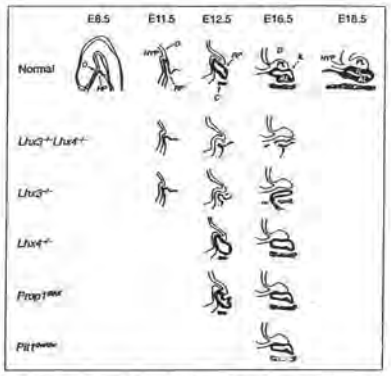


FIGURE 1. Normal embryonic morphology is altered in pituitary mutants. The abnormal morphology observed in mouse mutants is shown from the time point where it begins to differ from normal development until the time when development is arrested. In the most severe case (*Lhx3*$^{-/-}$*Lhx4*$^{-/-}$), the position of the pouch and cartilage are reversed, resulting in ectopic pituitary tissue. *Lhx3*$^{-/-}$ mice have incomplete separation of Rathke's pouch from the palate. *Lhx4*, *Prop1*, and *Pit1* mutations each arrest cell proliferation. The abnormalities in Rathke's pouch development are visible in *Prop1*$^{df/df}$ mice before the onset of *Pit1* transcription[34]. Abbreviations: AL, anterior lobe; C, cartilage; D, diencephelon; E, embryonic day; HP, hypophyseal placode; HYP, hypothalamus; IL, intermediate lobe; PL, posterior lobe; RP, Rathke's pouch.

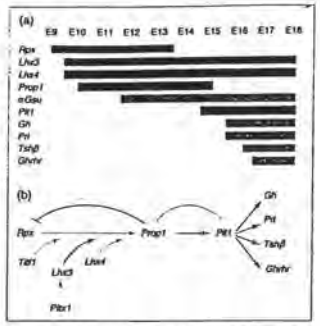
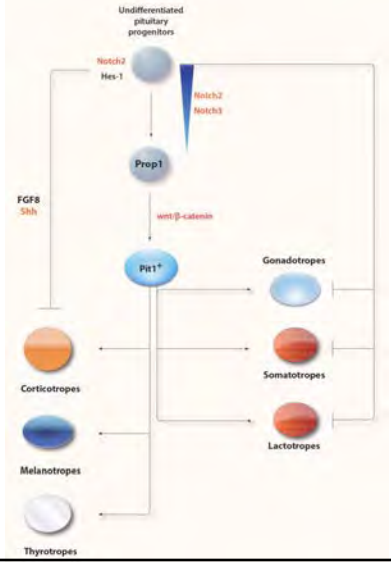


FIGURE 2. A cascade of transcription factors regulates anterior pituitary development. (a) The approximate timing of mRNA expression in the mouse is shown for transcription factors (black) and other marker genes (gray). (b) A genetic hierarchy is suggested by the effects of each gene on cell proliferation and differentiation. Arrows represent activation and truncated lines represent repression. Black solid lines indicate effects that are supported by analysis of pituitary mutants. The gray lines are hypothetical interactions that might be revealed by analysis of expression in other pituitary mutants. Future studies will determine which, if any, of the interactions are direct. Abbreviation: E, embryonic day.



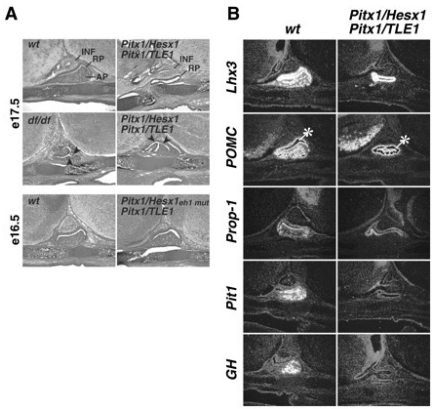
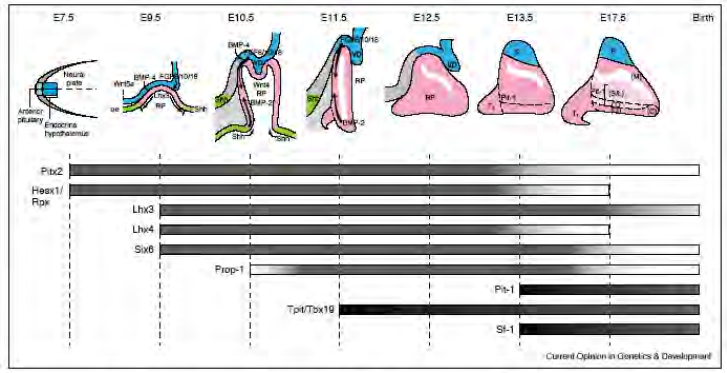
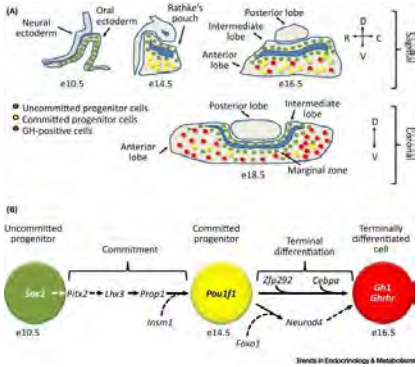


FIG. 5. Analysis of *Pitx1/Hesx1:Pitx1/TLE1* double-transgenic founder embryos. (A) Loss of anterior pituitary and morphological similarity to pituitary defects in Ames *df/df* mice, except when the *Pitx1/Hesx1* transgene encodes a mutated eh1 domain, which cannot interact with TLE1. H&E staining. (B) *In situ* hybridization showing loss of growth hormone (*GH*), *Pit-1,* and ventral *Prop-1*, while expression of proopiomelanocortin (*POMC*) appears unaffected and *Lhx3* and *Prop-1* continue to be expressed in the ectoderm of RP. Asterisk indicates the dorsal pouch ectoderm.



Ontogeny of signaling molecules and selected transcriptional factors during pituitary organogenesis. The most anterior neural ridge gives rise to primordia of pituitary and endocrine hypothalamus. Ventral diencephalon, which expresses BMP4, FGF8/10/18 and Wnt5, makes direct contact with oral ectoderm and induces the formation of Rathke's pouch. Shh is expressed throughout the oral ectoderm except in the Rathke's pouch, creating a boundary between two ectodermal domains of Shh-expressing and -nonexpressing cells. The opposing dorsal BMP4/FGF and ventral BMP2/Shh gradients convey proliferative and positional cues by regulating combinatorial patterns of transcription factor gene expression. Pit1 is induced at E13.5 in the caudomedial region of the pituitary gland, which ultimately gives rise to somatotropes (S), lactotropes (L) and thyrotropes (T). Rostral tip thyrotropes (T_1) are Pit1-independent. Corticotropes (C) and gonadotropes (G) are differentiated in the most ventral part of the gland. The dorsal region of the Rathke's pouch becomes the intermediate lobe, containing melanotropes (M). A number of transcription factors required for pituitary development and function are expressed in a distinct temporal order and spatial pattern (not shown).

Molecular Mechanisms Governing Embryonic Differentiation of Pituitary Somatotropes.
Ellsworth BS, Stallings CE.
Trends Endocrinol Metab. 2018 Jul;29(7):510-523.



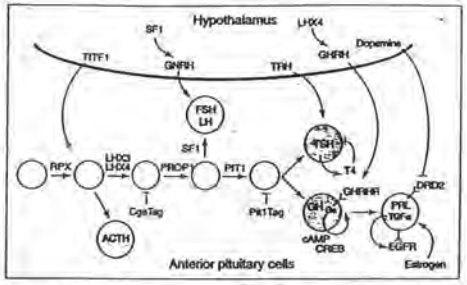


FIGURE 3. Proposed model for pituitary cell lineage and regulation of proliferation by secreted factors. The five endocrine cell types (gray) in the anterior pituitary are labeled with the hormone product that they secrete. Steps in precursor-cell differentiation that might be regulated by transcription factors are indicated. Possible regulation of cell proliferation by secreted factors (gray boxes) is also indicated. The points where SV40 T-Antigen transgenes are thought to block differentiation are shown in gray[53,54]. The block in differentiation results in pituitary tumors that have been immortalized for further study. Abbreviations: ACTH, adrenocorticotropin hormone; FSH, follicle-stimulating hormone; GH, growth hormone, LH, luteinizing hormone; PRL, prolactin; T4, thyroid hormone; TSH, thyroid-stimulating hormone.

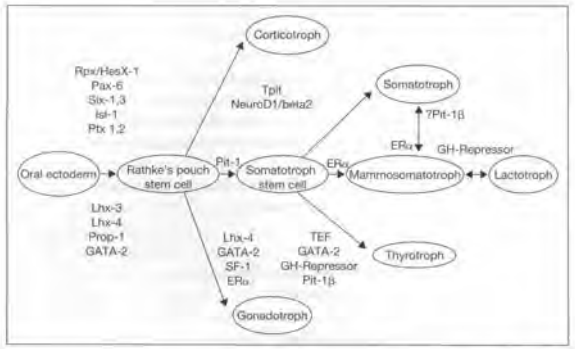


Table 1

Transcriptions factors associated with human pituitary disorders.

Gene	Class	Locus	Inheritance	Phenotype	Animal model	
					Mouse/zebrafish	Pituitary phenotypes
HESX1	Paired HD	3p21	Recessive Dominant	CPHD with SOD IGHD	Knockout	Absence of pituitary or multiple oral ectoderm invagination and cellular proliferation.
PITX2	Bicoid-like HD	4q25	Dominant	RIEG with occasional IGHD	Knockout	RP forms but fails to proliferate and differentiate at E12.5; lacks all cell types except corticotropes.
LHX3	LIM HD	9q34	Recessive	CPHD with rigid cervical spine	Knockout	Hypoplastic pituitary; RP forms but is unable to proceed; lacks all cell types except corticotropes.
LHX4	LIM HD	1q25	Dominant	CPHD with defects in sella turcica and cerebellar tonsil	Knockout	Hypoplastic anterior pituitary with reduction of all cell types; increased apoptosis.
GLI2	Kruppel	2q14	Dominant	CPHD with variable HPE features	Knockout *you-too*	Variable loss of pituitary; deletion of both *Gli1* and *Gli2* causes complete loss of pituitary. Transdifferentiation into a lens.
PROP1	Paired HD	5q35	Recessive	CPHD	Knockout Ames dwarf	Lack somatotropes, thyrotropes and lactotropes, reduced LH and FSH
PIT1	POU HD	3q11	Recessive Dominant	CPHD	*Snell* dwarf mutations	Loss of somatotropes, thyrotropes and lactotropes and increased gonadotropes. Loss of somatotropes, thyrotropes and lactotropes and expanded corticotropes.
TBX19	T-box	1q23	Recessive	ACTH deficiency	Knockout	Reduced corticotropes and melanotropes, melanotropes transdifferentiate into gonadotropes and Pit1-independent thyrotropes.
SF1	NR	9q33	Dominant Recessive	Adrenal failure, 46, XY gonadal dysgenesis	Knockout	Impaired pituitary FSH and LH expression.
SIX6	SIX HD	14q23	Dominant	Bilateral anophthalmia and pituitary anomalies	Knockout	Hypoplastic pituitary.
SOX3	HMG-box	Xq27	Recessive	IGHD with X-linked mental retardation	Knockout	Reduced GH levels and dysmorphic anterior lobe.

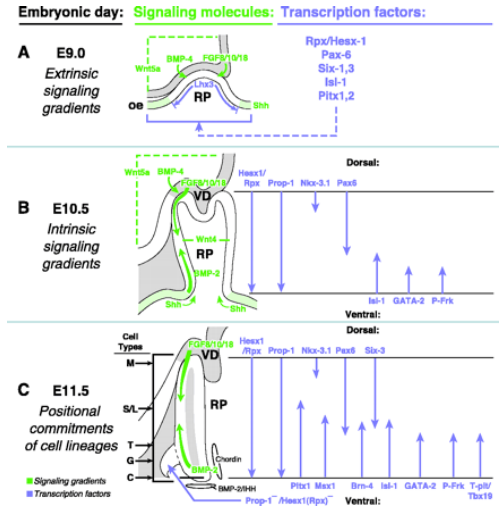
Abbreviations: HD, homeodomain; HMG, high mobility group; HPE holoprosencephaly, NR nuclear receptor.

Table 2

Signal pathways and other transcription factors critical for pituitary development and function.

Gene	Expression	Animal model Mouse/*zebrafish*	Pituitary phenotypes
Signaling molecules/receptors			
BMP4	VD	Knockoutand Ptx1- *Noggin Tg*	RP fails to form, embryonic lethal. RP arrested at E10 with loss of all cell types except corticotropes.
FGF10	VD	knockout	Anterior pituitary agenesis owing to increased apoptosis.
FGFR2-IIIb	RP	Knockout	Anterior pituitary agenesis owing to increased apoptosis.
FGF3, Zebrafish	VD	*Lia* (zebrafish)	Increased apoptosis leading to a complete loss of pituitary.
Wnt4	RP	Knockout	Hypoplastic pituitary with marked reduction of Pit1 lineages.
Wnt5	VD	Knockout	Pituitary dysmorphogenesis, cell differentiation occurs normally.
SHH	VD, oral ectoderm except RP	Ptx1-HIP Tg *sonic-you* (*syu*, zebrafish)	Pituitary hypoplasia with loss of expression of ventral transcription factors Hypoplastic pituitary with reduced *pomc*- and *prl*-positive cells and absence of *gh* and *tsh*-positive cells.
GHRH	Hypothalamus	Knockout	IGHD, hypoplastic pituitary with reduced production of GH.
GHRHR	Anterior pit	*little*, point mutation	IGHD, postnatal dwarf, reduced proliferation of caudomedial somatotropes.
GNRH2	Hypothalamus	*hpg*, deletion	Decreased LHβ, FSHβ, ACTH, PRL in pituitary.
D2R	Pituitary	Knockout	Prolactinomas.
ACVR2	Pituitary	Knockout	Reduced expression of *FSHβ*.
Transcription factors/cofactors			
Tltf1/Nkx2.1	VD	Knockout	Absence of pituitary, owing to ablation of FGFs expression domains in VD.
Brn2	Hypothalamus	Knockout	Loss of posterior pituitary, owing to defects in survival of hypothalamus neurons.
Gsh1	Hypothalamus	Knockout	Hypoplastic anterior pituitary; reduced production of GHRH, GH, PRL, LH.
Nhh2	Hypothalamus, Pituitary	Knockout	Hypogonadal; reduced production of FSH; adult-onset obesity. Deletion of both *Nhh1* and *Nhh2* results in significant reduction of GnRH-1 neurons.
Isl1	RP	Knockout	RP forms but remains primitive, thin pouch wall, embryonic lethal.
Pitx1	RP	Knockout	Decreased expression of *LHβ*, *FSHβ*, *TSHβ*; increased expression of ACTH.
Pax6	Dorsal region of RP	Knockout	Dorsal expansion of ventral cell types at the expense of dorsal cell types.
NeuroD1	RP	Knockout	Delayed corticotropes differentiation.
Aes	Dorsal region of RP	Knockout	Pituitary dysmorphogenesis.
Tcf4	ND	Knockout	Hyperplasic pituitary, prolonged Prop1 expression.
Egr1	Pit	Knockout	No *LHβ* expression, reduced number of somatotropes.
Otx1	Postnatal pituitary	Knockout	Transient dwarfism, delayed production of LHβ, FSHβ and GH.

Abbreviations: ND, not determined; RP, Rathke's pouch; Tg, transgenic; VD, ventral diencephalon.



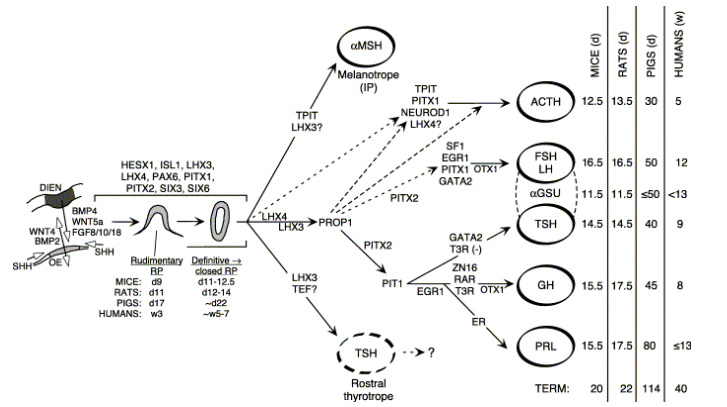


Fig. 2. Transcriptional regulation of anterior pituitary gland development. Inductive interactions involving the ventral diencephalon (DIEN) and oral ectoderm (OE) prime the expression of transcription factors that guide the development of Rathke's pouch (RP) into the specialized hormone-secreting cell types. The approximate developmental times (in days [d] or weeks [w] of gestation) at which key structures can be observed in various mammals are given. In addition, the approximate times at which hormone gene products can be detected are shown (times refer to the detection of mRNA, except human data and porcine PRL which represent protein detection; based on [Schwind, 1928; Clements et al., 1977; Osamura, 1977; Danchin and Dubois, 1982; Ikeda et al., 1988; Simmons et al., 1990; Stefanovic et al., 1993; Japon et al., 1994; Ma et al., 1994; Ma et al., 1996 and Granz et al., 1997]; and references therein). IP=intermediate pituitary lobe.

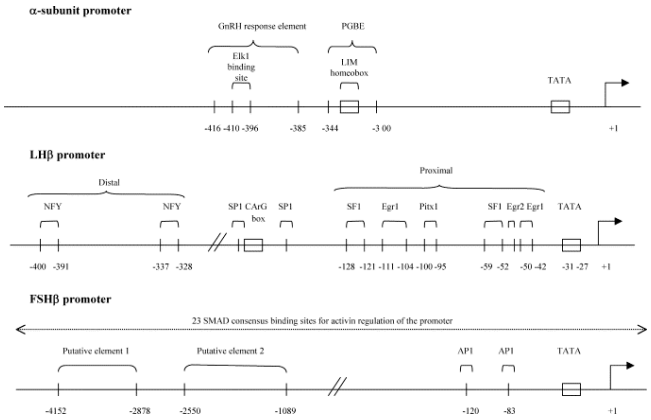


Fig. 2. Schematic of gonadotropin subunit promoters with major sites implicated in their regulation indicated. The consensus -subunit promoter map shown is based predominantly on the mouse gene sequence. The consensus LH map is based on the bovine and rat gene sequences and the FSH promoter map is based on the ovine gene sequence.

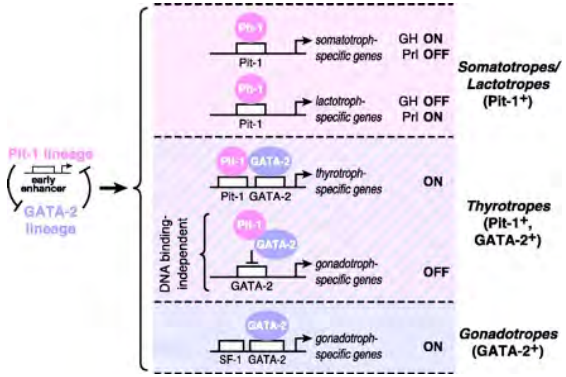


Fig. 4. A model of a proposed role of a BMP2-induced gradient of GATA-2 expression, acting with Pit-1, in determination of gonadotrope and thyrotrope lineages. In thyrotropes, Pit-1 exerts a DNA binding-independent transrepression to inhibit GATA-2-dependent activation of gonadotrope cell type-specific promoters; Pit-1 and GATA-2 synergistically activate TSH. GATA-2 may directly or indirectly inhibit activity of the Pit-1 early enhancer. Pit-1 but not GATA-2 is expressed and required in somatotropes and lactotropes. White boxes denote response elements.

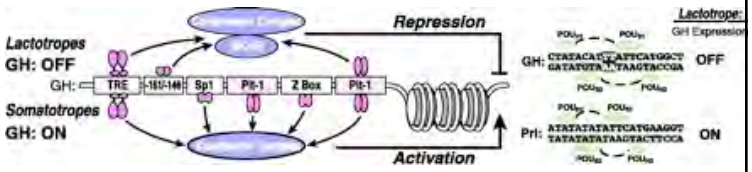
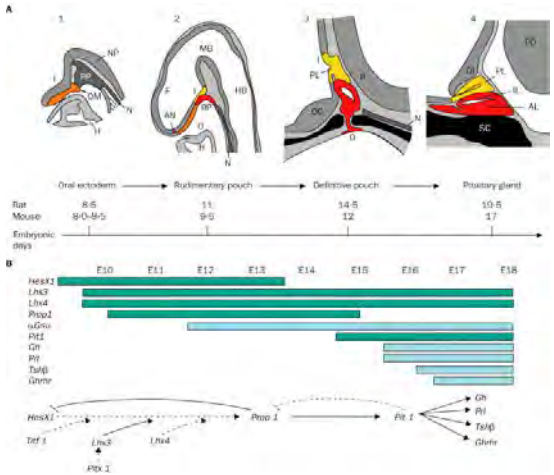
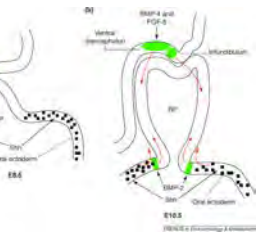


Fig. 5. Model of "repressosome"-based recruitment of a corepressor complex in cell type-specific long-term active repression of growth hormone gene expression in lactotropes. The altered spacing of the Pit-1 POUS and POUH on growth hormone and prolactin sites, in concert with additional DNA binding factors, dictates recruitment of an N-CoR-containing corepressor complex, causing restriction of growth hormone gene expression in the lactotrope.





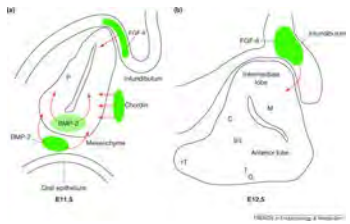
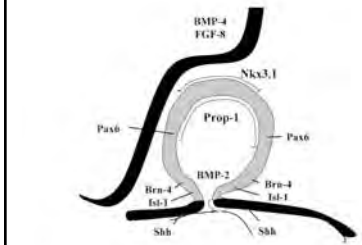
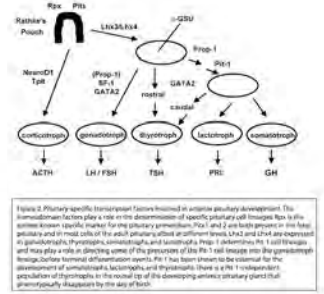


Fig. 1. Areas of expression (green or black) and action radius (indicated by red arrows) of bone morphogenetic protein 4 (BMP-4), BMP-2, fibroblast growth factor 8 (FGF-8) and sonic hedgehog (Shh) in Rathke's pouch (RP) and surrounding areas on embryonic day 8.5 (E8.5) (a) and E10.5 (b) in the mouse.

Fig. 2. Areas of expression (green) and action radius (indicated by red arrows) of bone morphogenetic protein 2 (BMP-2), fibroblast growth factor 8 (FGF-8) and chordin in embryonic pituitary (P) and surrounding areas on embryonic day 11.5 (E11.5) and E12.5 in the mouse. Areas in which corticotropes (C), gonadotropes (G), lactotropes (L), melanotropes (M), somatotropes (S), thyrotropes (T) and rostral thyrotropes (rT) first appear during embryonic development are indicated.

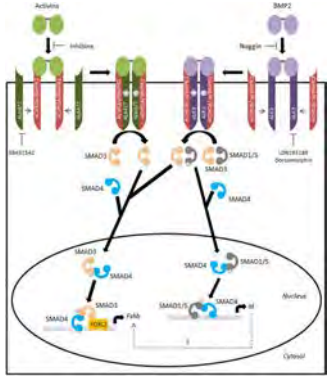




TGF-β Superfamily Regulation of Follicle-Stimulating Hormone Synthesis by Gonadotrope Cells: Is There a Role for Bone Morphogenetic Proteins?

Ongaro L, Schang G, Ho CC, Zhou X, Bernard DJ.

Endocrinology. 2019 Mar 1;160(3):675-683.



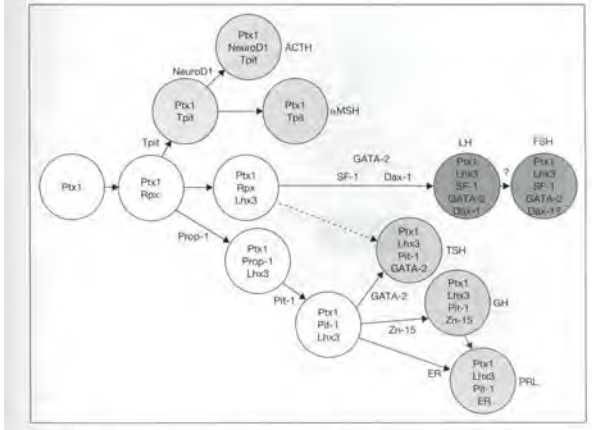
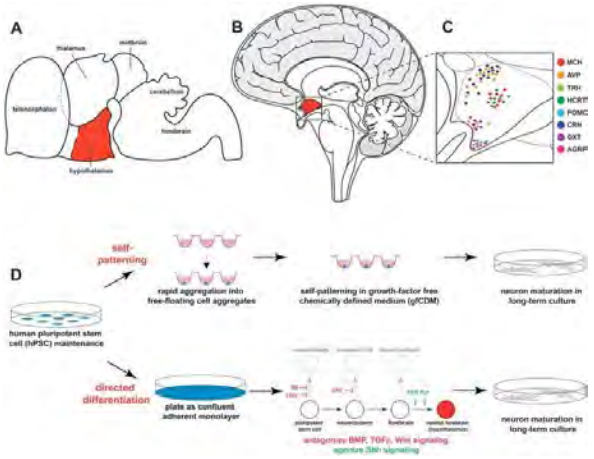
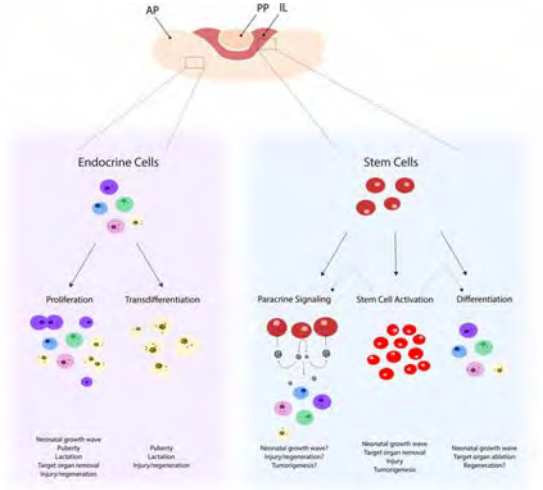


Fig. 3. Pituitary cell lineage. Several transcription factors have been reported to be active in all or a subset of cell lineages, in many cases during a specific period of development. The anterior pituitary cells are well known to be classified into three cells lineages, i.e. GH-PRL-TSH cells (Pit-1-dependent), POMC (ACTH-αMSH) (NeuroD1, Tpit-dependent) and FSH/LH (SF-1, Dax-1, GATA-2-dependent).

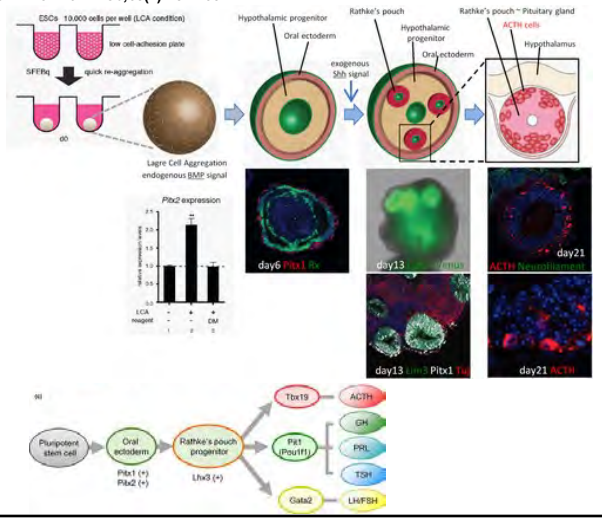
Generation of neuropeptidergic hypothalamic neurons from human pluripotent stem cells.
Merkle FT, Maroof A, Wataya T, et al.
Development. 2015, 142(4):633-43.



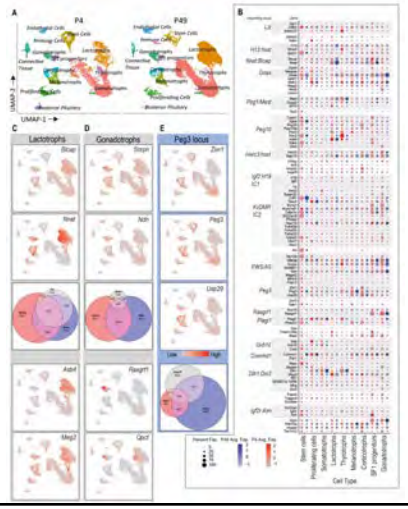
Pituitary Remodeling Throughout Life: Are Resident Stem Cells Involved?
Laporte E, Vennekens A, Vankelecom H.
Front Endocrinol (Lausanne). 2021 Jan 29;11:604519.



Hypothalamic-pituitary organoid generation through the recapitulation of organogenesis.
Ozaki H, Suga H, Arima H.
Dev Growth Differ. 2021 Feb;63(2):154-165.



Dynamic Expression of Imprinted Genes in the Developing and Postnatal Pituitary Gland.
Scagliotti V. Esse RCF, Willis TL, et al.
Genes (Basel). 2021 Mar 30;12(4):509.



Hypothalamus and Pituitary Hormones

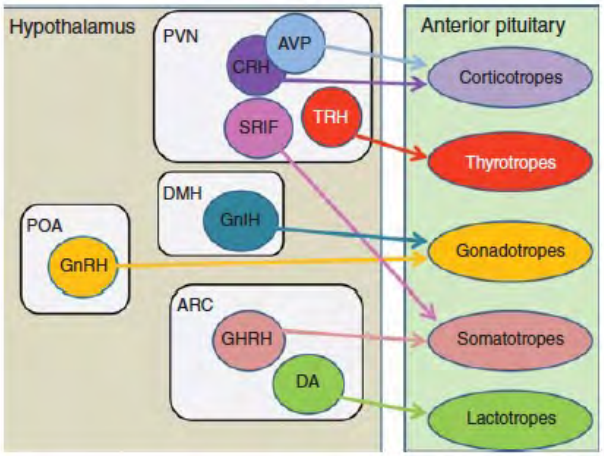
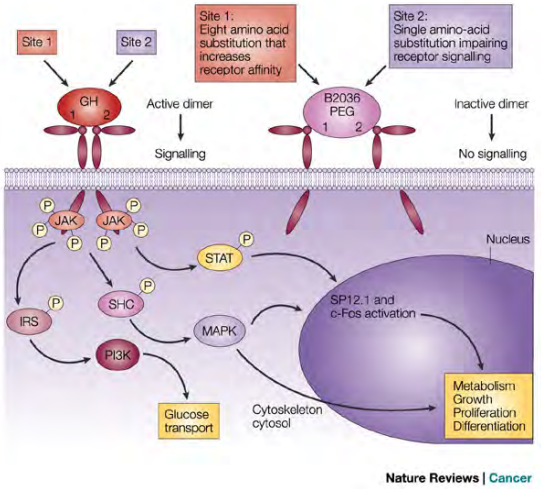


TABLE 1. Anterior pituitary cell types and hormone regulation

Somatotropes	Lactotropes	Thyrotropes	Corticotropes	Gonadotropes
Hormone product Growth hormone (GH)	Prolactin (PRL)	Thyroid-stimulating hormone (TSH)	Adrenocorticotropic hormone (ACTH)	Gonadotropins: luteinizing hormone (LH) and follicle-stimulating hormone (FSH)
Site of action Liver, kidney, most tissues	Mammary	Thyroid	Adrenal	Ovary, testis
Positive regulator Growth-hormone-releasing hormone	Estrogen, thyrotropin-releasing hormone	Thyrotropin-releasing hormone	Corticotropin-releasing hormone	Gonadotropin-releasing hormone
Negative regulator Somatostatin, insulin-like growth factor	Dopamine	Thyroid hormone	Corticosteroids	Gonad steroids, inhibins
Hypopituitarism phenotype Dwarfism	Failure to lactate	Thyroid hypoplasia, dwarfism, cretinism, hypothyroidism	Adrenal hypoplasia	Sexual immaturity
Hyperpituitarism phenotype Gigantism, acromegaly	Galactorrhea, infertility	Thyroid hyperplasia, hyperthyroidism	Cushing disease	Precocious puberty

Figure 22–4. Structure of the principal human growth hormone (continuous chain). The black bars indicate disulfide bridges. The 29 residues alongside the chain identify residues that differ in human chorionic somatomammotropin (hCS; see Chapter 23). All the other residues in hCS are the same, and hCS also has 191 amino acid residues. (Reproduced, with permission, from Parsons JA [editor]. *Peptide Hormones*. University Park Press, 1976.)



Nature Reviews | Cancer

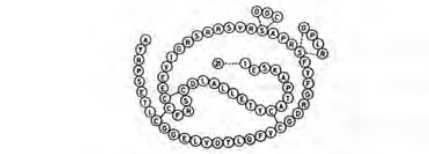
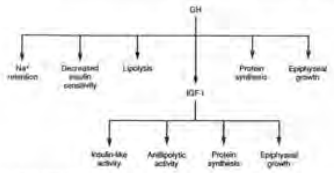


Figure 22–8. Primary structure of human IGF-II and 3 identified variants: a 21-amino-acid-residue extension of the C terminal, a des-peptide substitution at Ser-29, and a tripeptide substitution of Ser-33. Single-letter codes are used for amino acid residues. (Reproduced, with permission, from Sara VR, Hall K. Insulin-like growth factors and their binding proteins. *Physiol Rev* 1990;70:591.)



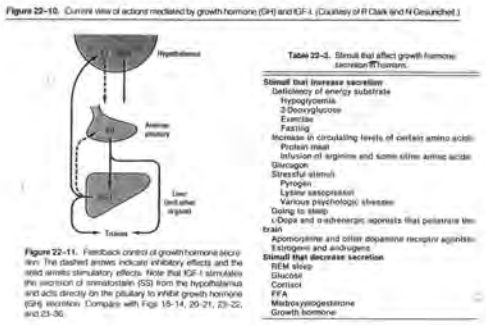
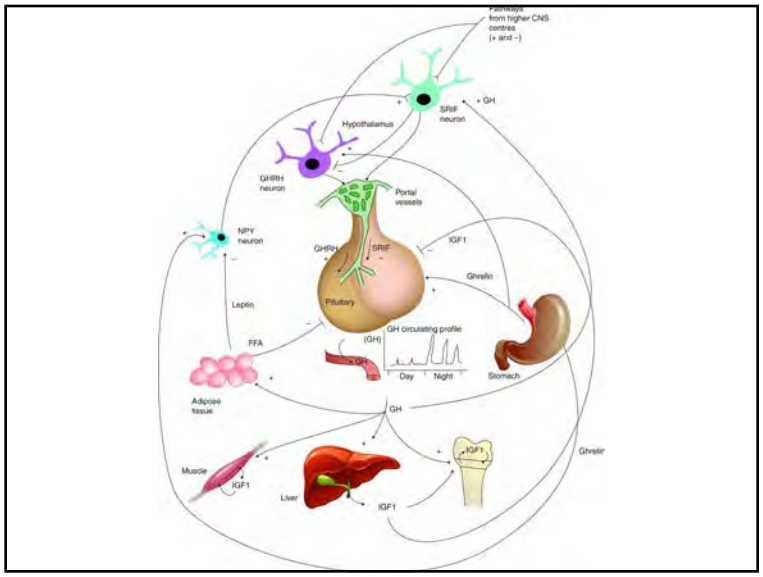


Figure 22–10. Current view of actions mediated by growth hormone (GH) and IGF-I. (Courtesy of R Clark and N Gesundheit.)

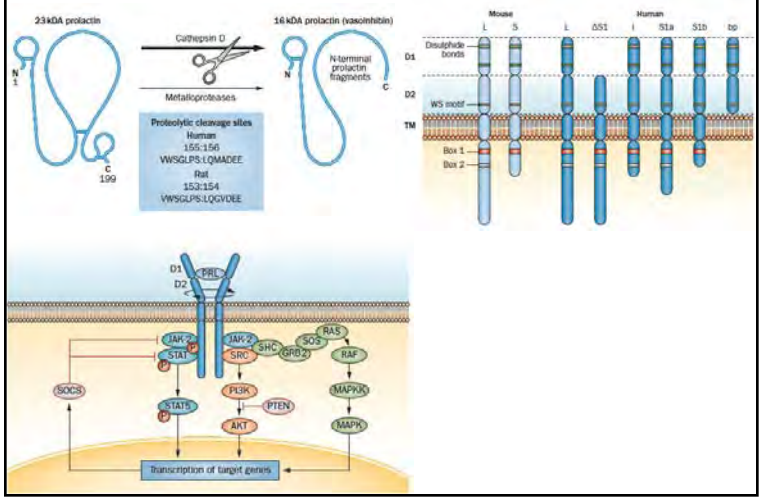
Figure 22–11. Feedback control of growth hormone secretion. The dashed arrows indicate inhibitory effects and the solid arrows stimulatory effects. Note that IGF-I stimulates the secretion of somatostatin (SS) from the hypothalamus and acts directly on the pituitary to inhibit growth hormone (GH) secretion. Compare with Figs 18–14, 20–21, 23–22, and 23–36.

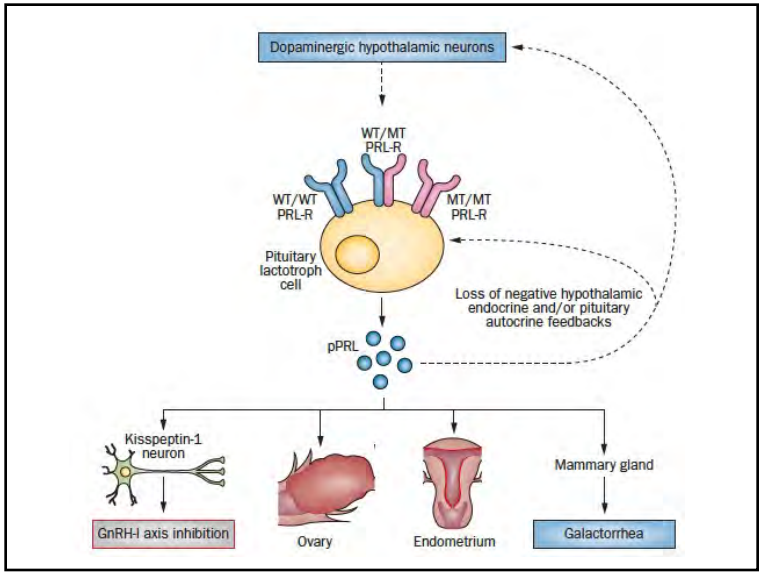
Table 22–3. Stimuli that affect growth hormone secretion in humans.

Stimuli that increase secretion
Deficiency of energy substrate
Hypoglycemia
2-Deoxyglucose
Exercise
Fasting
Increase in circulating levels of certain amino acids
Protein meal
Infusion of arginine and some other amino acids
Glucagon
Stressful stimuli
Pyrogen
Lysine vasopressin
Various psychologic stresses
Going to sleep
L-Dopa and α-adrenergic agonists that penetrate the brain
Apomorphine and other dopamine receptor agonists
Estrogens and androgens
Stimuli that decrease secretion
REM sleep
Glucose
Cortisol
FFA
Medroxyprogesterone
Growth hormone

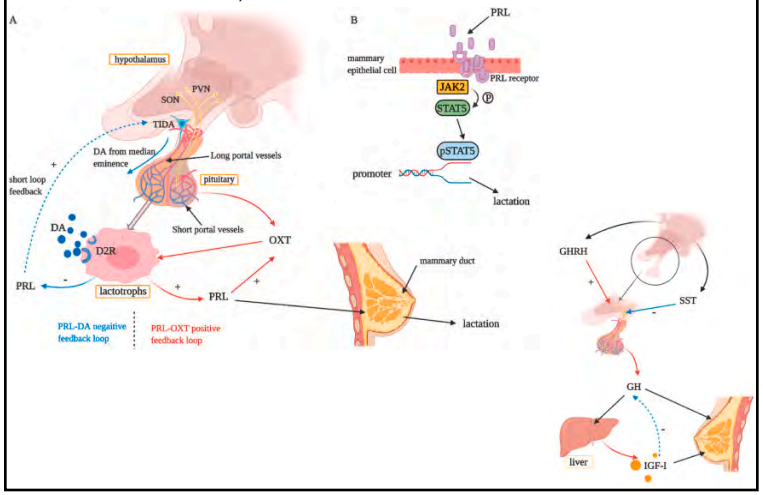


New insights in prolactin: pathological implications.
Bernard V, Young J, Chanson P, Binart N.
Nat Rev Endocrinol. 2015 May;11(5):265-75.





Three lactation-related hormones: Regulation of hypothalamus-pituitary axis and function on lactation.
Ni Y, Chen Q, Cai J, Xiao L, Zhang J.
Mol Cell Endocrinol. 2021 Jan 15;520:111084.



Macrophage colony-stimulating factor induces prolactin expression in rat pituitary gland.

Hoshino S, Kurotani R, Miyano Y, et al.

Zoolog Sci. 2014 Jun;31(6):390-7.

Abstract

We investigated the role of macrophage colony-stimulating factor (M-CSF) in the pituitary gland to understand the effect of M-CSF on pituitary hormones and the relationship between the endocrine and immune systems. When we attempted to establish pituitary cell lines from a thyrotropic pituitary tumor (TtT), a macrophage cell line, TtT/M-87, was established. We evaluated M-CSF-like activity in conditioned media (CM) from seven pituitary cell lines using TtT/M-87 cells. TtT/M-87 proliferation significantly increased in the presence of CM from TtT/GF cells, a pituitary folliculostellate (FS) cell line. M-CSF mRNA was detected in TtT/GF and MtT/E cells by reverse transcriptase-polymerase chain reaction (RT-PCR), and its expression in TtT/GF cells was increased in a lipopolysaccharide (LPS) dose-dependent manner. M-CSF mRNA expression was also increased in rat anterior pituitary glands by LPS. M-CSF receptor (M-CSFR) mRNA was only detected in TtT/M-87 cells and increased in the LPS-stimulated rat pituitary glands. In rat pituitary glands, M-CSF and M-CSFR were found to be localized in FS cells and prolactin (PRL)-secreting cells, respectively, by immunohistochemistry. The PRL concentration in rat sera was significantly increased at 24 h after M-CSF administration, and mRNA levels significantly increased in primary culture cells of rat anterior pituitary glands. In addition, TNF-α mRNA was increased in the primary culture cells by M-CSF. These results revealed that M-CSF was secreted from FS cells and M-CSF regulated PRL expression in rat pituitary glands.

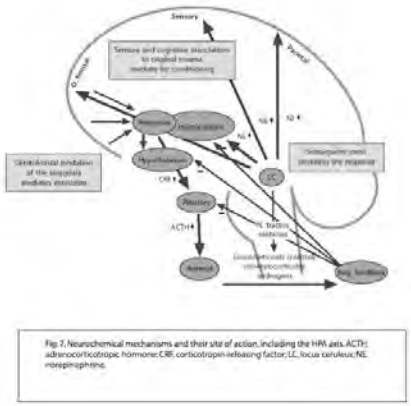


Fig. 7. Neurochemical mechanisms and their site of action, including the HPA axis. ACTH: adrenocorticotropic hormone; CRF: corticotropin-releasing factor; LC: locus ceruleus; NE: norepinephrine.

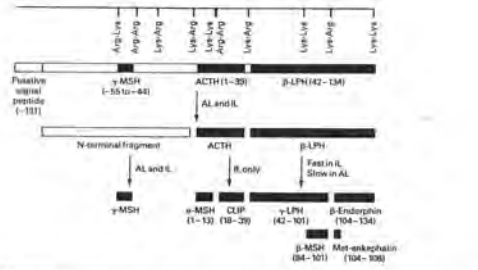
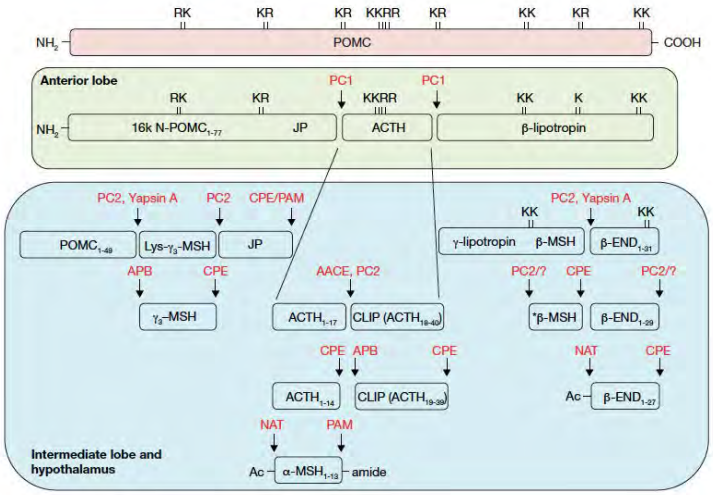
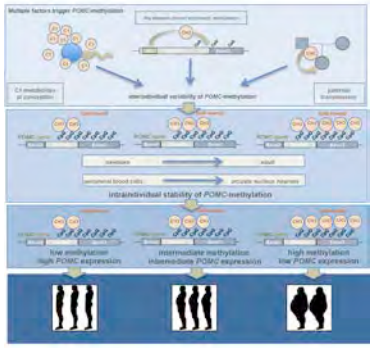


Figure 22–3. Schematic representation of the prepro-opiomelanocortin molecule formed in pituitary cells, neurons, and other tissues. The numbers in parentheses identify the amino acid sequences in each of the polypeptide fragments. For convenience, the amino acid sequences are numbered from the N terminal of ACTH and read toward the C-terminal portion of the parent molecule, whereas the amino acid sequences in the other portion of the molecule read to the left to ~131, the N terminus of the parent molecule. The locations of Lys-Arg and other pairs of basic amino acids residues are also indicated; these are the sites of proteolytic cleavage in the formation of the smaller fragments of the parent molecule. AL, anterior lobe; IL, intermediate lobe.



Interindividual Variation in DNA Methylation at a Putative POMC Metastable Epiallele Is Associated with Obesity.
Cell Metab. 2016 Sep 13;24(3):502-509.
Kühnen P, Handke D, Waterland RA, et al.

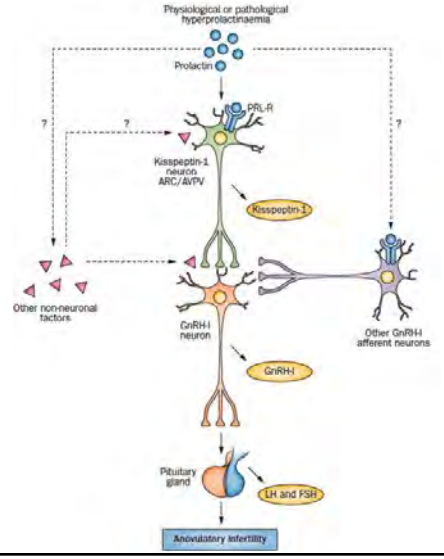


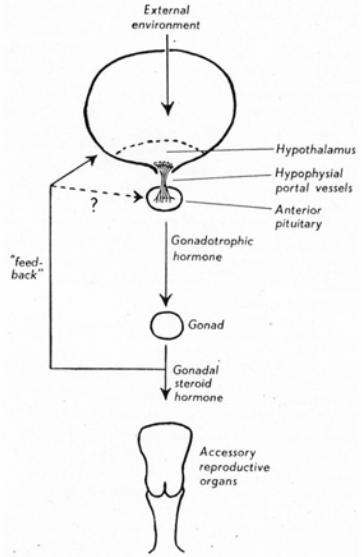
In Brief

Kühnen et al. explore the epigenetic regulation of body weight/BMI and identify a *POMC* DNA hypermethylation variant in obese individuals. This putative metastable epiallele is present after birth and leads to an increased individual risk of developing obesity later in life.

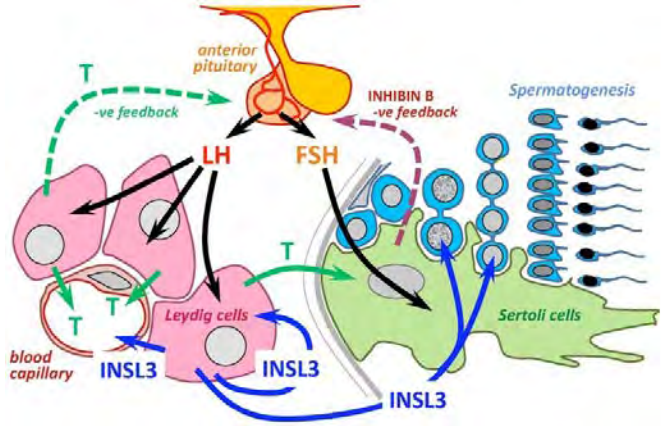
Highlights

- A *POMC* hypermethylation variant leads to increased risk for obesity development
- Maternal C1 metabolism at conception affects *POMC* methylation in the offspring
- Paternal *POMC* methylation correlates with methylation in the offspring
- This *POMC* region fulfills criteria for a putative metastable epiallele



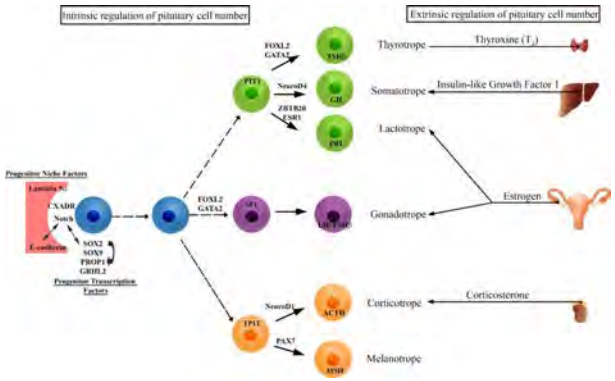


Insulin-Like Factor 3 and the HPG Axis in the Male.
Ivell R, Heng K, Anand-Ivell R. Front Endocrinol (Lausanne). 2014 Jan 27;5:6. eCollection 2014.

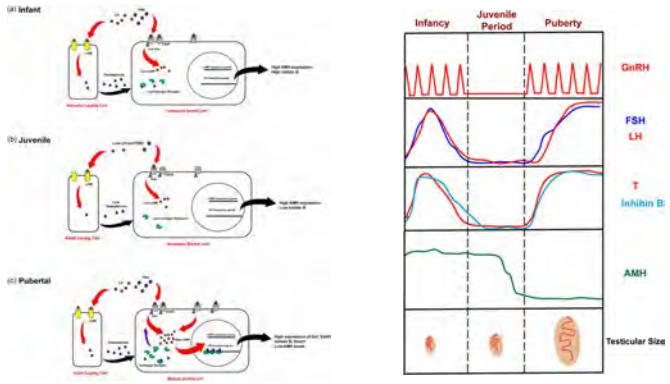


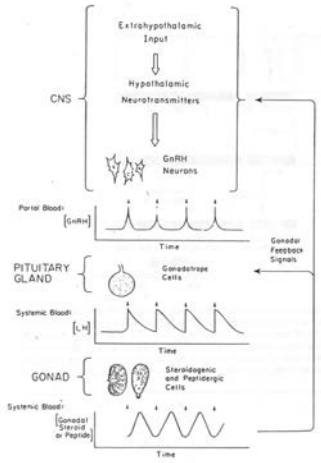
INSL3 and HPG axis. Scheme to show the relationship between the INSL3/RXFP2 system and testosterone as endpoint effectors of the HPG axis within the testis. Arrows are directed only to cells where there are known to be specific cognate receptors.

Complex integration of intrinsic and peripheral signaling is required for pituitary gland development.
Edwards W, Raetzman LT.
Biol Reprod. 2018 Sep 1;99(3):504-513.



Pubertal orchestration of hormones and testis in primates.
Bhattacharya I, Sen Sharma S, Majumdar SS.
Mol Reprod Dev. 2019 Nov;86(11):1505-1530.





VERTEBRATE HYPOTHALAMO-HYPOPHYSIO-GONADAL AXIS

TABLE I
GnRH Molecular Forms

GnRH	1	2	3	4	5	6	7	8	9	10
Mammal	pGlu	His	Trp	Ser	Tyr	Gly	Leu	Arg	Pro	Gly-NH_2
Guinea pig	—	Tyr	—	—	—	—	Val	—	—	—
Chicken II	—	—	—	—	His	—	Trp	Tyr	—	—
Chicken I	—	—	—	—	—	—	—	Gln	—	—
Frog	—	—	—	—	—	—	—	Trp	—	—
Salmon	—	—	—	—	—	—	Trp	Leu	—	—
Dogfish	—	—	—	—	His	—	Trp	Leu	—	—
Catfish	—	—	—	—	His	—	—	Asn	—	—
Seabream	—	—	—	—	—	—	—	Ser	—	—
Medaka	—	—	—	—	Phe	—	—	Ser	—	—
Herring	—	—	—	—	His	—	—	Ser	—	—
Lamprey I	—	—	Tyr	—	Leu	Glu	Trp	Lys	—	—
Lamprey III	—	—	—	—	His	Asp	Trp	Lys	—	—
Tunicate I	—	—	—	—	Asp	Tyr	Phe	Lys	—	—
Tunicate II	—	—	—	—	Leu	Cys	Hys	Ala	—	—

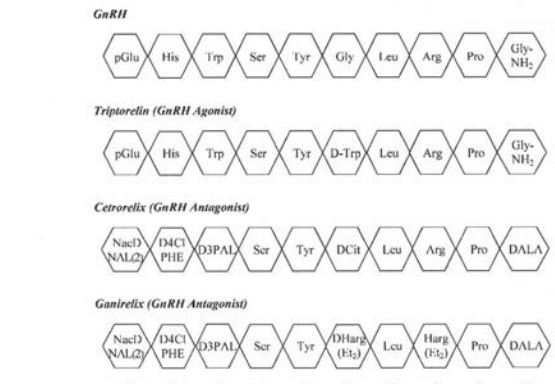
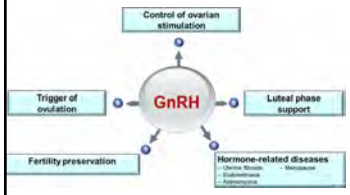


Figure 1. Structure of common GnRHant and GnRHag.

Gonadotropin-releasing hormone analogs: Mechanisms of action and clinical applications in female reproduction.
Wu HM, Chang HM, Leung PCK.
Front Neuroendocrinol. 2021 Jan;60:100876.



Amino acid sequences of the GnRH isoform, GnRH-I agonists and antagonists.

GnRH forms	
GnRH-I (mGnRH)	pGlu^1-His^2-Trp^3-Ser^4-Tyr^5-Gly^6-Leu^7-Arg^8-Pro^9-Gly^{10}-NH$_2$
GnRH-II (cGnRH-II)	pGlu^1-His^2-Trp^3-Ser^4-His^5-Gly^6-Trp^7-Tyr^8-Pro^9-Gly^{10}-NH$_2$
eGnRH-I	pGlu^1-His^2-Trp^3-Ser^4-Tyr^5-Gly^6-Leu^7-Gln^8-Pro^9-Gly^{10}-NH$_2$
rGnRH	pGlu^1-His^2-Trp^3-Ser^4-Tyr^5-Gly^6-Leu^7-Trp^8-Pro^9-Gly^{10}-NH$_2$
lGnRH-I	pGlu^1-His^2-Trp^3-Ser^4-Leu^5-Glu^6-Trp^7-Lys^8-Pro^9-Gly^{10}-NH$_2$
lGnRH-III	pGlu^1-His^2-Trp^3-Ser^4-His^5-Asp^6-Trp^7-Lys^8-Pro^9-Gly^{10}-NH$_2$
sGnRH	pGlu^1-His^2-Trp^3-Ser^4-Tyr^5-Gly^6-Trp^7-Leu^8-Pro^9-Gly^{10}-NH$_2$
cfGnRH	pGlu^1-His^2-Trp^3-Ser^4-His^5-Gly^6-Leu^7-Pro^8-Pro^9-Gly^{10}-NH$_2$
dfGnRH	pGlu^1-His^2-Trp^3-Ser^4-His^5-Gly^6-Trp^7-Leu^8-Pro^9-Gly^{10}-NH$_2$
GnRH agonists	
Triptorelin	pGlu^1-His^2-Trp^3-Ser^4-Tyr^5-D-Trp^6-Leu^7-Arg^8-Pro^9-Gly^{10}-NH$_2$
Leuprolide	pGlu^1-His^2-Trp^3-Ser^4-Tyr^5-D-Leu^6-Leu^7-Arg^8-Pro^9-NHC$_2$H$_5$
Buserelin	pGlu^1-His^2-Trp^3-Ser^4-Tyr^5-D-Ser(tBu)^6-Leu^7-Arg^8-Pro^9-NHC$_2$H$_5$
Goserelin	pGlu^1-His^2-Trp^3-Ser^4-Tyr^5-D-Ser(tBu)^6-Leu^7-Arg^8-Pro^9-AzGly^{10}-NH$_2$
Nafarelin	pGlu^1-His^2-Trp^3-Ser^4-Tyr^5-D-Nal(2)^6-Leu^7-Arg^8-pro^9-NHC$_2$H$_5$
GnRH antagonists	
Nal-Glu-GnRH	Ac-D-Nal^1-D-Cpa^2-D-Pal^3-Ser^4-Arg^5-D-Glu^6(AA)-Leu^7-Arg^8-Pro^9-D-Ala^{10}-NH$_2$
Cetrorelix	Ac-D-Nal^1-D-Cpa^2-D-Pal^3-Ser^4-Tyr^5-D-Cit^6-Leu^7-Arg^8-Pro^9-D-Ala^{10}-NH$_2$
Ganirelix	Ac-D-Nal^1-D-Cpa^2-D-Pal^3-Ser^4-Tyr^5-D-hArg(Et2)^6-Leu7-hArg (Et2)^8-Pro^9-D-Ala^{10}-NH$_2$
Abarelix	Ac-D-Nal^1-D-Cpa^2-D-Ala^3-Ser^4-Tyr^5-D-Asp^6-Leu^7-Lys(iPr)^8-Pro^9-D-Ala^{10}-NH$_2$
Azaline B	Ac-D-Nal^1-D-Cpa^2-D-Pal^3-Ser^4-Aph^5(Arz)-D-Aph^6(Arz)-Leu^7-ILys^8-Pro^9-D-Ala^{10}-NH$_2$

M, mammalian; c, chicken; r, amphibian; l, lamprey; s, salmon; cf, catfish and df, dogfish.

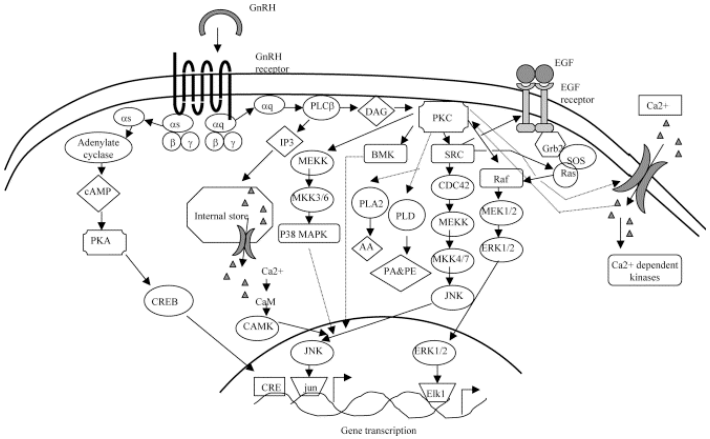
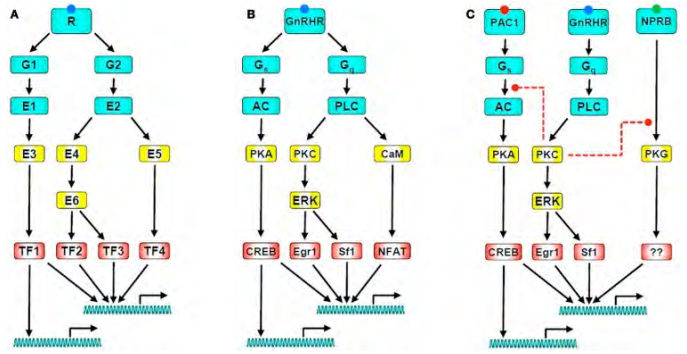


Fig. 1. Diagram of GnRH receptor modulated signaling network.

Molecular Mechanisms of Gonadotropin-Releasing Hormone Signaling: Integrating Cyclic Nucleotides into the Network.
Perrett RM, McArdle CA. Front Endocrinol (Lausanne). 2013 Nov 20;4:180.



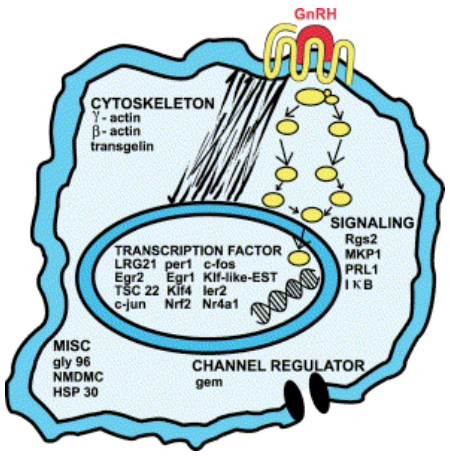


Fig. 3. Schematic of transcripts regulated by GnRH in LT2 cells. Reprinted from [196]. With permission of The American Society for Biochemistry and Molecular Biology.

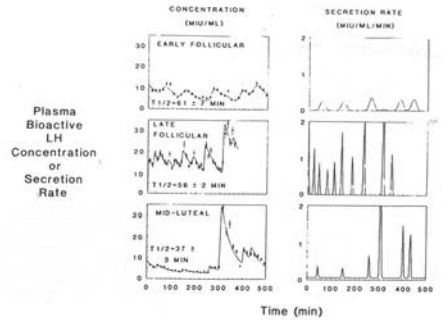


FIG. 5. Episodic secretion of biologically active LH as revealed by deconvolution analysis of pulsatile plasma bioactive LH profiles in normal women studied at three stages of the menstrual cycle. The stage of the menstrual cycle is noted in each subpanel. Plasma bioactive LH concentrations were measured in the rat interstitial cell testosterone bioassay in blood sampled at 10- or 15-minute intervals for 6 to 8 hours. **(Left panels)** Serial plasma bioactive LH concentrations and the computer-estimated reconvolution fit (continuous curve) and individual half-lives (± SD) of LH estimated in each data series. **(Right panels)** Calculated bioactive LH secretory rates, the units of which are mIU/mL/min (UI/L/min). Note that punctuated bursts of LH secretion without tonic release account for the pulsatile LH profiles. (Adapted from ref. 54, with permission.)

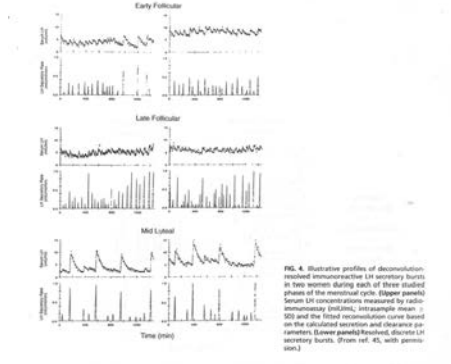


FIG. 4. Illustrative profiles of deconvolution-resolved immunoreactive LH secretory bursts in two women during each of three studied phases of the menstrual cycle. **(Upper panels)** Serum LH concentrations measured by radioimmunoassay (mIU/mL; intraassay mean ± SD) and the fitted reconvolution curve based on the calculated secretion and clearance parameters. **(Lower panels)** Resolved, discrete LH secretory bursts. (From ref. 45, with permission.)

Table 1. Mean (± SEM) LH Secretory Burst Characteristics during the Early Follicular, Late Follicular, and Midluteal Phases of the Menstrual Cycle

PHASE	SECRETORY BURST NUMBER (per 24 hours)	SECRETORY BURST HALF-DURATION* (minutes)	LH HALF-LIFE (minutes)	TOTAL DAILY SECRETION (mIU/mL/24 h)
Early follicular	17.5 ± 1.4ᵃ	6.5 ± 1.0ᵃ	131 ± 7ᵃ	49 ± 6ᵃ
Late follicular	16.9 ± 1.6ᵃ	3.5 ± 0.9ᵇ	128 ± 12ᵃ	56 ± 8ᵃ
Midluteal	10.1 ± 1.0ᵇ	11.0 ± 1.3ᶜ	303 ± 7ᵇ	52 ± 4ᵃ

The volume term (mL) represents unit distribution volume for LH. Entries within each column identified by different superscripts differ significantly (Duncan's multiple range test, $P < 0.05$).
* Duration of the deconvolution-resolved LH secretory burst at half-maximal amplitude.
(Adapted from ref. 45, with permission.)

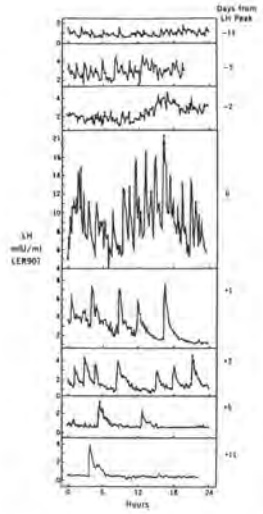


FIG. 4. Frequency and amplitude of LH pulses on selected days of the normal human menstrual cycle. The days of the cycle are indicated relative to the day of the LH surge (day 0). Significant LH pulses are indicated by a dot. Luteal phase progesterone levels are 1, 5, 6, and 12 ng/mL on days +1, +2, +5, and +11, respectively. During the follicular phase (days −11 to −2), low-amplitude LH pulses occur almost hourly. On the day of the LH peak, the frequency of the LH pulses remains circhoral, but the amplitude is increased. During the luteal phase, the LH pulse frequency is reduced. (From ref. 104.)

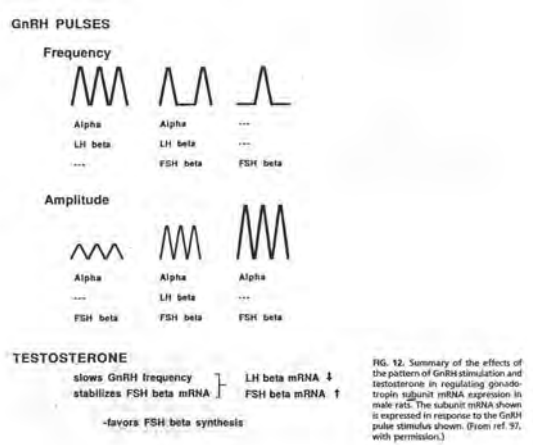
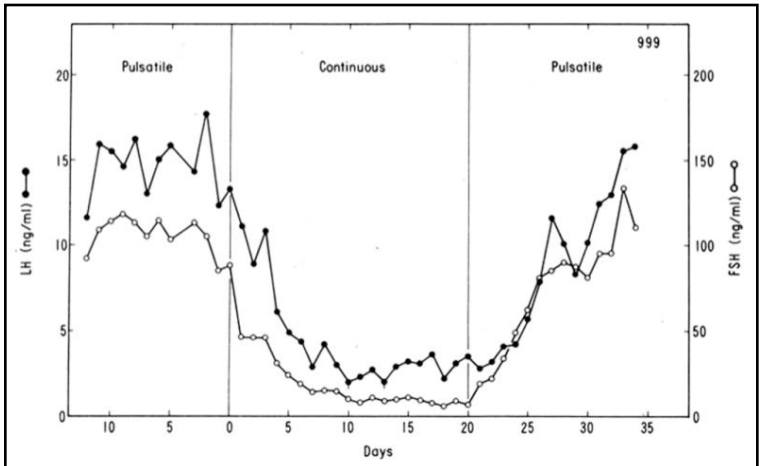
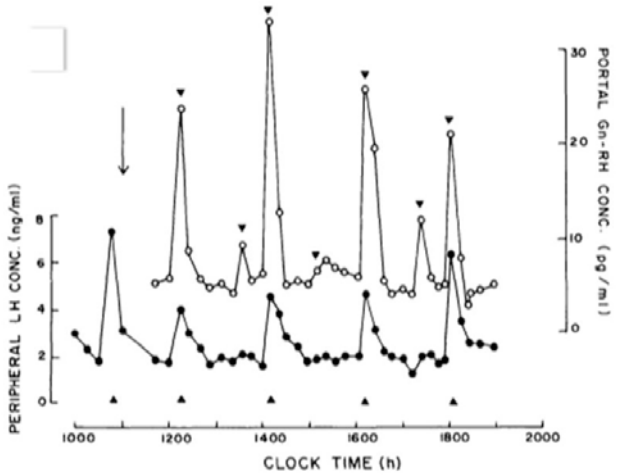


FIG. 12. Summary of the effects of the pattern of GnRH stimulation and testosterone in regulating gonadotropin subunit mRNA expression in male rats. The subunit mRNA shown is expressed in response to the GnRH pulse stimulus shown. (From ref. 97, with permission.)



Demonstration of the need of intermittent GnRH stimulation of the pituitary for sustained secretion of LH (closed data points) and FSH (open data points). A monkey rendered hypogonadotropic by a hypothalamic lesion was treated initially with an intermittent iv infusion of GnRH (1 µg/min for 6 min every h). On day 0 the pulsatile regimen was terminated and replaced with a continuous GnRH infusion (1 µg/min). On day 20 the pulsatile mode of GnRH stimulation was re-instituted (reprinted from Belchetz et al, 1978).



Relationship between pulsatile secretion of GnRH (open data points) into hypophysial portal blood and corresponding episodes of pituitary LH secretion (closed data points) into the systemic circulation in an ovariectomized ewe. Modified from Clarke and Cummins, 1982 – permission pending (Copyright 1982, The Endocrine Society).

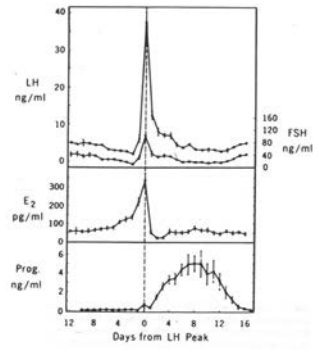


FIG. 1. Concentrations of LH (n = 9), FSH (n = 7), estradiol (E_2, n = 11), and progesterone (Prog, n = 7) in plasma samples taken daily throughout the menstrual cycle of rhesus monkeys (*Macaca mulatta*). The data are normalized to the day of the LH peak (day 0). (From ref. 7.)

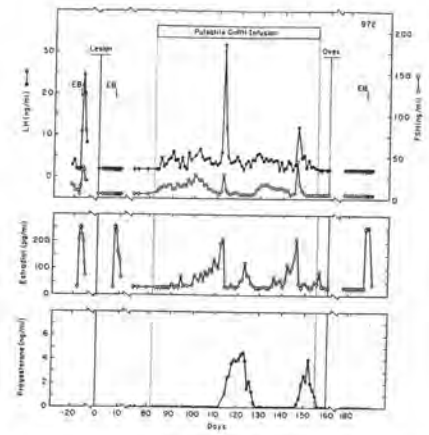


FIG. 12. The establishment of two ovulatory menstrual cycles in response to an unvarying pulsatile GnRH replacement regimen in a rhesus monkey subjected to a radiofrequency lesion in the MBH at time 0. Note that the lesion abolished the positive feedback action of administered estradiol benzoate (*EB*). Ovariectomy at the end of the experiment, to open a putative negative feedback loop, did not increase gonadotropin secretion, indicating the completeness of the lesion and the absence of reorganization or regeneration of the hypothalamic apparatus responsible for the control of gonadotropin secretion. *Small vertical lines* below some baseline points indicate concentrations below the limits of sensitivity of the assays. (From ref. 521.)

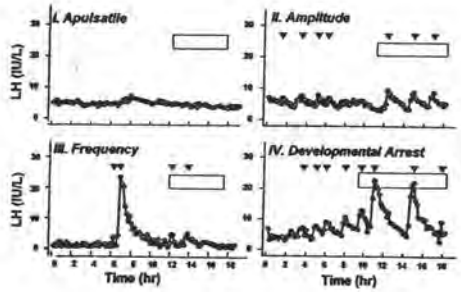
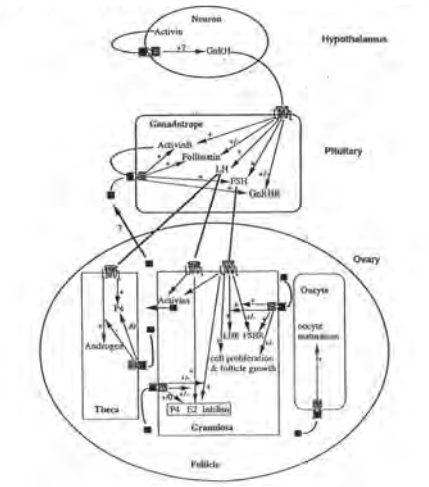
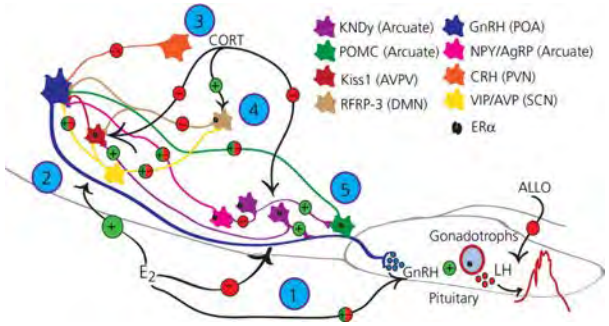


Fig. 4. Spectrum of GnRH abnormalities in 4 women with hypothalamic amenorrhea. ∇ = Detected LH pulsations. Note the predominance of LH pulsations during sleeping hours (open bars) [reproduced from 22].

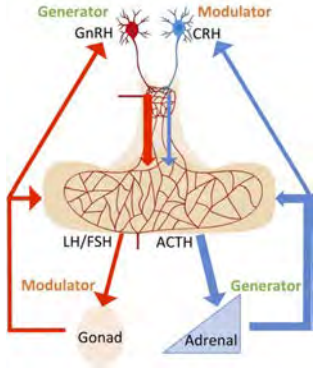


Regulation Hypothalamus and Pituitary Development

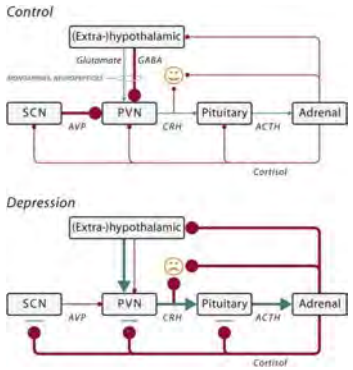
Emerging insights into hypothalamic-pituitary-gonadal axis regulation and interaction with stress signalling.
Acevedo-Rodriguez A, Kauffman AS, Cherrington BD, Borges CS, Roepke TA, Laconi M.
J Neuroendocrinol. 2018 Oct;30(10):e12590.



The Processes of Anterior Pituitary Hormone Pulse Generation.
Le Tissier P, Fiordelisio Coll T, Mollard P.
Endocrinology. 2018 Oct 1;159(10):3524-3535.



The human hypothalamus in mood disorders: The HPA axis in the center.
Bao AM, Swaab DF.
IBRO Rep. 2018 Dec 14;6:45-53.



Gene coexpression network analysis identifies genes and biological processes shared among anterior pituitary and brain areas that affect estrous behavior in dairy cows.
Kommadath A, Te Pas MF, Smits MA. (2013) J Dairy Sci. 2013 Apr;96(4):2583-95.

Table 1. Summary of steps taken in the analysis and their results

Steps	Results
Process data of 14 pairs of dye-swapped microarrays per tissue collected from 14 cows at start of estrous cycle	Gene expression values (M-values) of 23,496 probes per array obtained
Select good quality probes based on probe reannotation and average the M-values of probes representing the same gene	16,620 good-quality probes per array representing 13,234 genes obtained
Select the top 50% most variable genes per tissue and identify genes shared by each tissue within a tissue pair (assuming that genes affecting estrous behavior expression would have a variable expression across the experimental cows showing differing levels of estrous behavior)	Approximately 4,000 to 5,000 genes per tissue pair obtained : AM-DH, HC-DH, VH-DH, AM-HC, and AP-DH [1]
Perform coexpression network analysis on gene expression data of shared genes within each tissue pair and identify consensus modules	Gene coexpression networks constructed for tissues within each pair and consensus modules identified
Identify consensus modules within tissue pairs whose module eigengenes correlate with estrous behavior scores	Consensus modules that correlated with estrous behavior identified: AM-DH: 1 of 3, HC-DH: 5 of 10, VH-DH: 0 of 2, AM-HC: 3 of 8, and AP-DH: 10 of 23
Test for enriched gene ontology and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway terms within estrous behavior-correlated consensus modules	Significant enriched terms obtained (summary of the significant terms per module are reported in Figure 1)
Identify hub genes within the estrous behavior correlated consensus modules	Hub genes per module obtained (the top 3 hub genes per module are reported in Table 3)

[1]Tissues are abbreviated as follows: anterior pituitary (AP), dorsal hypothalamus (DH), ventral hypothalamus (VH), amygdala (AM), and hippocampus (HC).

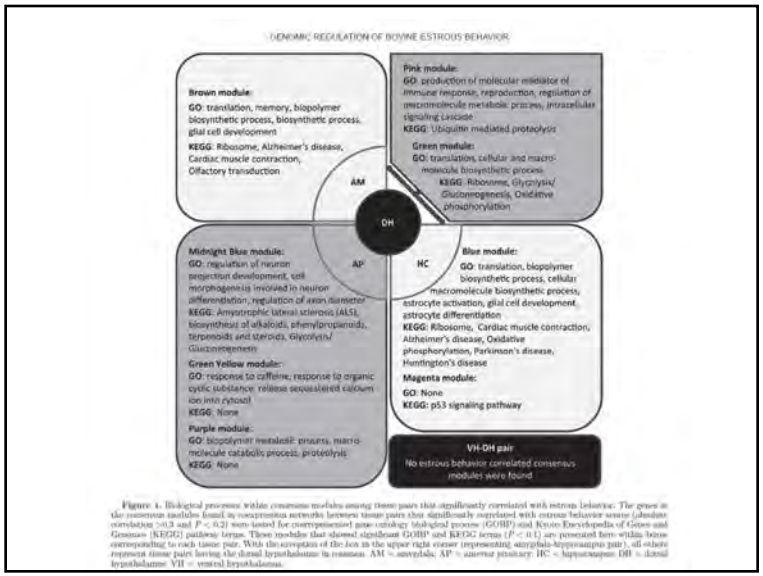
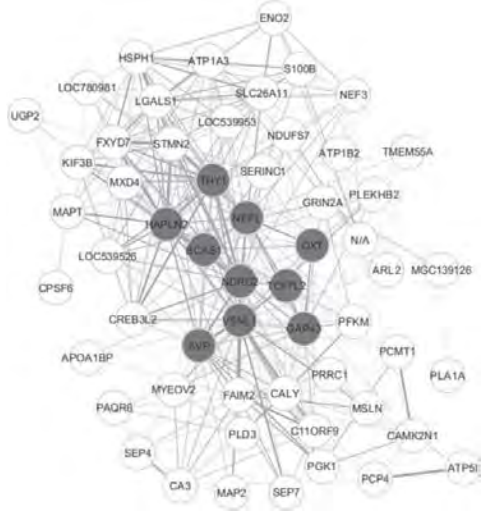


Figure 4. Biological processes within consensus modules among tissue pairs that significantly correlated with estrous behavior. The genes in the consensus modules found in comparison networks between tissue pairs that significantly correlated with estrous behavior source (absolute correlation >0.3 and $P < 0.2$) were tested for overrepresented gene ontology biological process (GOBP) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway terms. Those modules that showed significant GOBP and KEGG terms ($P < 0.1$) are presented here within boxes corresponding to each tissue pair. With the exception of the box in the upper right corner (representing amygdala-hippocampus pair), all others represent tissue pairs having the dorsal hypothalamus in common. AM = amygdala; AP = anterior pituitary; HC = hippocampus; DH = dorsal hypothalamus; VH = ventral hypothalamus.

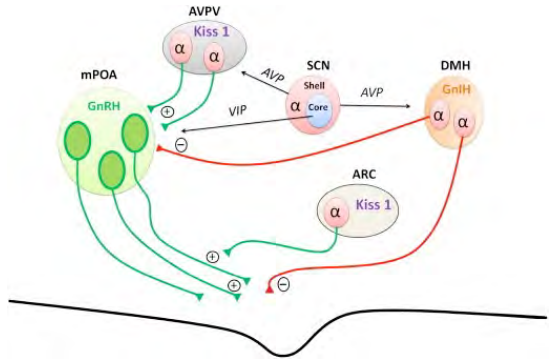


GENOMIC REGULATION OF BOVINE ESTROUS BEHAVIOR

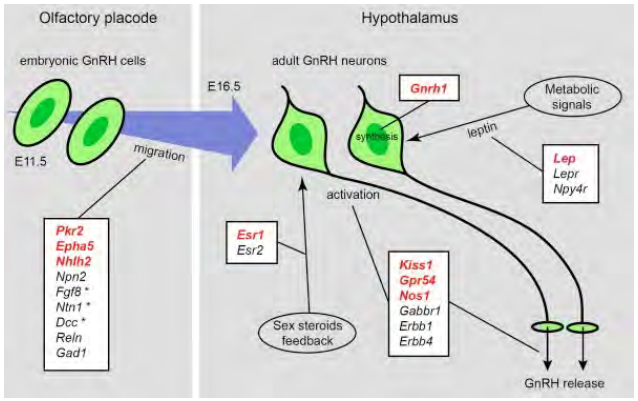
Table 4. Estrous behavior-associated genes and processes in dairy cows known to correspond to processes within the growth, amplification, preparation, permission, and synchronization (GAPPS) modules

GAPPS module	Characteristics	Corresponding genes and processes in cows (with reference in parentheses)
Growth	Increase in the input/output connections for behavior-directing hypothalamic neurons	Synaptic plasticity: Immune related genes: *CTLA4, IL1RL1, MARCO* (Kommadath et al., 2011) Neurotransmitter receptors: *CHRM1, CHRM3, CHRNA5* (Kommadath et al., 2011). Ribosomal genes: *RPL14, RPL18, RPL24, RPS11, RPS18* (this study) Others: *NEFL, NDRG2, THY1, GAP43* (this study)
Amplification	Amplification of estrogen effect by progesterone mediated by progesterone receptor	*PGR* gene upregulated in the anterior pituitary at d 0 (Kommadath, 2012)
Preparation	Preparation for mating	Female sexual receptivity: *OXT, AVP, HTR2A, DRD2, GABRA6* (this study and Kommadath et al., 2011) Anxiolytic effect: *OXT, TTR, KCNN2* (this study and Kommadath et al., 2011) Altered feeding motivation and mood: *POMC, MCHR1, MOBP, LTA4H* (Kommadath et al., 2011)
Permission	Permissive actions by hypothalamic neurons for the mating behavior to occur	Arousal, activation of protein kinases and release of Ca^{2+}: *CHRM1, CHRM3, CHRNA5, PLCB2, ITPKA* (Kommadath et al., 2011)
Synchronization	Synchronize mating behavior with ovulation	Prostaglandin regulators: *PTGDS, PTGIS, PTGFB* (Kommadath et al., 2011)

[1]This table is adapted from the PhD thesis of the first author (Kommadath, 2012).

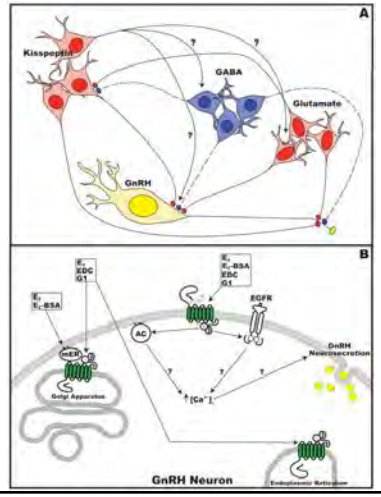


Sex steroids and hypothalamic control of the HPG-axis. Hypothalamic nuclei involved in regulation of gonadotropin release at the level of the hypothalamus. Neurons expressing estrogen receptors (ER), red, with ER subtype (α or β) indicated. Axons depicted in green represent neuronal inputs promoting the release of gonadotropins and axons depicted in red represent neuronal inputs inhibiting their release. The gonadotropin releasing hormone (GnRH) neurons, green, of the medial pre optic area (mPOA), light green, release gonadotropins into the medial eminence. Excitatory inputs upstream of the GnRH neurons include Kisspeptin (Kiss1) producing neurons in the anteroventral paraventricular nucleus (AVPV), grey, which project onto the somas of GnRH neurons, as well as Kisspeptin neurons of the arcuate nucleus (ARC), silver, which project onto the axons of GnRH neurons. The major inhibitory signals come from gonadotropin inhibiting hormone (GnIH) releasing neurons of the dorsomedial hypothalamus (DMH), light orange. The SCN influences multiple sites involved in control of gonadotropin release throughout the hypothalamus. Black arrows indicate monosynaptic projections from the shell of the SCN, to the positive (kisspeptin, and GnRH) as well as the negative signal of the GnIH. Adapted from Williams and Kriegsfeld (2012).

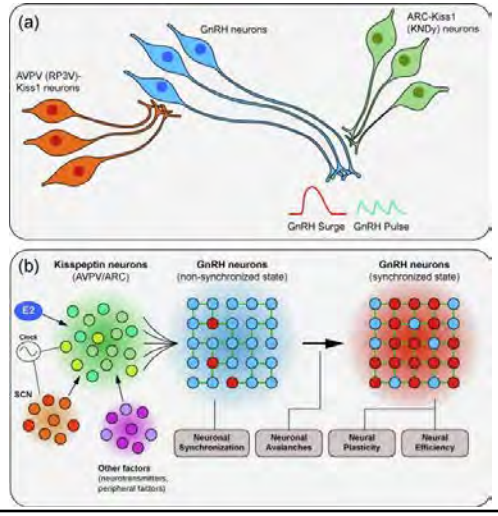


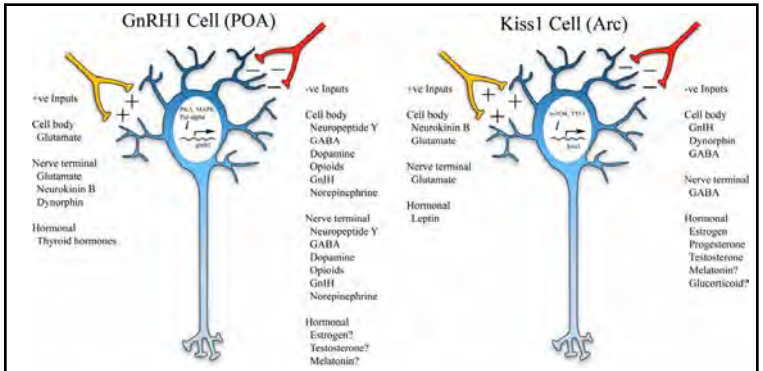
Schematic diagram summarizing the genes involved in the central regulation of puberty as identified from transgenic studies. GnRH neurons originate in the olfactory placodes from where they start migrating at embryonic day 11.5 (E11.5) towards the hypothalamus to finally achieve the adult spatial distribution by E16.5. In the adult, GnRH neurons integrate information from sex steroid feedback, metabolic status, local neurotransmitters and growth factors to release GnRH. The genes shown in red/bold are those where disruption in the mouse leads to absence of puberty and hypogonadotropic hypogonadism. The other genes have a mild effect on reproductive function, such as delayed puberty and lower fecundity. Asterisks denote genes where mutations lead to severely disrupted GnRH neuron migration but their role in puberty cannot be assessed due to perinatal death of the mice.

Recent discoveries on the control of gonadotrophin-releasing hormone neurones in nonhuman primates.
Terasawa E, et al. J Neuroendocrinol. 2010 Jul;22(7):630-8.

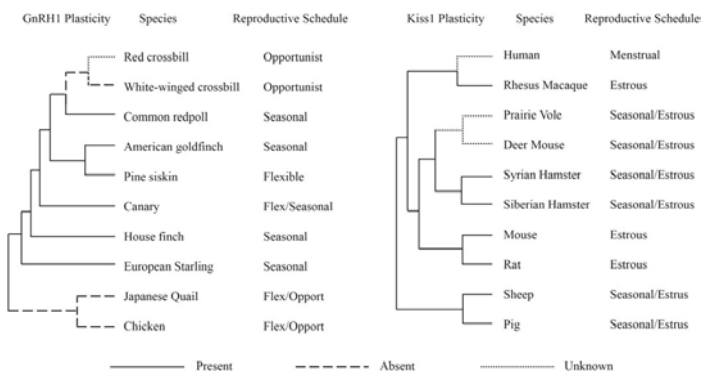


Heterogeneity in GnRH and kisspeptin neurons and their significance in vertebrate reproductive biology.
Ogawa S, Parhar IS.
Front Neuroendocrinol. 2022 Jan;64:100963.



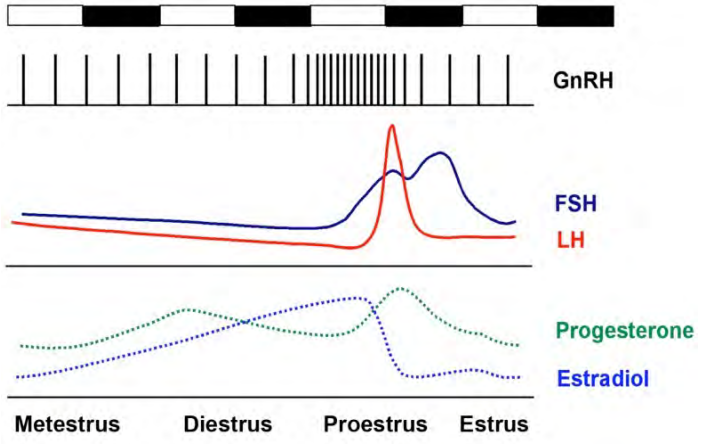


Schematic representation of the neuromodulatory and harmonal inputs that regulate GnRH1 in the preoptic area (POA) in birds and Kiss1 in the Arcuate nucleus (Arc) in mammals. The annual change in photoperiod is the primary signal that governs the predictability in neuropeptide expression. However, the precise hormonal (i.e. melatonin and/or thyroid hormones) and neural signals that integrate the photoperiodic cue with a physiological effect on the GnRH1 and Kiss1 cell activity are not known. There are several neural candidate inputs that regulative GnRH1 and Kiss1 mRNA/protein expression. The photoperiodic regulation of GnRH1 and Kiss1 expression most likely involves a switch from a net balance of excitation to inhibition and vice versa. It is important to note that the majority of the information on GnRH1 mRNA expression is derived from mammalian and cell line experiments. One marked difference between avian and mammalian regulation of GnRH1 is the absence of Kiss1 input onto GnRH1 cells, as kisspeptin has not been identified in birds. Abbreviations: Protein Kinase A (PKA), and Mitogen-activated protein kinase (MAPK), Purine-rich element binding protein alpha (pur-alpha). Mammalian target of rapamycin (mTOR), thyroid transcription factor 1 (TTF1). Data compiled from Dawson et al., (2001), Tillbrook and Clarke (2001), Popa et al., (2008) Oakley et al., (2009), Xu et al., (2009), Zhao et al., (2009), Mueller et al., (2011), Hameed et al., (2011), Dalvi et al., (2011), True et al., (2011), Smith (2011), Navarro & Tena-Sempere (2012).

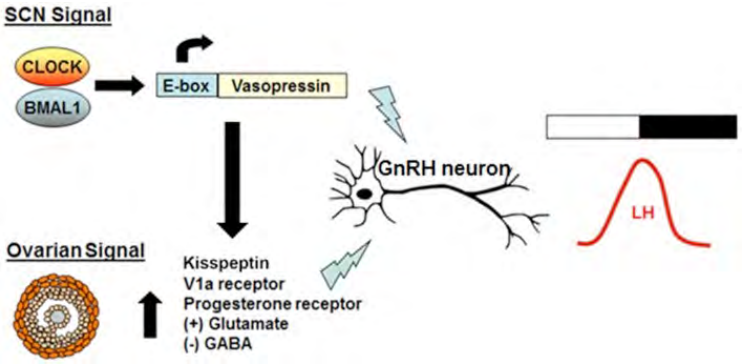


Phylogenetic analysis of GnRH1 and Kiss1 plasticity in bird and mammalian species, respectively. Kiss1 plasticity occurs in both the Arc and POA/AvPv in all mammalian species studied to date. Data was compiled using MacDougall-Shackleton et al., 2009, Revel et al., (2006), Greives et al., (2007), Gottsch et al., (2011), Adachi et al., (2007), Smith et al., (2007), Chalivoix et al., (2010), Smith et al., (2010). Phylogeny was adapted from Marten and Johnson (1986) Badyaev (1997), Arnaiz-Villena et al., (2001) Jansa & Weksler (2004) and Prasad et al., (2008).

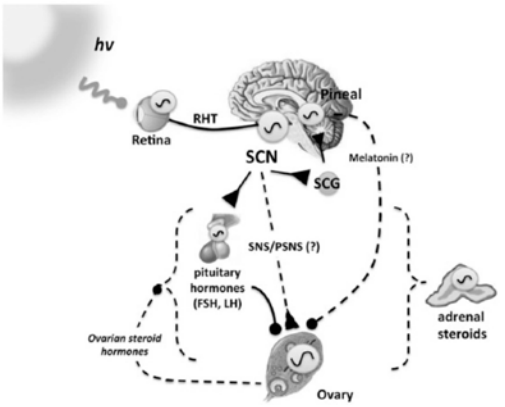
Central Circadian Control of Female Reproductive Function.
Miller BH, Takahashi JS. Front Endocrinol (Lausanne). 2014 Jan 22;4:195.



The rodent estrous cycle. In the mouse, ovulation occurs every 4–5 days. Metestrus and diestrus are characterized by low but slowly increasing levels of estradiol. On the late afternoon of proestrus, elevated estradiol levels induce a bolus of GnRH release from the hypothalamus, which induces the proestrus LH and FSH surge at approximately the start of the active (dark) period. Ovulation occurs 12–14 h later.

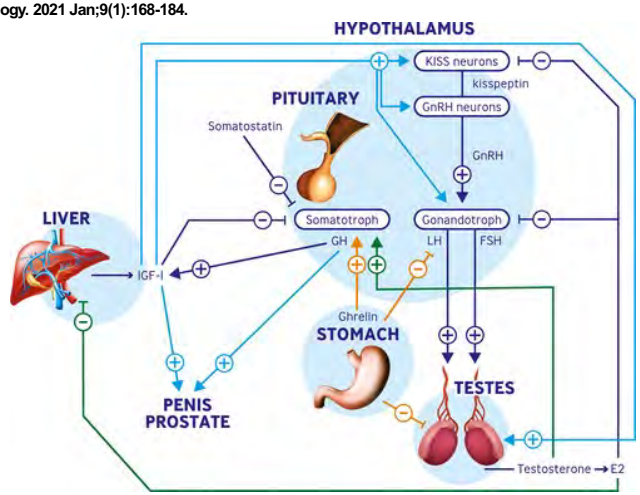


Model of the interaction between the daily timing signal and the ovarian signal on GnRH release. AVP is rhythmically transcribed in the SCN and forms the basis for the strong neural daily timing signal from the SCN. On the day of proestrus, estradiol produced by the developing follicles in the ovary upregulates expression of hypothalamic AVP and VIP receptors and primes kisspeptin neurons to become more sensitive to the SCN-derived signal. The end result is an increase in excitatory input to GnRH neurons, elevated GnRH release, and a subsequent surge in LH.

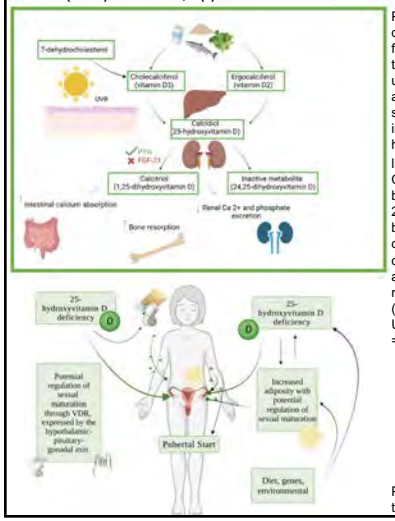


The circadian timing system in the hypothalamo-pituitary-ovarian (HPO) axis. A schematic diagram of the HPO axis indicating the integration of the circadian timing system in HPO axis function. The ovary shows phasic sensitivity to gonadotropins (LH and FSH that may depend on the timing of the ovarian clock and/or numerous timing cues of central and peripheral origin. Time of day or "photic" cues are passed to the central pacemaker in the SCN via the RHT. The SCN then conveys this information to the pineal via the SCG and the pituitary indirectly via the activity of releasing hormone neurons in the basal hypothalamus and forebrain. The SCN may also modulate the timing of the ovarian clock more directly via autonomic nervous cues (SNS, PSNS). Cells of the ovarian follicle also express melatonin receptors, and melatonin could indirectly modulate the timing of the ovarian clock. Adrenal glucocorticoids (e.g., corticosterone) may also act to synchronize the timing of the molecular clock in the pituitary and ovary. Ovarian steroid feedback affects the timing of clock gene expression in several tissues, including the uterus, pituitary, and ovary, and could further gate the response to gonadotropins. Nervous signals are indicated by lines ending in triangles, while lines ending in solid dots indicate hormonal pathways. hv indicates light, RHT, retinohypothalamic tract; SNS/PSNS, sympathetic nervous system, parasympathetic nervous system; FSH, follicle-stimulating hormone; LH, luteinizing hormone; SCN, suprachiasmatic nucleus; SCG, superior cervical ganglion.

Somatotropic-Testicular Axis: A crosstalk between GH/IGF-I and gonadal hormones during development, transition, and adult age.
Tenuta M, Carlomagno F, Cangiano B, et al.
Andrology. 2021 Jan;9(1):168-184.



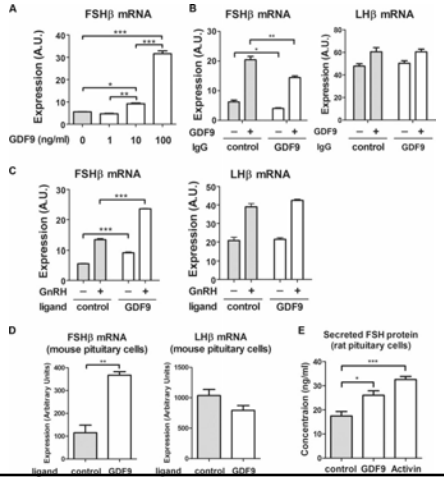
Association between Vitamin D Levels, Puberty Timing, and Age at Menarche.
Calcaterra V, Magenes VC, Tagi VM, Grazi R, Bianchi A, Cena H, Zuccotti G, Fabiano V.
Children (Basel). 2023 Jul 19;10(7):1243.



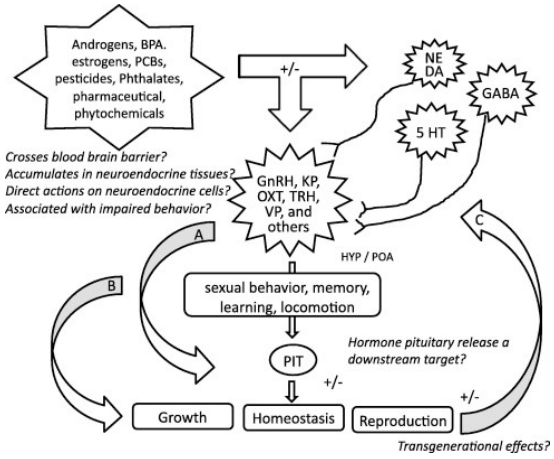
Pathways of vitamin synthesis and function. Cholecalciferol derives from animal products and supplements. It originates from the conversion of 7-dehydrocholesterol to vitamin D3 through isomerization and thermo-conversion mediated by ultraviolet B radiation in epidermal and dermal keratinocytes and fibroblasts. Ergocalciferol derives from plants and supplements. It originates from the conversion of ergosterol in plants mediated by irradiation. Calcidiol derives from 25-hydroxylation of cholecalciferol and ergocalciferol in the liver mediated by vitamin D-25-hydroxylase (CYP2R1). Calcidiol reaches the kidneys and is converted into bioactive calcitriol through hydroxylation mediated by 25(OH)D-1alfa-hydroxylase (CYP27B1), which is activated by PTH and inhibited by FGF-23. Calcitriol modulates calcium–phosphorus balance: in response to low dietary calcium intake, calcitriol induces maturation of osteoclasts and calcium–phosphorus absorption by bone and reduces renal calcium and phosphate excretion [11,12,13,14] (created with biorender.com, accessed on 10 July 2023). UVB = ultraviolet type B; PTH = parathyroid hormone; FGF = Fibroblast Growth Factors.

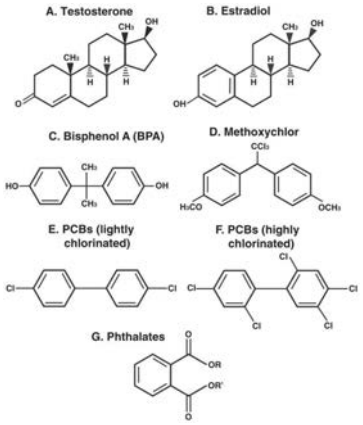
Potential mechanisms linking vitamin D and pubertal timing. VDR = vitamin D receptor.

Growth differentiation factor 9 (GDF9) forms an incoherent feed-forward loop modulating follicle-stimulating hormone β-subunit (FSHβ) gene expression.
Choi SG, Wang Q, Jia J, Pincas H, Turgeon JL, Sealfon SC.
J Biol Chem. 2014 Jun 6;289(23):16164-75.

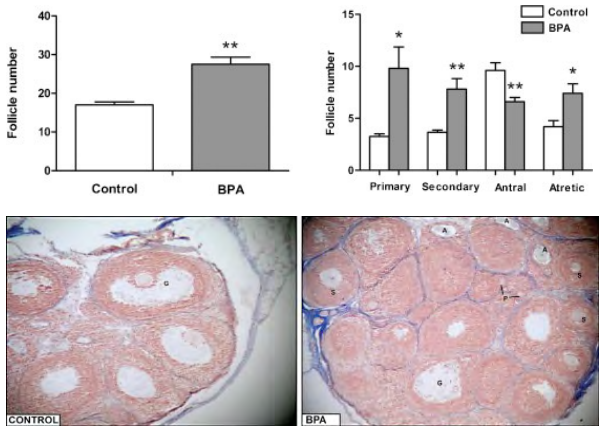


Current concepts in neuroendocrine disruption.
León-Olea M, et al. (2014) Gen Comp Endocrinol. (Epub ahead of print).

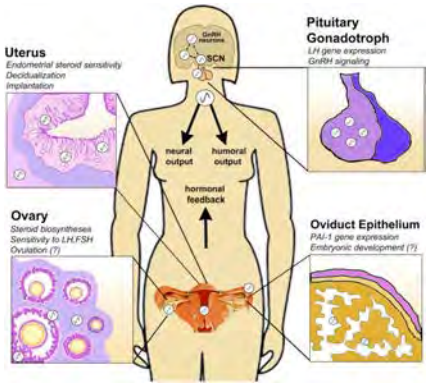




Exposure to a low dose of bisphenol A impairs pituitary-ovarian axis in prepubertal rats: effects on early folliculogenesis.
Gámez JM, Penalba R, Cardoso N, et al.
Environ Toxicol Pharmacol. 2015 Jan;39(1):9-15.

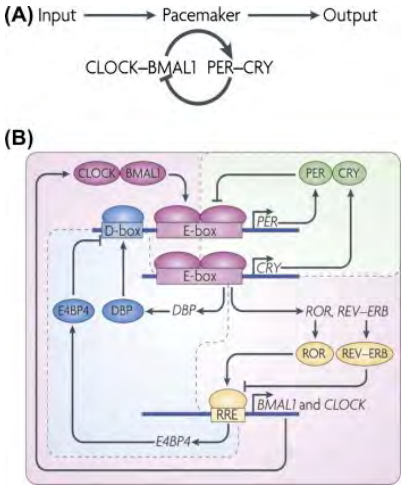


Clocks underneath: the role of peripheral clocks in the timing of female reproductive physiology.
Sellix MT. Front Endocrinol (Lausanne). 2013 Jul 23;4:91.

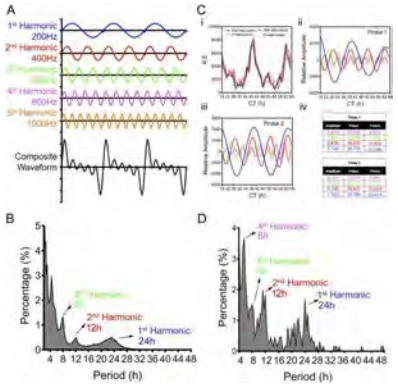


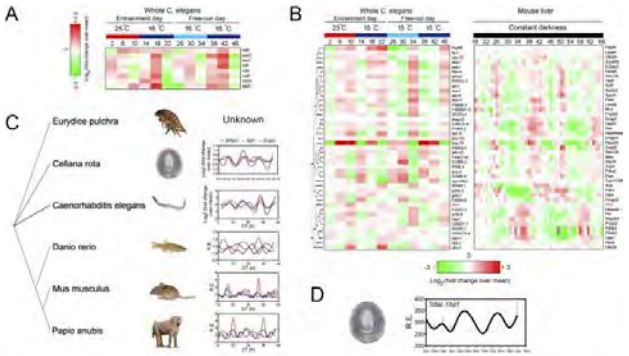
Circadian clock function in the peripheral tissues of the female HPG axis. The central circadian clock in the suprachiasmatic nucleus (SCN) drives rhythmic GnRH secretion and subsequent gonadotropin secretion from the pituitary. In addition to these neuroendocrine pacemakers, clocks are also present in the pituitary gonadotroph, uterine endometrium and myometrium, oviduct epithelial cells and ovarian theca, interstitial, and granulosa cells. Clock function has been implicated in GnRH signaling, gonadotropin sensitivity, ovulation, steroid hormone synthesis, embryonic maturation, implantation, and decidualization. Synchronization of central and peripheral oscillators is mediated by several putative humoral and neural cues, driven either directly or indirectly by the SCN. Moreover, feedback signals from the periphery, e.g., steroid hormones of ovarian origin, modulate the timing of the clock in both central and peripheral tissues of the HPG axis.

Sex differences in circadian timing systems: implications for disease.
Bailey M, Silver R. Front Neuroendocrinol. 2014 Jan;35(1):111-39.

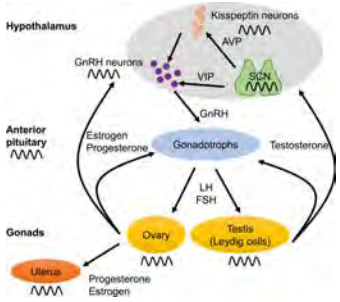


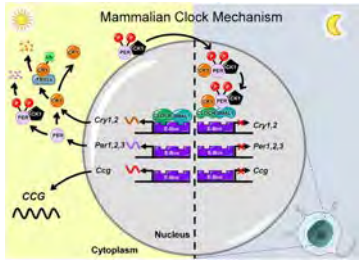
Unveiling "Musica Universalis" of the Cell: A Brief History of Biological 12-Hour Rhythms.
Zhu B, Dacso CC, O'Malley BW.
J Endocr Soc. 2018 Jun 6;2(7):727-752.



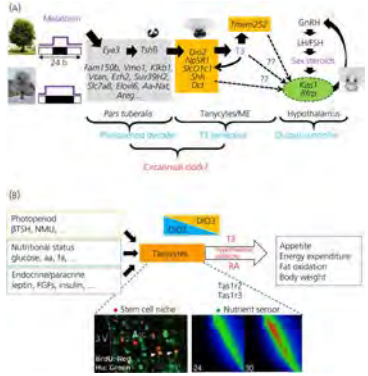


Role of core circadian clock genes in hormone release and target tissue sensitivity in the reproductive axis.
Sen A, Hoffmann HM.
Mol Cell Endocrinol. 2020 Feb 5;501:110655.

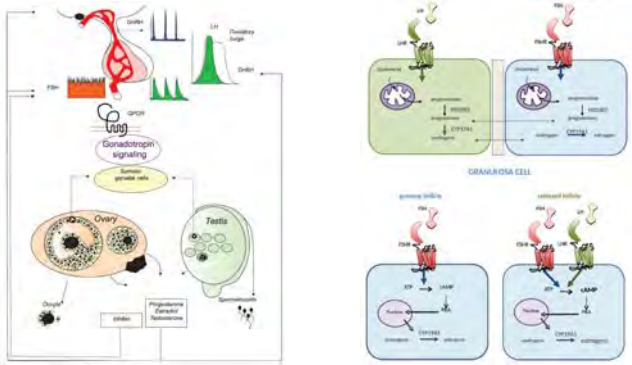




An integrative view of mammalian seasonal neuroendocrinology.
Dardente H, Wood S, Ebling F, Sáenz de Miera C.
J Neuroendocrinol. 2019 May;31(5):e12729.



Advances in computational modeling approaches of pituitary gonadotropin signaling.
Yvinec R, Crépieux P, Reiter E, Poupon A, Clément F.
Expert Opin Drug Discov. 2018 Sep;13(9):799-813.



"Systems Biology of Reproduction"

Spring 2024 (Even Years) – Course Syllabus
Biol 475/575 Undergraduate/Graduate (3 Credit)
SLN: (475) – 06763, (575) – 06764
Time - Tuesday and Thursday 10:35 am-11:50 am
Course Lectures in person and recorded on Canvas/Panopto and Discussion Sessions live in person and on WSU Zoom for all campuses (Hybrid Course)
Room – CUE 418
Course Director – Michael Skinner, Abelson Hall 507, 335-1524, skinner@wsu.edu
Co-Instructor – Eric Nilsson, Abelson Hall 507, 225-1835, nilsson@wsu.edu
Learning Objective -
Current literature based course on the Systems Biology of Reproduction. Learning Systems approaches to the biology of reproduction from a molecular to physiological level of understanding.
Schedule/Lecture Outline –

January	9 & 11	Week 1	Systems Biology Introduction
	16 & 18	Week 2	Molecular/ Cellular/ Reproduction Systems
	23 & 25	Week 3	Sex Determination Systems
Jan /Feb	30 & 1	Week 4	Male Reproductive Tract Development & Function
February	6 & 8	Week 5	Female Reproductive Tract Development & Function
	13 & 15	Week 6	Gonadal Developmental Systems Biology
	20 & 22	Week 7	Testis Systems Biology
	27 & 29	Week 8	Ovary Systems Biology
March	5 & 7	Week 9	Epigenetics and Transgenerational Gonadal Disease
	11 – 15	**Week 10**	**Spring Break**
	19 & 21	Week 11	Gametogenesis/ Stem Cells/ Cloning
	26 & 28	Week 12	Hypothalamus-Pituitary Development & Function
April	2 & 4	Week 13	Reproductive Endocrinology Systems
	9 & 11	Week 14	Fertilization & Implantation Systems
	16 & 18	Week 15	Fetal Development & Birth Systems
	23 & 25	Week 16	Assisted Reproduction/Contraception
Apr/May	30 & 2	Week 17	Exam or Grant Review