Spring 2018 – 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 27, 2018
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
- GnHR Actions / Signaling
- LH/FSH Pulsitive Secretion/Menstrual Cycle

Regulation of Development
- Cyclisity / Estrous Cycle / Circadian Systems

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Hypothalamus-Pituitary Development & Function

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

Hormones
- Growth Hormone / Receptors / GHRH
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Spring 2018 – 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 29, 2018
Week 12

Hypothalamus-Pituitary Development & Function

Primary Papers:

1. Belchetz et al. (1978) Science 202:631
2. Houlahan et al. (2015) Toxicology 328:93-101
3. Kuhnen et al. (2016) Cell Metabolism 24:502-509

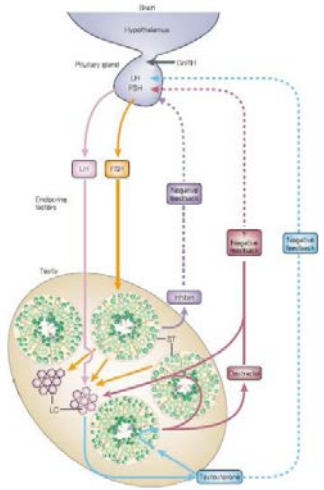
Discussion

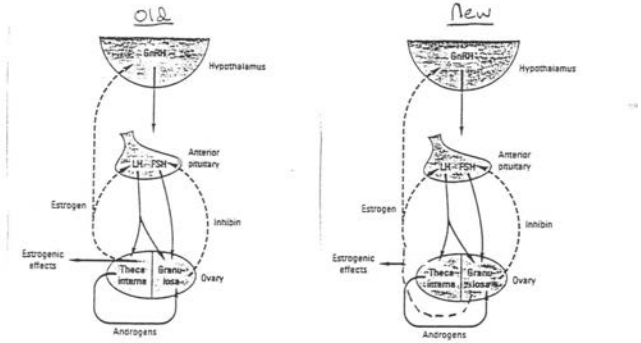
Student 4: Reference 1 above
- What unique endocrine parameter was identified in the hypothalamic regulation of pituitary function?
- What physiological advantage does this have?
- How does this information fit into the understanding of Brain-Pituitary-Gonadal axis?

Student 5: Reference 2 above
- What was the experimental design and objectives of the study?
- What cellular processes and pathways were identified to be effected?
- What insights into dioxin actions on the hypothalamus were obtained?

Student 6: Reference 3 above
- What was the experimental design and objective of study?
- What alteration in the POMC was identified and how?
- What mechanism is suggested for the etiology of obesity?

Hypogonadal – pituitary – testis axis





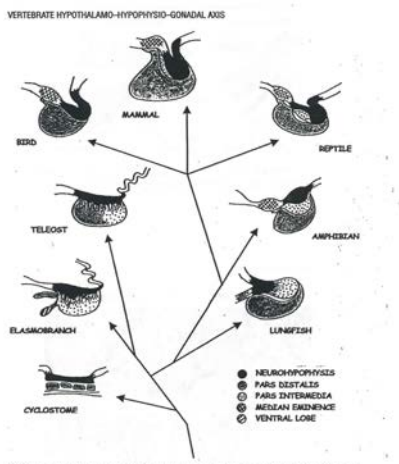


FIG. 1 Evolutionary scheme showing pituitary composition and relationship with the median eminence.

Hypothalamus and Pituitary Cell Biology

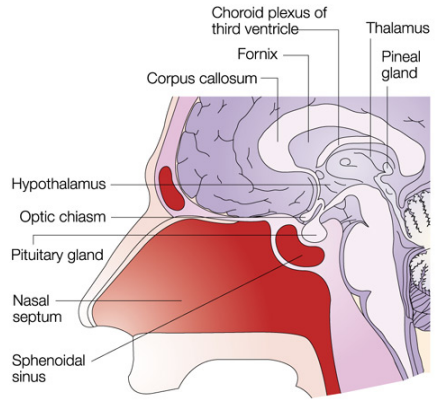


Figure 1 | **Anatomy of the pituitary gland.** Sagittal section through the midline shows the pituitary gland within the diaphragma sella (a fold that encases the pituitary), situated immediately posterior to the sphenoid sinus.

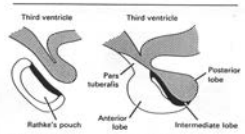


Figure 22–1. Diagrammatic outline of the formation of the pituitary and the various parts of the organ in the adult.

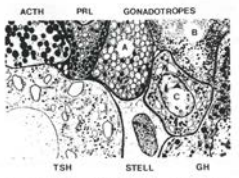


Figure 22–2. Ultrastructure of the anterior pituitary, showing the characteristics of 5 types of secretory cells. Note that in this illustration, 3 morphologically different subtypes of gonadotropes (A, B, and C) have been identified. STELL, folliculostellate cell. (Reproduced, with permission, from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

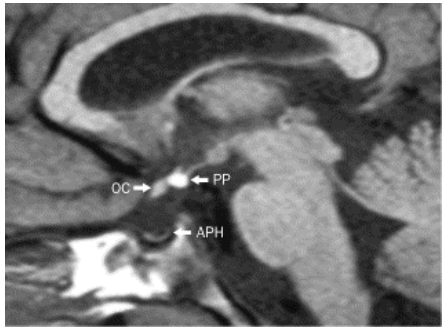


Figure 2. Sagittal MRI scan showing anterior pituitary hypoplasia. APH=anterior pituitary hypoplasia. PP=posterior pituitary, which is ectopic on this image. OC=optic chiasm., normal here. The infundibulum connecting the pituitary to the hypothalamus is not shown.

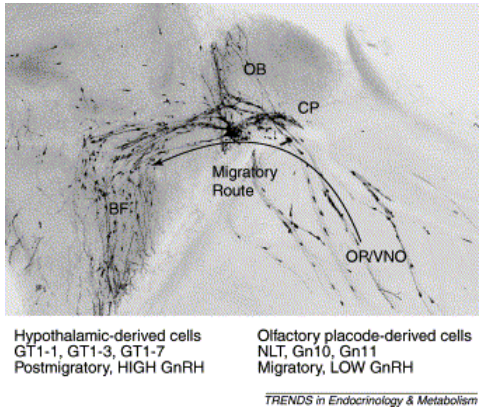


Figure 1. GnRH neuronal migration in the mouse and targeting of immortalized GnRH neuronal cell lines at specific windows across development. Immortalized NLT and Gn GnRH neuronal cells were derived from a tumor in the olfactory region to cribiform plate, whereas the GT GnRH neuronal cells were derived 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.

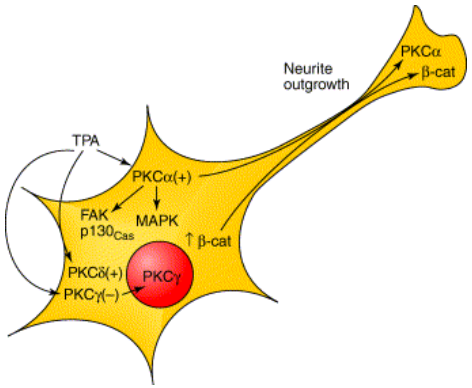
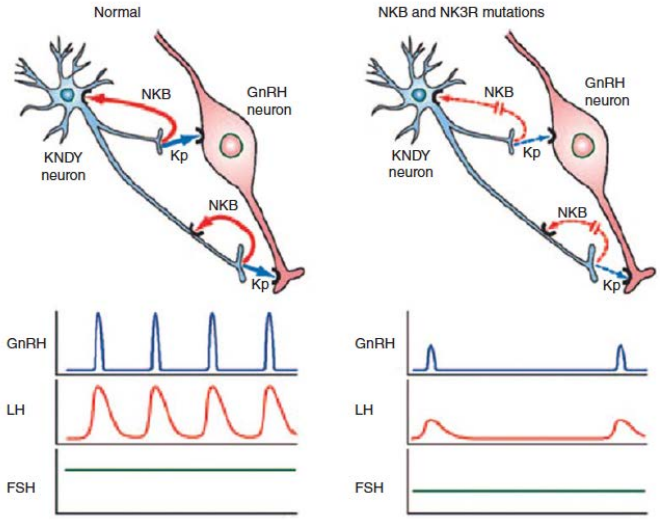


Figure 4. Phorbol ester signaling in GT1 GnRH neurons promotes neurite outgrowth. 12-O-tetradecanoylphorbol-13 acetate (TPA) signals to PKC, and in GT GnRH neurons. PKC promotes neurite outgrowth, translocates to the growth cone and activates MAPK. It also localizes to focal adhesions to stimulate FAK and $p130_{cas}$ 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.

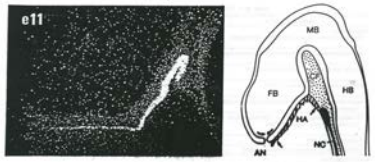


★ hypophyseal - portal system

(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

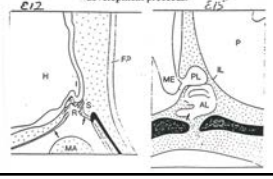
hypophyseal placode
embedded in roof of mouth

Active proliferation of A.L.

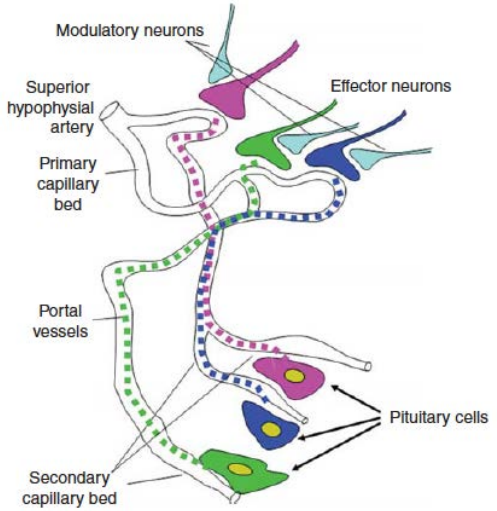
E12 3rd week in humans

Note: Proximity of A.L. and infundibulum will disappear as development proceeds.

E17 Blood vessels from that surround Pit axon terminals come in from the hypothalamus to median eminence (ME)



← RAT PIT Development



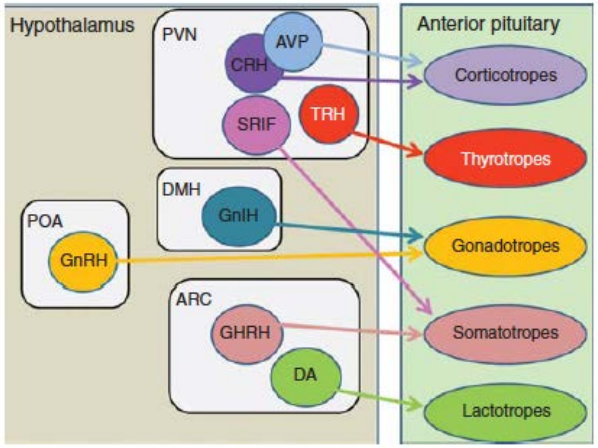


Table 22-1. Pituitary hormones in mammals.[1]

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

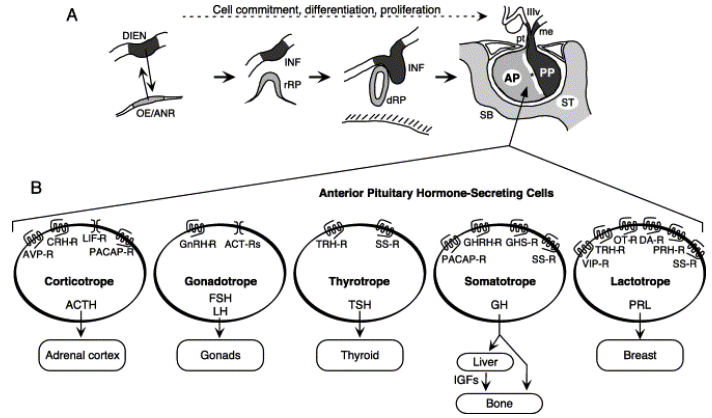


Fig. 1. Development of the mammalian anterior pituitary gland. (A) Inductive signaling between and within the ventral diencephalon (DIEN) of the brain and oral ectoderm/anterior neural ridge (OE/ANR) promotes the formation of a rudimentary Rathke's pouch (rRP), and the infundibulum (INF), the respective 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.

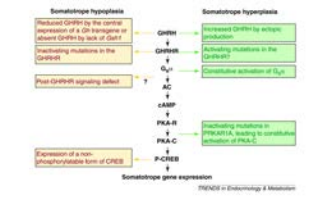


Fig. 1. Spontaneous and experimental alterations in the GHRH signaling pathway that result in either somatotrope hypoplasia or hyperplasia. Abbreviations: AC, adenylyl cyclase; cAMP, cyclic adenosine monophosphate; GHRH, growth hormone-releasing hormone; GHRH-R, GHRH receptor; $G_{\alpha s}$ a subunit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

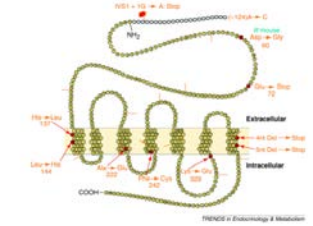


Fig. 2. Sequence of the human GHRHR, demonstrating the amino acid changes resulting from the reported loss-of-function mutations associated with GH deficiency and somatotrope hypoplasia. The exon splice sites are shown by straight lines. The mouse *Ghrhr* mutation (*lit*) is shown in the position corresponding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

Hypothalamus and Pituitary Development

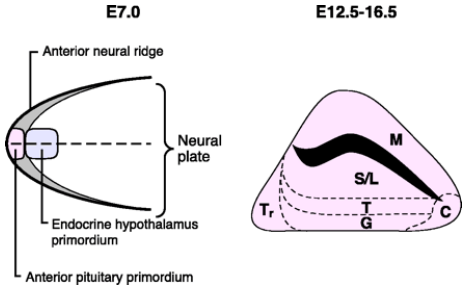
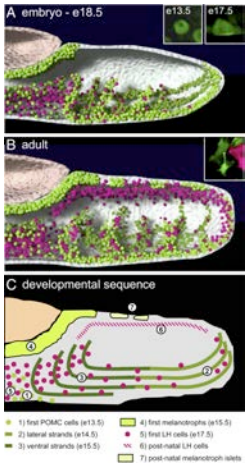


Fig. 1. Development of the hypothalamic-pituitary axis. The midline embryological primordia of the pituitary in the anterior neural ridge and of the endocrine hypothalamus in the neural plate are indicated. Cell types later arise in a temporally and spatially specific fashion: E12.5 corticotrope (C), 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.



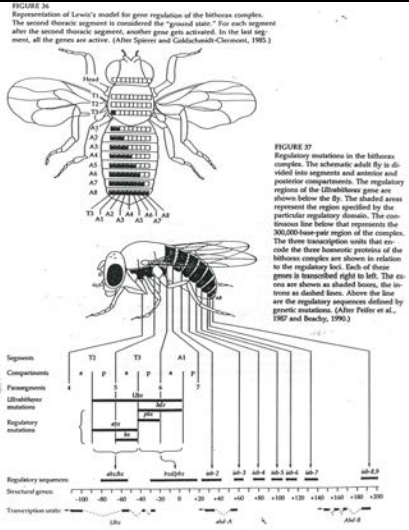


FIGURE 36
Representation of Lewis's model for gene regulation of the bithorax complex. The second thoracic segment is considered the "ground state." For each segment after the second thoracic segment, another gene gets activated. In the last segment, all the genes are active. (After Spierer and Goldschmidt-Clermont, 1985.)

FIGURE 37
Regulatory mutations in the bithorax complex. The schematic adult fly is divided into segments and anterior and posterior compartments. The regulatory regions of the *Ultrabithorax* gene are shown below the fly. The shaded areas represent the region specified by the particular regulatory domain. The continuous line below that represents the 300,000-base-pair region of the complex. The three transcription units that encode the three homeotic proteins of the bithorax complex are shown in relation to the regulatory loci. Each of these genes is transcribed right to left. The exons are shown as shaded boxes, the introns as dashed lines. Above the line are the regulatory sequences defined by genetic mutations. (After Peifer et al., 1987 and Beachy, 1990.)

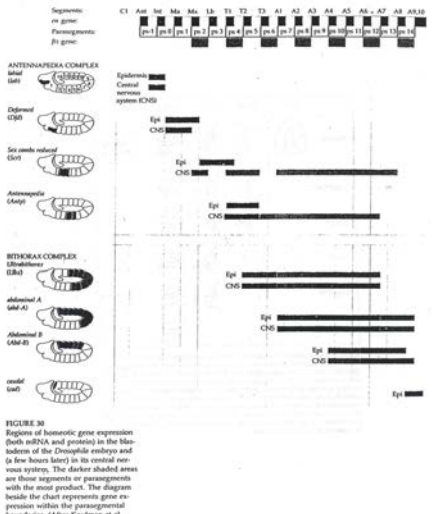


FIGURE 38
Regions of homeotic gene expression (both mRNA and protein) in the blastoderm of the *Drosophila* embryo and (a few hours later) in its central nervous system. The darker shaded areas are those segments or parasegments with the most product. The diagram beside the chart represents gene expression within the parasegmental boundaries. (After Kaufman et al., 1990.)

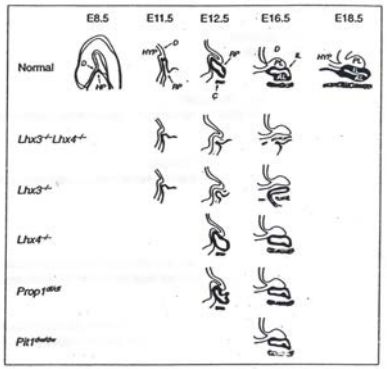


FIGURE 1. Normal embryonic morphology is altered in pituitary mutants. The abnormal morphology observed in mouse mutants is shown from the time point where it begins to differ from normal development until the time when development is arrested. In the most severe case (*Lhx3*$^{-/-}$*Lhx4*$^{-/-}$), 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[24]. 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.

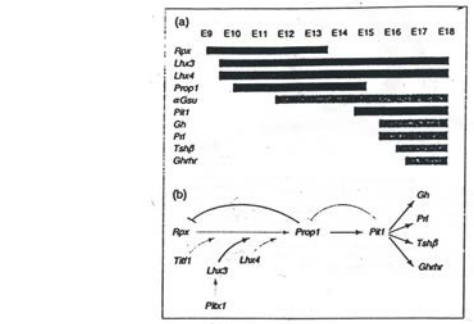
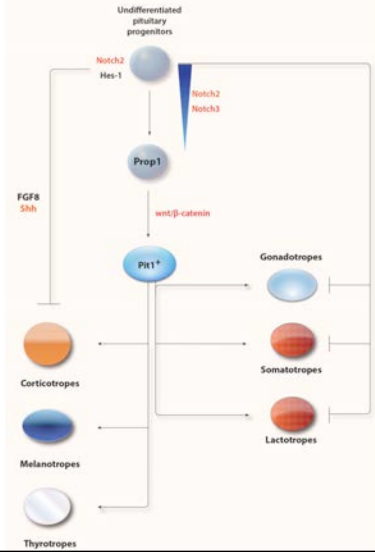


FIGURE 2. A cascade of transcription factors regulates anterior pituitary development. (a) The approximate timing of mRNA expression in the mouse is shown for transcription factors (black) and other marker genes (gray). (b) A genetic hierarchy is suggested by the effects of each gene on cell proliferation 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.



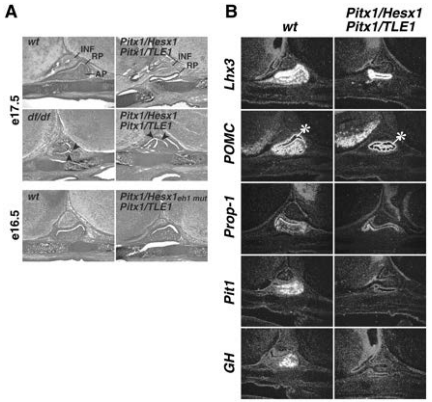
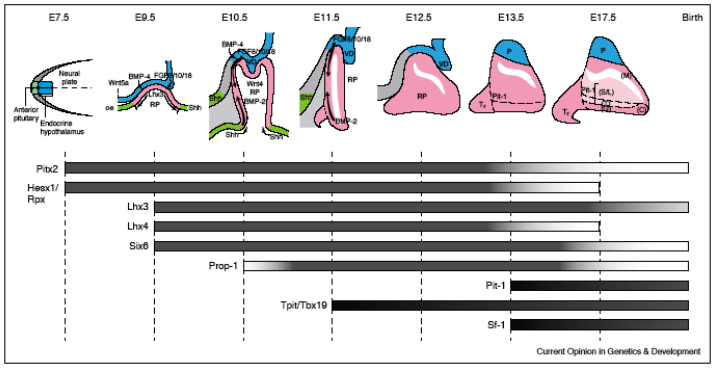


FIG. 5. Analysis of *Pitx1/Hesx1:Pitx1/TLE1* double-transgenic founder embryos. (A) Loss of anterior pituitary and morphological similarity to pituitary defects in Ames *df/df* mice, except when the *Pitx1/Hesx1* transgene encodes a mutated eh1 domain, which cannot interact with TLE1. H&E staining. (B) *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_x) 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).

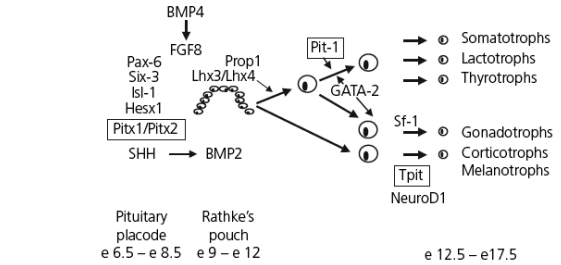


Fig. 1. Anterior pituitary gland development: transcription factors known to be involved in the development of the anterior pituitary gland. The morphogene FGF8 is necessary for the determination of dorsal cells in the anterior pituitary. BMP4 induces the exclusion of SHH expression in the pituitary primordium. Pax6, Six3, Isl-1 and Hesx1 are transcription factors expressed in the primordium. BMP2 contributes importantly to the expression of transcription factors such as GATA-2. Pit-1, SF-1 and Tpit are expressed just before the terminal differentiation of the endocrine cells. Pituitary development involves the following three steps: (i) induction of the pituitary placode; (ii) formation of Rathke's pouch, the primordium of the anterior pituitary, which undergoes cell proliferation and determination; and (iii) terminal differentiation of the five hormone-secreting lineages.

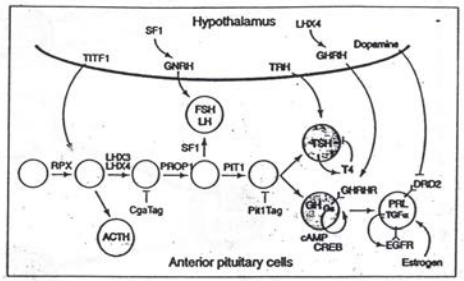


FIGURE 3. Proposed model for pituitary cell lineage and regulation of proliferation by secreted factors. The five endocrine cell types (gray) in the anterior pituitary are labeled with the hormone product that they secrete. Steps in precursor-cell differentiation that might be regulated by transcription 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.

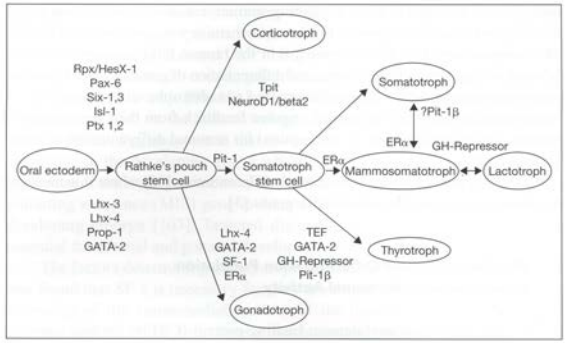


Table 1

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.

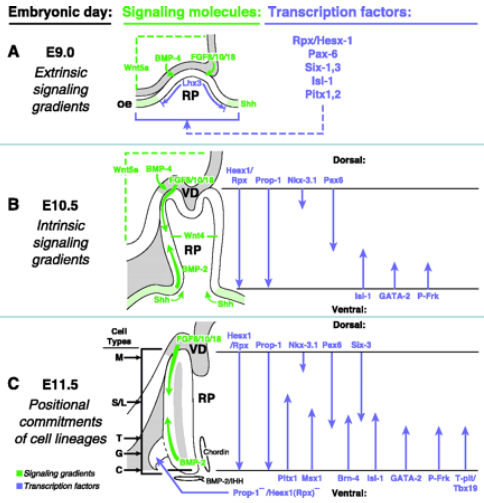
Abbreviations: HD, homeodomain; HMG, high mobility group; HPE holoprosencephaly, NR nuclear receptor.

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 Pitx1-*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	Pitx1-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			
Titf1/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 *Nhlh1* and *Nhlh2* 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.



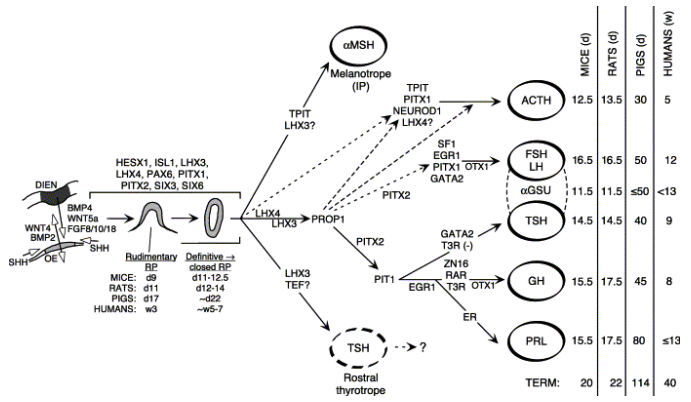


Fig. 2. Transcriptional regulation of anterior pituitary gland development. Inductive interactions involving the ventral diencephalon (DIEN) and oral ectoderm (OE) prime the expression of transcription factors that guide the development of Rathke's pouch (RP) into the specialized hormone-secreting cell 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.

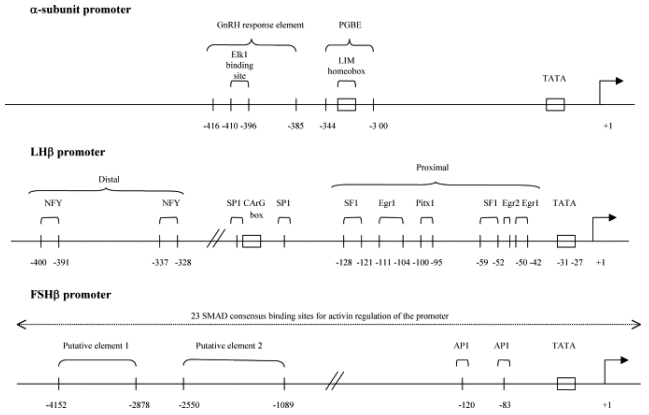


Fig. 2. Schematic of gonadotropin subunit promoters with major sites implicated in their regulation indicated. The consensus -subunit promoter map shown is based predominantly on the mouse gene sequence. The consensus LH map is based on the bovine and rat gene sequences and the FSH promoter map is based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

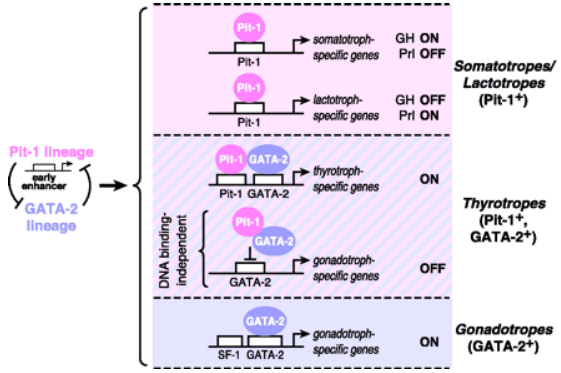


Fig. 4. A model of a proposed role of a BMP2-induced gradient of GATA-2 expression, acting with Pit-1, in determination of gonadotrope and thyrotrope lineages. In thyrotropes, Pit-1 exerts a DNA binding-independent transrepression to inhibit GATA-2-dependent activation of gonadotrope cell type-specific 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.

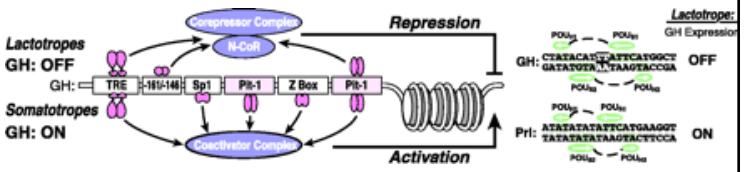
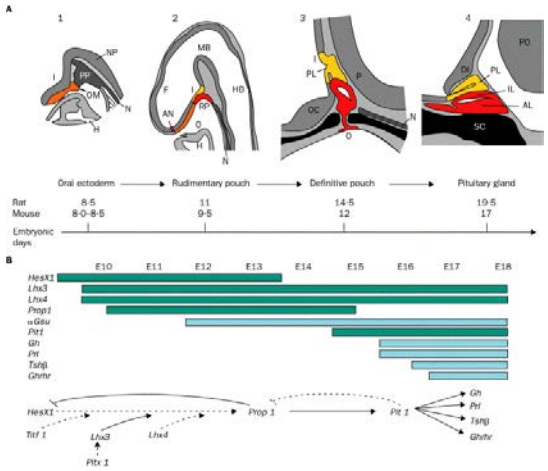


Fig. 5. Model of "repressosome"-based recruitment of a corepressor complex in cell type-specific long-term active repression of growth hormone gene expression in lactotropes. The altered spacing of the Pit-1 POUS and POUH on growth hormone and prolactin sites, in concert with additional DNA binding factors,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



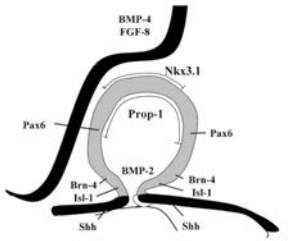


Figure 1. Pituitary development in the mouse (at e11). Dorsal signals (including BMP-4, FGF-8, Prop-1, Nkx3.1, and Pax6) and ventral signals (including BMP-2, Isl-1, and Brn-4) form gradients that appear to determine overlapping patterns of specific transcription factors. (Modified from C. Kioussi et al. Mech Dev 81:23–35, 1999 [102].) Pax6 has a role in the sharp boundary of attenuation of the ventral signals that dictate thyrotroph and gonadotroph cell lineages. An additional poulation of thyrotrophs is found in the rostal tip and probably derives from Isl-1-expressing cells.

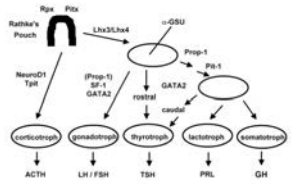


Figure 2. Pituitary specific transcription factors involved in anterior pituitary development. The homeodomain factors play a role in the determination of specific pituitary cell lineages. Rpx is the earliest known specific marker for the pituitary primordium. Ptx1 and 2 are both present in the fetal pituitary and in most cells of the adult pituitary, albeit at different levels. Lhx3 and Lhx4 are expressed in gonadotrophs, thyrotrophs, somatotrophs, and lactotrophs. Prop-1 determines Pit-1 cell lineages and may play a role in directing some of the precursors of the Pit-1 cell lineage into the gonadotroph lineage, before terminal differentiation events. Pit-1 has been shown to be essential for the development of somatotrophs, lactotrophs, and thyrotrophs. There is a Pit-1-independent population of thyrotrophs in the rostral tip of the developing anterior pituitary gland that phenotypically disappears by the day of birth.

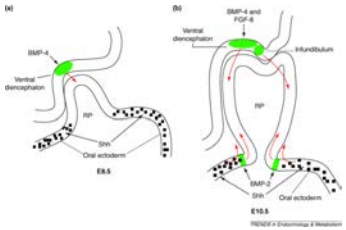


Fig. 1. Areas of expression (green or black) and action radius (indicated by red arrows) of bone morphogenetic protein 4 (BMP-4), BMP-2, fibroblast growth factor 8 (FGF-8) and sonic hedgehog (Shh) in Rathke's pouch (RP) and surrounding areas on embryonic day 8.5 (E8.5) (a) and E10.5 (b) in the mouse.

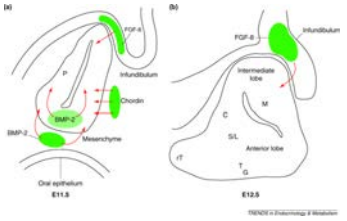


Fig. 2. Areas of expression (green) and action radius (indicated by red arrows) of bone morphogenetic protein 2 (BMP-2), fibroblast growth factor 8 (FGF-8) and chordin in embryonic pituitary (P) and surrounding areas on embryonic day 11.5 (E11.5) and E12.5 in the mouse. Areas in which corticotropes (C),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

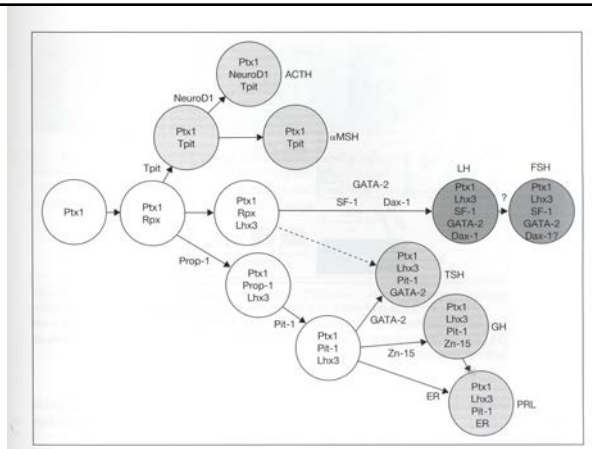
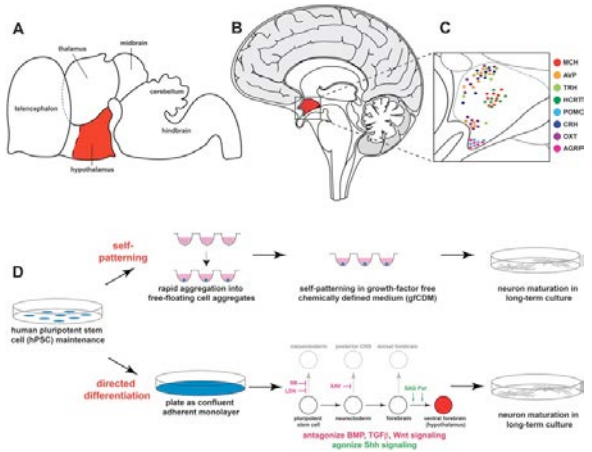


Fig. 3. Pituitary cell lineage. Several transcription factors have been reported to be active in all or a subset of cell lineages, in many cases during a specific period of development. The anterior pituitary cells are well known to be classified into three cells lineages, i.e. GH-PRL-TSH cells (Pit-1-dependent), 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.



Hypothalamus and Pituitary Hormones

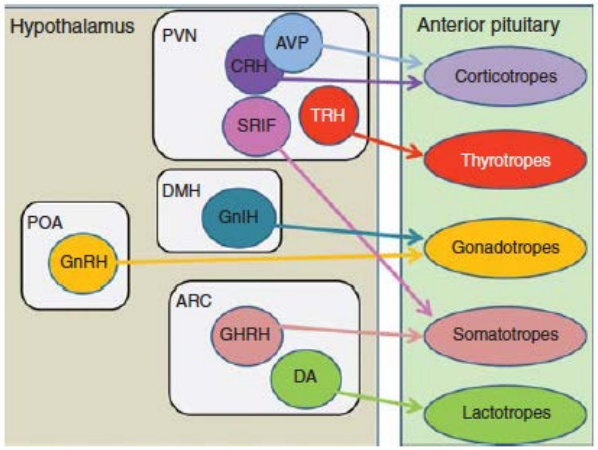


TABLE 1. Anterior pituitary cell types and hormone regulation

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

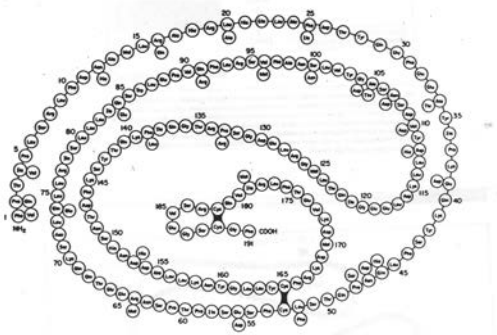
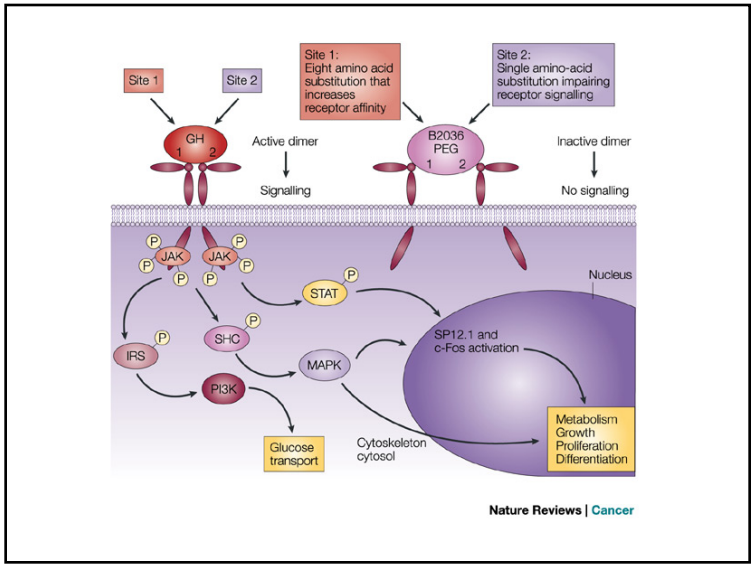


Figure 22–4. Structure of the principal human growth hormone (continuous chain). The black bars indicate disulfide bridges. The 29 residues alongside the chain identify residues that differ in human chorionic somatomammotropin (hCS; see Chapter 23). All the other residues in hCS are the same, and hCS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


Site 1
Site 2
Site 1:
Eight amino acid substitution that increases receptor affinity
Site 2:
Single amino-acid substitution impairing receptor signalling
GH
1 2
Active dimer
Signalling
B2036
PEG
1 2
Inactive dimer
No signalling
JAK
JAK
STAT
Nucleus
IRS
SHC
MAPK
PI3K
SP12.1 and
c-Fos activation
Glucose transport
Cytoskeleton
cytosol
Metabolism
Growth
Proliferation
Differentiation
Nature Reviews | Cancer

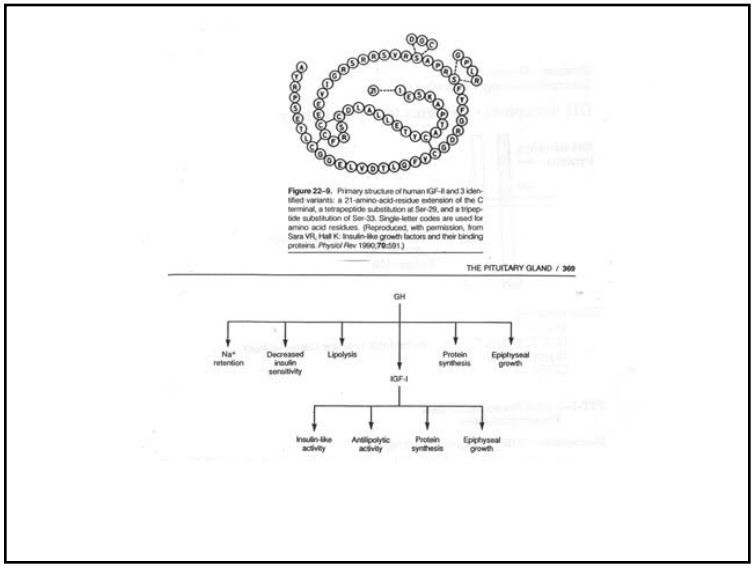


Figure 22–9. Primary structure of human IGF-II and 3 identified variants: a 21-amino-acid-residue extension of the C terminal, a tetrapeptide substitution at Ser-29, and a tripeptide substitution of Ser-33. Single-letter codes are used for amino acid residues. (Reproduced, with permission, from Sara VR, Hall K: Insulin-like growth factors and their binding proteins. Physiol Rev 1990;70:591.)
THE PITUITARY GLAND / 369
GH
Na+ retention
Decreased insulin sensitivity
Lipolysis
Protein synthesis
Epiphyseal growth
IGF-I
Insulin-like activity
Antilipolytic activity
Protein synthesis
Epiphyseal growth

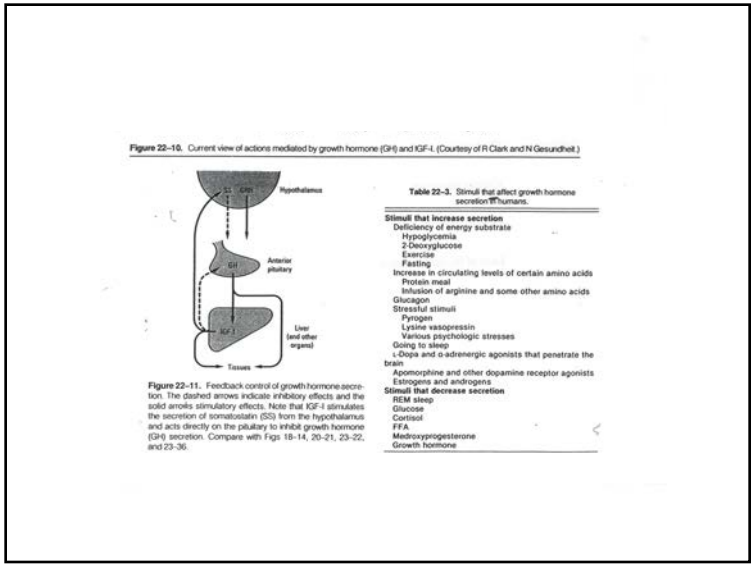
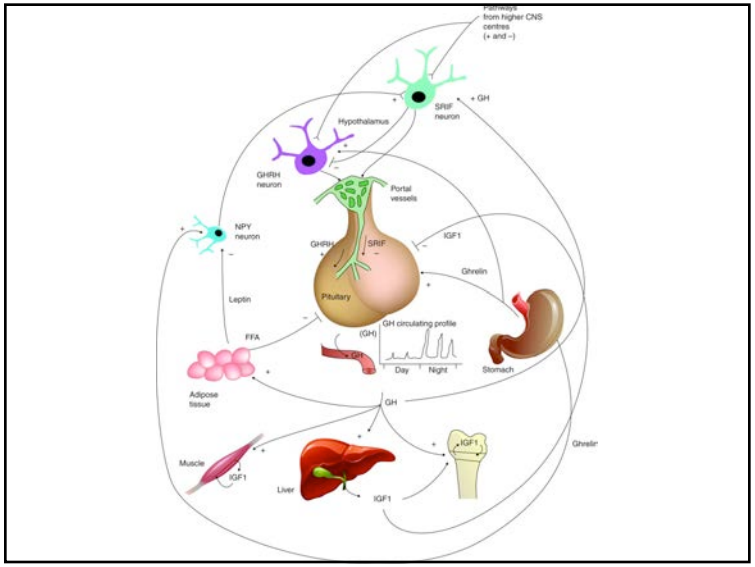
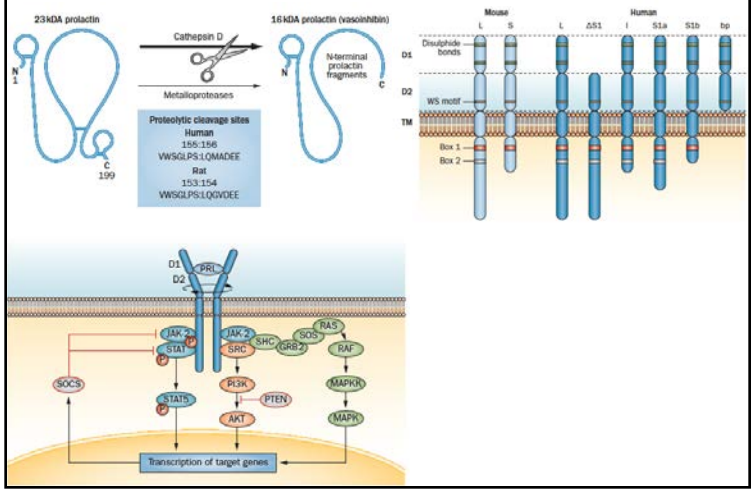
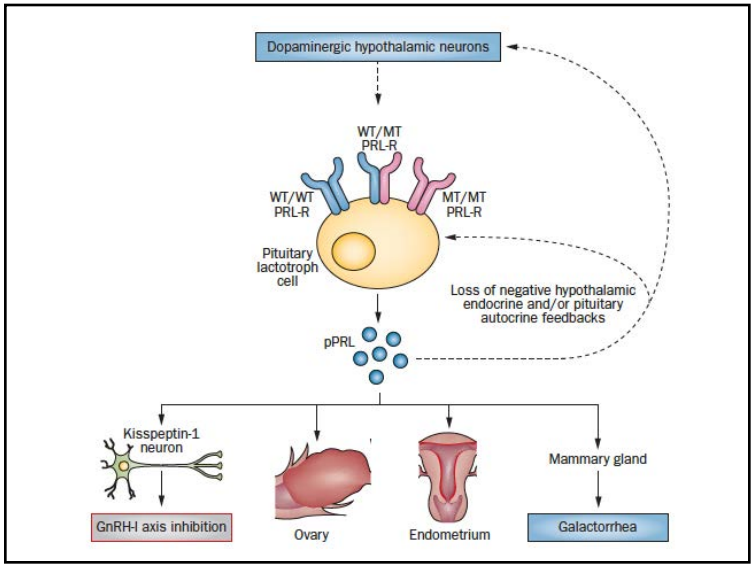


Figure 22–10. Current view of actions mediated by growth hormone (GH) and IGF-I. (Courtesy of R Clark and N Gesundheit.)
Hypothalamus
GH
Anterior pituitary
IGF-1
Liver (and other organs)
Tissues
Figure 22–11. Feedback control of growth hormone secretion. The dashed arrows indicate inhibitory effects 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


Hypothalamus
SRIF neuron
+ GH
GHRH neuron
Portal vessels
NPY neuron
GHRH
SRIF
IGF1
Ghrelin
Leptin
Pituitary
GH circulating profile
(GH)
Day
Night
Stomach
FFA
Adipose tissue
GH
Muscle
IGF1
Liver
IGF1
IGF1
Ghrelin

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





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.

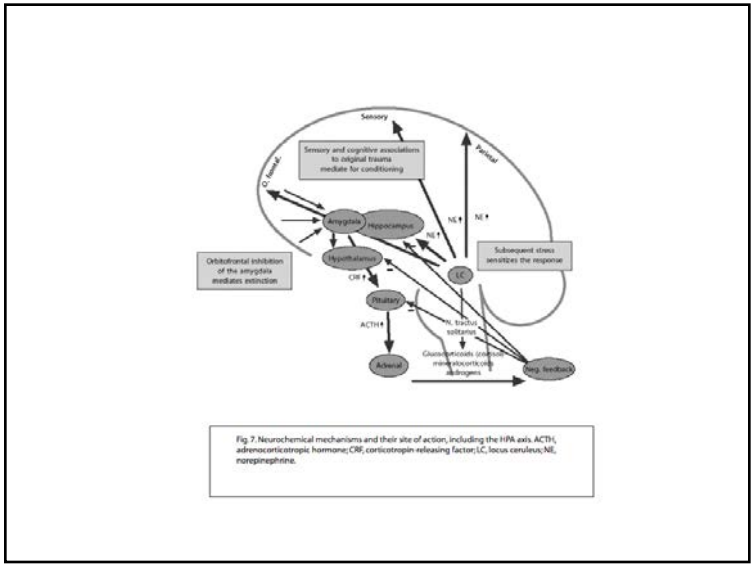


Fig. 7. Neurochemical mechanisms and their site of action, including the HPA axis. ACTH, adrenocorticotropic hormone; CRF, corticotropin-releasing factor; LC, locus ceruleus; NE, norepinephrine.

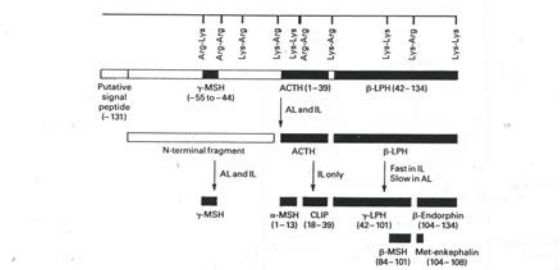
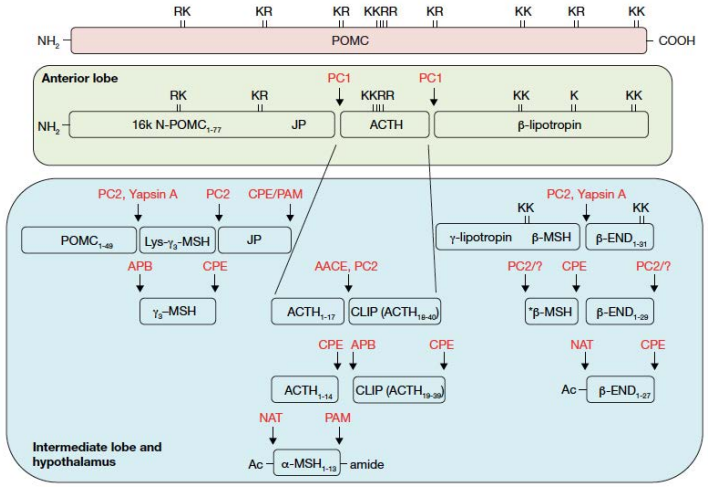
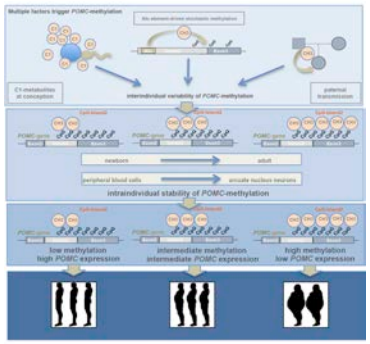


Figure 22–3. Schematic representation of the prepro-opiomelanocortin molecule formed in pituitary cells, neurons, and other tissues. The numbers in parentheses identify the amino acid sequences in each of the polypeptide fragments. For convenience, the amino acid sequences are numbered from the N terminal 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 terminal 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.

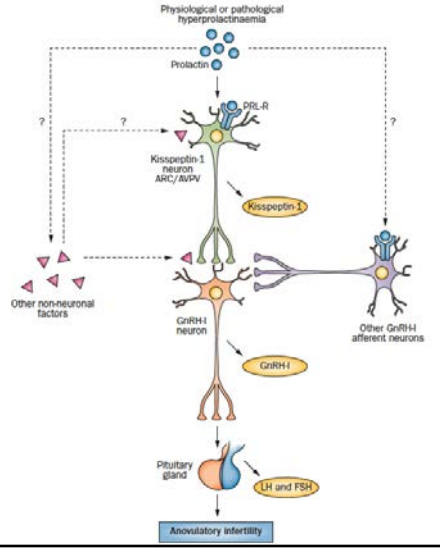


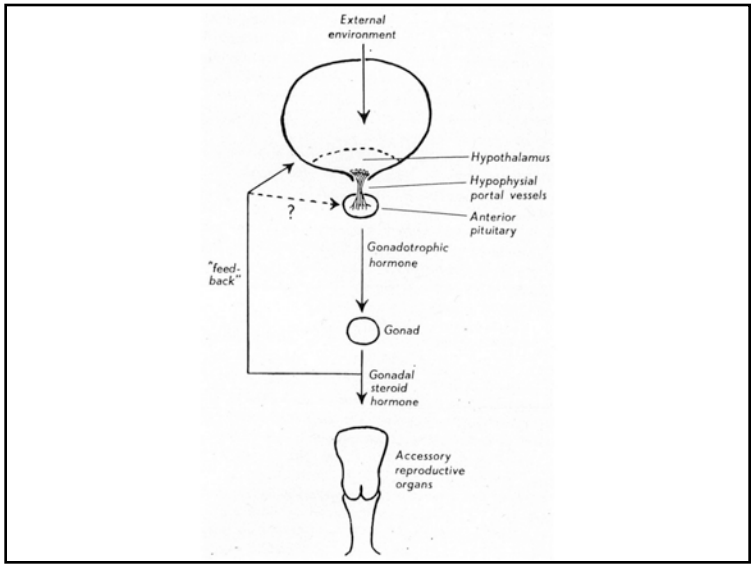
In Brief

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.

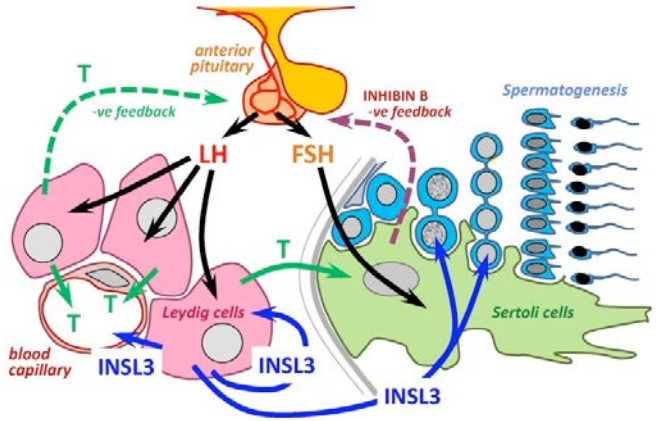
Highlights

- 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

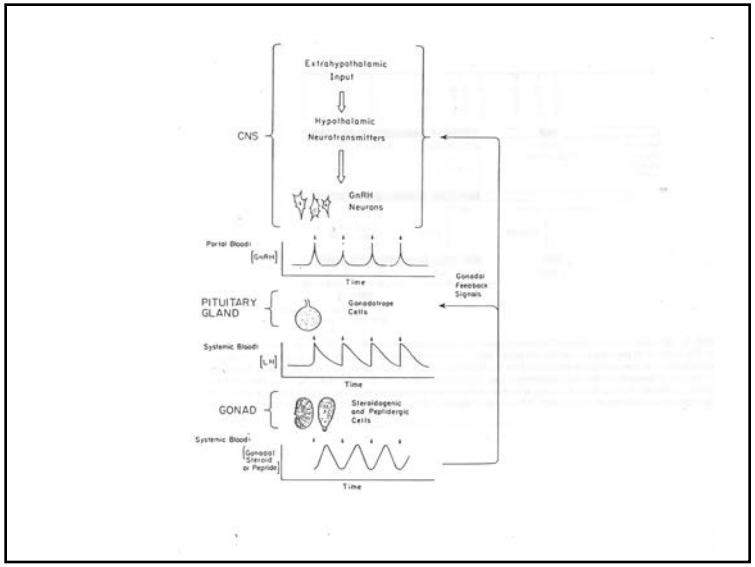




Insulin-Like Factor 3 and the HPG Axis in the Male.
Ivell R, Heng K, Anand-Ivell R. Front Endocrinol (Lausanne). 2014 Jan 27;5:6. eCollection 2014.



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.



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	—	—

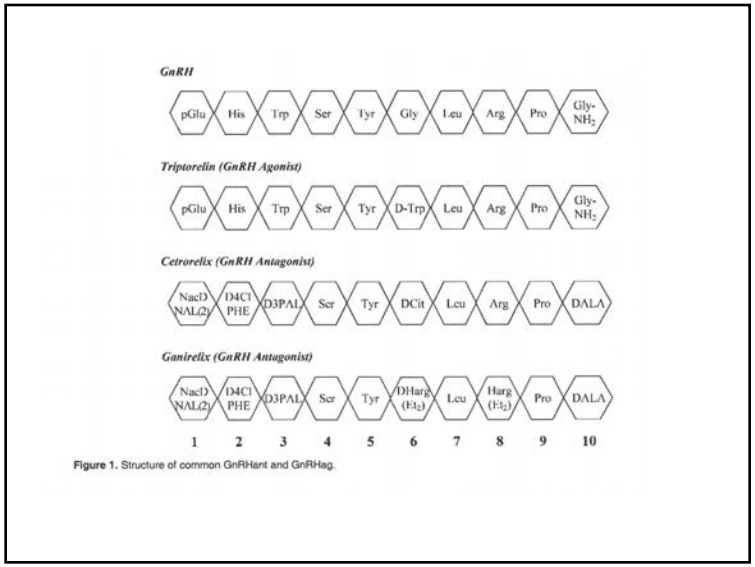


Figure 1. Structure of common GnRHant and GnRHag.

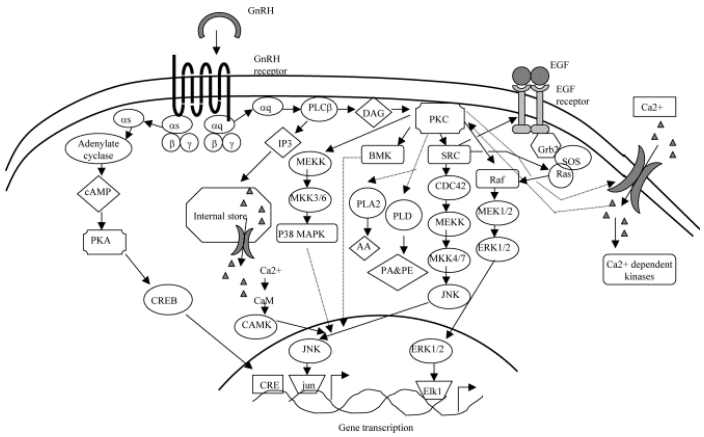
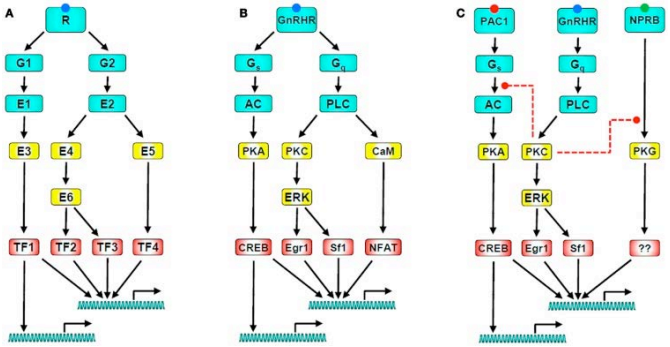


Fig. 1. Diagram of GnRH receptor modulated signaling network.

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.



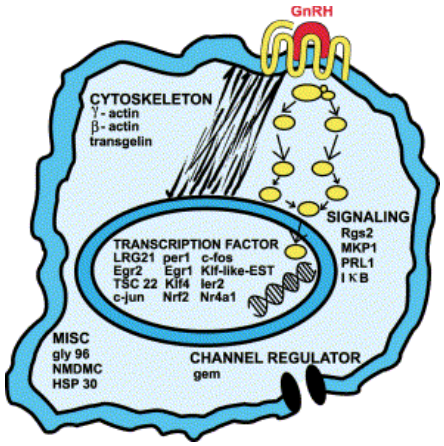


Fig. 3. Schematic of transcripts regulated by GnRH in LT2 cells. Reprinted from [196]. With permission of The American Society for Biochemistry and Molecular Biology.

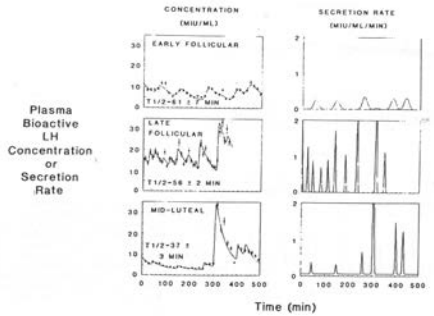


FIG. 5. Episodic secretion of biologically active LH as revealed by deconvolution analysis of pulsatile plasma bioactive LH profiles in normal women studied at three stages of the menstrual cycle. The stage of the menstrual cycle is noted in each subpanel. Plasma bioactive LH concentrations were measured 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 (U/L/min). Note that punctuated bursts of LH secretion without tonic release account for the pulsatile LH profiles. (Adapted from ref. 54, with permission.)

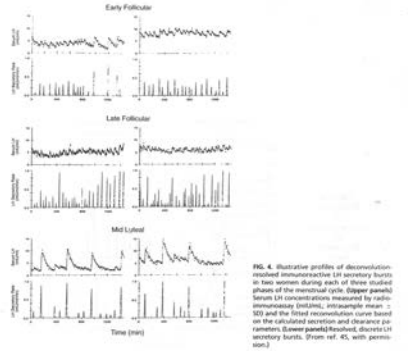


FIG. 4. Illustrative profiles of deconvolution-resolved immunoreactive LH secretory bursts in two women during each of three studied phases of the menstrual cycle. **(Upper panels)** Serum LH concentrations measured by radioimmunoassay (mIU/mL; intra-sample mean ± SD) and the fitted reconvolution curve 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 ± 1.4[a]	6.5 ± 1.0[a]	131 ± 13[a]	49 ± 6[a]
Late follicular	26.9 ± 1.6[b]	3.5 ± 0.9[b]	128 ± 12[a]	56 ± 8[a]
Midluteal	10.1 ± 1.0[c]	11.0 ± 1.3[c]	103 ± 7[a]	52 ± 4[a]

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.)

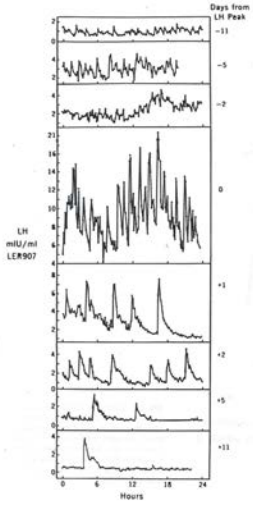


FIG. 4. Frequency and amplitude of LH pulses on selected days of the normal human menstrual cycle. The days of the cycle are indicated relative to the day of the LH surge (day 0). Significant LH pulses are indicated by a dot. Luteal phase progesterone levels are 1, 5, 6, and 12 ng/mL on days +1, +2, +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.)

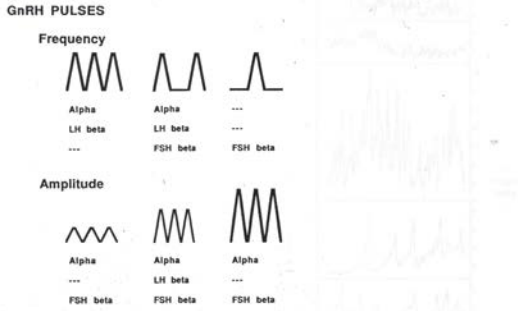
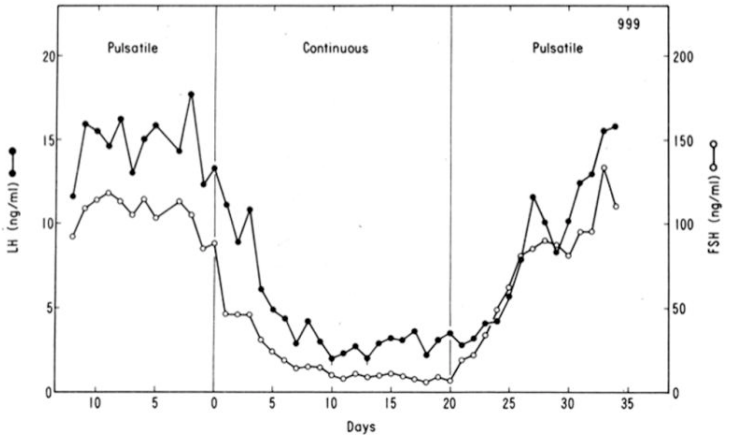
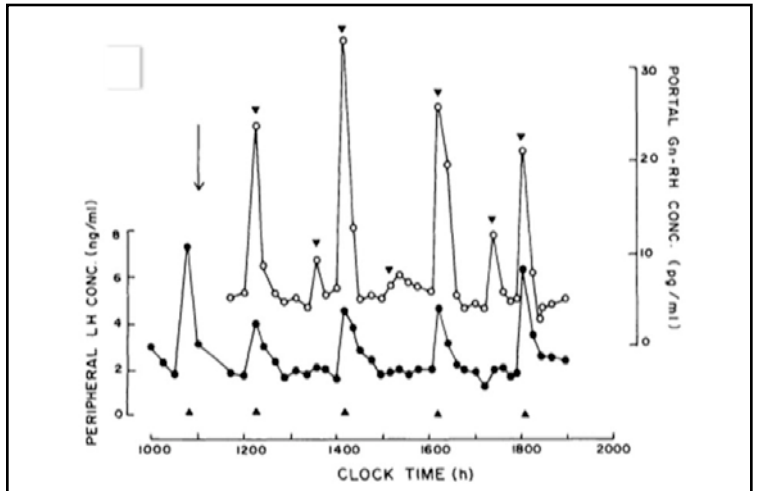


FIG. 12. Summary of the effects of the pattern of GnRH stimulation and testosterone in regulating gonadotropin subunit mRNA expression in male rats. The subunit mRNA shown is expressed in response to the GnRH pulse stimulus shown. (From ref. 97, with permission.)



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).

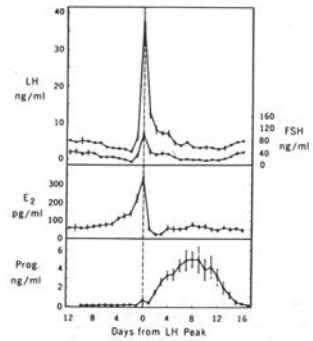


FIG. 1. Concentrations of LH (n = 9), FSH (n = 7), estradiol (E_2, n = 11), and progesterone (Prog, n = 7) in plasma samples taken daily throughout the menstrual cycle of rhesus monkeys *(Macaca mulatta)*. The data are normalized to the day of the LH peak (day 0). (From ref. 7.)

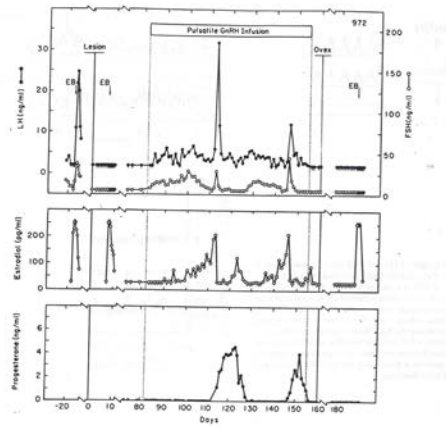


FIG. 12. The establishment of two ovulatory menstrual cycles in response to an unvarying pulsatile GnRH replacement regimen in a rhesus monkey subjected to a radiofrequency lesion in the MBH at time 0. Note that the lesion abolished the positive feedback action of administered estradiol benzoate *(EB)*. 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.)

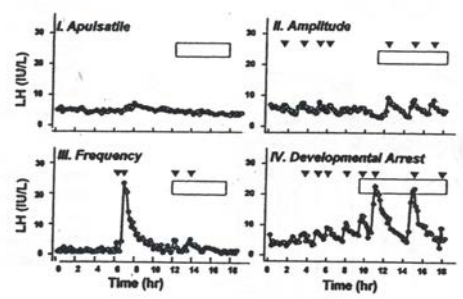
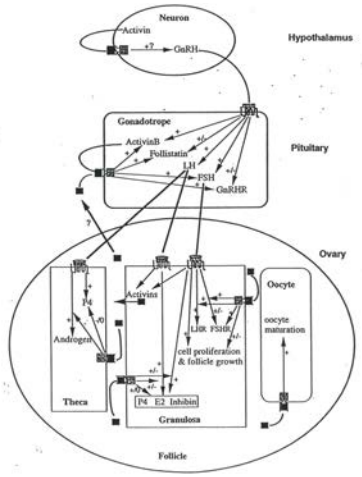


Fig. 4. Spectrum of GnRH abnormalities in 4 women with hypothalamic amenorrhea. ∇ = Detected LH pulsations. Note the predominance of LH pulsations during sleeping hours (open bars) [reproduced from 22].



Regulation Hypothalamus and Pituitary Development

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).

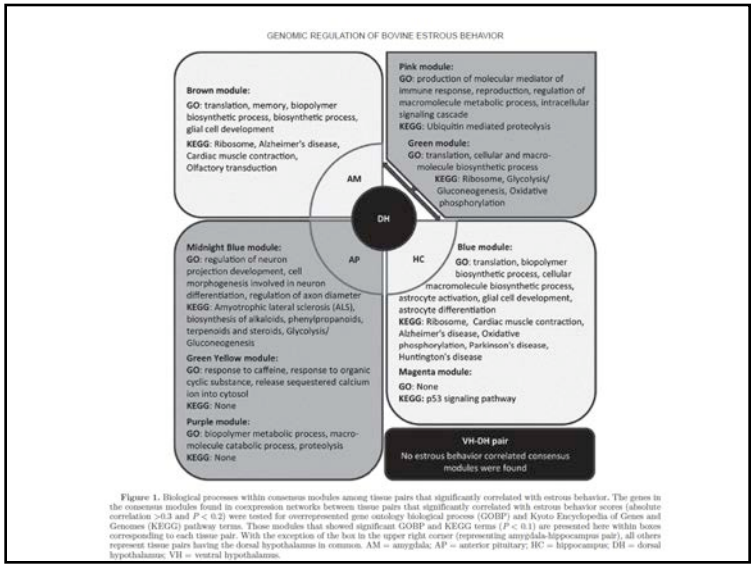
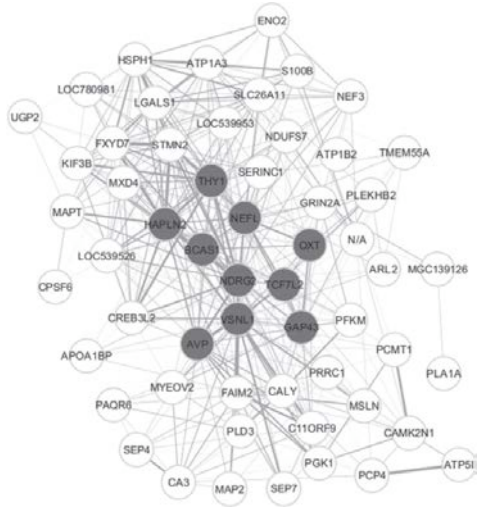


Figure 1. Biological processes within consensus modules among tissue pairs that significantly correlated with estrous behavior. The genes in the consensus modules found in coexpression networks between tissue pairs that significantly correlated with estrous behavior scores (absolute correlation >0.3 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.



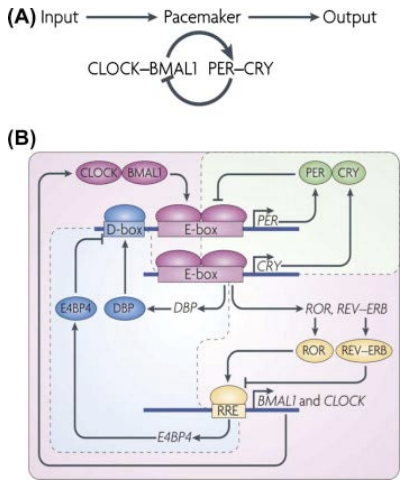
GENOMIC REGULATION OF BOVINE ESTROUS BEHAVIOR

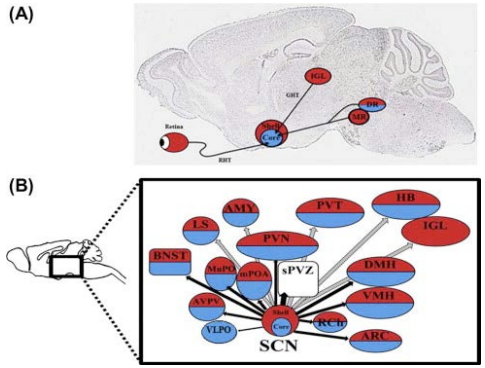
Table 4. Estrous behavior-associated genes and processes in dairy cows known to correspond to processes within the growth, amplification, preparation, permission, and synchronization (GAPPS) modules

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, PTGFR* (Kommadath et al., 2011)

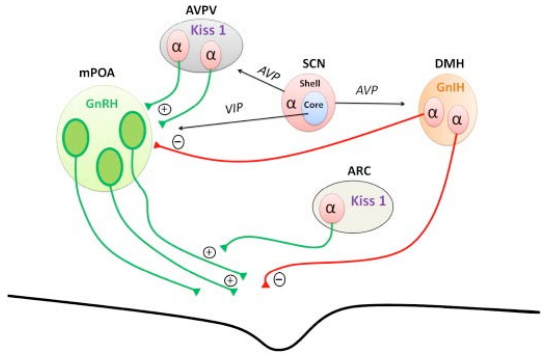
[1]This table is adapted from the PhD thesis of the first author (Kommadath, 2012).

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



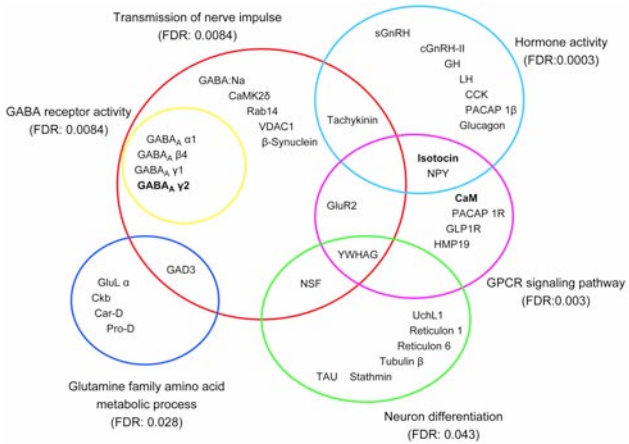


Gonadal hormone receptor expression in SCN afferents and efferents. (A) The main afferent pathways of the SCN, with nuclei expressing estrogen receptors (ER), red, or androgen receptors (AR), blue, or both ER and AR, red/blue. Light information from the Retina is sent to the SCN core via the retinohypothalamic tract (RHT). Non-photic information is sent to the SCN core from the intergeniculate leaflet (IGL) via the geniculohypothalamic tract (GHT), and the dorsal and medial raphe nuclei (DR and MR). (B) Main efferent pathways of the SCN to hypothalamic nuclei (black arrows) and extra hypothalamic sites (grey arrowss), which express ER, red, AR, blue, or both, red/blue. Nuclei receiving inputs from the SCN core and shell include: the pre optic area (POA) – specifically the medial preoptic area (mPOA), the median preoptic area (MnPO), and the anteroventral periventricular nucleus (AVPA); as well as sparse connections with the ventrolateral peroptic area (VLPO). Projections extending dorsally heavily innervate the sub paraventricular zone (sPVZ) – including ventral sPVZ; as well as the paraventricular nucleus of the hypothalamus (PVN). Caudal projections innervate the the retrochiasmatic area (Rch), the arcuate nucleus (ARC), ventromedial nucleus of the hypothalamus (VMH), the dorsomedial hypothalamus (DMH). Extra hypothalamic regions receiving direct SCN input include: the lateral septum (LS), the bed nucleus of the stria terminalis (BNST), the anterior paraventricular thalamic nuclei (PVA), the amygdala (AMY), the habenula (HB), and the intergeniculate leaflet (IGL) (Simerly et al., 1990, Simerly, 2002, Zhang et al., 2002, Shughrue et al., 1992, Shughrue et al., 1997 and Shughrue and Merchenthaler, 2001) (Kriegsfeld et al., 2004a, Kriegsfeld et al., 2004b, Abrahamson et al., 2001, Leak and Moore, 2001, Morin, 2013 and Dibner et al., 2010).

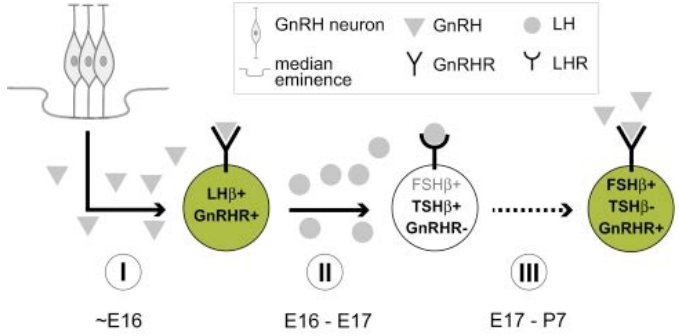


Sex steroids and hypothalamic control of the HPG-axis. Hypothalamic nuclei involved in regulation of gonadotropin release at the level of the hypothalamus. Neurons expressing estrogen receptors (ER), red, with ER subtype (α or β) indicated. Axons depicted in green represent neuronal inputs promoting 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).

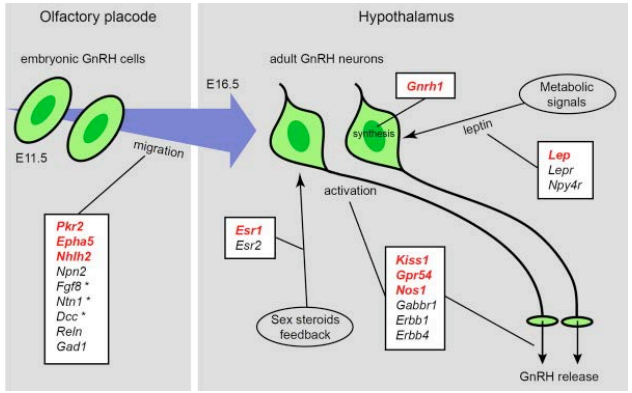
Defining global neuroendocrine gene expression patterns associated with reproductive seasonality in fish.
Zhang D, et al. PLoS One. 2009 Jun 5;4(6):e5816.



Embryonic gonadotropin-releasing hormone signaling is necessary for maturation of the male reproductive axis.
Wen S, Ai W, Alim Z, Boehm U. Proc Natl Acad Sci U S A. 2010 Sep 14;107(37):16372-7.

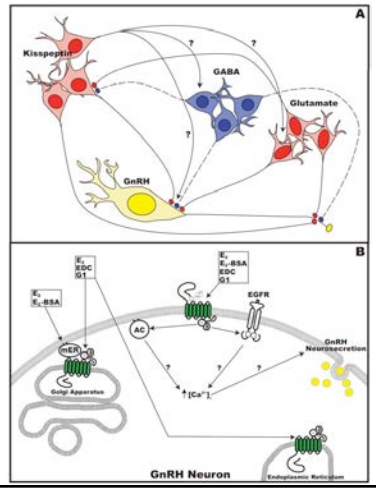


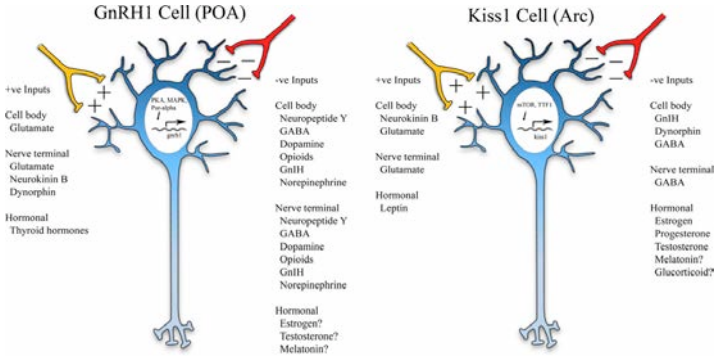
Proposed model of embryonic GnRH signaling–dependent gonadotrope development in male mice. Increased GnRH release from axon terminals at the median eminence triggers an increase in LH secretion around E16 (I). At this stage, only LH+ cells express GnRHR (green) and are GnRH-responsive. The embryonic increase in LH secretion promotes proper development of FSH+ gonadotropes in the anterior pituitary. FSH+ gonadotropes coexpress TSH+ and LHR, suggesting a direct LH effect on FSH+ gonadotrope development (II). Between E17 and P7 (III), FSH+ gonadotropes up-regulate FSHβ and lose TSHβ expression and start to express GnRHR (green).



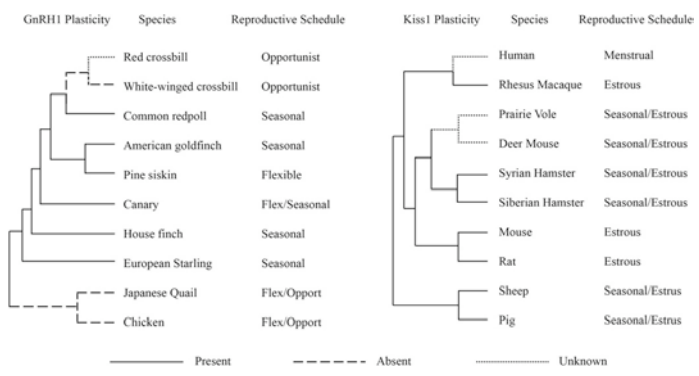
Schematic diagram summarizing the genes involved in the central regulation of puberty as identified from transgenic studies. GnRH neurons originate in the olfactory placodes from where they start migrating at embryonic day 11.5 (E11.5) towards the hypothalamus to finally achieve the adult spatial distribution 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.



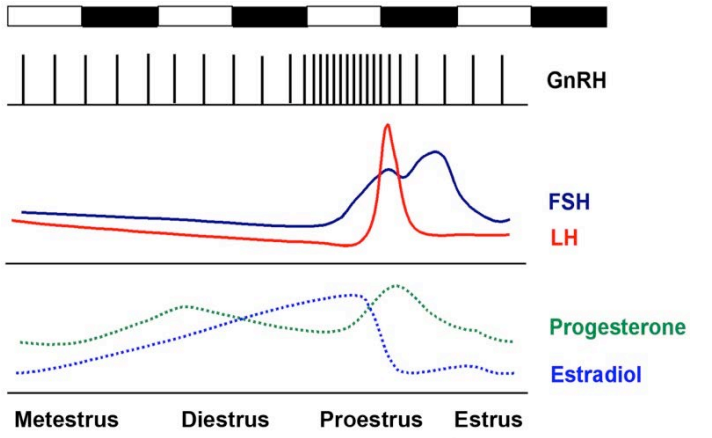


Schematic representation of the neuromodulatory and harmonal inputs that regulate GnRH1 in the preoptic area (POA) in birds and Kissl in the Arcuate nucleus (Arc) in mammals. The annual change in photoperiod is the primary signal that governs the predictability in neuropeptide expression. However, the 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 Kissl cell activity are not known. There are several neural candidate inputs that regulative GnRH1 and Kissl mRNA/protein expression. The photoperiodic regulation of GnRH1 and Kissl 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 Kissl 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).

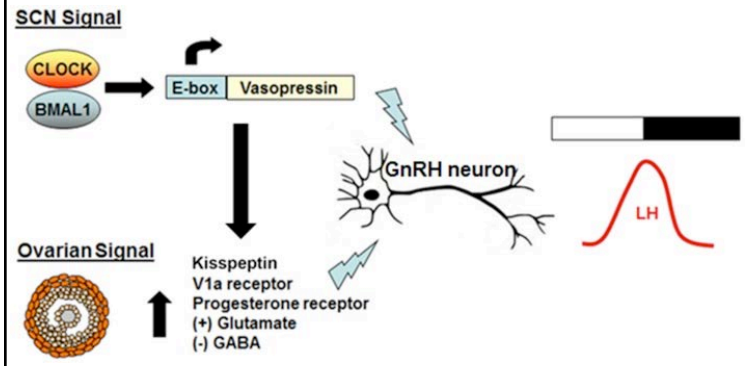


Phylogenetic analysis of GnRH1 and Kissl plasticity in bird and mammalian species, respectively. Kissl plasticity occurs in both the Arc and POA/AvPv in all mammalian species studied to date. Data was compiled using MacDougall-Shackleton et al., 2009, Revel et al., (2006), Greives et al., (2007), Gottsch 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).

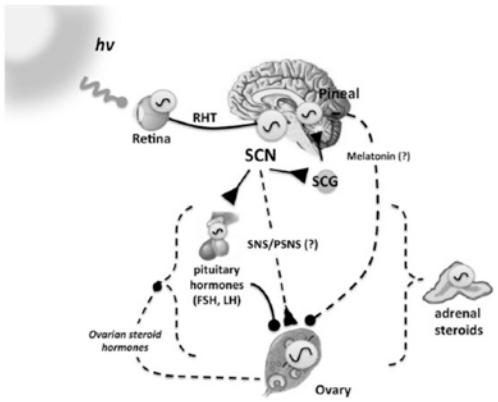
Central Circadian Control of Female Reproductive Function.
Miller BH, Takahashi JS. Front Endocrinol (Lausanne). 2014 Jan 22;4:195.



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.

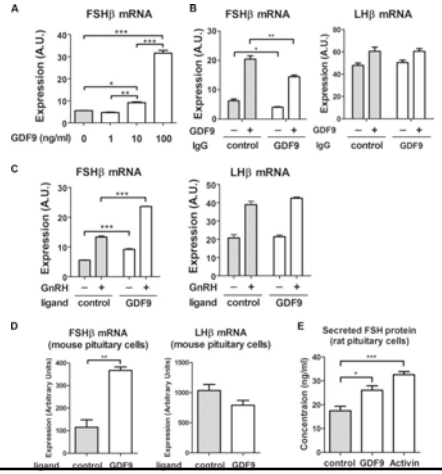


Model of the interaction between the daily timing signal and the ovarian signal on GnRH release. AVP is rhythmically transcribed in the SCN and forms the basis for the strong neural daily timing signal from the SCN. On the day of proestrus, estradiol produced by the developing follicles in the ovary 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.

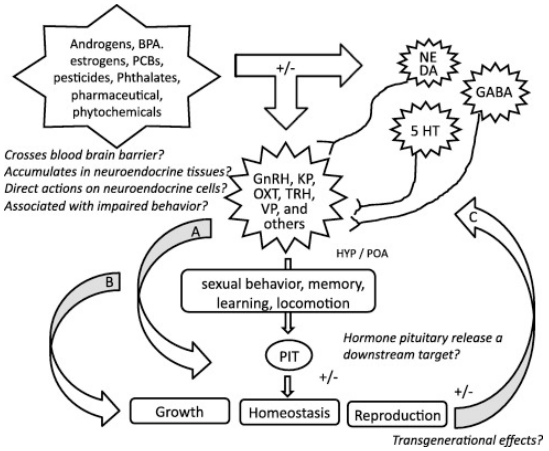


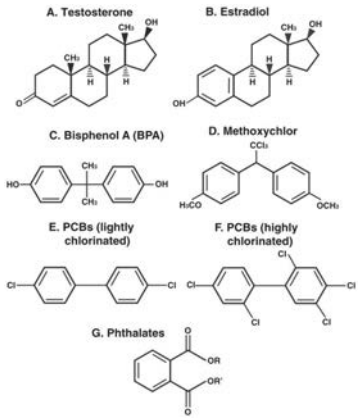
The circadian timing system in the hypothalamo-pituitary-ovarian (HPO) axis. A schematic diagram of the HPO axis indicating the integration of the circadian timing system in HPO axis function. The ovary shows phasic sensitivity to gonadotropins (LH and FSH that may depend on the timing of the ovarian 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.

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.

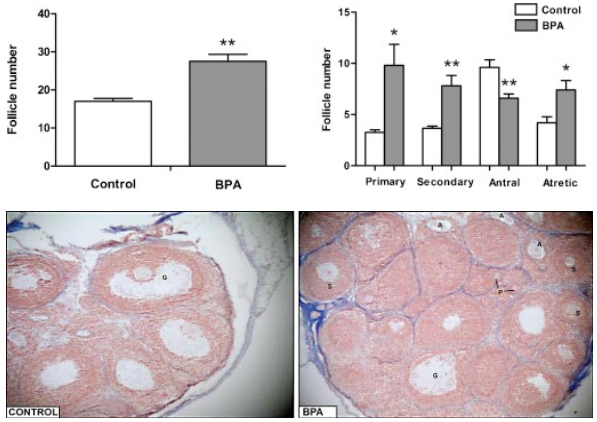


Current concepts in neuroendocrine disruption.
León-Olea M, et al. (2014) Gen Comp Endocrinol. (Epub ahead of print).

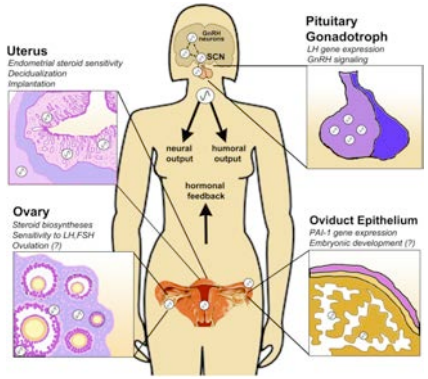




Exposure to a low dose of bisphenol A impairs pituitary-ovarian axis in prepubertal rats: effects on early folliculogenesis.
Gámez JM, Penalba R, Cardoso N, et al.
Environ Toxicol Pharmacol. 2015 Jan;39(1):9-15.



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.