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REVIEW

Extrapituitary production of anterior pituitary hormones: an overview

S. Harvey · C. Arámburo · E. J. Sanders

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Abstract Protein hormones from the anterior pituitary gland have well-established endocrine roles in their peripheral target glands. It is, however, now known that these proteins are also produced within many of their target tissues, in which they act as local autocrine or paracrine factors, with physiological and/or pathophysiological significance. This emerging concept is the focus of this brief review.

Keywords Growth hormone · Prolactin · Adrenocorticotropin · Thyrotropin · Luteinizing hormone · Follicle-stimulating hormone

Introduction

Plasma hormones are typically derived from a single endocrine gland, although the same factors may be expressed more widely. For instance, insulin-like factors (IGFs) in circulation are primarily derived from the liver, although IGFs are produced in most, if not all, tissues [1–3]. Similarly, while plasma ghrelin is largely derived from the gastric mucosa, ghrelin production occurs widely throughout the diffuse endocrine system, including the pituitary, thyroid, pancreas, adrenal, intestine, lung, gonads, and placenta [4]. Plasma insulin is similarly largely derived from cells in the pancreas, but extrapancreatic insulin expression occurs in the liver, adipose tissue, spleen, bone marrow, thymus, and brain [5].

The ectopic expression of these hormones in "aberrant" locations reflects the fact that all cells have the potential to express every gene present in the genome. While this may sometimes reflect "leaky gene" phenomena, it may reflect the acquisition of autocrine or paracrine physiological roles of some endocrines in physiological or pathophysiological function [6]. The endocrine (whole body) activity of some hormones may similarly be acquired developmentally by factors initially involved in local growth and differentiation [7]. In this brief review, the expression and physiological or pathophysiological roles of anterior pituitary hormones in extra-pituitary tissues is considered. In this review, expression refers to transcription of the gene and not to translation of the named protein.

Growth hormone

The extrapituitary production of growth hormone (GH) and its functional relevance was the subject of a recent review [8] and will not be detailed here. In addition to the anterior pituitary, GH and GH mRNA are present in the central (CNS) and peripheral (PNS)-nervous systems, in the respiratory system, immune system, gastrointestinal system, reproductive system, cardiovascular system and in integumentary tissues. As the GH receptor (GHR) gene is expressed in all of these sites, extrapituitary GH may have local autocrine or paracrine actions in all of these tissues. Indeed, functional roles for GH within most of these sites have been demonstrated by the local blockade of its production or by local blockade of its receptor-mediated actions. Autocrine actions of GH in carcinogenesis are

S. Harvey (✉) · E. J. Sanders
Department of Physiology, University of Alberta, Edmonton, AB T6G 2H7, Canada
e-mail: steve.harvey@ualberta.ca

C. Arámburo
Departmento de Neurobiología Celular Y Molecular, Instituto de Neurobiología, Campus Juriquilla, Universidad Nacional, Autónoma de Mexico, Querétaro, Qro 76230, Mexico

particularly well described by the voluminous work from Peter Lobie's group [9–12]. Autocrine or paracrine roles for extrapituitary GH are therefore now well established [8].

Prolactin

Ben Jonathan was amongst the first to review the widespread presence of prolactin in extrapituitary tissues [13]). These authors suggested the pleiotropic actions of prolactin (including the regulation of mammary development, initiation and maintenance of lactation, immune modulation, osmoregulation and behavioral modulation) reflected its circulating role as an endocrine and local roles as a cytokine. It was classified as a cytokine based upon its shared properties with hematopoietic growth factors, including comparable structural motifs, multiple sites of synthesis, ubiquitous receptor distributions, homologous receptor structures, and similar signal transduction pathways that promote cell growth and cell survival.

Within the immune system, prolactin gene expression in man occurs in lymphocytes in response to cytokines produced by monocyte-macrophage activation [14] and in response to calcitriol, the active form of vitamin D [15]. It is similarly produced in helper T cells and in B cells in the mouse spleen [16]. Within the immune system, prolactin, in turn, has autocrine or paracrine immunoregulatory roles that promote lymphoid tissue development and stimulate cytokine synthesis [17]. In T-lymphocytes, in particular, prolactin release enhances NK cell function and the secretion of IL-2 and IFN gamma [18]. The importance of autocrine prolactin in the activation of T-lymphocytes is further demonstrated by the knockdown of the prolactin receptor gene, which impairs T-lymphocyte proliferation and the production of IL-2 and IL-4 [19]. Enhanced prolactin production in lymphocytes occurs in patients with autoimmune disease [20] and has been causally related to the induction of autoimmunity [21] and cancer [22].

Increased expression of prolactin and its receptor is similarly associated with an increase in tumorigenesis in many tissues, particularly reproductive tissues [22–24]. For instance, prolactin is an established risk factor for breast cancer [24], and it has long been known to be expressed in mammary glands during pregnancy and lactation (in rats [25, 26], mice [27], rabbits [28], sheep and goats [29]) and prolactin is present at high concentrations in milk [13, 30]. Blocking local prolactin signaling has therefore been proposed as a therapeutic approach in the treatment of breast and prostate cancer [31–33]. The prostate, like the mammary gland, is another reproductive tissue in which prolactin as its receptors are expressed [34] and increased expression of prostate prolactin results in hyperplasia [35, 36] and provides a marker for prostate cancer prognosis and metastasis [31].

Prolactin immunoreactivity (IR) is similarly present in the interstitial tissue of the rodent testis and in Sertoli cells and germ cells [37]. This reflects the expression of the prolactin gene, since prolactin mRNA has been demonstrated in mouse Leydig cells and in germ cells, particularly in spermatogonia [38]. Although the nucleotide sequence of the testicular transcript is the same as that in the pituitary, two forms of prolactin were detected in the testis: one was the 23 kDa moiety similarly found in the pituitary gland and the other was an N-terminal truncated form. The intact, full-length protein was localized in the nucleus of round spermatids, while the truncated protein was localized in the Golgi apparatus of round spermatids and in the cytoplasm of elongated spermatids spermatozoa tails. These prolactin moieties may therefore account for the actions of prolactin in testicular function and spermatogenic development [39, 40].

In females, extrapituitary prolactin gene expression has been demonstrated in decidualized uterine stromal cells during pregnancy [7], in which it is thought to regulate uterine epithelial cell differentiation, trophoblast growth, angiogenesis and the modulation of the immune response [41]. Decidual prolactin additionally inhibits the expression of interleukin 6 (IL-6), a pro-inflammatory cytokine, and the expression of 20 α-hydroxysteroid dehydrogenase (20α-HSD), an enzyme that promotes inflammation by catabolizing progesterone, thereby maintaining pregnancy [42].

Extrapituitary prolactin is also synthesised and secreted by breast, visceral, and subcutaneous adipose tissue [43, 44], in which the expression and release of adipose prolactin increases during early pre-adipocyte differentiation [45]. The release of prolactin from subcutaneous adipose explants is reduced during obesity, suggesting its production is related to metabolic state [46]. Both the long and short forms of the prolactin receptor are expressed in rodent and human adipose tissue [47–49] and prolactin is involved in adipogenesis, lipolysis, metabolism and the release of adipokines such as leptin, adiponectin and IL-6 [44, 46, 49].

Extrapituitary prolactin is also widely synthesised within cutaneous tissues [50]. Prolactin and/or prolactin mRNA are, for instance, present in skin fibroblasts [51], keratinocytes [52, 53], in dermal endothelial cells [54], in sebaceous glands [55], sweat glands [50] and hair follicles [53]. As prolactin receptors are expressed in these sites [50], prolactin is likely to have autocrine or paracrine actions in cutaneous function.

The presence of prolactin and prolactin mRNA in vascular endothelium is of interest, because of the actions of prolactin moieties in angiogenesis [56, 57]. While all endothelium cells express full-length prolactin mRNA and

synthesize 23 kDa prolactin, umbilical vein and brain capillary cells additionally express a smaller prolactin mRNA and proteins with a molecular mass of ~21, 16, and 14 kDa [49, 53, 54, 58, 59]. These smaller moieties have a reduced capacity to activate classical prolactin receptors and have actions dissimilar to the full-length molecule [58, 59]. The actions of these prolactin moieties on endothelial cells occur in the absence of the classical prolactin receptor, as this is not expressed in rat retinal endothelial cells [59]. Thus, while 23 kDa has no effect on the proliferation of endothelial cells in vitro [60] the 16 and 14 kDa moieties exert an autocrine anti-mitogenic effect on endothelial cell proliferation and the 21 kDa protein is pro-mitogenic [52].

Prolactin synthesis also occurs in the brain [13], particularly the hypothalamus [61–63], although prolactin is similarly found in extrahypothalamic limbic brain regions, such as the bed nucleus of stria terminals, the amygdala and the locus coeruleus [63]. Within the hypothalamus the paraventricular nucleus (PVN) and the supraoptic nucleus (SON) neurons express prolactin mRNA and contain 14 kDa prolactin IR that likely results from proteolysis of 23 kDa prolactin. As the nerve terminals from the PVN and SON neurons are in the neurohypophysis on systemic blood vessels, the presence of 14 kDa prolactin in rat and human serum may be derived from the hypothalamo-neurophypophyseal system [64], although 14 kDa prolactin is synthesised by mammary epithelial and endothelial cells [54, 58, 65].

In addition to prolactin, prolactin receptors are also present throughout the brain and mediate numerous physiological and behavioral actions [63, 66]. However, as pituitary prolactin can enter the brain through a receptor-mediated active transport system in the choroid plexus [67, 68], these CNS target sites may respond to pituitary or brain-derived prolactin.

Outside the brain, prolactin immunoreactivity (IR) has been found within the eye. Prolactin-IR has, for instance, been detected in the cytoplasm of chick embryo retinal ganglion cells, in the choroid and in the endothelial cells of choroid blood vessels [69]. In the rat, 23 and 16 kDa prolactin have been detected in aqueous humor and in corneal homogenates [70]. Prolactin is similarly present in the sub-retinal fluid of patients with premature retinopathy [71], which may originate from newly formed intra-ocular blood vessels, since these actively produce and release full-length prolactin [60] and prolactin mRNA is expressed in the retinal blood vessels (and leukocytes) of humans with retinopathy of prematurity [72] and within fibrovascular tissue within the vitreous compartment [66]. The concentration of prolactin in retinal blood vessels is 300-fold higher than that in other blood vessels [72], suggesting important roles in ocular function, especially as receptors for prolactin have been localized in the retina and cornea, in which exogenous 16 kDa prolactin has anti-angiogenic activity [70].

The presence of prolactin proteins of different molecular size indicates that its processing may be tissue-specific. The expression of the prolactin gene in many extrapituitary tissues is thought to differ from that in the pituitary gland, although prolactin mRNA identical to that in the pituitary gland has been found in prostate and breast cancer cells [31, 43, 73]. The mRNA for prolactin in lymphocytes and decidual cells is, however, longer than that in the pituitary gland, since prolactin transcription in these tissues is driven by an alternative promoter, which is located 5.8 bp upstream for the pituitary transcription start site, resulting in the transcription of an extra exon, exon 1a [74]. Prolactin mRNA in many extrapituitary tissues is therefore 150 bp larger than that in the pituitary gland [50, 51]. This extra exon could contribute to the expansion of the transcriptional and/or translational "repertoire" of the prolactin gene [74]. The regulation of the alterative promoter differs from that in the pituitary gland, since it's activation in extrapituitary tissue is independent of the pituitary specific transcription factor, Pit-1, which is required for prolactin expression in lactotrophs. Other tissue-specific factors also regulate extrapituitary prolactin expression [38]. For instance, while dopamine, thyrotropin-releasing hormone (TRH), vasoactive intestinal peptide (VIP), and estrogen are the classical regulators of pituitary prolactin, they are ineffective regulators of the alternate promoter [13]. The alternate promoter in decidual cells, lymphocytes and adipocytes is, however, stimulated by cAMP and by autocrine or paracrine factors [13, 75, 76]. Decidual prolactin, for example, is stimulated by the feto-placenta unit and the production of progesterone, although this is not due to direct effects of progesterone on the prolactin gene, but to its stimulation of decidual fibrobalsts [13]. In contrast, progesterone is ineffective at regulating pituitary prolactin expression [13]. Local proteins that stimulate and inhibit decidual prolactin but have no effect on pituitary prolactin have been reported, although these are not fully identified [13]. Nur 77, a transcription factor, may be one of these proteins as it induces decidual prolactin expression and is, in turn, stimulated by cAMP and progesterone [77].

Extrapituitary prolactin, at least in decidual cells further differs from that in the pituitary gland in that it is not packaged into dense secretory granules and is rapidly released after synthesis [78]. The release of decidual prolactin is thus not affected by increased extracellular calcium concentrations [79], which is unusual for cells that secrete protein hormones [13].

Prior to organogenesis, extrapituitary prolactin or prolactin-like proteins may be involved in early development. For instance, prolactin receptors are expressed in oocytes and preimplantation rodent embryos lacking pituitary

glands [80] and the immuneneutralization of endogenous prolactin from cultured rat embryos significantly suppresses embryonic growth [81], whereas embryonic growth is improved in the presence of exogenous prolactin [81, 82]. These actions may, however, be due to prolactin-like proteins rather than to prolactin itself, as at least 18 distinct prolactin GH-like genes have been identified in rodents [83–86]. A novel prolactin-like protein (PRL-L) with homology to prolactin in chickens, zebrafish, xenopus, rats, and humans is similarly present in chickens and zebrafish [87]. However, unlike the predominant expression of prolactin in the pituitary gland, PRL-L is widely expressed in extrapituitary tissues and only minimally present in the pituitary gland.

POMC-derived peptides

Pro-opiomelanocortin (POMC) is a gene expressed in the anterior and intermediate lobes of the pituitary gland and in many extrapituitary tissues [88, 89]. Its encoded protein is a 285 amino acid polypeptide that undergoes tissue-specific, post-translational processing to produce λ MSH (melanocyte stimulating hormone), ACTH, β-LPH (lipotropin), MSH, CLIP (corticotropin-like intermediate peptide), λ lipotropin, β-endorphin, and β-MSH. The full length POMC polypeptide is primarily translated into ACTH and β-LPH in pituitary corticotrophs but mainly into α-MSH in the intermediate lobe. POMC can additionally be cleaved by proteases into other fragments that are not found in the circulation. An adrenal protease, for instance, cleaves α-MSH into smaller fragments that act as potent mitogens within the adrenal gland [90].

Although α-MSH is mainly produced in the intermediate lobe of the pituitary gland, it is nevertheless present in birds, which lack an intermediate lobe [91]. In birds, α-MSH has been found in neural tissue, especially within the eye [91], where it may act as an autocrine or paracrine in ocular development. Indeed, α-MSH is present in the retinal pigmented epithelium (RPE) of chick embryos from embryonic day 10 of the 21-day incubation period, although melanocortin receptors are found outside the RPE, in the choroid and neural retina [92], and likely mediate cell proliferation and neurite outgrowth [93].

In the brain, Larsson [94] was amongst the first to document the presence of ACTH and closely related peptides, particularly in opoid-containing nerves. Larsson [94] additionally found CLIP (lacking adrenocortical activity) to be present in the pars intermedia of the pituitary gland. The extrapituitary forms of ACTH and β-endorphin in the brain were of larger molecular weight than in the pituitary gland, a finding confirmed by Saito et al. [95] for ACTH-like peptides in the brain [95], as in other tissues (including the stomach, kidney, colon, small intestine, heart and placenta [96, 97]).

In addition to these tissues, POMC gene expression and protein processing occurs in cells of the immune system, including rat mononuclear leukocytes and macrophages [98]. The presence of corticotrophin and melanocortin receptors in these cells [99] supports the possibility that they may have local or autocrine or paracrine roles in immune regulation. α-MSH has similarly been found in the chicken thymus and bursa of Fabricius, together with other POMC-derived peptides [100].

Skin is the principle target site of MSH action, but melanocortins and other POMC-derived peptides also have biological activity [101]. These peptides are produced by keratinocytes, melanocytes, dermal microvascular epithelial cells and hair follicles [102, 103]. As receptors for all of these peptides are also present within skin [104], they are likely autocrine or paracrine regulators of dermal function, including vascular, immune and pigmentary actions, the cutaneous stress response and the growth or loss of hair [105]. The local production of POMC-derived peptides in skin has also been demonstrated in melanoma, in which their autocrine or paracrine actions have been implicated with cancer progression [106]. Another pathophysiological consequence of extrapituitary POMC production is Cushing's syndrome, as ectopic ACTH production is an established cause of this disease [107].

Thyroid-stimulating hormone (TSH)

There are a number of established extrapituitary sites of TSH expression. These are first apparent in several tissues during early embryonic chick development at embryonic day 7 (ED7), before the functional differentiation of the pituitary thyrotropes [108]. Sites of early expression during development include: brain, otic vesicle, crop, liver, and the respiratory system. This embryonic extrapituitary expression appears to be dependent on the Pit-1 transcription factor, as it is in the pituitary gland [109]. Like several other hormones [6, 69], TSH is found in the developing chick retina, commencing at approximately ED7 [110, 111]. This retinal TSH is found in the synaptic processes of retinal ganglion cells, where it is hypothesized to act as a neuromodulator involved in the control of synaptic transmission or local blood flow. TSH also increases cyclic AMP accumulation in retinal pigmented epithelial cells [112].

Other regions of the brain reported to show TSH immunoreactivity include cells of the mammalian hypothalamus [113], from where it may be released from a membrane-bound compartment, at least in vitro, by electrical stimulation of the tissue [114]. Interestingly, this

hypothalamic TSH appears to be regulated by the levels of thyroxine (T4), which increase hypothalamic TSH immunoreactivity, but not by tri-iodothyronine (T3). This regulation by T4 is, however, dependent on local deiodination of T4 to T3, and indicates that hypothalamic TSH immunoreactivity is regulated independently of pituitary and serum TSH [115]. Developmentally, rat brain TSH may be detected before pituitary TSH, and it undergoes a transient increase in concentration prior to birth, independent of pituitary TSH levels, again indicating that brain and pituitary TSH represent two distinct pools [116].

The immune system is another a rich source of extrapituitary TSH [117, 118]. Elements of the immune system implicated in TSH synthesis and secretion include splenic dendritic cells [119], intestinal T cells [120, 121], bone marrow hematopoietic cells [122], and T cell lines [123], implying that TSH may act as an immune system cytokine. The best characterized such system is the intestinal immune system [118], where TSH synthesis is localized epithelial cells in the subvillus crypts. Within these crypts, T-cell differentiation and TSH synthesis occurs in response to viral infection [124], suggesting the presence of a local paracrine TSH network.

Immune TSH, like pituitary TSH, may also have thyroid activity, as bone marrow transplantation disrupts thyroid function [118], indicating that there is a bone marrow-thyroid TSH network which contributes to the control of thyroid function. This is supported experimentally by the demonstration that bone marrow cells are able to migrate to the thyroid gland, where they express TSH transcripts and secrete TSH [125, 126]. Within the thyroid, bone marrow cells additionally produce a TSH splice variant [127, 128], which likely has paracrine actions on T3 and T4 secretion [125, 126]. The expression of this variant, but not the native form of TSH β, is significantly upregulated in the thyroid during systemic infections. This variant which includes a 27 nucleotide portion of intron 2 and all of axon 3, coding for 71.2% of the native human TSH β polypeptide [128] is also present in the pituitary gland. Extrapituitary TSH could therefore be responsible for thyroid autoimmunity triggered by viral infection and may indicate that the immune system participates in the regulation of basal metabolism.

Extrapituitary TSH is also thought to be a local growth factor in the human epidermis, in which TSH mRNA and protein are expressed intradermally in the scalp and the TSH receptor is present in the adjacent dermis [129]. The expression of TSH in the skin is increased by TRH and reduced by thyroid hormones. Actions of TSH in the skin include an upregulation of the genes for involucrin, loricrin and veratins 5 and 14. It also stimulates mitochondrial proliferation and biogenesis in the perinuclear region of human skin epidermal keratinocytes and upregulates mitochondrial biogenesis in this non-classical target site [130].

Luteinizing hormone (LH)

In the chick embryo, luteinizing hormone (LH) is found in the epithelial cells of the developing lung and stomach as early as ED3 of the 21-day incubation period, indicating a potential paracrine role for LH in early embryogenesis [131]. There are also indications that LH and LH receptors [132] are present in the developing retina [69], suggesting possible roles in early retinal development or maintenance. Transcripts for LH receptors additionally occur in oocytes and pre-implantation embryos, suggesting further paracrine roles for LH in embryogenesis [133]. A role for extrapituitary LH in embryogenesis is similarly indicated in zebra fish embryos, in which antisense morpholino oligonucleotides suppress LH gene expression and embryo development [134].

Like TSH, LH is also found in the fetal rat brain and persists in the adult rat and human [116, 135], in the hypothalamus [136] and pineal gland [137]. Indeed, the presence of LH in the brain cortex, hypothalamus, hippocampus, medulla oblongata as well as its presence in the heart, liver, and pancreas is thought to explain the continued presence of LH in the circulation of hypophysectomized rats [138]. LH is produced in differentiated embryonic rat cortical neurons and neuroblastoma cells and is increased in response to GnRH treatment [139]. This was thought to account for the accumulation of LH in the pyramidal neurons of aged human and rat brains following post-reproductive surges in GnRH secretion. Expression of LH receptors in cultured neonatal rat brain glial cells may indicate local paracrine actions [140]. The presence of LH receptors in the hippocampus [141], suggest that LH may stimulate this region of the brain and possibly influence hippocampal synaptic function. It appears that cells producing LHβ subunit protein, and transcripts, may have developmental origins in the brain as well as in the pituitary gland, and may act as a neuromodulator of reproductive behavior [142, 143].

Other extrapituitary locations of LH include lymphocytes [144], where it may act as a cytokine-like determinant of T-cell proliferation [145]. It is also present in the gonads [146] and placenta [147] and in lung carcinoma [148, 149], where the significance, if any, is unclear.

Follicle-stimulating hormone (FSH)

There is a scarcity of reports on the occurrence of extrapituitary follicle-stimulating hormone (FSH), however, FSH

Table 1 Extrapituitary production of anterior pituitary hormone

	GH	PRL	POMC-derived peptides	TSH	LH	FSH
Brain	+	+	+	+	+	+
Retina	+	+	+	+	+	
Immune cells	+	+	+	+	+	+
Gut	+		+	+	+	+
Mammary glands	+	+				
Placenta	+		+		+	
Ovary	+	+			+	
Uterus	+	+				+
Testis	+	+			+	+
Adipose		+				
Skin	+	+	+	+		
Lung	+				+	
Pancreas	+				+	+
Embryo	+	+		+	+	
Cancer	+	+	+		+	

+ As indicated by the presence of mRNA or immunoreactive protein

protein and its transcripts have been shown to be present in the brain [142], particularly the preoptic area [143], the hypothalamus [150] and the hippocampus [151]. Although brain receptors for FSH were previously thought to be absent [141], they have now been reported to be present in the hippocampus [151], suggesting functional significance. Indeed, as hippocampal neurons are extrapituitary sites of FSH expression [150], FSH is likely to have local autocrine or paracrine roles. Immunoreactive FSH is additionally present in human Sertoli cells and in rounded germinal cells, both of which express FSH receptor transcripts [152], suggesting autocrine or paracrine roles in testicular function that may complement its endocrine actions. Autocrine or paracrine actions of FSH are similarly indicated in the rat pancreas, in which FSH and its receptors are co-localized in islet cells, in which FSH regulates the secretion of insulin and glucagon [153]. The expression of FSH in the pancreas occurs in response to the activation of GnRH receptors that are co-localized with FSH in islet cells. Transcripts for FSH receptors also occur during early human and mouse development (embryos at the 2 cell, morula and blastocyst stages, [133, 154] indicating possible early paracrine activity for this hormone.

Like LH, FSH has also been reported in stomach [155] placenta [147] and immune system [156], with uncertain significance. The presence of FSH in human prostate [157, 158] and breast [159] tissue has been linked to possible roles in malignant transformation. The presence of receptors in uterine tubal epithelium [160], and the cervix [161, 162] further suggests actions of FSH unrelated to gonadal activity.

Conclusion

Somatotrophs, lactotrophs, corticotrophs, thyrotrophs and gonadotrophs in the pituitary gland are primarily responsible for the production of GH, prolactin, ACTH, TSH, LH and FSH and their presence in the circulation, but all of these hormones are also produced in many extrapituitary tissues (Table 1). The extrapituitary production of these hormones is mostly at concentrations too low to induce the endocrine activities of the pituitary hormones, although hypophysectomized rats retain 10–50% of their biologically active prolactin concentrations, [163, 164] which may compensate for the lack of pituitary prolactin. Extrapituitary sources may similarly account for the persistence of measurable amounts of GH [165–167], TSH [168], LH [169], FSH [170], and ACTH [165, 166, 171] in systemic plasma after hypophysectomy. Indeed, hypersecretory disease states can result from the overproduction of pituitary hormones in extrapituitary tissues, as demonstrated by the induction of acromegaly by mammary GH in progesterone treated dogs [172, 173]. Progesterone induced mammary GH secretion similarly restores growth in dogs with pituitary dwarfism [174]. Hypersecretion of immune TSH during viral infections could similarly result in hypo- or hyperthyroid states, as hypothesized by Schaefer and Klein [126]. The tumerous production of ACTH can similarly result in adrenal overactivity and Cushings disease [175] and the tumerous production of LH can result in excess testosterone production and a hypogonadal state [176].

In addition to possible endocrine roles, the extrapituitary production of pituitary hormones is likely to have local non-endocrine (autocrine or paracrine) roles that may be of physiological or pathophysiological significance. Indeed, as most of the pituitary hormones are present in early development prior to the ontogenetic appearance of the pituitary gland, it is likely that they act as growth or differentiation factors [6] before they assume their classical endocrine roles.

In many cases, the widespread distribution of these extrapituitary hormones is in tissues that are target sites for the pituitary hormones. This is particularly evident for neural and immune tissues, which regulate these hormones in the pituitary gland and are target sites of the pituitary hormones. The extrapituitary production of these hormones in the "neuro-immune axis" may therefore provide a mechanism for rapid and discrete actions that compliment those under strategic control by their pituitary counterparts [99, 177–179]. In some cases, the extrapituitary production of pituitary hormones could, alternatively, be the cause or consequence of abnormal (tumerous) development. The local expression of GH is, for instance, particularly associated with cancer progression [9–12], but it is of note that aberrant gene expression occurs in cancer and that most of the pituitary hormones are present in tumerous tissue. The extrapituitary production of pituitary hormones may thus have physiological or pathophysiological relevance.

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References

1. D. Le Roith. The insulin-like growth factor system. Exp. Diabetes Res. **4**, 205–212 (2003)
2. D. Le Roith, C. Bondy, S. Yakar, J.L. Liu, A. Butler, The somatomedin hypothesis: 2001. Endocr. Rev. **22**, 53–74 (2001)
3. K. Sjogren, J.O. Jansson, O.G. Isaksson, C. Ohlsson, A model for tissue-specific inducible insulin-like growth factor-I (IGF-I) inactivation to determine the physiological role of liver-derived IGF-I. Endocrine **19**, 249–256 (2002)
4. G. Rindi, A. Torsello, V. Locatelli, E. Solcia, Ghrelin expression and actions: a novel peptide for an old cell type of the diffuse endocrine system. Exp. Biol. Med. **229**, 1007–1016 (2004)
5. H. Kojima, M. Fujimiya, K. Matsumura, T. Nakahara, M. Hara, L. Chan, Extra-pancreatic insulin-producing cells in multiple organs in diabetes. Proc. Natl. Acad. Sci. USA **101**, 2458–2463 (2004)
6. E.J. Sanders, S. Harvey, Peptide hormones as developmental growth and differentiation factors. Dev. Dyn. **237**, 1537–1552 (2008)
7. M.V. Urgrumov, Developing brain as an endocrine organ: a paradoxical reality. Neurochem. Res. **35**, 837–850 (2010)
8. S. Harvey, Extrapituitary growth hormone. Endocrine **38**, 335–359 (2010)
9. J.K. Perry, K.M. Mohankumar, B.S. Emerald, H.C. Mertani, P.E. Lobie, The contribution of growth hormone to mammary neoplasia. J. Mammary Gland Biol. Neoplasia. **13**, 131–145 (2008)
10. V. Pandey, J.K. Perry, K.M. Mohankumar, X.J. Kong, S.M. Liu, Z.S. Wu, M.D. Mitchell, T. Zhu, P.E. Lobie, Autocrine human growth hormone stimulates oncogenicity of endometrial carcinoma cells. Endocrinology **149**, 3909–3919 (2008)
11. S.E. Brunet-Dunand, C. Vouyovitch, S. Araneda, V. Pandey, L.J. Vidal, C. Print, H.C. Mertani, P.E. Lobie, J.K. Perry, Autocrine human growth hormone promotes tumor angiogenesis in mammary carcinoma. Endocrinology **150**, 1341–1352 (2009)
12. Z.S. Wu, K. Yang, Y. Wan, P.X. Qian, J.K. Perry, J. Chiesa, H.C. Mertani, T. Zhu, P.E. Lobie, Tumor expression of human growth hormone and human prolactin predict a worse survival outcome in patients with mammary or endometrial carcinoma. J. Clin. Endocrinol. Metab. **96**, E1619–E1629 (2011)
13. N. Ben-Jonathan, J.L. Mershon, D.L. Allen, R.W. Steinmetz, Extrapituitary prolactin: distribution, regulation, functions, and clinical aspects. Endocr. Rev. **17**, 639–669 (1996)
14. L. Matera, Endocrine, paracrine and autocrine actions of prolactin on immune cells. Life Sci. **59**, 599–614 (1996)
15. L. Diaz, I. Martinez-Reza, R. Garcia-Becerra, L. Gonzalez, F. Larrea, Calcitriol stimulates prolactin expression in non-activated human peripheral blood mononuclear cells: breaking paradigms. Cytokine **55**, 188–194 (2011)
16. K. Horiguchi, S. Yagi, K. Ono, Y. Nishiura, M. Tanaka, M. Ishida, T. Harigaya, Prolactin gene expression in mouse spleen helper T cells. J. Endocrinol. **183**, 639–646 (2004)
17. K.W. Kelley, D.A. Weigent, R. Kooijman, Protein hormones and immunity. Brain Behav. Immun. **21**, 384–392 (2007)
18. L. Matera, Action of pituitary and lymphocyte prolactin. Neuroimmunomodulation **4**, 171–180 (1997)
19. D. Xu, F. Lin, X. Lin, Z. Huang, Z. Lei, Immunoregulation of autocrine prolactin: suppressing the expression of costimulatory molecules and cytokines in T-lymphocytes by prolactin receptor knockdown. Cell. Immunol. **263**, 71–78 (2010)
20. I. Mendez, J. Alcocer-Varela, A. Parra, A. Lava-Zavala, D.A. de la Cruz, D. Alarcon-Segovia, F. Larrea, Neuroendocrine dopaminergic regulation of prolactin release in systemic lupus erythematosus: a possible role of lymphocyte-derived prolactin. Lupus **13**, 45–53 (2004)
21. I. Mendez, C. Clarion, L. Diaz, Prolactin in the immunological system: synthesis and biological effects. Rev. Invest. Clin. **57**, 447–456 (2005)
22. N. Ben-Jonathan, K. Liby, M. McFarland, M. Zinger, Prolactin as an autocrine/paracrine growth factor in human cancer. Trends Endocrinol. Metab. **13**, 245–250 (2002)
23. C. Manhes, V. Goffin, P.A. Kelly, P. Touraine, Autocrine prolactin as a promoter of mammary tumour growth. J. Dairy Res. **72**, 58–65 (2005)
24. S. Bernichtein, P. Touraine, V. Goffin, New concepts in prolactin biology. J. Endocrinol. **206**, 1–11 (2010)
25. A. Kurtz, L.A. Bristol, B.E. Toth, E. Lazar-Wesley, L. Takacs, B. Kacsoh, Mammary epithelial cells of lactating rats express prolactin messenger ribonucleic acid. Biol. Reprod. **48**, 1095–1103 (1993)
26. R.W. Steinmetz, A.L. Grant, P.V. Malven, Transcription of prolactin gene in milk secretory cells of the rat mammary gland. J. Endocrinol. **136**, 271–276 (1993)
27. T. Harigaya, E. Imata, Y. Mori, Prolactin gene expression in mouse mammary gland during late pregnancy and lactation. Anim. Sci. Technol. **67**, 484–485 (1996)
28. L. Gabou, M. Boisnard, I. Gourdou, H. Jammes, J.P. Dulor, J. Djiane, Cloning of rabbit prolactin cDNA and prolactin gene expression in the rabbit mammary gland. J. Mol. Endocrinol. **16**, 27–37 (1996)

29. F. Le Provost, C. Leroux, P. Martin, P. Gaye, J. Djiane, Prolactin gene expression on ovine and caprine mammary gland. Neuroendocrinology **60**, 305–313 (1994)
30. P.V. Malven, Prolactin and other protein hormones in milk. J. Anim. Sci. **45**, 609–616 (1977)
31. A. Dagvadorj, S. Collins, J.-B. Jomain, J. Abdulghani, I. Karras, T. Zellweger, H. Li, M. Nurmi, K. Alanen, T. Mirtti, T. Visakorpi, L. Bubendorf, V. Goffin, M.T. Nevalainen, Autocrine prolactin promotes prostate cancer cell growth via Janus kinase-2-signal transducer and activator of transcription-5a/b signaling pathway. Endocrinology **148**, 3089–3101 (2007)
32. V. Rouet, R.L. Bogorad, C. Kayser, K. Kessal, C. Genestie, A. Bardier, D.R. Grattan, B. Kelder, J.J. Kopchick, P.A. Kelly, V. Goffin, Local prolactin is a target to prevent expansion of basal/stem cells in prostate tumors. Proc. Natl. Acad. Sci. (USA) **107**, 15199–15204 (2010)
33. E.M. Jacobson, E.R. Hugo, D.C. Borcherding, N. Ben-Jonathan, Prolactin in breast and prostate cancer: molecular and genetic perspectives. Discov. Med. **11**, 315–324 (2011)
34. M.T. Nevalainen, E.M. Valve, P.M. Ingleton, M. Nurmi, P.M. Martikainen, P.L. Hardonen, Prolactin and prolactin receptors are expressed and functioning in human prostate. J. Clin. Invest. **99**, 618–627 (1997)
35. H. Wennbo, J. Kindblom, O.G. Isaksson, J. Tornell, Transgenic mice over-expressing the prolactin gene develop dramatic enlargement of the prostate gland. Endocrinology **138**, 4410–4415 (1997)
36. J. Kindblom, K. Dillner, L. Sahlin, F. Roberson, D. Ormandy, J. Tornell, H. Wennbo, Prostate hyperplasia in a transgenic mouse with prostate-specific expression of prolactin. Endocrinology **144**, 2269–2278 (2003)
37. M. Roux, N. Martinat, J.P. Richoux, G. Grignon, Histoimmunological identification of a prolactin-like substance in rodent testis. Cell. Tissue Res. **240**, 663–667 (1985)
38. M. Ishida, M. Yoshida, S. Fukuta, K. Uemura, M. Iijima, K. Horiguchi, T. Harigaya, Analysis of prolactin gene expression and cleaved prolactin variants in the mouse testis and spermatozoa. J. Reprod. Dev. **56**, 567–574 (2010)
39. S. Nag, S. Sanyal, K.K. Ghosh, N.M. Biswas, Prolactin suppression and spermatogenic developments in maturing rats. A quantitative study. Horm. Res. **15**, 72–77 (1981)
40. P. Guillaumot, E. Tabone, M. Benahmed, Sertoli cells as potential targets of prolactin action in the testis. Mol. Cell. Endocrinol. **122**, 199–206 (1996)
41. H.N. Jabbour, H.O. Critchley, Potential roles of decidual prolactin in early pregnancy. Reproduction **121**, 197–205 (2001)
42. L. Bao, C. Tessier, A. Prigent-Tessier, F. Li, O.L. Buzzio, E.A. Callegari, N.D. Horseman, G. Gibori, Decidual prolactin silences the expression of genes detrimental to pregnancy. Endocrinology **148**, 2326–2334 (2007)
43. M. Zinger, M. McFarland, N. Ben-Jonathan, Prolactin expression and secretion by human breast glandular and adipose tissue explants. J. Clin. Endocrinol. Metab. **88**, 689–696 (2003)
44. T. Brandebourg, E. Hugo, N. Ben-Jonathan, Adipocyte prolactin: regulation of release and putative functions. Diabetes Obes. Metab. **9**, 464–476 (2007)
45. M. McFarland-Mancini, E. Hugo, J. Loftus, N. Ben-Jonathan, Induction of prolactin expression and release in human preadipocytes by cAMP activating ligands. Biochem. Biophys. Res. Commun. **344**, 9–16 (2006)
46. E.R. Hugo, D.C. Borcherding, K.S. Gersin, J. Loftus, N. Ben-Jonathan, Prolactin release by adipose explants, primary adipocytes, and LS14 adipocytes. J. Clin. Endocrinol. Metab. **93**, 4006–4012 (2008)
47. C. Ling, G. Hellgren, M. Gebre-Medhin, K. Dillner, H. Wennbo, B. Carlsson, H. Billig, Prolactin (PRL) receptor gene expression in mouse adipose tissue: increases during lactation and in PRL-transgenic mice. Endocrinology **141**, 3564–3572 (2000)
48. C. Ling, L. Svensson, B. Oden, B. Weijdegard, B. Eden, S. Eden, H. Billig, Identification of functional prolactin (PRL) receptor gene expression: PRL inhibits lipoprotein lipase activity in human white adipose tissue. J. Clin. Endocrinol. Metab. **88**, 1804–1808 (2003)
49. T.D. Brandebourg, J.L. Bown, N. Ben-Jonathan, Prolactin upregulates its receptors and inhibits lipolysis and leptin release in male rat adipose tissue. Biochem. Biophys. Res. Comm. **357**, 408–413 (2007)
50. E.A. Langan, K. Foitzik-Lau, V. Goffin, Y. Ramot, R. Paus, Prolactin: an emerging force along the cutaneous-endocrine axis. Trends Endocrinol. Metab. **21**, 569–577 (2010)
51. R.G. Richards, S.M. Hartman, Human dermal fibroblast cells express prolactin in vitro. J. Invest. Dermatol. **106**, 1250–1255 (1996)
52. K. Foitzik, E.A. Langan, R. Paus, Prolactin and the skin: a dermatological perspective on an ancient pleiotropic peptide hormone. J. Invest. Dermatol. **129**, 1071–1087 (2009)
53. K. Foitzik, K. Krause, F. Conrad, M. Nakamura, W. Funk, R. Paus, Human scalp hair follicles are both a target and a source of prolactin, which serves as an autocrine and/or paracrine promoter of apoptosis-driven hair follicle regression. Am. J. Pathol. **168**, 748–756 (2006)
54. C. Clapp, F.J. Lopez-Gomez, G. Nava, A. Corbacho, L. Torner, Y. Macotela, Z. Dueñas, Z. Ochoa, G. Noris, E. Acosta, E. Garay, G.M. de la Escalera, Expression of prolactin mRNA and of prolactin-like proteins in endothelial cells: evidence for autocrine effects. J. Endocrinol. **158**, 113–160 (1998)
55. M. Koizumi, K. Horiguchi, Y. Tomita, Y. Kato, T. Harigaya, Prolactin gene expression in the mouse nipple. J. Reprod. Dev. **49**, 465–472 (2003)
56. C. Clapp, G.Martinez. de la Escalera, Prolactins: novel regulators of angiogenesis. News Physiol. Sci. **12**, 231–237 (1997)
57. A.M. Corbacho, G.Martinez. de la Escalera, C. Clapp, Roles of prolactin and related members of the prolactin/growth hormone/placental lactogen family in angiogenesis. J. Endocrinol. **173**, 219–238 (2002)
58. A.M. Corbacho, Y. Macotela, G. Nava, L. Torner, Z. Dueñas, G. Noris, M.A. Morales, G.Martinez. de la Escalera, C. Clapp, Human umbilical vein endothelial cells express multiple prolactin isoforms. J. Endocrinol. **166**, 53–62 (2000)
59. A.M. Corbacho, G. Nava, J.P. Eiserich, G. Noris, Y. Macotela, I. Struman, G.M. de la Escalera, B.A. Freeman, C. Clapp, Proteolytic cleavage confers nitric oxide synthase inducing activity upon prolactin. J. Biol. Chem. **275**, 13183–13186 (2000)
60. A. Ochoa, P.Montes. de Oca, J.C. Rivera, Z. Dueñas, G. Nava, G.M. de la Escalera, C. Clapp, Expression of prolactin gene and secretion of prolactin by rat retinal capillary endothelial cells. Investig. Ophthalmol. Vis. Sci. **42**, 1639–1645 (2001)
61. C. Clapp, L. Torner, G. Gutierrez-Ospina, E. Alcantara, F.J. Lopez-Gomez, M. Nagano, P.A. Kelly, S. Mejia, M.A. Morales, G.M. de la Escalera, The prolactin gene is expressed in the hypothalamic-neurohypophyseal system and the protein is processed into a 14 kDa fragment with activity like 16 kDa prolactin. Proc. Natl. Acad. Sci. (USA) **91**, 10384–10388 (1994)
62. B.L. Hansen, G.N. Hansen, C. Hagen, Immunoreactive material resembling ovine prolactin in perikarya and nerve terminals of the rat hypothalamus. Cell Tissue Res. **226**, 121–131 (1982)
63. L. Torner, I.D. Neumann, The brain prolactin system: involvement in stress response adaptations in lactation. Stress **5**, 249–257 (2002)
64. L. Torner, S. Mejia, F.J. Lopez-Gomez, A. Quintanar, G. Martinez. de la Escalera, C. Clapp, A 14-kilodalton prolactin-

like fragment is secreted by the hypothalamo-neurohypophyseal system of the rat. Endocrinology **136**, 5454–5460 (1995)
65. M. Lkhider, S. Delpal, F. Le Provost, M. Ollivier-Bousquet, Rat prolactin synthesis by lactating mammary epithelial cells. FEBS Lett. **401**, 117–122 (1997)
66. D.R. Grattan, I.C. Kokay, Prolactin: a pleiotropic neuroendocrine hormone. J. Neuroendocrinol. **20**, 752–763 (2008)
67. R.J. Walsh, L.P. Mangurian, B.I. Posner, Prolactin receptors in the primate choroid plexus. J. Anat. **168**, 137–141 (1990)
68. R.J. Walsh, F.J. Slaby, B.I. Posner, A receptor-mediated mechanism for the transport of prolactin from blood to cerebrospinal fluid. Endocrinology **120**, 1846–1850 (1987)
69. S. Harvey, D. Rattray, M.-L. Baudet, E.J. Sanders, Ocular pituitary hormones in the chick embryo, in *Functional avian endocrinology*, ed. by A. Dawson, P.J. Sharp (Narosa Publishing House, New Delhi, 2005), pp. 403–414
70. Z. Dueňas, L. Torner, A.M. Corbacho, G. Gutierrez-Ospina, F. Lopez-Barrera, F.A. Barrios, P. Berger, G.Martinez. de la Escalera, C. Clapp, Inhibition of rat corneal angiogenesis by 16 kDa prolactin and by endogenous prolactin-like molecules. Investig. Ophthalmol. Vis. Sci. **40**, 2498–2505 (1999)
71. H. Quiroz, Z. Dueňas, F. Lopez-Barrera, G. Nava, A. Ochoa, G. Noris, G.Martinez. de la Escalera, C. Clapp, Detection of prolactin and prolactin mRNA in the eye of patients with retinopathy of prematurity. Investig. Ophthalmol. Vis. Sci. **41**, 12 (2000). (abstract 1766)
72. Z. Dueňas, J.C. Rivera, H. Quiroz-Mercado, J. Aranda, Y. Macotela, P.M. de Oca, F. Lopez-Barrera, G. Nava, J.L. Guerrero, A. Suarez, M. De Regil, G.M. del la Escalera, C. Clapp, Prolactin in eyes of patients with retinopathy of prematurity: implications of vascular regression. Investig. Ophthalmol. Vis. Sci. **45**, 2049–2055 (2004)
73. C.M. Shaw-Bruha, S.J. Pirrucello, J.D. Shull, Expression of the prolactin gene in normal and neoplastic human breast tissues and human mammary cell lines: promoter usage and alternative mRNA splicing. Breast Cancer Res. Treat. **44**, 243–253 (1997)
74. S. Gerlo, J.R.E. Davis, D.L. Mager, R. Kooijman, Prolactin in man: a tale of two promoters. BioEssays **28**, 1051–1055 (2006)
75. R. Telgmann, E. Maronde, K. Tasken, B. Gellersen, Activated protein kinase A is required for differentiation-dependent transcription of the decidual prolactin gene in human endometrial stromal cells. Endocrinology **138**, 929–937 (1997)
76. G.H. Reem, D.W. Ray, J.R. Davis, The human prolactin gene upstream promoter is regulated in lymphoid cells by activators of T-cells and by cAMP. J. Mol. Endocrinol. **22**, 285–292 (1999)
77. Y. Jiang, Y. Hu, J. Zhao, X. Zhen, G. Yan, H. Sun, The orphan nuclear receptor Nur77 regulates decidual prolactin expression in human endometrial stromal cells. Biochem. Biophys. Res. Commun. **404**, 628–633 (2011)
78. S. Handweger, R.G. Richards, E. Markoff, The physiology of decidual prolactin and other decidual protein hormones. Trends Endocrinol. Metab. **3**, 91–95 (1992)
79. E. Markoff, S. Barry, S. Handwerger, Influence of osmolality and ionic environment on the secretion of prolactin by human decidua in vitro. J. Endocrinol. **92**, 103–110 (1982)
80. E. Kiapekou, D. Loutradis, E. Patsoula, G.A. Koussidis, V. Minas, R. Bletsa, A. Antsaklis, S. Michalas, A. Makrigiannakis, Prolactin receptor mRNA expression in oocytes and preimplantation mouse embryos. Reprod. Biomed. Online **10**, 339–346 (2005)
81. A.K. Karabulut, R. Layfield, M.K. Pratten, The mechanism of growth-promoting effects of prolactin in embryogenesis—links to growth factors. Cell Tissue Organs **164**, 2–13 (1999)
82. A.K. Karabulut, M.K. Pratten, Species-specificity of growth-promoting effects of prolactin during rat embryogenesis. J. Anat. **192**, 1–12 (1998)
83. K. Ishibashi, M. Imai, Identification of four new members of the rat prolactin/growth hormone gene family. Biochem. Biophys. Res. Commun. **262**, 575–578 (1999)
84. D.J. Toft, D.I. Linzer, Identification of three prolactin-related hormones as markers of invasive trophoblasts in the rat. Biol. Reprod. **63**, 519–525 (2000)
85. N. Sahgal, G.T. Knipp, B. Liu, B.M. Chapman, G. Dai, M.J. Soares, Identification of two new nonclassical members of the rat prolactin family. J. Mol. Endocrinol. **24**, 95–108 (2000)
86. D.O. Wiemers, R. Ain, S. Ohboshi, M.J. Soares, Migratory trophoblast cells express a newly identified member of the prolactin gene family. J. Endocrinol. **179**, 335–345 (2003)
87. Y. Wang, J. Li, A.H. Yan Kwok, W. Ge, F.C. Leung, A novel prolactin-like protein (PRL-L) gene in chickens and zebrafish: cloning and characterization of its tissue expression. Gen. Comp. Endocrinol. **166**, 200–210 (2010)
88. B.A. Eipper, R.E. Mains, Structure and biosynthesis of pro-adenocorticotropin/endorphin and related peptides. Endocr. Rev. **1**, 1–27 (1980)
89. A.N. Eberle, Structure and chemistry of the peptide hormones of the intermediate lobe. Ciba Found. Symp. **81**, 13–31 (1981)
90. A.B. Bicknell, Identification of the adrenal protease that cleaves pro-gamma-MSH: the dawning of a new era in adrenal physiology? J. Endocrinol. **172**, 405–410 (2002)
91. S. Takeuchi, S. Takahashi, R. Okimoto, H.B. Schioth, T. Boswell, Avian melanocortin system: α-MSH may act as an autocrine/paracrine hormone. Ann. N.Y. Acad. Sci. **994**, 366–372 (2003)
92. K. Teshigawara, S. Takahashi, T. Boswell, Q. Li, S. Tanaka, S. Takeuchi, Identification of avian α-melanocyte-stimulating hormone in the eye: temporal and spatial regulation of expression in the developing chicken. J. Endocrinol. **168**, 527–537 (2001)
93. N. Lindqvist, U. Napankangas, J. Lindblom, F. Hallbook, Proopiomelanocortin and melanocortin receptors in the adult rat retino-tectal system and their regulation after optic nerve transaction. Euro. J. Pharmacol. **482**, 85–94 (2003)
94. L.-I. Larsson, Corticotropin-like peptides in central nerves and in endocrine cells of gut and pancreas. Lancet **2**, 1321–1323 (1977)
95. E. Saito, S. Iwasa, W.D. Odell, Widespread presence of large molecular weight adrenocorticotropin-like substances in normal rat extrapituitary tissues. Endocrinology **113**, 1010–1019 (1983)
96. E.S. Orwoll, J.W. Kendall, Beta-endorphin and adrenocorticotropin extrapituitary sites: gastrointestinal tract. Endocrinology **107**, 438–442 (1980)
97. S.I. Grigorakis, E. Anastasiou, K. Dai, A. Souvatzoglou, M. Alevizaki, Three mRNA transcripts of the proopiomelanocortin gene in human placenta at term. Eur. J. Endocrinol. **142**, 533–536 (2000)
98. P.D. Lyons, J.E. Blalock, Proopiomelanocortin gene expression and protein processing in rat mononuclear leukocytes. J. Neuroimmunol. **78**, 47–56 (1978)
99. D.A. Weigent, J.E. Blalock, Interactions between the neuroendocrine and immune systems: common hormones and receptors. Immunol. Rev. **100**, 79–108 (1987)
100. A. Franchini, E. Ottaviani, Immunoreactive POMC-derived peptides and cytokines in the chicken thymus and bursa of Fabricius microenvironments: age-related changes. J. Neuroendocrinol. **11**, 685–692 (1999)
101. A. Slominski, J. Wortsman, Neuroendocrinology of the skin. Endocr. Rev. **21**, 457–487 (2000)
102. R. Paus, V.A. Botchkarev, N.V. Botchkareva, L. Mecklenburg, T. Luger, A. Slominski, The skin POMC system (SPS). Leads and lessons from the hair follicle. Ann. N. Y. Acad. Sci. **20**, 350–363 (1999)

103. K. Seiffert, R. Granstein, Neuropeptides and neuroendocrine hormones in ultraviolet radiation-induced immunosuppression. Methods **28**, 97 (2002)
104. T.E. Scholzen, T. Brzoska, D.H. Kalden, M. Hartmeyer, M. Fastrich, T.A. Luger, C.A. Armstrong, J.E. Ansel, Expression of functional melanocortin receptors and proopiomelanocortin peptides by human dermal microvascular endothelial cells. Ann. N. Y. Acad. Sci. **20**, 239–253 (1999)
105. M. Tsatmali, J. Ancans, J. Yukitake, A.J. Thody, Skin POMC peptides: their actions at the human MC-1 receptor and roles in the tanning response. Pigment Cell Res. **13**, 125–129 (2000)
106. M. Nagahama, Y. Funasaka, M.L. Fernandez-Frez, A. Ohashi, A.K. Chakraborty, M. Ueda, M. Ichihashi, Immunoreactivity of alpha-melanocyte-stimulating hormones and beta-endorphin in cutaneous malignant melanoma and benign melanocytic naevi. Br. J. Dermatol. **138**, 981–985 (1998)
107. M. De Martin, F. Pecori Giraldi, F. Cavagnini, Cushing's disease. Pituitary **9**, 279–287 (2006)
108. A.E. Murphy, S. Harvey, Extrapituitary beta TSH and GH in early chick embryos. Mol. Cell. Endocrinol. **185**, 161–171 (2001)
109. A.E. Murphy, S. Harvey, Extrapituitary TSH in early chick embryos: Pit-1 dependence? J. Mol. Neurosci. **18**, 77–87 (2002)
110. F.J. Fernandez-Trujillo, A. Prada, C. Verastegui, Thyrotropin-like immunoreactivity in human retina: immunoreactive colocalization in ganglion cells in perivascular fibers. Neurochem. Int. **28**, 381–384 (1996)
111. J.A. Prada, C. Verastegui, N. Perez-Rios, M. Gonzalez-Moreno, F.J. Fernandez-Trujillo, Thyrotropin-like immunoreactivity in the developing chicken retina. Eur. J. Morphol. **38**, 34–40 (2000)
112. S.W. Kohl, G.J. Chader, Agonist effects on the intracellular cyclic AMP concentration of retinal pigment epithelial cells in culture. J. Neurochem. **42**, 287–289 (1984)
113. S.A. Joseph, K.M. Knigge, Localization and content of TSH in median eminence of the hypothalamus. Am. J. Physiol. **226**, 630–633 (1974)
114. W.J. DeVito, T.N. Spearman, J.M. Connors, G.A. Hedge, Subcellular localization of immunoreactive thyroid-stimulating hormone in the rat hypothalamus. Neuroendocrinology **42**, 459–466 (1986)
115. W.J. DeVito, Comparison of brain and pituitary immunoreactive prolactin by peptide mapping and lectin affinity chromatography. Endocrinology **125**, 2439–2444 (1989)
116. S. Hojvat, N. Emanuele, G. Baker, E. Connick, L. Kirsteins, A.M. Lawrence, Growth hormone (GH), thyroid-stimulating hormone (TSH), and luteinizing hormone (LH)-like peptides in the rodent brain: non-parallel ontogenetic development with pituitary counterparts. Brain Res. **256**, 427–434 (1982)
117. E.M. Smith, M. Phan, T.E. Kruger, D.H. Coppenhaver, J.E. Blalock, Human lymphocyte production of immunoreactive thyrotropin. Proc. Natl. Acad. Sci. USA **80**, 6010–6013 (1983)
118. J.R. Klein, The immune system as a regulator of thyroid hormone activity. Exp. Biol. Med. **231**, 229–236 (2006)
119. E.U. Bagriacik, Q. Zhou, H.C. Wang, J.R. Klein, Rapid and transient reduction in circulating thyroid hormones following systemic antigen priming: implications of functional collaboration between dendritic cells and thyroid. Cell. Immunol. **212**, 92–100 (2001)
120. J. Wang, M. Whetsell, J.R. Klein, Local hormone networks and intestinal T cells homeostasis. Science **275**, 1937–1939 (1997)
121. V.L. Scofield, D. Montufar-Solis, E. Cheng, M.K. Estes, J.R. Klein, Intestinal TSH production is localized in crypt enterocytes and in villus 'hotblocks' and is coupled to IL-7 production: evidence for involvement of TSH during acute enteric virus infection. Immunol. Lett. **99**, 36–44 (2005)
122. H.C. Wang, J. Dragoo, Q. Zhou, J.R. Klein, An intrinsic thyrotropin-mediated pathway of TNF-alpha production by bone marrow cells. Blood **101**, 119–123 (2003)
123. D.V. Harbour, T.E. Kruger, D. Coppenhaver, E.M. Smith, W.J. Meyer 3rd, Differential expression and regulation of thyrotropin (TSH) in T cells lines. Mol. Cell. Endocrinol. **64**, 229–241 (1989)
124. S. Varghese, D. Montufar-Solis, B.H. Vincent, J.R. Klein, Virus infection activates thyroid stimulating hormone synthesis in intestinal epithelial cells. J. Cell. Biochem. **105**, 271–276 (2008)
125. J.R. Klein, H.C. Wang, Characterization of a novel set of resident intrathyroidal bone marrow-derived hematopoietic cells: potential for immune-endocrine interactions in thyroid homeostasis. J. Exp. Biol. **207**, 55–65 (2004)
126. J.S. Schaefer, J.R. Klein, Immunological regulation of metabolism—a novel quintessential role for the immune system in health and disease. FASEB J. **25**, 29–34 (2011)
127. B.H. Vincent, D. Montufar-Solis, B.B. Teng, B.A. Amendt, J. Schaefer, J.R. Klein, Bone marrow cells produce a novel TSHbeta splice variant that is upregulated in the thyroid following systemic virus infection. Genes Immun. **10**, 18–26 (2009)
128. J.S. Schaefer, J.R. Klein, A novel thyroid stimulating hormone beta-subunit isoform in human pituitary, peripheral blood leukocytes, and thyroid. Gen. Comp. Endocrinol. **162**, 241–244 (2009)
129. E. Bodo, B. Kany, E. Gaspar, J. Knuver, A. Kromminga, Y. Ramot, T. Biro, A. Tiede, N. van Beek, B. Poeggeler, K.C. Meyer, B.E. Wenzel, R. Paus, Thyroid-stimulating hormone, a novel, locally produced modulator of human epidermal functions, is regulated by thyrotropin-releasing hormone and thyroid hormones. Endocrinology **151**, 1633–1642 (2010)
130. B. Poeggeler, J. Knuever, E. Gaspar, T. Biro, M. Klinger, E. Bodo, R.J. Wiesner, B.E. Wenzel, R. Paus, Thyrotropin powers human mitochondria. FASEB J. **24**, 1525–1531 (2010)
131. N. Shirasawa, M. Shiino, Y. Shimizu, H. Nogami, S. Ishii, Immunoreactive luteinizing hormone (ir-LH) cells in the lung and stomach of chick embryos. Cell Tissue Res. **283**, 19–27 (1996)
132. D.A. Thompson, M.I. Othman, Z. Lei, X. Li, Z.H. Huang, D.M. Eadie, C.V. Rao, Localization of receptors for luteinizing hormone/chorionic gonadotropin in neural retina. Life. Sci. **63**, 1057–1064 (1998)
133. E. Patsoula, D. Loutradis, P. Drakakis, K. Kallianidis, R. Bletsa, S. Michalas, Expression of mRNA for the LH and FSH receptors in mouse oocytes and preimplantation embryos. Reproduction **121**, 455–461 (2001)
134. J.Y. Chen, M.J. Chiou, Molecular cloning and functional analysis of the zebrafish luteinizing hormone beta subunit (LH<beta>) promoter. Fish Physiol. Biochem. **36**, 1253–1262 (2010)
135. R.L. Bowen, M.A. Smith, P.L. Harris, Z. Kubat, R.N. Martins, R.J. Castellani, G. Perry, C.S. Atwood, Elevated luteinizing hormone expression colocalizes with neurons vulnerable to Alzheimer's disease pathology. J. Neurosci. Res. **70**, 514–518 (2002)
136. H. Croxatto, J. Arrau, H. Croxatto, Luteinizing hormone-like activity in human median eminence extracts. Nature **204**, 584–585 (1964)
137. H.P. Noteborn, J. de Koning, F.H. de Jong, I. Ebels, C.A. Salemink, Identification of luteinizing hormone-like proteins in the ovine pineal gland. J. Pineal Res. **12**, 118–127 (1992)
138. V.A. Isachenkov, O.G. Krivosheev, E.P. Badosov, N.A. Nabatchikova, Extrapituitary localization of luteinizing hormone in rats. Vopr. Med. Khim. **27**, 527–534 (1981)
139. A.C. Wilson, M.S. Salamat, R.J. Haasl, K.M. Roche, A. Karande, S.V. Meethal, E. Terasawa, R.L. Bowen, C.S. Atwood,

Human neurons express type I GnRH receptor and respond to GnRH I by increasing luteinizing hormone expression. J. Endocrinol. **191**, 651–663 (2006)
140. A.A. Al-Hader, Z.M. Lei, C.V. Rao, Novel expression of functional luteinizing hormone/chorionic gonadotropin receptors in cultured glial cells from neonatal rat brains. Biol. Reprod. **56**, 501–507 (1997)
141. R. Lathe, Hormones and the hippocampus. J. Endocrinol. **169**, 205–231 (2001)
142. I.S. Parhar, T. Soga, S. Ogawa, Y. Sakuma, FSH and LH-beta subunits in the preoptic nucleus: ontogenic expression in teleost. Gen. Comp. Endocrinol. **132**, 369–378 (2003)
143. M. Pandolfi, A.G. Pozzi, M. Canepa, P.G. Vissio, A. Shimizu, M.C. Maggese, G. Lobo, Presence of beta-follicle-stimulating hormone and beta-luteinizing hormone transcripts in the brain of *Cichlasoma dimerus* (Perciformes: Cichlidae): effect of brain-derived gonadotropins on pituitary hormone release. Neuroendocrinology **89**, 27–37 (2009)
144. P.K. Hotakainen, E.M. Serlachius, S.I. Lintula, H.V. Alfthan, J.P. Schroder, U.E. Stenman, Expression of luteinizing hormone and chorionic gonadotropin beta-subunit messenger-RNA and protein in human peripheral blood leukocytes. Mol. Cell. Endocrinol. **162**, 79–85 (2000)
145. P. Sabharwal, S. Varma, W.B. Malarkey, Human thymocytes secrete luteinizing hormone: an autocrine regulator of T-cell proliferation. Biochem. Biophys. Res. Commun. **187**, 1187–1192 (1992)
146. So. W-K, H.-F. Kwok, W. Ge, Zebrafish gonadotropins and their receptors: II. Cloning and characterization of zebrafish follicle-stimulating hormone and luteinizing hormone subunits—their spatial-temporal expression patterns and receptor specificity. Biol. Reprod. **72**, 1382–1396 (2005)
147. A. Al-Timimi, H. Fox, Immunohistochemical localization of follicle-stimulating hormone, luteinizing hormone, growth hormone, adrenocorticotrophic hormone and prolactin in the human placenta. Placenta **7**, 163–172 (1986)
148. G.D. Sorenson, O.S. Pettengill, T. Brinck-Johnsen, C.C. Cate, L.H. Maurer, Hormone production by cultures of small-cell carcinoma of the lung. Cancer **47**, 1289–1296 (1981)
149. M. Fukayama, Y. Hayashi, M. Koike, H. Hajikano, S. Endo, H. Okumura, Human chorionic gonadotropin in lung and lung tumors. Immunohistochemical study on unbalanced distribution of subunits. Lab. Investig. **55**, 433–443 (1986)
150. A.G. Davies, I.F. Duncan, S.S. Lynch, Autoradiographic localization of 125I-labeled follicle-stimulating hormone in the rat hypothalamus. J. Endocrinol. **66**, 301–302 (1975)
151. C. Chu, G. Gao, W. Huang, A study on colocalization of FSH and its receptor in rat hippocampus. J. Mol. Histol. **39**, 49–55 (2008)
152. B. Baccetti, G. Collodel, E. Costantino-Ceccarini, A. Eshkol, L. Gambera, E. Moretti, M. Strazza, P. Piomboni, Localization of human follicle-stimulating hormone in the testis. FASEB J. **12**, 1045–1054 (1998)
153. C. Chu, B. Xu, H. Weiquan, A study on expression of FSH and its effects on the secretion of insulin and glucagon in rat pancreas. Tissue Cell **42**, 370–375 (2010)
154. E. Patsoula, D. Loutradis, P. Drakakis, L. Michalas, R. Bletsa, S. Michalas, Messenger RNA expression for the follicle-stimulating hormone receptor and luteinizing hormone receptor in human oocytes and preimplantation-stage embryos. Fertil. Steril. **79**, 1187–1193 (2003)
155. P.S. Mandrekar, A.R. Sheth, V.M. Doctor, J.P. Zaveri, N.A. Sheth, Immunocytochemical localization of follicle stimulating hormone in normal human stomach. Anat. Rec. **227**, 334–339 (1990)
156. S.K. Shahani, S.M. Gupta, P.K. Meherji, Lymphocytes—their possible endocrine role in the regulation of fertility. Am. J. Reprod. Immunol. **35**, 1–4 (1996)
157. K.S. Hurkadli, M.G. Shah, D.S. Pardanani, A.R. Sheth, De novo biosynthesis of FSH like peptide by the human prostate. Life Sci. **47**, 391–400 (1990)
158. S.V. Garde, A.R. Sheth, M.G. Shah, S.A. Kulkarni, Prostate—an extrapituitary source of follicle-stimulating hormone (FSH): occurrence, localization, and de novo biosynthesis and its hormonal modulation in primates and rodents. Prostate **18**, 271–287 (1991)
159. S.V. Garde, A.R. Sheth, R. Joseph, C.J. Panchal, R.F. Chinoy, N.A. Sheth, Occurrence and de novo biosynthesis of follicle stimulating hormone (FSH) in benign and malignant conditions of human breast. Cancer Lett. **75**, 1–9 (1993)
160. W. Zheng, M.S. Magid, E.E. Kramer, Y.T. Chen, Follicle-stimulating hormone receptor is expressed in human ovarian surface epithelium and fallopian tube. Am. J. Pathol. **148**, 47–53 (1996)
161. D. Mizrachi, M. Shemesh, Follicle-stimulating hormone receptor and its messenger ribonucleic acid are present in the bovine cervix and can regulate cervical prostanoid synthesis. Biol. Reprod. **61**, 776–784 (1999)
162. M. Shemesh, D. Mizrachi, M. Gurevich, Y. Stram, L.S. Shore, M.J. Fields, Functional importance of bovine myometrial and vascular LH receptors and cervical FSH receptors. Semin. Reprod. Med. **19**, 87–96 (2001)
163. C. Bole-Feysot, V. Goffin, M. Edery, N. Binart, P.A. Kelly, Prolactin (PRL) and its receptor: action, signal transduction pathways and phenotypes observed in PRL receptor knockout mice. Endocr. Rev. **19**, 225–268 (1998)
164. E. Nagy, I. Berczi, Hypophysectomized rats depend on residual prolactin for survival. Endocrinology **128**, 2776–2784 (1991)
165. B.P. Meij, J.A. Mol, T.S. van den Ingh, M.M. Bevers, H.A. Hazewinkel, A. Rijnberk, Assessment of pituitary function after transsphenoidal hypophysectomy in beagle dogs. Domest. Anim. Endocrinol. **14**, 81–97 (1997)
166. B.P. Meij, J.A. Mol, M.M. Bevers, A. Rijnberk, Residual pituitary function after transsphenoidal hypophysectomy in dogs with pituitary-dependent hyperadrenocorticism. J. Endocrinol. **155**, 531–539 (1997)
167. D. Morishita, M. Wakita, S. Hoshino, Effect of hypophysectomy on insulin-like growth factor (IGF)-1 binding activity of serum in chickens. Comp. Biochem. Physiol. Comp. Physiol. **104**, 261–265 (1993)
168. P.S. Hopkins, A.L. Wallace, G.D. Thorburn, Thyrotrophin concentrations in the plasma of cattle, sheep, and foetal lambs as measured by radioimmunoassay. J. Endocrinol. **64**, 371–387 (1975)
169. S.H. Shin, S.G. Vincent, C. Maltman, M.C. Obonsawin, J.C. Stokreef, C.W. Reifel, Pulsatile release of immunoreactive luteinizing hormone (irLH) in hypophysectomized male rats. Biol. Reprod. **35**, 1115–1122 (1986)
170. P.P. Morosini, N. Campanella, G.F. Ferretti, P. Carletti, Hypophyseal gonadotropins after GnRH in patients with hypophyseal tumors and after hypophysectomy. Boll. Soc. Ital. Biol. Sper. **56**, 1248–1251 (1980)
171. J.M. Hanson, H.S. Kooistra, J.A. Mol, E. Teske, B.P. Meij, Plasma profiles of adrenocorticotropic hormone, cortisol, alpha-melanocyte-stimulating hormone, and growth hormone in dogs with pituitary-dependent hyperadrenocorticism before and after hypophysectomy. J. Endocrinol. **190**, 601–609 (2006)
172. P.J. Selman, J.A. Mol, G.R. Rutteman, E. van Garderen, A. Rijnberk, Progestin-induced growth hormone excess in the dog originates in the mammary gland. Endocrinology **134**, 287–292 (1984)

173. J.E. Eigenmann, Acromegaly in the dog. Vet. Clin. North Am. Small Anim. Pract. **14**, 827–836 (1984)
174. H.S. Kooistra, G. Voorhout, P.J. Selman, A. Rijnberk, Progestin-induced growth hormone (GH) production in the treatment of dogs with congenital GH deficiency. Domest. Anim. Endocrinol. **15**, 93–102 (1998)
175. K.I. Alexandraki, A.B. Grossman, The ectopic ACTH syndrome. Rev. Endocr. Metab. Disord. **11**, 117–126 (2010)
176. M.N. Dizon, D.L. Vesely, Gonadotropin-secreting pituitary tumor associated with hypersecretion of testosterone and hypogonadism after hypophysectomy. Endocr. Pract. **8**, 225–231 (2002)
177. D.A. Weigent, J.E. Blalock, Associations between the neuroendocrine and immune systems. J. Leukoc. Biol. **58**, 137–150 (1995)
178. H.O. Besedovsky, A.D. Rey, Physiology of psychoneuroimmunology: a personal view. Brain Behav. Immun. **21**, 34–44 (2007)
179. K.L. Hull, F. Nette, S. Harvey, Bidirectional communication between the immune and neuroendocrine systems: role of growth hormone, in *Avian endocrinology*, ed. by A. Dawson, C.M. Chaturvedi (Narosa Publishing Hourse, New Delhi, 2001), pp. 437–446