Title: Multiple signaling pathways convey central and peripheral signals to regulate pituitary function: lessons from human and non-human primate models

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Abstract

The anterior pituitary gland is a key organ involved in the control of multiple physiological functions including growth, reproduction, metabolism and stress. These functions are controlled by five distinct hormone-producing pituitary cell types that produce growth hormone (somatotropes), prolactin (lactotropes), adrenocorticotropin (corticotropes), thyrotropin (thyrotropes) and follicle stimulating hormone/luteinizing hormone (gonadotropes). Classically, the synthesis and release of pituitary hormones was thought to be primarily regulated by central (neuroendocrine) signals. However, it is now becoming apparent that factors produced by pituitary hormone targets (endocrine and non-endocrine organs) can feedback directly to the pituitary to adjust pituitary hormone synthesis and release. Therefore, pituitary cells serve as sensors to integrate central and peripheral signals in order to fine-tune whole-body homeostasis, although it is clear that pituitary cell regulation is species-, age- and sex-dependent. The purpose of this review is to provide a comprehensive, general overview of our current knowledge of both central and peripheral regulators of pituitary cell function and associated intracellular mechanisms, focusing on human and non-human primates.

Outline

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1. Introduction: the complexity and versatility of actions of the pituitary gland.

The pituitary gland, also known as the “master gland”, is a fundamental regulator of a plethora of relevant physiological functions such as growth, puberty, reproduction, lactation, metabolism and stress. To exert its function, the pituitary receives and processes the information originating from central and peripheral signals (as illustrated in **Figure 1**) and appropriately conveys it to several, key target endocrine and non-endocrine organs [1]. Thus, to achieve their goal, these complex networks of multiple regulatory signals must be integrated together to finely modulate the synthesis and release of various pituitary hormones, which, in turn, will be responsible to control the function of various organs involved in the vital processes mentioned above [1].

The pituitary gland is located at the *sella turcica*, a depression in the sphenoid bone, at the base of the brain [2] and is comprised of the adenohypophysis [consisting of the anterior (subject of this review) and intermediate lobes] and the neurohypophysis (or posterior lobe), which are two distinct structures from the morphological and functional point of view, which display a strong developmental and functional interplay [3].The adenohypophysis develops from an upward invagination of the oral ectoderm, named the Rathke’s pouch [4], which contains undifferentiated proliferative progenitors that differentiate into five hormone-producing cell types: growth hormone (GH)-producing or somatotrope cells, prolactin-producing or lactotrope cells, adrenocorticotropin (ACTH)-producing or corticotrope cells, thyrotropin (TSH)-producing or thyrotrope cells, and follicle stimulating hormone (FSH)/luteinizing hormone (LH)-producing or gonadotrope cells [1]. Remarkably, the synthesis and release of these pituitary hormones (GH, PRL, ACTH, TSH, FSH and LH) and the subsequent fundamental actions on the numerous physiological processes cited above are finely tuned by an intricate interplay among many primary regulators (**Figure 1**). Specifically, the actions of multiple central (mainly hypothalamic) and peripheral signals, with their specific receptors located at the pituitary cells, are directly orchestrated and integrated at the intracellular signal transduction level to subsequently regulate pituitary hormone secretion.

Classically, the primary control of pituitary hormone secretion was thought to reside in the hypothalamus. The hypothalamic hormones involved in pituitary cell regulation have changed during vertebrate evolution. For example, for somatotropes, somatostatin (SST), GH-releasing factor (GHRH), and PACAP are considered the main regulators in teleosts, amphibians and reptiles. In contrast, PACAP does not have an obvious role in birds and mammals, wherein GHRH and SST regulate GH secretion through a tight interplay (for review, see [5]). There are many other examples of evolutionary differences in the number and nature of regulatory molecules implicated in the control of species-dependent pituitary hormone synthesis and release. Although a plethora of data has been generated using non-primate models (rats, mice, etc.), more limited information has been generated in humans due to the obvious intrinsic research limitations to explore pituitary physiology; however, non-human primates have emerged as suitable tools to

model human pituitary function. Therefore, the present review provides a comprehensive overview of the different central and peripheral regulators of pituitary function and their associated intracellular mechanisms, primarily focusing on studies performed in humans and non-human primates.

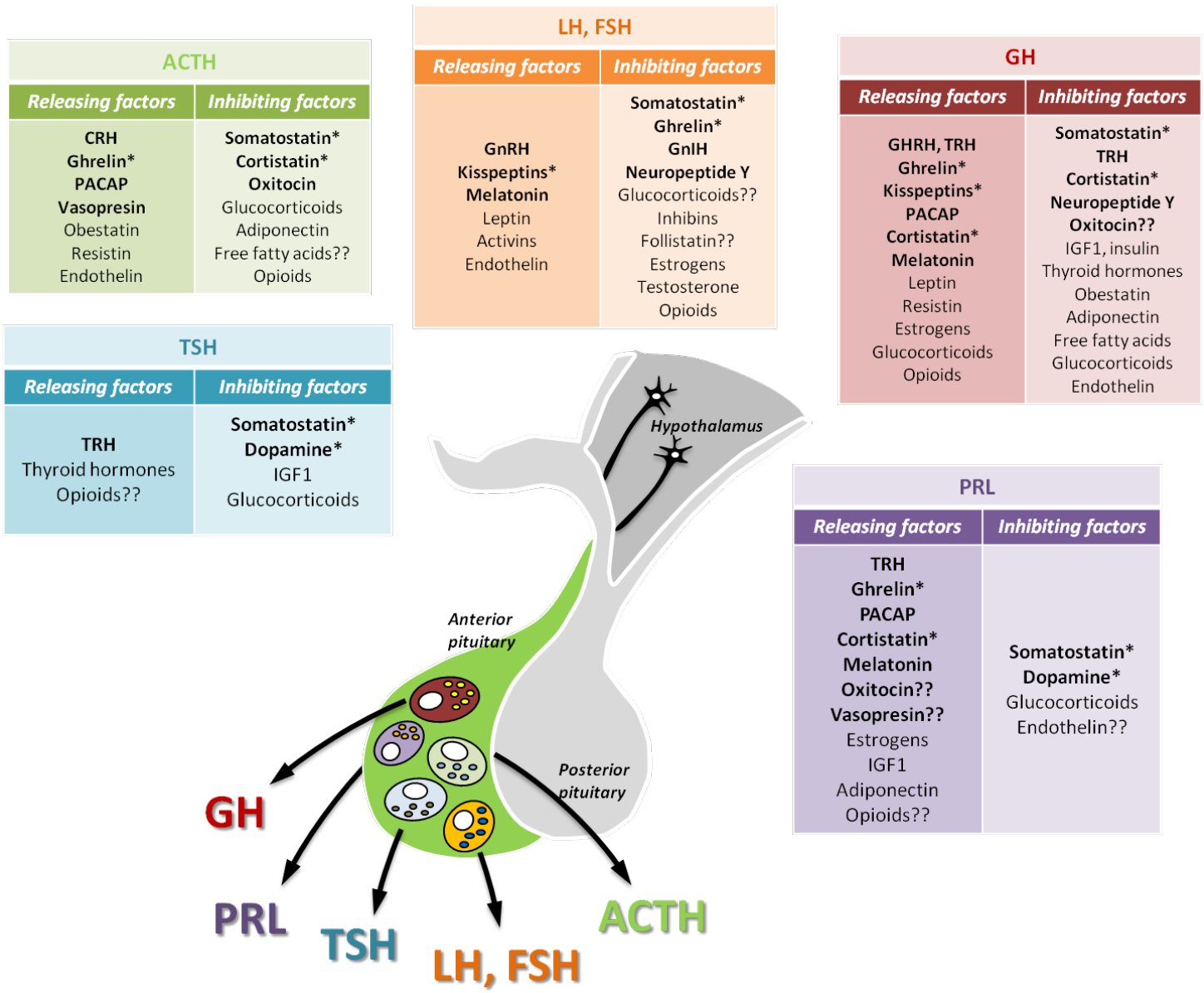

Figure 1. Representative model summarizing central and peripheral regulators involved in the modulation of the function of different cell types comprising the anterior pituitary gland. This model is based on the studies performed in human and non-human primates. Question marks (?) indicate regulators whose action have not been fully defined. Those factors shown in bold are primarily considered neuroendocrine factors, while those shown in standard type are considered coming from systemic sources. Those factors demarcated by asterisks (*) can be produced by central and systemic tissues.

2. Non-human primates as suitable model for the study of human physiology.

The vast majority of the knowledge gathered to date about the regulation of human pituitary cell function has been generated through the use of laboratory rodents and human (patho)physiological samples (such as fetal and tumoral cell cultures). However, despite the significant information generated using these approaches, there are still a number of aspects of the regulation of normal adult human pituitary physiology that remain unclear. Therefore, our laboratory and others have used pituitary cells obtained from non-human primates. Specifically, baboons (*Papio sp*) and rhesus monkeys

(*Macaca mulatta* and *Macaca fascicularis*), three species belonging to the *Cercopithecoidea* family (the Old World monkeys) [6], are the most commonly used non-human primates in biomedical research. Indeed, results obtained from non-human primate models are used for translational research to humans [7-9]. Comparative genomic analyses exploring their molecular phylogeny and their evolutionary process have revealed that the separation of this family from the *Hominoidea* family occurred approximately 25 million years ago, which is relatively recent compared to the separation of rodent lineages with eutherian mammals that happened between 65 and 85 million years ago [10, 11]. Indeed, *Macaca mulatta* and *Macaca fascicularis* show a genetic identity of 93,54% and 92,83% with *Homo sapiens*, respectively [12, 13]. Additionally, the fact that olive baboon (*Papio anubis*) also shares a high fidelity at genomic, proteomic and physiological levels, together with the *in vivo* and *in vitro* conservation of the pituitary regulatory systems (as discussed below), makes these species suitable models to study the effects of different peptides/hormones on pituitary cell function, which cannot be evaluated in healthy human subjects. Hence, current evidence supports the notion that non-human primates can be considered as valuable and useful models to study normal, non-pathological, human physiology [7, 14-18].

3. Central modulators of pituitary cell function.

3.1. Hypothalamic modulators of pituitary cell function.

In 1965, it was shown for the first time that hypothalamic extracts induced GH release [19]. Since that time, the understanding of the neuroendocrine control of the somatotrope, as well as other pituitary cell types has led to the identification of a plethora of central factors that regulate pituitary function. Below is an overview of these central factors, shown in bold in Figure 1.

3.1.1. GH-Releasing Hormone (GHRH)

GHRH is a 44-amino acid peptide hormone originally isolated and identified from a pancreatic tumour causing acromegaly [20, 21] and subsequently shown to be produced by neurons located in the arcuate nucleus (ARC) of the human hypothalamus [22]. GHRH has been unequivocally accepted as the main hypophysiotropic neuropeptide in the generation and maintenance of pulsatile/episodic GH secretion in humans [23, 24], as well as in female rhesus monkey [25]. Specifically, either GHRH antagonism or ARC nucleus ablation results in an impairment of GH pulsatility or complete loss of GH secretion, respectively [24, 26]. In addition, administration of synthetic GHRH reliably increases GH release in humans [26], as well as in female baboon pituitary cultures (*Papio anubis*) [27]. Previous studies have shown that GHRH specifically couples to GHRH receptor in somatotrope cells to activate multiple intracellular signaling mechanisms. Thus, in several species, including humans and baboons, it has been described that GHRH/GHRH-R coupling significantly stimulates GH release by activating adenylate cyclase (AC), increasing cAMP production, which in turn leads to an increase in protein kinase A (PKA) activity [15, 27, 28]. Additionally, it has been described that GHRH also requires other signaling pathways such as intracellular and extracellular Ca^{2+}, NOS/NO/GC/cGMP and/or PKC/PLC pathways to stimulate GH release in other species including non-human primates [15, 29].

3.1.2. Somatostatin (SST)

SST or somatotropin-release inhibitory factor (SRIF) is derived from a 116 precursor that produces two different cyclic forms by alternative post-translational processing: somatostatin-14 and somatostatin-28. SST biological actions are mediated by its specific interaction with at least 5 receptor subtypes (SST_{1-5} receptors), which exhibit the structure of typical G-protein-coupled receptors (GPCRs) with seven transmembrane domains. Similar expression profile for all five receptor subtypes has been reported in human and baboon pituitary extracts and pituitary cell cultures, where subtypes 2 and 5 are the predominant subtypes [30-32]. Specific SST binding elicits the recruitment of several downstream transduction pathways including AC, protein phosphatases, cGMP dependent protein kinases, and calcium and other ion channels [33-35]. Overall, SST exhibits inhibitory actions on virtually all (neuro)endocrine secretions. At the anterior pituitary, SST is the main inhibitory signal for somatotrope function by directly inhibiting GH release as well as antagonizing the GH stimulatory effect elicited by either GHRH or ghrelin [23, 33]. Interestingly, in non-human primates, it has been shown that SST can exert both negative and positive effects on GH release [31]. Specifically, it has been documented that high doses of SST do not alter basal GH secretion but block both GHRH- and ghrelin-induced GH release [31]. In contrast, low doses of SST significantly stimulate GH release, to a similar extent to that elicited by GHRH or ghrelin, in primary pituitary cultures from female adult baboons (*Papio anubis*) [31]. In this

experimental model, SST inhibitory actions were shown to be mediated through activation of SST_1 and SST_2 receptors, which involved AC and MAPK signaling. In contrast, SST5 receptor signaling through AC/cAMP/PKA and intracellular calcium pathways mediated the stimulatory action of low doses of SST on GH release. In addition, it has been reported that the main regulators of the hypothalamic-GH axis (GHRH, ghrelin and SST) in baboons can also regulate the expression of their receptors by both homologous and heterologous mechanisms [27].

Besides the well described SST role on somatotrope function, it has also been documented that SST regulates other anterior pituitary cell types in several animal models, as well as humans [36]. Specifically, in human fetal pituitary cultures, SST has been reported to exert an inhibitory effect on TSH, PRL and ACTH release, which mainly involves the differential participation of SST_2 and SST_5 receptors [36, 37]. SST-mediated inhibition of PRL, ACTH, TSH, LH or FSH has also been described in healthy humans [38-43]. However, contradictory results have been published showing no significant effects of SST on spontaneous PRL or ACTH secretion [44].

3.1.3. Ghrelin

Ghrelin is a 28 amino acid peptide hormone originally isolated from the stomach of humans and rats [45] based on its strong GH-releasing ability, which is mediated through the activation of the GH-secretagogue receptor 1a (GHSR1a), first identified as anorphan GPCR and later identified as the receptor for synthetic GH-secretagogues. Soon after its discovery and isolation, ghrelin was also found to be present in multiple organs and tissues. At the level of the central nervous system, ghrelin expression has been detected in the pituitary and hypothalamus [46, 47]. Ghrelin circulates in two main forms, octanoylated (acylated) and deoctanoylated (deacylated). Acyl-ghrelin was the first form to be identified, based on its ability to stimulate GH release upon GHSR1a activation. In contrast, unacylated-ghrelin lacks the GH stimulatory action elicited by acyl-ghrelin on somatotrope cells. Although acylated ghrelin stimulates GH secretion directly acting on human [48] and monkey pituitaries [15], an indirect hypothalamic-mediated mechanism involving an increase in GHRH and a weak inhibition of SST neurons, has also been documented [15, 49-51]. In terms of signal transduction, ghrelin/GHSR1a interaction at the pituitary level has been shown to activate multiple signaling cascades, including phospholipase C (PLC), protein kinase C (PKC), PKA [52], intracellular and extracellular Ca^{2+} or mitogen-activated protein kinases [50, 53, 54]. Interestingly, besides its action on somatotrope function, studies in humans and non-human primate models have revealed that ghrelin also regulates anterior pituitary function by inhibiting LH and FSH secretion and consequently modulating reproductive function [51, 55, 56], as well as stimulating PRL and ACTH release [51, 57-61].

3.1.4. Pituitary Adenylate Cyclase Activating Polypeptide (PACAP)

PACAP is a C-terminally amidated peptide with two forms of 38 and 27 residues, which belongs to the VIP/secretin/glucagon superfamily of peptides. It was first isolated from ovine hypothalamic extracts based on its ability to stimulate AC activity in rat pituitary cells. In mammals, contradictory findings about the role of PACAP on GH secretion have been documented. Some studies report a stimulatory action while others, show no effect on GH release [23]. In human somatotrope tumour cells, PACAP was able to increase both cAMP production and GH release similarly to that previously reported for GHRH although in a less potent manner [62]. This stimulatory action was shown to involve the activation of voltage-operated/gated Ca^{2+}channels via AC-PKA pathway [23, 63]. Conversely, in healthy human volunteers, intravenous PACAP administration was unable to induce GH and gonadotropins release [64]. However, it has been described that intravenous PACAP administration can regulate ACTH and PRL secretion in different mammalian species including humans [64-66]. PACAP elicits its biological action by coupling to different G-protein-coupled receptors classified into three groups based on their differential affinity for PACAP or VIP. Thus, PACAP type 1 receptors (PAC1R) are more specific for PACAP while VPAC1 and VPAC2 receptors present similar affinity for either PACAP isoforms or VIP. Additionally, PAC1R alternative splicing generates at least five different PAC1R subtypes that seem to trigger different signalling pathways as well as their relative affinity for PACAP isoforms [66, 67]. All these receptors are widely distributed throughout the brain, including hypothalamus and pituitary, as well as in peripheral organs [66, 67].

3.1.5. Gonadotropin Releasing Hormone (GnRH)

GnRH is a hypothalamic decapeptide released in a pulsatile manner that is essential in the maintenance of reproductive function throughout the episodic secretion of gonadotropic pituitary hormones [68]. Indeed, the direct effect of GnRH on LH and FSH release in healthy subjects is firmly established [69]. In line with this, a stimulation of LH secretion in response to exogenous GnRH has been also reported in macaques [70]. Additionally, a significant increase on LH secretion after GnRH treatment has been observed in primary pituitary cell cultures from baboons. In most vertebrates,

including humans, at least two GnRH receptor (GnRH-R) isoforms have been described, type I and type II GnRH-R. Both isoforms are expressed at the pituitary and non-pituitary level, including reproductive and non-reproductive tissues. Type I GnRH-R is the functional receptor isoform that belongs to the G-protein-coupled receptor superfamily with seven transmembrane domains, a hydrophilic extracellular domain and a hydrophobic cytosolic tail. This GnRH-R differs from others GPCRs in its short cytosolic tail that slows receptor internalization and prevents rapid desensitation [71] Human type II GnRH-R is a non-functional isoform due to the presence of a frameshift and a premature stop codon in its sequence [71, 72]. The signaling pathways involved in the GnRH actions cited above were NOS/NO/GC/cGMP pathway and extracellular Ca^{2+} mobilization but not AC pathway [73]. On the other hand, in higher vertebrates, including humans and non-human primates, no data have been documented on the effect of GnRH on GH release under normal conditions, while several studies documented a modulatory effect of GnRH on GH release under different pathological disorders [74].

3.1.6. Kisspeptins

Kisspeptin (KISS1) is an amidated neurohormone first identified as a key regulator involved in GnRH control at the level of the hypothalamus. KISS1 gene encodes a 145 amino acids precursor protein that can originate four possible derivate peptides with 54, 14, 13 or 10 amino acids [75-78]. All these peptides have the same efficacy and affinity for their receptor, GPR54, being kisspeptin-10 the most commonly used in biomedical research [79, 80]. In addition to its central effects, KISS1 and its receptor (GPR54, KISS1R or AXOR12) are widely distributed in different tissues including pituitary gland, suggesting that this neurohormone system could play an important role in the control of hypophyseal hormone release [75, 76, 79, 81-83]. Specifically, in non-human primates (*Macaca mulatta*), kisspeptin-positive cells have been described to be present in intermediate lobe co-localizing with α-MSH, in neural lobe with GnRH axons, and, only in 50% with ACTH-positive cells in the periphery of anterior lobe of pituitary [79, 84]. In humans, kisspeptin-54 and kisspeptin-10 were able to similarly induce LH and FSH levels. However, both kisspeptins were less potent in stimulating gonadotropins levels than GnRH [69, 85]. Furthermore, intravenous administration of kisspeptin-10 in *Macaca mulatta* increased LH levels, an effect apparently mediated by hypothalamic actions (GnRH-induced), while other hypophyseal hormones were not altered [79]. In addition, results from studies on women did not confirm a role of kisspeptinson GH, TSH and PRL release after acute or chronic administration [86]. However, kisspeptins seem to exert a direct effect on primary pituitary cell cultures from baboons. Specifically, kisspeptin-10 stimulated GH and LH secretion and mRNA levels after short- and long-term exposure (4 to 48 h), at a broad range of doses (10^{-14} to 10^{-6}) [73]. In contrast, kisspeptin-10 did not alter FSH, PRL, ACTH or TSH secretion/expression. The signaling pathways involved in the regulation of GH and LH pituitary hormones by kisspeptins were phospholipase C, protein kinase C, MAPK, and intracellular Ca^{2+} mobilization. Interestingly, LH, but not GH, release also involved mammalian target of rapamycin (mTOR) and PI3K [73]. Taken together, *in vitro* and *in vivo* evidences suggest that kisspeptins could play a relevant role, at least, on LH regulation and seems to exert the effects not only through hypothalamic actions but also directly on the pituitary gland.

3.1.7. Gonadotropin-inhibitory Hormone (GnIH)

Gonadotropin-inhibitory hormone (GnIH) was initially discovered in the quail hypothalamus, wherein its inhibitory action on gonadotropin secretion from cultured anterior pituitary cells was documented [87, 88]. Subsequent studies described that avian GnIH was well conserved across various mammals and primates including humans, in which an inhibitory action on reproductive function was also reported for these GnIH orthologs [87, 88]. In particular, the functional human GnIH ortolog, RFRP-3, as well as other GnIH peptides are called RF-related peptides (RFRPs) in that they share a common structural feature with kisspeptins: the presence of a C-terminal Arg-Phe-NH2 (RFamide) motif, thus belongings to the RFamide peptide family members. In humans and non-human primates, GnIH/RFRP neural cell bodies are located at the dorsomedial region and intermediate periventricular nucleus of the hypothalamus, respectively. In addition, human GnIH/RFRP expression in cell bodies was also documented in other areas of the brain and in neuronal fibres projected to the median eminence [89-93]. GPR147 (NPFF1, OT7T022) has been identified as the cognate receptor that mediates GnIH/RFRPs inhibitory actions. In this sense, it has been reported in a rodent ovarian cell line that RFRPs action reduces intracellular cAMP levels, suggesting that GPR147 couples to Gi protein [94]. Additionally, in a mouse gonadotrope cell line, it has been reported that the inhibitory action of RFRPs on gonadotropin secretion is mediated by the inhibition of AC/cAMP/PKA/ERK pathway [95]. Moreover, human RFRP-3 is able to inhibit, *in vivo* and *in vitro*, GnRH-induced gonadotropin release in sheep through inhibition of intracellular calcium mobilization [93].

3.1.8. Corticotropin-releasing hormone (CRH)

CRH is a 41 amino acid peptide hormone produced by neuroendocrine cells of the paraventricular nucleus of the hypothalamus. At the anterior pituitary, CRH induces ACTH secretion, which, in turn, stimulates the secretion of glucocorticoid hormones (mainly cortisol in humans) from the adrenal cortex. CRH exerts its biological actions by coupling to specific receptors that recruit several intracellular effectors such as cAMP and protein kinases [96]. In addition, a role for CRH on somatotrope function/GH release has also been described in lower vertebrates [97, 98]. However, in humans and non-human primates, in the absence of pathological conditions, there is not much evidence of such effect to date. Interestingly, in patients suffering from acromegaly, two independent groups have previously reported an increase in circulating GH concentration after treatment with either CRH or dexamethasone (DEX, a synthetic glucocorticoid). However, such stimulatory effect on GH has not been confirmed by other studies [23]. On the other hand, it has been suggested a role for CRH in the regulation of gonadotropin secretion based on the presence of its receptor in pituitary gonadotropes [99]. However, these results are not conclusive due to the fact that CRH infusion in male rhesus macaques produced a clear increase on ACTH and cortisol levels, but the LH levels were not different from those observed in untreated control macaques [100].

3.1.9. Thyrotropin-releasing hormone (TRH)

TRH is a short neuropeptide (pGlu-His-Pro-NH2) initially isolated from hypothalamic extracts based on its ability to stimulate the release of thyroid-stimulating hormone. In mammals, it has been documented that TRH not only stimulates TSH but also PRL and GH release, although with species-specific differences [23, 101]. In humans, TRH induction induces GH release in adenomatous cell cultures from acromegalic subjects [23, 102]. Under this experimental setting, TRH-induced GH release was dependent on the calcium influx through L-type calcium channels, with an attenuation in such calcium events elicited by a PKC inhibitor [102]. In lactotrope cells, activation of the TRH receptor by TRH recruits the participation of Gq protein and stimulation of IP production, which in turn activates PKC pathway as well as the release of Ca^{2+} from different stores. Other signaling mechanisms triggered by TRH action includes ERK and MAPK [101].

3.1.10. Neuropeptide Y (NPY)

NPY is a 36-amino acid peptide widely distributed throughout the central nervous system, with highest density of producing-neurons located at the hypothalamic arcuate nucleus [103]. In some mammalian species, NPY seems to elicit a stimulatory effect on GH secretion [23]. NPY actions are mediated by multiple receptors that belong to the GPCR family [104]. NPY administration to patients with prolactin-secreting pituitary adenomas, significantly increased GH levels in 60% of patients. However, in a different study, NPY administration did not alter GH release when administered to healthy young men [33]. In several animal species, it has been described that NPY indirectly regulates different pituitary hormones secretion by acting first at the hypothalamic level by regulating the activity of GnRH, CRH, TRH and GHRH neurons [104, 105]. In fact, it was described that administration of human NPY to the third cerebroventricle in ovariectomized (OVX) rhesus monkeys produced a marked LH suppression through the alteration of GnRH/LH secretory system [106]. Moreover, it was also shown that NPY acts at the level of the median eminence to stimulate the release of GnRH or directly enhancing the LH secretion in response to GnRH through the transportation into the hypophyseal portal blood. Both of these mechanisms seems to involve the mobilization of intracellular calcium [107].

3.1.11. Dopamine (DA)

It has been previously reported that either DA precursor or DA agonist administration stimulated GH release in humans when administered subcutaneously, while decreased blood PRL concentration [108]. However, such effect was partially or totally antagonized by an alpha-adrenergic component in monkeys and humans [109]. Conversely, inhibitory actions of DA on GH release have also been reported [109, 110]. To date, five DA receptors ($D_{1\text{-}5}$ receptors) coupled to diverse downstream signaling pathways have been described [111]. Lactotropes present the highest expression level of DRD2 while, in somatotropes, the DRD2 expression is significantly lower to that observed in adenomatous somatotropes [30, 112,113]. Hetero- or oligomerization of SST receptors and DRs has been studied in non-pituitary cell models and was thus suggested as a molecular mechanism in somatotrope cells for the inhibition of GH release [113]. In addition, DRD2 expression was also found in a high percentage of other pituitary cells, thus indicating that DRD2 expression is not confined to lactotrope cells. Consistent with the broad pituitary expression of DRs, one study reported DA can regulate ACTH release [114]. Although DA receptors have been widely associated with multiple signaling pathways [111], to the best of our knowledge the specific routes responsible of DA effects on human or primate pituitary gland remain to be determined.

3.1.12. Oxytocin (OT) and arginine-vasopressin (AVP)

OT and AVP are two hypothalamic hormones well known to exert post-hypophyseal (systemic) actions. However, OT and AVP have been also related with the modulation of anterior pituitary hormones, which could be anticipated by the high concentrations of both neurohormones found in the hypophyseal portal blood of non-human primates [115, 116]. Indeed, AVP administration increases ACTH levels in healthy humans, wherein AVP seems to enhance CRH-stimulated ACTH release [117-121]. In fact, it was reported that AVP from pituitary portal circulation is more important altering ACTH levels than AVP derived from peripheral circulation. Similarly, a stimulation of GH secretion has also been related with AVP infusion in human and non-human primates [120, 122-125] and probably these effects are mediated through stimulation of cholinergic-muscarinic mechanisms and/or mediated in part through catecholamines [126, 127]. Regarding PRL secretion, it was reported a significant increase on PRL release after AVP administration compared with saline infusions [121]. However, these results are not in agreement with other reports whereno alterations of PRL levels were observed in response to AVP [120, 128,129]. Finally, the rest of anterior pituitary hormones do not seem to be significantly affected by AVP infusion in humans [121, 129].

On the other hand, OT has been described to exert the opposite role of AVP on ACTH secretion in humans. In this regard, several studies have reported an inhibition of basal and stimulated ACTH release in normal human subjects [130-134]. In contrast, other reports have not found changes on plasma ACTH levels after increasing doses of OT in men even when the OT doses and administration routes were the same as the studies mentioned above [135-137]. In line with this, OT infusions did not alter basal or CRH-induced ACTH release in women, but was able to inhibit the potentiating effect of AVP on CRH-stimulated ACTH release [138]. Regarding other anterior pituitary hormones, OT administration did not relevantly alter GH, PRL, TSH or LH and FSH responses in healthy humans [128, 134, 137, 139,140]. However, other studies reported no changes on basal GH release, but a significant reduction on AVP-stimulated GH secretion [141]. Additionally, OT administration enhanced PRL release in response to vasoactive intestinal polypeptide [142] and TRH in women [140].

Although the above data demonstrate AVP and OT can mediate anterior pituitary hormone secretion, *in vitro* data is lacking whether these effects are direct or also represent the combined actions of these peptides on central neuronal function, which may in part help to explain the contradictory results currently available.

3.2. Other central modulators of pituitary cells function.

3.2.1. Melatonin

Melatonin (MT) or N-acetyl-5-methoxy tryptamine is a hormone produced by the pineal gland. The presence of MT receptors at the pituitary gland suggested a possible influence of this hormone on the regulation of anterior pituitary hormones [143, 144]. Indeed, the secretion of pituitary hormones show a circadian rhythm [145] and it has been suggested that these patterns could be a consequence of nocturnal MT secretion [146]. Specifically, *in vivo* studies suggest the influence of melatonin on the secretion of GH and other pituitary hormones in primates and healthy humans [147-151]. However, the available data is not consistent. First, MT had a different effect depending on the stage of human growth. In infants, diurnal cycles seem to be beneficial for growth, which suggests a negative correlation between MT and GH at this age [147]. At puberty, oral administration of MT treatment resulted in decrease GH [148], which may explain a greater growth in this age range in summer when MT levels are lower [149]. On the other hand, in adults, MT administration increased basal GH levels [150] and seemed to increase sensitivity to GHRH via altering the SST inhibitory pathway. However, other studies have shown that in young men, MT does not influence GH release but correlates with PRL and cortisol [151], which was also observed by others in both women and men [152, 153]. Exogenous MT administration can also influence PRL, LH and TSH secretion in women [154], wherein MT could lead to hyperprolactinemia [155]. In men, MT administration has also been associated with a reproductive role, by regulating LH and FSH secretion. Particularly, MT increases LH amplitude pulse in a dose-independent manner without altering FSH values [156] and its decrease may lead to sterility [157, 158]. Interestingly, the effect of MT on pituitary secretions seems to be dose- and time-dependent, in that MT causes an increase on neurohypophysial hormones (AVP and OT) and GH at low doses (0,5 mg), whereas at high doses (5 mg) the only GH levels are impacted [146]. In addition, an acute MT administration increases GH levels [159, 160] and modulates the secretion of other pituitary hormones (LH and/or PRL) in men and women [161-163]. Surprisingly, chronic MT administration, does not cause any effect on GH [150]. Studies performed on non-human primates have shown that MT only was able to slightly affect the insulin-stimulated GH release without producing any change in basal or stimulated PRL, TSH, LH or FSH secretion [164]. However, it has been recently described the role of MT on primary pituitary cell cultures obtained from baboons

(*Papio anubis*), where MT showed clear stimulatory actions on GH and PRL expression and secretion in a dose and time-dependent manner through common and distinct signaling pathways. Specifically, the effects of MT on GH and PRL levels were mediated through AC/PKA and extra-/intracellular calcium pathways, although the effects on GH, but not PRL release also required the activation of PLC route. Regarding other pituitary hormones, MT did not produce any change on ACTH, LH, FSH or TSH synthesis or release on baboon primary pituitary cell cultures [18]. Finally, it has been suggested that the action of MT at the pituitary level could be mediated through the MT1 receptor [18, 165].

3.2.2. Cortistatin (CORT)

CORT is a neuropeptide produced by post-translational cleavage, which can lead to the generation of two mature products CORT-17 and CORT-29 in humans [166]. CORT, as well as SST, is distributed and expressed in wide variety of human and rodent tissues (including pituitary gland), even more than that previously assumed [167, 168]. Additionally, CORT shares with SST a high structural homology that explains their similar capacity to bind the same family of receptors (SST_{1-5} receptors) [169-173]. Despite the structural and functional similarities of these molecules, they display crucial differences [174, 175], including the capacity of CORT, but not SST, to bind to other receptors such as GHSR1a [176, 177], or Mrgx2 (an orphan G-protein-coupled receptor belonging to Mas-related genes family) [178]. Also CORT is able to mediate different/opposite actions compared to SST such as the effect on immune cells, the increase on slow wave sleep, the reduction in the synthesis of inflammatory mediators, as well as differential effects on pituitary function (see below) [179]. At the pituitary level, CORT inhibits GH release through the activation of SST receptors in young males and, indeed, CORT and SST show equal inhibition of GH release induced by GHRH, ghrelin and synthetic analogues [44, 166, 180-182]. However, CORT, as well as SST, did not affect ghrelin-stimulated PRL, ACTH and cortisol levels [166] even when both showed the same inhibitory effect on ghrelin release [181]. Interestingly, CORT-8, a synthetic CORT-analogue that binds GHSR1a but not SST receptors, was not able to modulate ghrelin- or hexarelin-stimulated GH, PRL and ACTH release, suggesting a predominant role of SST receptors on the known actions of CORT on GH release [183], which seems to be further supported by *in vitro* studies [176, 184]. Indeed, *in vitro* observations in human fetal pituitary cells using CORT showed an inhibitory effect on GH release, which was even greater than that elicited by SST [182, 185]. In female baboons (*Papio anubis*), CORT blunted GH and ACTH basal secretion and also decreased GH and POMC mRNA expression. Surprisingly, CORT stimulated, while SST inhibited, PRL release in baboon primary pituitary cell cultures without altering mRNA expression. This stimulatory effect seems to be mediated through GHSR1a, since the treatment with an antagonist of this receptor completely blocked this stimulatory response to CORT [31, 182]. Finally, in primate pituitary cell cultures, low concentrations of both CORT-17 and SST-14 (10^{-17} and 10^{-15} M) are able to stimulate GH release through SST5 receptor requiring activation of AC/cAMP/PKA and intracellular Ca^{2+} pathways. Therefore, all this information indicates that CORT directly modulates the function of different pituitary cell types and these actions in humans and non-human primate models are dose- and cell type-dependent and receptor-specific [27].

4.Peripheral modulators of pituitary cell function.

4.1. Glucocorticoids (GCs)

Glucocorticoids, the end products of the CRH (hypothalamic) –ACTH (pituitary)- adrenal axis, negatively feedback to suppress its own axis function, where many reports demonstrate GC suppress ACTH secretion *in vivo* and in primary pituitary cell cultures [186-189]. GCs have also been shown to regulate GH secretion [190] *in vitro* and *in vivo* in humans and non-human primates [16, 191, 192]. *In vivo* observations in healthy humans support the hypothesis that GCs are able to stimulate or inhibit GH secretion depending on the specific conditions (dual effect) [190, 193-197]. Especially, during short-term incubations (1h), GCs produce an inhibition of GHRH-stimulated GH secretion probably due to an increase of endogenous SST secretion [194]. This inhibitory effect was corroborated using acetylcholinesterase inhibitors, which are known to elicit GH secretion through a decrease in the hypothalamic release of SST [198-200]. Thus, the presence of acetylcholinesterase inhibitors, alone or in combination with GHRH, blocked the inhibitory effect of GCs on GH release [201]. In contrast, a rise of GH values was detected after 3h treatment with DEX (iv. or oral administration) in normal subjects. Interestingly, after 12h incubation with DEX, the GH release was again inhibited [195, 196]. In fact, the GC prednisone was able to blunt GHRH-stimulated GH response after 4 days of treatment in healthy subjects [197]. Although the mechanisms behind these effects are not yet clear, there are potential reasons that could explain these responses: 1) a rise of GHRH secretion and inhibition of negative feedback of IGF-I in a short period of treatment; 2) a stable increase of SST release due to a sustained hypercortisolemia and; 3) the time of administration. In contrast, the effects of GCs on PRL secretion in healthy humans are still unclear inasmuch as several reports showed a suppression

on basal and TRH-stimulated PRL levels after DEX administration [202, 203], which is in accordance with *in vitro* results described in baboon [204]. However, TRH-stimulated, but not basal, PRL is reduced by DEX in women [188], and no effect on basal or stimulated PRL was found in normal subjects [205]. These differences between studies could be due to the dose of GCs, route of administration, experimental design or even sensitivity limit of PRL radioimmunoassays. In addition, GCs have been shown to alter TSH secretion in humans, where clear inhibition has been observed in baseline and TRH-stimulated levels in response to a short or a long-term GCs treatment and this suppression was reflected by a fall in T_3 concentration in adults and preterm infants [203, 205-211]. The use of hypothalamic somatostatinergic and dopaminergic inhibitory compounds revealed that these mechanisms are involved in the TSH response to GCs treatment [212]. In addition to ACTH and GH, GCs also modulated LH and FSH levels in humans. It has been reported that DEX cannot alter basal LH or FSH, but decreased LH levels after GnRH stimulation, but not confirmed in another study [213, 214].

Interestingly, one of the first evidences showing the direct effect of GCs on GH secretion *in vitro* was the demonstration of a marked increase of GH production after the treatment with cortisol in primary pituitary cell cultures obtained from *Macaca mulatta* [191]. Interestingly, the use of an inactive analogue (11 α-hydroxycortisol) blunted the GH response, and the mechanisms behind this effect involved protein and probably RNA synthesis [191]. In line with this, treatment with DEX also produced a significant increase in GH secretion when fetal rhesus monkey pituitary cells were treated [192]. These results have been corroborated in another primate model, *Papio anubis*, in which DEX and hydrocortisone (HY) caused a clear increase of GH release in primary pituitary cell cultures after a 24h incubation period. Moreover, both GCs significantly stimulated GH, GHRH-R and GHS-R mRNA levels in baboon primary pituitary cell cultures, which could suggest that the increase in GH mRNA is translated into an increase of GH production and secretion [16]. Furthermore, similar results were obtained in cultures of normal human pituitaries from patients with metastatic breast carcinoma [215] and in human fetal anterior pituitary cell cultures [192]. In both cases, GCs (cortisol or DEX) were able to produce a marked increase of GH release under basal and GHRH stimulated conditions in a time-dependent manner [192, 215]. In contrast, in the case of PRL secretion, different concentrations of cortisol significantly decreased PRL secretion in tissue fragments from baboon pituitary glands even when TRH was used to stimulate PRL release [204]. To date, the vast knowledge about the mechanisms and signaling pathways underlying these effects have been described mainly in rodents and involve the activation of cAMP/PKA or PKC signaling pathways and intracellular free calcium mobilization [216]; however, whether the actions of GCs on human or primate pituitary hormone secretions are mediated through these signaling pathways remains to be fully elucidated.

4.2. Thyroid hormones (THs)

THs are produced and secreted by the thyroid gland and are mainly regulated by thyrotropin (TSH). Likewise, THs regulate TSH through a direct negative feedback on pituitary gland [210]. In this sense, T3 and T4 administration significantly reduced serum TSH levels without any alteration on its pulsatility in healthy humans [210]. Moreover, TRH-stimulated TSH response can be suppressed by THs alone or by T3 combined with ipodate (iodinated radiocontrast agent that inhibits the conversion of T4 to T3). Conversely, combination of T4 and ipodate did not alter the TSH response to TRH. These results suggest that the conversion of T4 to T3 could be important for the THs feedback action [210, 217]. In this regard, it is important to mention that among thyroid hormone analogues such as tetraiodothyroaceticacid (TETRAC) or triiodothyroaceticacid (TRIAC), only TRIAC is known to be able to partially inhibits the synthesis and secretion of TSH and PRL in normal subjects [218, 219]. Interestingly, THs also seem to play a role in the regulation of GH as several studies have described that an increase in THs levels in humans is able to produce a strong reduction of pituitary GH release probably due to a rise of hypothalamic SST tone (which blunted any stimulatory effect) or, to a reduction on GHRH release [220, 221]. However, THs could also play a direct role in the regulation of somatotropes as T3 can decrease the expression of hGH gene in transfected GC cell cultures [222]. Moreover, the negative effect of T3 on GH secretion was also described in pituitary cultures from fetal rhesus monkey and humans. Specifically, treatment of rhesus monkey cells with T3 produced a significant inhibition of GH release after GHRH stimulation but did not alter basal GH secretion [192]. Conversely, the results with human cells showed a strong reduction of basal and GHRH-stimulated GH secretion [192]. In the same line, T3 treatment was also able to decrease hGH RNA levels without a clear effect at the protein level in transgenic (171hGH/CS-TG) mice expressing the human GH gene [223]. However, to the best of our knowledge, the signaling pathways and mechanisms associated with the effects of THs and its analogues in humans and non-human primate pituitaries have not been identified.

4.3. Insulin and IGF-I

Insulin/IGF-I system comprises a complex family of related peptides, membrane receptors and high-affinity IGF binding proteins (IGFBP) [224, 225], which have been directly associated with a strong regulation of pituitary cell function in several models [226, 227]. Indeed, IGF-I and IGFBP-3 are positively correlated with spontaneous 24h GH secretion (expressed as AUC) in different healthy humans subgroups (sex or pubertal stage) [228]. IGF-I in turn acts via negative feedback to the hypothalamus, as well as the pituitary to control GH secretion. For example, low doses of recombinant IGF-

I infusion were able to blunt the fasting-stimulated GH secretion in men fasted for 32h [229]. In the same line, the administration of recombinant IGF-I at physiological doses diminished GH response to GHRH without any alteration on spontaneous GH levels [230]. Moreover, it has been shown that circulating free and not total IGF-I could be a key mediator of GH secretion since the rise of GH levels after 24h was negatively correlated with the reduction of free IGF-I [231]. However, a single dose of recombinant IGF-I is not sufficient to alter basal or pulsatile GH release or impact FSH, LH and PRL levels, but does suppress TSH [232]. This discrepancy between different studies could be due to the dose or route of administration.

Insulin infusion, like IGF-I, has been shown to reduce GH response to GHRH in healthy humans [233]. Also, an increase of insulin concentration observed in healthy humans undergoing overeating, is accompanied by a reduction of GH levels [234]. The action of both IGF-I and insulin could be in part due to direct suppression of somatotrope function. Specifically, IGF-I and IGF-II dose dependently decreased GH release in both fetal and adults cultures [235]. In that same study, IGF also reduced PRL levels in adult, but not in fetal pituitary cultures, while having no impact on ACTH or LH release [235]. In another study, IGF-I was able to suppress GH mRNA levels induced by cAMP plus hydrocortisone and, to reduce stimulated GH secretion without altering basal GH secretion in human choriocarcinoma cells transfected with hGH gene [236]. Moreover, a suppression of somatrotrope function has been reported in baboon primary pituitary cell cultures wherein IGF-I was able to significantly blunt GH release and mRNA levels in a dose-dependent manner after 24 hours of treatment. Like IGF-I, insulin also inhibited GH secretion and mRNA levels at physiological concentrations in baboon primary pituitary cell cultures although with a different dose-dependent pattern [16]. In another study by the same group, the inhibitory actions of insulin and IGF-I required distinct intracellular signaling pathways to suppress somatotrope function in baboon pituitary cell cultures (i.e. IGF-I acted through PI3K, mTORC1 and MEK routes while insulin required PI3K), and that these pathways might be common across mammalian species in that they observed similar results using mouse primary pituitary cell cultures [226, 227]. Taken together these studies demonstrate IGF-I and insulin can directly regulate somatotrope function under normal conditions [16], and since both IGF-I and insulin are regulated by nutritional status, may suggested changes in circulating GH levels observed during starvation or obesity (overeating) may in part be mediated by direct actions of these hormones on somatotrope function.

4.4. Fatty acids

Free fatty acids (FFAs) have also been described as regulators of pituitary function. Specifically, the majority of the information available about the capacity of FFAs to regulate pituitary gland function is related with the modulation of GH secretion. Thus, in primates (rhesus monkeys), it was described a complete inhibition of acute insulin-induced GH secretion after a soybean oil emulsion, which produce an elevation of serum FFAs [237]. Consistently, elevation of plasma FFAs produced a strong reduction in GH release in rhesus and Java monkeys and lowering plasma FFAs led to an increase in GH secretion, without altering PRL levels [238]. In healthy humans, as in primates, a reciprocal relationship between FFAs and GH release has been reported [239-246]. Elevations in FFAs induced by different types of lipid infusions are able to mediate a significant inhibition of GHRH-stimulated GH secretion, where it has been hypothesized that this effect is due to suppressing GHRH and/or stimulating SST secretion, or to a direct effect of FFAs on somatotrope cells [239-246]. In support of a direct effect was a report showing that 24h treatment of baboon primary pituitary cell cultures with oleic and linoleic acids markedly reduced GH release and mRNA levels. In contrast to GH, no association between FFAs concentrations and PRL levels has been observed in primates or humans [238, 244]. However, like GH, lipid infusion-induced elevations in circulating plasma FFAs evoked a strong inhibitory effect of spontaneous ACTH and cortisol secretion in humans, although the lipid load did not affect CRH-stimulated ACTH levels [244, 247]. In contrast, another study indicated that FFAs did not alter basal ACTH and cortisol secretion in normal men even when the FFAs levels obtained in response to lipid load were comparable in both studies [248]. Therefore, further investigations are required to clearly understand the specific role of FFAs at the level of the pituitary gland and the mechanisms involved in such actions.

4.5. Adipokines

Adipokines comprise a family of increasingly important cytokines, mainly released from the adipose tissue, which includes leptin, adiponectin or resistin. However, although certain studies have reported the connection between leptin or adiponectin and pituitary hormones, the precise implication of adipokines on the modulation of human (or primate) anterior pituitary hormones remains to be fully characterized. Indeed, exogenous treatment with leptin in female rhesus monkeys (*Macaca mulatta*) caused a rapid rise in LH concentration, which was followed by an increase in serum

estradiol and advanced puberty [249]. In addition, leptin was also associated with an elevation of GH secretion in this model [249]. Similarly, adiponectin has been directly associated with GH pulse secretion in healthy men, although it remains to be proven whether this is a direct effect [250]. Of note, leptin, adiponectin or resistin receptors are expressed in a wide variety of tissues and organs including pituitary gland, wherein they seem to be involved in its regulation [251, 252]. In order to determine if leptin mediated changes in pituitary hormone secretion is due to direct pituitary actions, a recent report explored the impact of adiponectin, leptin and resistin on primary pituitary cell cultures from two primates species (*Macaca fascicularis* and *Papio anubis*). This study demonstrated that adiponectin reduces GHRH-stimulated but not ghrelin-stimulated GH release, and that it is able to increase PRL and decrease ACTH without altering LH/FSH/TSH-release. Conversely, leptin increased GH, PRL, ACTH and FSH secretion but did not alter LH or TSH secretion. Finally, resistin, like leptin, produced an elevation of GH and ACTH levels without any alteration of PRL, LH, FSH or TSH secretion. In addition, only leptin was able to increase GH, PRL and POMC at mRNA expression levels. Interestingly, the direct effects induced by these adipokines were mediated by common signaling pathways such as AC/PKA, but also involved distinct and specific signaling cascades. Indeed, in addition to AC/PKA, leptin exerted its effects by activating intra-/extra-cellular calcium and PLC/PKC, adiponectin also involved intra-/extra-cellular calcium, and resistin also induced its effects through mTOR pathway [253]. Taken together, these data demonstrate that adipokines could directly modulate the function of anterior pituitary hormones in non-human primates, which could help to explain the results obtained *in vivo* in humans and primates.

4.6. Obestatin

Obestatin is an amidated peptide hormone encoded by the ghrelin gene and mainly produced in the gastrointestinal tract [254, 255]. However, the use of human fetal and adult tissue samples has revealed that obestatin is widely distributed throughout human tissue, with prominent expression in lung, pancreas, thyroid, gastrointestinal tract and pituitary gland. Interestingly, a strong correlation between obestatin and ghrelin mRNA levels has been found in these tissues [256]. The data available in the literature about this hormone is confusing, quite limited and mainly generated in rodent models; however, one study has been recently published exploring the direct, *in vitro*, effect of obestatin on the function of all pituitary cell types using baboon primary pituitary cell cultures as model. Specifically, obestatin treatment did not alter GH or ACTH release or expression after 4h. However, GH was inhibited, while ACTH/POMC secretion and expression was stimulated, in baboon primary cultures after 24h of treatment. Additionally, obestatin also blunted ghrelin-stimulated GH release. In contrast, other pituitary hormones (PRL, FSH, LH and TSH) were not affected by obestatin treatment at any time point tested. All these observations suggest that obestatin can directly regulate somatotrope/corticotrope function in primary pituitary cell cultures from baboons, and that these actions are mediated through the activation of AC and MAPK routes [17].

4.7. Inhibins

Inhibins are glycoprotein hormones constituted by two different subunits (α- and β_A- or β_B-subunit), which are linked to form inhibin A or inhibin B. These glycoproteins are secreted by the granulosa and theca cells of the ovary and by the Sertoli cells of the testis [257]. One of the first evidence demonstrating the effect of inhibins on non-human primate models was published by Medhamurthy et al., where they showed the direct role of inhibins in the regulation of FSH secretion in the male rhesus monkey (*Macaca mulatta*). Specifically, the administration of ovine antiserum against inhibin α-subunit produced a hypersecretion and an increase of pulse amplitude of FSH, but did not alter LH secretion or pattern [258, 259]. In the same line, pituitary FSH secretion and expression were maintained at control values by the infusion of recombinant inhibin in orchidectomized monkeys, preventing the postcastration hypersecretion and overexpression of FSH [260]. In addition, a significant reduction of circulating FSH levels was detected after 54 hours when recombinant inhibin was administered by infusion to adult male rhesus monkeys. However, and in line with previous results, the infusion of inhibin A did not alter the circulating LH concentrations in monkeys, which suggests that testicular inhibin actions are specific for FSH at the pituitary level [261]. Likewise, exogenous inhibin administration to female rhesus monkeys specifically reduced FSH secretion during the mid-to-late luteal phase of the menstrual cycle [262]. Furthermore, the direct effect of inhibin on FSH and LH secretion in pituitary cell cultures from male rhesus monkeys and one cynomolgus monkey was studied during 48 hours of incubation, showing a reduction of 50,8 % of FSH release compared with controls while no effect was observed on LH secretion [263]. These results were corroborated by another study developed with human fetal primary pituitary cell cultures. In this case, inhibin treatment clearly reduced FSH levels but the effect on LH was inconsistent [264]. Regarding the presence and role of inhibins in humans, important gender differences have been described, being inhibin A and B present at physiological concentrations in females, whereas only inhibin B was observed in males [265]. In this sense, inhibin B secretion was found to be decreased in older ovulatory women who showed a monotropic FSH increase. On the contrary, inhibin A release in these women was found similar to that in younger women. These results in women suggest that inhibin B has an important role in the modulation of the intercycle FSH changes [266]. In men, results

obtained from an acute sex withdrawal model (declined testosterone and estradiol levels) showed that inhibin B is the major regulator of FSH release in the human male [267]. Finally, with regard to the action mechanisms, the knowledge about the inhibin effects is quite limited. One of the hypothesis proposed has been that inhibins could act as a dominant negative regulator of the activin signal transduction pathways (see below) through the binding of β_A subunit to the activin type II receptors with lower affinity than activin [268]. On the other hand, several reports have found non-overlapping binding sites for activin A and inhibin A in different tissues suggesting the existence of inhibin-specific receptors. In this sense, two different candidates has been identified as inhibin receptors, betaglycan (TGF-β type III receptor) and inhibin binding protein/p120 (INHBP/P120). However, none of them seem to satisfy all the criteria required since betaglycan are not expressed in pituitary gonadotrope cells and INHBP/P120 did not bind to inhibins in receptor binding assays [268, 269]. For that reasons, additional studies are necessary to undoubtedly identify inhibins receptor(s) and signaling mechanisms behind the observed effects.

4.8. Activins

Activins, like inhibins, are glycoproteins that belong to TGF-β superfamily. Activins are dimers composed by two different β subunits, which can generate three isoforms: activin A (β_A β_A), activin B (β_B β_B) or activin AB (β_A β_B) [257, 270]. The presence of activins has been detected in some, but not all, Leydig, Sertoli and granulosa cells of fetal primate gonads [271]. Likewise, β_A subunit was found in FSH-, GH- and in a few PRL-positive cells in human pituitary gland [272]. In the same way, β_B subunit was detected in TSH-cells, FSH- and LH-positive gonadotrophs [272]. In primates, the first results showing the effect of activins in the function of pituitary gland were obtained from *Macaca fascicularis.* Specifically, 2-days infusion of activin A to adult male macaques produced a significantly increase of basal FSH levels, without changes in basal LH levels. However, GnRH-stimulated FSH and LH levels were significantly increased after 48 hours of activin A administration, showing a physiological role of activins on gonadotropin secretion in non-human primates [273]. In the same way, the infusion of exogenous activin to female rhesus monkeys stimulated FSH and LH production during the early follicular phase of the menstrual cycle [274]. On the other hand, the specific direct role of activins on pituitary gland was studied using human fetal primary pituitary cell cultures. In this case, treatment with recombinant activin A produced a potent increase on FSH and LH release, being activin-stimulated LH secretion less potent compared to GnRH treatment [264]. To date, the knowledge about the mechanisms and signaling pathways underlying these effects involve the binding of activins to two activin type II receptors (ActRII and ActRIIB), and one type I receptor (ActIR/ALK4). Downstream signaling is mediated by the SMAD signaling pathway, where these SMAD proteins are phosphorylated and translocated to the nucleus as multimeric complexes to regulate gene transcription [275, 276].

4.9. Follistatin

Follistatin (FST), originally called the FSH suppressing protein, is a monomeric polypeptide considered a key regulator of the biological actions of activin. Therefore, this molecule regulates the expression and secretion of gonadotropins contributing to their importance as modulators of the reproductive axis [277]. FST is secreted from mature gonadal cells, particularly its secretion has been associated to gonadotrophs and folliculostellate cells probably in an autocrine or paracrine manner [277]. Alternative splicing of this molecule produce two polypeptide variants with different number of aminoacids (FST315 and FST288), although with the same mechanisms of action [278]. The long-variant is distributed throughout the body, while the short-variant is located in secretory tissues [279]. Each molecule of FST binds to an activin subunit. The complex activin-follistatin undergoes internalization and lysosomal degradation causing an irreversible activin inhibition, downregulating FSH secretion and avoiding activin-activin receptor binding [280]. Regarding to the effect of FST in non-human primates, castration of rhesus monkeys produced an increase on FSHβ, LHβ and α-subunit mRNA levels and an increase of FSH secretion, which was related to an unaltered pituitary FST expression in these monkeys [281]. In humans, a slight decrease of both basal and GnRH-stimulated LH and FSH concentrations in response to FST was detected in human fetal primary pituitary cell cultures, which might be due to the fact that FST could act directly blocking activin actions as it has been described in other species [264].

4.10. Estrogens

There is increasing evidence demonstrating estrogens directly regulate pituitary cell function. In fact, estrogen receptors are expressed in baboon lactotropes and gonadotropes, and to a lesser extent in somatotropes and thyrotropes [282, 283]. The first observations about the relationship between estrogens and GH levels were not conclusive. Specifically, the effect of physiological or pharmacological estradiol doses on the concentration of IGF-I and GH was explored in castrate and intact adult female baboons. These studies demonstrated that only with intact baboons and physiological

doses, estradiol was able to increase plasma IGF-I levels, associated with an increase in GH concentrations [284]. Likewise, castrated macaques treated with estradiol revealed an increase on GH concentrations. However, estradiol treatment on castrated adult female and male or juvenile female macaques pituitary cell cultures did not show any effect on GH levels, although adult female monkeys showed an increase on PRL secretion. Interestingly, only juvenile male (< 2 years), but not adult or juvenile female pituitary cultures presented a mild increase on GH release, and a double immunocytochemistry corroborated a different cell composition between adult and juveniles pituitary cell cultures. Based on these results, the authors suggested that estradiol was acting on a GH-secreting cell population that was present in young male but not in adult monkeys, and that this population was probably composed by mamosomatotrope stem cells, which expressed estrogen receptors [285]. In humans, treatment with estradiol decreased IGF-I and elevated basal GH and PRL concentrations in men [286]. In postmenopausal women, estrogen treatment was able to enhance basal and exercise-induced GH release and decreased IGF-I levels. The mechanisms behind these effects in humans are not clear although possible options could be central effects or a negative feedback related with IGF-I levels [287]. Regarding the role of estrogens on other pituitary hormones, a direct effect of estradiol and progesterone on PRL secretion has been reported using pituitary cell cultures from male and female monkeys. Thus, estradiol administration significantly increased PRL release compared to vehicle-treated controls. However, estradiol and progesterone combined treatment did not produce any difference in PRL secretion levels compared to estradiol treatment suggesting that progesterone did not exert any effect on PRL secretion [288]. In contrast, PRL levels were not altered in ovariectomized female cynomolgus monkeys treated with estradiol [289]. On the other hand, estradiol has been described as the predominant regulator of FSH secretion in men through the aromatization of testosterone to estradiol [290]. Taken together, further studies are necessary to clearly elucidate the role estrogens play on anterior pituitary hormones and the signaling pathways underlying these effects.

4.11. Testosterone

In human and monkeys, testosterone acts as a gonadal component of the negative feedback that regulate LH and FSH secretion; however, the precise actions of testosterone on gonadotropin secretion in humans and non-human primates seem not to be the same [263, 291]. In this sense, it has been demonstrated that testosterone replacement after orchidectomy failed to prevent the postcastration FSH hypersecretion in male rhesus monkeys without altering LH levels, which suggests that circulating testosterone concentrations are not essential for the testicular inhibition of FSH secretion in rhesus monkeys [292]. In the same line, treatment with testosterone did not produce any change on basal or GnRH-stimulated FSH or LH levels in primate pituitary cell cultures [263, 293]. In contrast to these data, the results reported in humans reveal that testosterone or its metabolites are able to inhibit FSH and LH secretion acting at the pituitary and hypothalamus level. Moreover, although the effect of testosterone on LH release appears to be through a direct or indirect feedback, the aromatization of testosterone to estradiol seem to be necessary to produce an effect on FSH secretion [290, 291, 294, 295]. However, the signaling pathways associated to these effects have not been described. For these reasons, further investigations are necessary to clarify the effects of testosterone on gonadotropin hormones and the mechanisms underlying these effects.

4.12. Endothelin

Endothelin (ET) is a peptide that contributes to constrict the blood vessel and to rise blood pressure and, consequently, overexpression of this molecule is associated with heart diseases. In human, three different ET isopeptides encoded by three different genes were identified and designated as ET-1, ET-2 and ET-3 [296]. The presence of ET-3 in gonadotrophs cells has been detected using immunoreactivity suggesting a potential role of ETs in gonadotropins secretion [297-299]. *In vivo* assays with healthy human male volunteers showed that ET-1 intravenous administration produced an increase on basal serum ACTH levels without altering the rest of pituitary hormones. However, the increase of pituitary hormones secretion stimulated by pituitary hormones releasing factors (GHRH, CRH, GnRH, TRH) was altered in some cases after ET-1 administration. Thus, TSH-stimulated PRL levels and GHRH-stimulated GH levels were decreased after ET-1 administration. In contrast, ACTH, FSH and LH were enhanced and TSH was unaltered in response to ET-1 treatment [300]. In a different study, the effect of ET-1 and ET-3 administration was further studied in men. In this sense, ET-1, but not ET-3, increased plasma ACTH and PRL levels [301]. Regarding the mechanisms involved in ET actions, it is known that ACTH and GH concentrations decreased when nifepidine (a calcium channel blocker) was administered before ET-1 infusion, without any alteration on other pituitary hormones. Based on these data, it has been suggested that the effect observed in human in response to ET could be, at least in part, mediated by calcium mobilization at the pituitary level [302].

4.13. Opioids

Opioids encompass any endogenous or exogenous agent that binds to opioid receptors, which are located mainly in the central nervous system. A significant amount of reports have identified the main types of receptors as mu-μ, kappa-κ and delta-δ opioid receptors [303]. The effect of opioids at the pituitary level depend on the cell type implicated. For instance, intrathecal administration of opioids was able to modulate different pituitary hormones in a group of 73 patients. The consequence of the chronic and acute administration was a significant decrease on serum LH concentrations and, only in the chronic administration, FSH levels [304-306] through the μ-opioid receptor pathway [307]. The effect observed on LH release was dependent on the sexual maturation stage of patients due to the sex steroid hormones, which are required for major modulating effects [308-310]. The effect of chronic opioid administration on PRL levels is not clear since the information in the literature is contradictory. Likewise, PRL levels were not modified in chronic patients (males and females) that received opioids either intrathecally or orally [304, 311]. However, acute dose of morphine caused an increase on PRL levels, demonstrating that this effect is achieved through dopaminergic mechanisms [305]. In this sense, in non-human primates, PRL release was enhanced by dopaminergic pathways [312]. The use of opioid antagonists showed an increase of LH levels that could be caused by a change on GnRH levels [313]. On the other hand, opioids increased plasma GH level through a reduction of somatostatin tone in healthy males. This conclusion was obtained after two studies using naloxone administration [314, 315]. In addition, TSH was elevated after opioids administration as it is demonstrated in different studies [305, 306, 316]. Specifically, the use of opioids and their antagonists had greater effects in modifying the nocturnal pulses of TSH by altering the circadian rhythm of this hormone [317, 318]. However, these results regarding TSH levels were not corroborated by another study [304]. Regarding ACTH levels, several reports indicated that the use of these compounds reduced the pituitary ACTH response to CRH through κ-receptor [319-326]. Altogether, the opiods seem to have a direct role at the hypophyseal level in humans. Nevertheless, the information found in the literature is contradictory in many cases, which suggests that additional studies are necessary to clarify the real effect on pituitary hormones and the mechanisms involved in these effects.

5. Signaling pathways involved in the regulation of pituitary gland.

As reviewed in detail above, the vast majority of the information and knowledge regarding the signaling pathways involved in the regulation of the synthesis and release of the different anterior pituitary hormones has been generated using primary pituitary cell cultures from non-human primate species. Indeed, almost all the studies referenced in this review report the effect of the different regulators on hormone release; however, not all of them explored the effect on hormone expression. For this reason, it would be necessary to further explore this particular question in order to better understand the differential regulation of pituitary hormonal synthesis and release by these regulators. On the other hand, the major findings regarding signaling pathways of all studies included in this review are summarized in **Table 1**. In particular, in these studies, the main approach used to explore the signaling pathways activated or inhibited in response to different pituitary regulators has been the direct measurement of key second messengers coupled to the use of specific pharmacological inhibitors to block selected components of relevant routes. An overall view of all the information available reveals that most of the data reported hitherto in the literature is mainly focused in the mechanisms involved in the regulation of GH release by different central and peripheral modulators (**Table-1**). When taken together, these data indicate that the regulation of GH release by different modulators is carried out through the modulation of multiple, common and distinct, signaling pathways. Specifically, most of the GH regulators act through two common signaling pathways such as AC/PKA (except for kisspeptins) [15, 18, 23, 27, 28, 31, 63, 253] and extra- and/or intracellular calcium mobilization (except for PACAP, resistin and obestatin) [15, 18, 27, 31, 73, 253, 302]. In addition, most of the modulators of GH secretion simultaneously elicit the activation and/or inhibition of additional routes. Indeed, ghrelin and kisspeptins modulate GH release also through PLC/PKC and MAPK pathways [15, 73], while MT also regulate PLC/PKC pathway [18]. Alternatively, GHRH-mediated GH release required NOS/NO/GC/cGMP pathway [15], obestatin is also able to inhibit GH release through MAPK signaling pathways [17], and adipokines use PI3K,whereas resistin activates the mTOR pathway to regulate GH release [253].

Regarding PRL regulation, MT, leptin and adiponectin are able to exert their effects on PRL secretion through AC/PKA pathway and extra-/intracellular Ca^{2+} mobilization [18, 253]. The stimulation of PRL release by leptin and adiponectin also involves the activation of PI3K pathway [253]. On the other hand, the regulation of ACTH is mediated through AC/PKA by ghrelin, obestatin and adipokines, through MAPK by ghrelin and obestatin, through PI3K by adipokines [15, 17, 253], and also through extracellular Ca^{2+} mobilization by endothelins [302]. In the case of gonadotropins, both LH and FSH hormones are differentially regulated by distinct but also by some common signaling pathways. Likewise, LH is modulated through PLC/PKC, intracellular Ca^{2+} mobilization, MAPK, mTOR and PI3K by kisspeptins, through extracellular Ca^{2+} mobilization and NOS/NO/GC/cGMP pathway by GnRH [73], through intracellular Ca^{2+} mobilization and AC/PKA by GnIH [93, 95] and through SMAD signaling by activins [275, 276]. Additionally, FSH release

mediated by GnIH involve intracellular Ca^{2+} mobilization and AC/PKA [93, 95], by leptin involve AC/PKA, PLC/PKC, extra-/intracellular Ca^{2+} mobilization and PI3K [253] and by activins also involve SMAD signaling [275, 276]. Taken together, all this information suggests that the central and peripheral modulators mentioned above, in most cases, converge in multiple and similar signaling pathways to regulate the function of different anterior pituitary cell types (**Table-1**). However, only some selected signaling pathways have been explored in these studies, which suggest that more *in vitro* studies are necessary to understand the full landscape of signaling pathways involved in the regulation of pituitary gland function in humans and in non-human primate models.

Table 1: Summary of the signaling pathways modulated by different regulators on the secretion of anterior pituitary hormones.

Hormone	Signaling pathways	Regulators	References
GH	AC/cAMP	GHRH, Ghrelin, CORT, SST, PACAP, MT, Leptin, Adiponectin, Resistin, Obestatin	[15, 17, 18, 23, 27, 28, 31, 63, 253]
	Extra- and/or intracellular Ca^{2+} mobilization	GHRH, Ghrelin, CORT, SST, MT, Kisspeptins, Leptin, Adiponectin, Endothelin	[15, 18, 27, 31, 73, 253, 302]
	PLC/PKC	GHRH, Ghrelin, MT, Kisspeptins	[15, 18, 29, 73]
	PI3K	Leptin, Adiponectin, Resistin	[253]
	MAPK	Ghrelin, Kisspeptins, Obestatin	[15, 17, 73]
	mTOR	Resistin	[253]
	NOS/GC	GHRH	[15]
PRL	AC/cAMP	MT, Leptin, Adiponectin	[18, 253]
	Extra- and/or intracellular Ca^{2+} mobilization	MT, Leptin, Adiponectin	[15, 253]
	PI3K	Leptin, Adiponectin	[253]
ACTH	AC/cAMP	Ghrelin, Obestatin, Leptin, Adiponectin, Resistin	[17, 54, 59, 253]
	MAPK	Ghrelin, Obestatin	[17, 53, 54]
	PI3K	Leptin, Adiponectin, Resistin	[253]
	Extracellular Ca^{2+} mobilization	Endothelin	[302]

LH	Extra- and/or intracellular Ca^{2+} mobilization	GnRH, Kisspeptins, GnIH	[73, 93, 95]
	PLC/PKC	Kisspeptins	[73]
	MAPK	Kisspeptins	[73]
	mTOR	Kisspeptins	[73]
	PI3K	Kisspeptins	[73]
	NOS/GC	GnRH	[73]
	SMAD	Activins	[275, 276]
FSH	AC/cAMP	GnIH, Leptin	[95, 253]
	PLC/PKC	Leptin	[253]
	PI3K	Leptin	[253]
	Extra- and intracellular Ca^{2+} mobilization	GnIH, Leptin	[93, 95, 253]
	SMAD	Activins	[275, 276]

6. Concluding remarks

This review summarizes what we know to date regarding both central and peripheral factors involved in the regulation of pituitary cell function (**Figure 1**), specially focusing on studies performed in humans and non-human primates, and paying special attention to intracellular mechanisms underlying this regulation. Although some regulators seem to exert discrepant results depending on the study, it seems solidly demonstrated that the regulation of pituitary function is triggered by an integration of multiple factors acting simultaneously and/or sequentially at this gland, which converge, and ultimately result, in the activation and/or inhibition of multiple, common and distinct, signaling pathways to finely modulate the synthesis and secretion of the different anterior pituitary hormones. The broad perspective gained through this review highlight the importance of the pituitary gland, often referred to as the "master endocrine gland" of the organism, as a true sensor of whole body function, able to gauge the status of growth, reproduction, lactation, stress, metabolism and in turn adjust pituitary hormone synthesis and release to finely control the whole-body homeostasis. This growing number of regulators, interactions and mechanisms, supports the view that the control of pituitary function is far more complex than originally envisioned, and that future studies will need to be implemented in order to elucidate the precise effects of various regulators mentioned in this review, the complete set of their underlying mechanisms, and the network of interactions among them.

7. References

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