Role of pituitary adenylate cyclase-activating polypeptide in modulating hypothalamic-pituitary system

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Abstract

**Background:** Pituitary adenylate cyclase-activating polypeptide (PACAP) is a multifunctional peptide that is isolated and identified from the ovine hypothalamus, whose effects and mechanisms have been elucidated in numerous studies. The PACAP and its receptor are widely expressed, not only in the hypothalamus but also in peripheral organs.

**Methods:** The studies on the role of PACAP in the hypothalamic-pituitary system, including those by the authors, were summarized.

**Results:** In the pituitary gonadotrophs, PACAP increases the gonadotrophin α-, luteinizing hormone β-, and follicle-stimulating hormone β-subunit expression and the expression of gonadotropin-releasing hormone (GnRH) receptor and its own receptor, PAC1R. Moreover, a low-frequency GnRH pulse increases the expression of PACAP and PAC1R more than a high-frequency GnRH pulse in the gonadotrophs. The PACAP stimulates prolactin synthesis and secretion and increases PAC1R in the lactotrophs. In the hypothalamus, PACAP increases the expression of the GnRH receptors, although it is unable to increase the expression of GnRH in the GnRH-producing neurons.

**Conclusion:** The PACAP not only acts directly in each hormone-producing cell, it possibly might regulate hormone synthesis via the expression of its own receptors or those of other hormones.

**KEYWORDS**
gonadotropin, gonadotropin-releasing hormone, hypothalamus, pituitary, pituitary adenylate cyclase-activating polypeptide

1 | INTRODUCTION

Pituitary adenylate cyclase-activating polypeptide (PACAP) was isolated from ovine hypothalamic extracts as a novel peptide hormone that could stimulate cyclic adenosine monophosphate (cAMP) synthesis in anterior pituitary cells. Although PACAP was first discovered in the hypothalamic area, PACAP actually is widely distributed in various brain regions, including the cerebral cortex, substantia nigra, pineal gland, hippocampus, amygdala, cerebellum, and pons. Thereafter, it was revealed that PACAP also is expressed broadly in the peripheral nervous system and in many peripheral organs, including the pituitary gland, adrenal gland, pancreas, gonads, and placenta. Furthermore, PACAP has been reported to act as a hormone, neurotransmitter, and neuromodulator. For example, in the central and peripheral nervous systems, PACAP is involved in neuronal differentiation and activation of the neurosecretory system and plays roles in the differentiation of neural progenitor cells, regulation of neuronal synaptic...
plasticity, glucose-dependent insulin secretion, and many other physiological effects.

There are two functional isoforms, PACAP-38 and PACAP-27. Both are derived from the same precursor protein that is encoded by the Adcyap1 gene. It shares 68% amino acid sequence homology with vasoactive intestinal polypeptide (VIP) and 37% homology with secretin and thus PACAP belongs to the VIP-secretin-glucagon peptide superfamily. The primary structure of PACAP38 has been remarkably conserved among most mammals, suggesting that PACAP plays important roles in maintaining life. The distribution ratio of PACAP27 and PACAP38 varies from tissue to tissue. PACAP null female mice had lowered implantation rates and decreased prolactin and progesterone levels. In another report, PACAP knockout female mice showed decreased mating frequency and reduced fertility (the number of pairings). In contrast, the overexpression of PACAP in the anterior pituitary gland of transgenic male mice delayed puberty and reduced fertility (the number of parturitions relative to the number of pairings). In contrast, the overexpression of PACAP in the anterior pituitary gland of transgenic male mice delayed puberty and suppressed luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels and gonadotropin-releasing hormone (GnRH) receptor expression. Thus, PACAP plays important roles in the hypothalamic-pituitary system.

This review focuses on the modulatory role that is played by PACAP in the hypothalamic-pituitary system in reproduction. Interactions between PACAP and the principle regulators of the hypothalamic-pituitary system—kisspeptin, GnRH, gonadotropin, and prolactin—are discussed, based on the authors’ observations using cell models.

2 ROLE OF PITUITARY ADENYLATE CYCLASE-ACTIVATING POLYPEPTIDE IN THE ANTERIOR PITUITARY GLAND

Gonadotropins, namely LH and FSH, are secreted from the anterior pituitary gland and regulate puberty and reproductive function through the production of sex steroids in the gonads. The LH and FSH are controlled primarily by GnRH, which is released from the hypothalamus in a pulsatile manner. However, several reports suggested that PACAP also modulates the secretion of gonadotropins as it is present in the hypothalamus with a dense PACAP-immunoreactive fiber network in the external and internal zone of the median eminence in close contact with the hypophyseal portal vein and PACAP has been detected in portal blood at a higher concentration than in the peripheral blood. Moreover, PACAP receptors are found in the anterior pituitary gland and PACAP stimulates the anterior pituitary hormones, such as growth hormone, adrenocorticotropic hormone, prolactin, thyroid-stimulating hormone (TSH), and gonadotropins in normal pituitary cells. In addition, PACAP is expressed by gonadotrophs and folliculostellate cells and is synthesized and released from the anterior pituitary gland. Moreover, i.v. injection of PACAP increases its own expression in the pituitary gland. These results suggest that PACAP might act not only as a paracrine factor through the hypothalamus, but also as an autocrine factor in the pituitary gland.

3 REGULATION OF THE GONADOTROPHS BY PITUITARY ADENYLATE CYCLASE-ACTIVATING POLYPEPTIDE IN THE ANTERIOR PITUITARY GLAND

With regard to the effects of PACAP on gonadotrophs, many studies have been conducted by using model cells. αT3-1 cells, which are immortalized cells that are derived from transgenic mice, synthesize and secrete the α-subunit gene even though they do not express the β-subunit and cannot synthesize LH or FSH. The PACAP dose-dependently increases the cAMP accumulation and increases the basal levels of the α-subunit through the PAC1 receptors and has a synergistic effect on GnRH in the αT3-1 cells. The LpT2 cells are another gonadotropin-producing cell model. These cells, also immortalized cells that are derived from transgenic mice, contain α-, LHβ-, and FSHβ-subunits and can be induced to express each subunit by GnRH stimulation. The PACAP increases the intracellular cAMP levels and stimulates the α-, LHβ-, and FSHβ-subunit promoter activities in the LpT2 cells, although the effects were more modest than those of GnRH. The effects of GnRH on gonadotropin expression were not altered by the presence of PACAP.

Continuous PACAP stimulates α-subunit messenger (m) RNA levels but decreases FSHβ-subunit mRNA without affecting the LHβ-subunit mRNA in rat primary pituitary culture. Additionally, if PACAP is administered in a pulsatile manner, PACAP stimulates the α- and LHβ-subunit mRNA but has no effect on the FSHβ-subunit mRNA in rat pituitary cells. Continuous GnRH stimulation fails to restore sustained LH and FSH secretion, whereas gonadotropin secretion can be induced by pulsatile GnRH administration. In addition, it is generally accepted that FSH is predominantly secreted after low-frequency GnRH pulses and LH is predominantly secreted after high-frequency GnRH pulses. The GnRH pulse frequency-dependent regulation of gonadotropin production was also investigated in the gonadotroph-immortalized cell line, LpT2. It is suggested that the effects of
GnRH on gonadotroph regulation are altered by the stimulation mode of PACAP, although it is unclear how PACAP is released from the hypothalamus to the anterior pituitary gland. As above, pulsatile stimulation with PACAP specifically induces the expression of gonadotropin subunits in gonadotrophs. More interestingly, stimulation with high-frequency PACAP pulses (pulse interval of 30 minutes) increases the LHβ-subunit mRNA more than the low-frequency PACAP pulses, whereas the low-frequency PACAP pulses (pulse interval of 120 minutes) increase the FSHβ-subunit mRNA in a preferential manner in the Lj/T2 cells.43

4 | PITUITARY ADENYLATE CYCLASE-ACTIVATING POLYPEPTIDE AND GONADOTROPIN-RELEASING HORMONE CROSS-TALK IN THE GONADOTROPHS

The PACAP receptors are present not only in the hypothalamus, but also in the anterior pituitary gland.44 There are two types of receptors—PAC1R and VPAC2R—in the anterior pituitary gland and gonadotrophs.55,46 The PACAP mainly acts via the PAC1R in rat gonadotrophs.34 The GnRH promotes the expression of its own receptors in the gonadotrophs41 and PACAP also regulates PAC1R expression.42,47 Moreover, the stimulation of PACAP increases the expression of the GnRH receptor in Lj/T2 cells.45 Interestingly, the expression of PAC1R is markedly increased by low-frequency PACAP stimulation in the Lj/T2 cells. In contrast, the GnRH receptor expression increases with high-frequency PACAP stimulation and does not increase with low-frequency PACAP stimulation.43 The results of these studies suggest that PACAP regulates not only the expression of the gonadotropin subunits, but also that of its own receptors and GnRH receptors. Larger numbers of GnRH receptors tended to increase the expression of LHβ, but tended to decrease that of FSHβ.48 However, the expression of both the LHβ- and FSHβ-subunit mRNA was promoted as the number of PAC1Rs increased in the Lj/T2 cells.48 In addition, previous studies have shown that GnRH increases the expression of PACAP and PAC1R in the gonadotrophs and primary pituitary culture.43,49 The authors also have observed that low-frequency GnRH pulses increase the expression of PACAP and PAC1R more than the high-frequency GnRH pulses. Moreover, the GnRH-induced expression of the FSHβ-subunit is significantly prevented by the PAC1R antagonist.50 Thus, GnRH and PACAP each display receptor-mediated cross-talk and might be involved in gonadotropin production.

4.1 | Role of pituitary adenylate cyclase-activating polypeptide in prolactin synthesis and secretion in the pituitary gland

Prolactin is released from the lactotrophs and somatolactotrophs in the anterior pituitary gland and has a wide variety of functions. Prolactin plays important roles in reproduction and is involved in mammary gland development during pregnancy and breast milk synthesis and secretion.51 The frequency and amplitude of LH pulses decrease in patients with hyperprolactinemia, resulting in menstrual cycle dysfunction and amenorrhea.52 In addition, prolactin suppresses LH pulses in rats.53 Prolactin-receptor null female mice fail embryonic implantation and have irregular cycles and reduced fertilization rates.54

Prolactin secretion is predominantly inhibited by dopamine from the tuberoinfundibular dopaminergic neurons.55 This means that if prolactin increases in circulation, dopamine is secreted from the hypothalamus and prolactin production is suppressed in the anterior pituitary gland. However, other factors promote prolactin synthesis and secretion. One such factor is TRH. The structure of TRH has been elucidated and the hormone has been proven to induce the rapid release of pituitary thyrotropin.56 Subsequently, TRH was shown to induce prolactin secretion from rat pituitary cell culture57 and its i.v. administration has induced the release of prolactin in humans.58 The TRH binds TRH receptor-coupled G protein on the lactotrophs and activates the PKC-related pathway.59 Extracellular signal-regulated kinase (ERK) is also activated by TRH and activated ERK is inactivated by dual-specificity threonine/tyrosine mitogen-activated protein kinase (MAPK) phosphatase.60,61 The activation of ERK signaling is important for TRH-induced prolactin expression.62 However, it is not yet clear how TRH regulates the production and secretion of prolactin.

The PACAP receptors are expressed in most types of cells in the anterior pituitary gland and PAC1R mainly is expressed in the lactotrophs.23 It was shown initially that PACAP promotes prolactin secretion from superfused rat pituitary cells.5 Although there have been reports that PACAP does not affect prolactin secretion in sheep63 or rat64 pituitary cells, subsequent studies have observed that PACAP can increase prolactin release from rat pituitary cells.65,66 Moreover, PACAP increases the plasma prolactin levels in hypothalamus-lesioned rats.67 A previous study showed that PACAP stimulated prolactin gene expression in the prolactin-producing GH3 cell model, although the effect was mild, compared with TRH stimulation.68 The GH3 cells are immortalized cells that are derived from rat pituitary tumor that synthesizes and secretes prolactin and growth hormone69 and PACAP can stimulate prolactin and growth hormone release.70 It increases prolactin gene expression in GH3 cells through the ERK and cAMP/PKA pathways.71

Although the effect of PACAP on prolactin gene expression in GH3 cells is limited, the degree of prolactin promoter activity is similar to that of TRH stimulation if there is sufficient PAC1R due to its overexpression. In addition, PACAP and TRH have a synergistic effect on the expression of the prolactin gene. Increased PAC1R expression via overexpression potentiates the effect of TRH on prolactin promoter activity.72 This suggests that the presence of PAC1R itself might enhance the effect of TRH on prolactin expression. Moreover, PACAP itself increases PAC1R expression, although TRH cannot stimulate PAC1R expression in GH3 cells. Desensitization occurs in the GnRH receptor due to prolonged continuous stimulation with GnRH, suppressing gonadotropin secretion.73 Similar to the GnRH receptor, prolonged TRH stimulation
decreases the number of TRH receptors in the pituitary cells. In the authors’ work, the response of prolactin promoter activity to TRH and PACAP was diminished with prolonged TRH stimulation in the GH3 cells. In contrast, prolonged PACAP stimulation counteracted the response of prolactin promoter activity, not only to PACAP but also to TRH. This means that PACAP and TRH desensitize their own and each other’s receptor in prolactin-producing cells.

5 | PITUITARY ADENYLATE CYCLASE-ACTIVATING POLYPEPTIDE AND PITUITARY ADENYLATE CYCLASE-ACTIVATING POLYPEPTIDE RECEPTOR IN THE HYPOTHALAMUS

High levels of PACAP are found in the hypothalamus of different species by radioimmunoassay. Thereafter, there have been several reports on the localization of PACAP in the hypothalamus and it was clear that PACAP is present in the supraoptic nuclei, paraventricular nuclei, arcuate nucleus, and in a wide area in the hypothalamus. The PACAP receptors are distributed in the arcuate nucleus, supraoptic nuclei, paraventricular nuclei, suprachiasmatic nucleus, and preoptic area. The presence of PACAP and the PACAP receptors in the hypothalamus suggests that PACAP acts as a paracrine and autocrine factor.

5.1 | Role of pituitary adenylate cyclase-activating polypeptide in the hypothalamus

As GnRH is synthesized and secreted by parvocellular neurons that extend from the preoptic area and PACAP is also present in this area, it is possible that PACAP regulates gonadotropin synthesis and secretion via the control of GnRH neurons. The release of LH and ovulation are inhibited in female rats by the intracerebroventricular administration of PACAP and the injection of PACAP into the medial basal hypothalamus reduces the LH concentration, LH pulse...

FIGURE 1  Schematic summary of the role of pituitary adenylate cyclase-activating polypeptide (PACAP) in reproductive function regulation in the hypothalamus-pituitary system. The PACAP is not only released from the hypothalamus but also expresses in gonadotrophs and folliculostellate cells in the anterior pituitary gland, in which PACAP type1 receptors (PAC1R) exist in the gonadotrophs and PACAP increases the expression of the gonadotropin α-, luteinizing hormone (LH)β-, and follicle-stimulating hormone (FSH)β-subunits. The PACAP increases the expression of the gonadotropin-releasing hormone (GnRH) receptor (GnRHR) and its own PAC1R in the gonadotrophs. The PAC1R receptor is also present in the lactotrophs and PACAP increases the expression of prolactin and PAC1R. In addition, PACAP enhances thyrotropin-releasing hormone receptor (TRHR)-induced prolactin production. In the hypothalamus, both PACAP and kisspeptin increase GnRHR expression. The GnRHR expression by kisspeptin stimulation is potentiated in the presence of PACAP.
frequency, and pulse amplitude in ovariectomized ewes. Moreover, the intracerebroventricular injection of PACAP increases the GnRH mRNA levels in male rats. These results suggest that PACAP has an effect on gonadotropin secretion at the hypothalamus.

6 | ROLE OF PITUITARY ADENYlate CYCLASE-ActivATING POLYPEPTIDE IN GONADOTROPIN-RELEASING HORMONE-PRODUCING NEURONS

In studies of the response of GnRH neurons, GT1-7 cells, which are mouse hypothalamic immortalized cells, are widely used as a model. The PACAP receptors are expressed in the GT1-7 cells and cAMP accumulation is dose-dependently increased by PACAP stimulation.

The GnRH had been thought to be the primary regulator of the hypothalamus-pituitary-sex axis, but it has become clear that kisspeptin is positioned upstream of GnRH and controls GnRH secretion from the hypothalamus. The kisspeptin neuron fibers are located close to the GnRH neuronal cell bodies and processes and make synaptic contacts with the GnRH neurons. Kisspeptin causes depolarization of the GnRH neurons and increases their firing frequency. These results show that kisspeptin directly activates GnRH neurons. Indeed, GnRH is released after stimulation by kisspeptin from the hypothalamic explants of male rats.

In a study using Chinese hamster ovary cells, kisspeptin receptor (Kiss1R) coupled to Gq protein and stimulated intracellular calcium mobilization through the activation of the PLC pathway. Kisspeptin also strongly phosphorylated ERK and p38 MAPK. The authors previously reported that kisspeptin activates ERK- and cAMP/PKA-mediated pathways in GT1-7 cells. Several studies have reported that Kiss1R is expressed in GT1-7 cells and that kisspeptin is able to stimulate GnRH synthesis and secretion from the GT1-7 cells. However, in the authors’ experiments, the effect of kisspeptin stimulation on GnRH expression in the GT1-7 cells was unable to be confirmed, although the cells did express Kiss1R. However, it was observed that kisspeptin increased the expression of the GnRH receptors in Kiss1R-overexpressing GT1-7 cells.

It is unclear how PACAP directly affects GnRH-producing neurons. In GT1-7 cells, PACAP also increased the expression of the GnRH receptor, similar to kisspeptin. The increase in the GnRH receptor expression by kisspeptin stimulation was potentiated by PACAP. Pulsatile GnRH secretion is dependent on an autocrine interaction between GnRH and its receptors that are expressed in GnRH-producing neurons. These results suggest that PACAP could regulate GnRH expression by modulating GnRH receptor expression.

7 | CONCLUSION

This review summarized the roles of PACAP in the hypothalamus-pituitary system and reproductive function, focusing on experiments using cell models (Figure 1). Regarding gonadotropin production, GnRH is the major regulator, but PACAP also increases the expression of the gonadotropin subunit gene and further stimulates GnRH receptor expression in gonadotrophs. The PACAP is also a prolactin synthesis-stimulating factor and the presence of PAC1R itself promotes TRH-induced prolactin production in lactotrophs. In the GnRH-producing neurons, PACAP is involved in GnRH receptor expression. It is suggested that PACAP not only acts directly in each hormone-producing cell, but also influences the production of each hormone by regulating the expression of its own receptors or those of other hormones.

DISCLOSURES

Conflict of interest: The authors declare no conflict of interest. Human Rights Statement and Animal studies: This study has been approved by a suitably constituted Ethics Committee. This article does not contain any studies with human and animal participants that have been performed by the any of the authors.

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