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Signaling pathways regulating pituitary functions

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The pituitary gland is composed of two distinct parts, the posterior pituitary and the anterior pituitary, which differ in origin, structure and function. The posterior pituitary derives from neural ectoderm and consists of neuronal projections of neurosecretory cells from the hypothalamus that produce vasopressin (AVP) and oxytocin and pituicytes, specialized glial cells that resemble astrocytes. The anterior pituitary derives from oral ectoderm giving rise to non-secretory folliculostellate cells and six lineages of secretory cell types, which can be classified into three groups. The first group is composed of two cell types expressing proopiomelanocortin gene (*Pomc*), which cleave POMC protein differentially: melanotrophs from the intermediate lobe produce α -melanocyte-stimulating hormone and β -endorphin, whereas corticotrophs from the anterior lobe produce adrenocorticotrophic hormone. The second group is composed of gonadotrophs, secreting luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and thyrotrophs, secreting thyroid-stimulating hormone (TSH). These hormones are the heterodimeric glycoproteins comprised of a common α -subunit derived by *Cga* gene, and a specific LH β , FSH β , and TSH β subunits, derived by *Lhb*, *Fshb*, and *Tshb* genes, respectively. Third, two structurally similar monomeric peptides, prolactin and growth hormone (GH), are produced by lactotrophs and somatotrophs, respectively. The heterogeneity of secretory cell types includes lacto-somatotrophs, releasing both prolactin and GH, and gonadotrophs secreting LH and FSH only, or both hormones.

This issue is focused on the anterior pituitary cell signaling. The issue starts with an article introducing multiple signaling pathways accounting for central and peripheral control of secretory pituitary cells in human and non-human primates. The authors first introduce hypothalamic modulators of pituitary cell functions, including GH-releasing hormone (GHRH), somatostatin, Ghrelin, gonadotropin-releasing hormone (GnRH), kisspeptins, corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH), dopamine, oxytocin and AVP. They also discuss the roles of melatonin and cortistatin in control of pituitary functions. This is followed by detailed analysis of peripheral modulators of pituitary cells functions, including glucocorticoids, estrogens, thyroid hormones, insulin, and fatty acids. The article also introduces intracellular signaling pathways triggered by these regulators that accounts for pituitary gene expression and hormone secretion (Vazquez-Borrego et al., 2017).

All secretory pituitary cells are excitable and fire action potentials spontaneously or in the response to hypothalamic neurohormones, including GHRH, TRH, CRH, AVP, and GnRH, whereas somatostatin and dopamine silence electrical activity. Action potential firing is accompanied with calcium influx through voltage-gated calcium channels, resulting in localized and global increase in intracellular calcium concentration. This in turn leads to

activation of plasma membrane, cytosolic and nuclear effectors involved in control of numerous cellular processes, including electrical activity, gene expression, and exocytosis. In their article, Fletcher et al. (2017) discuss common and diverse elements of voltage-gated ion channels and G protein-coupled receptors underlying electrical activity in all endocrine pituitary cell type. Using experimental recordings and mathematical modeling, they argue that a common set of ionic currents unites these cells, while differential expression of another subset of ionic currents could underlie cell type-specific patterns. The authors suggest that the collection of voltage-gated ion channels and transporters underlying electrical activity and calcium signaling should be considered an important part of cell type identity reached during embryogenesis and development, and provide a rationale how they are coordinated with hormone synthesis and secretion.

Calcium-activated potassium channels are plasma membrane effectors of localized and global calcium signals triggered by action potentials or by calcium release from intracellular stores. In his article, Michael Shipston (2017) discusses in details the role of these channels in control of anterior pituitary cell excitability. These cells express large (BK), small (SK) and intermediate (IK) calcium activated potassium channels. BK channels can both promote electrical bursting and terminate bursting and spiking dependent upon intrinsic BK channel properties and proximity to voltage-gated calcium channels in somatotrophs, lactotrophs and corticotrophs. In contrast, SK channels are predominantly activated by calcium released from intracellular inositol trisphosphate-sensitive calcium stores and mediate membrane hyperpolarization in endocrine cells, including gonadotrophs and corticotrophs. IK channels appear to be corticotroph-specific, where they limit membrane excitability. Future studies should clarify the cell-type specific molecular composition of these channels and how they control anterior pituitary calcium-dependent processes, including exocytosis.

The excitability of endocrine pituitary cells is also controlled by ligands that operates as neurotransmitters in neuronal cells by activating both G protein-coupled receptors (GPCRs) and ligand-gated receptor channels. These include acetylcholine, γ -aminobutyric acid and ATP, three neurotransmitters that are also secreted by pituitary cells, where they act in autocrine/paracrine manner. In her article, Hana Zemkova (2017) summarizes the current knowledge about the cell type-specific expression and functions of neurotransmitter receptor and channels in native and immortalized anterior pituitary cells. The main function of ligand-gated receptor channels, including γ -aminobutyric acid, is to facilitate electrical activity and calcium signaling, which further emphasizes the importance of voltage-and ligand-gated channels as signaling platforms in the pituitary gland. Further studies are needed to clarify the physiological relevance of cell type-specific ligand synthesis, expression of neurotransmitter receptors and channels and the interactions between major pathways activated by other GPCRs.

The coupling of spontaneous and receptor-controlled electrical activity to hormone secretion by regulated exocytosis also requires the presence of a large channel, called the exocytotic fusion pore. As described in article by Kreft et al. (2017), the fusion pore is an aqueous channel connecting the vesicle lumen with the plasma membrane. Once the channel is formed, it may stay closed (not being permeable for hormone stored in vesicle), providing a pathway for a rapid and transient hormone release when stimulus arrives. The article

describes biophysical properties of this channel, the role of soluble-N-ethylmaleimide-sensitive factor-attachment protein receptor proteins in their formation, and their potential relevance of stimulus-secretion coupling in pituitary cells, including lactotrophs.

The following two reviews discuss the intracellular messengers controlled by GPCRs in endocrine pituitary cells. The article by Hernandez-Ramirez et al. (2017) is focused on cyclic 3',5'-adenosine monophosphate (cAMP), the first intracellular messenger identified 1957, which is synthesized from ATP by adenylyl cyclases, and used in organisms from prokaryotes to mammals, including all mammalian secretory pituitary cells. Most of the physiologic actions of cAMP are mediated by cAMP-dependent protein kinase, which controls multiple aspects of cell function through phosphorylation of protein substrates, including electrical activity in pituitary cells. cAMP also directly regulates certain guanine nucleotide exchange factors, the cyclic nucleotide-gated channel, and the hyperpolarization-activated nonselective cation channels, which are also expressed in endocrine pituitary cells. The article describes physiological roles of this signaling pathway in pituitary cells as well as abnormal signaling in pituitary adenomas. The review by Roof and Gutierrez-Hartmann (2017) highlights the role of two signaling pathways, Ras/ERK and PI3K/AKT/mTORM, in each pituitary cell type, as well as in other endocrine tissues. These pathways are implicated in some of the most malignant cancers. The authors discuss evidence that a balance of ERK and PI3K signaling is required to maintain pituitary homeostasis. The authors also concluded that it is unlikely that one sole oncogene will be identified as being responsible for sporadic pituitary adenoma formation.

Two articles discuss GnRH receptor-dependent signaling pathways, one from experimental (Mugami et al., 2017) and the other from theoretical (Voliotis et al., 2017) points of view. The first article describes findings on the role of protein kinase C isoforms (PKCs) in mitogen-activated protein kinase (MAPK) phosphorylation (ERK1/2, JNK1/2 and p38) in mouse gonadotroph-derived cell lines: α T3-1 and L β T2. The authors show that GnRH induced a protracted activation of ERK1/2 and a slower and more transient activation of JNK1/2 and p38MAPK. They also showed a differential role for PKC α , PKC β II, PKC δ and PKC ϵ in ERK1/2, JNK1/2 and p38MAPK phosphorylation in a ligand- and cell context-dependent manner. The other paper is focused on the dynamic of GnRH receptor signaling and its impact on cellular functions during pulsatile GnRH delivery and of cell-cell heterogeneity in responses to GnRH. In general, ordinary differential equation-based mathematical models to explore the decoding of pulse dynamics and information theory-derived statistical measures are frequently used to address the influence of cell-cell variability on the amount of information transferred by signaling pathways. In this study, the authors describe both approaches for GnRH receptor signaling, with emphasis on novel insights gained from the information theoretic approach, which could be helpful in further experimental work on the fundamental question of why this neuropeptide is secreted in pulses.

Two reviews summarized the current knowledge about *Lhb* and *Fshb* expression in immortalized L β T2 gonadotrophs and compared these findings with limited studies previously done with native gonadotrophs. Djurdjica Coss' (2017) article focuses on coupling of GnRH receptor signaling pathways to *Lhb* and *Fshb* expression and crosstalk of

GnRH with other hormones that regulate gonadotropin gene expression. Stamatiades and Kaiser (2017) summarize literature describing the role of pulsatile GnRH in intracellular signaling and expression of genes relevant for control of gonadotropin gene expression. The common conclusion of these reviews is that high GnRH pulse frequency is coupled to stimulation of *Lhb* transcription, whereas low GnRH pulse frequency predominantly stimulates *Fshb* expression. There is also agreement in the field that GnRH-induced expression of immediately-early response gene *Egr-1* is sustained during high GnRH pulse frequency, which is critical for *Lhb* transcription. However, there is disagreement about signaling pathways accounting for expression of this gene: calmodulin kinase II alone or together with ERK1/2. There is also disagreement in findings about signaling pathways and transcriptional factors responsible for *Fshb* expression: protein kinase A-dependent phosphorylation of CREB vs. calmodulin kinase II/ERK1/2-dependent phosphorylation of FOS. In general, immortalized cells have tendency to change with the age of cell culture, which could contribute to different conclusions in the field. Also, L β T2 cells differ from native gonadotrophs with respect to GnRH-induced electrical activity and calcium signaling and of coupling to G_s signaling pathway. Together, these reviews provide a solid base for further work in this field, including renewal of experimentation with native gonadotrophs.

The final review nicely summarizes comparative aspects of GnRH-stimulated signal transduction in the vertebrate pituitary (Chang and Pemberton, 2017). The main part of review is focused on GnRH-stimulated signaling, gene expression and secretion in gonadotrophs from teleost fishes, amphibians, reptiles, birds and mammals. Not only several forms of GnRH control GnRH receptor signaling in gonadotrophs from teleost fishes, but also GnRH control somatotroph and lactotroph functions in these species. The authors also review literature about GnRH effects on somatotroph and lactotroph functions in mammals, suggesting that heterogeneity of cells with operative GnRH receptor signaling is reduced but not abolished during evolution.

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