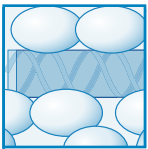# CELLULAR AND MOLECULAR SPECIFICITY OF PITUITARY GLAND PHYSIOLOGY

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Laboratorio de Regulación de la Expresión Génica en el Crecimiento, Supervivencia y Diferenciación Celular, Departamento de Química Biológica, and Laboratorio de Fisiología y Biología Molecular, Departamento de Fisiología y Biología Molecular y Celular, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires; Max Planck Institute of Psychiatry, Department of Endocrinology, Munich, Germany; and Instituto de Investigación Biomedicina de Buenos Aires (IBioBA)-CONICET-Partner Institute of the Max Planck Society, Buenos Aires, Argentina

Perez-Castro C, Renner U, Haedo MR, Stalla GK, Arzt E. Cellular and Molecular Specificity of Pituitary Gland Physiology. *Physiol Rev* 92: 1–38, 2012; doi:10.1152/physrev.00003.2011.—The anterior pituitary gland has the ability to respond to complex signals derived from central and peripheral systems. Perception of these signals and their integration are mediated by cell interactions and cross-talk of multiple signaling transduction pathways and transcriptional regulatory networks that cooperate for hormone secretion, cell plasticity, and ultimately specific pituitary responses that are essential for an appropriate physiological response. We discuss the physiopathological and molecular mechanisms related to this integrative regulatory system of the anterior pituitary gland and how it contributes to modulate the gland functions and impacts on body homeostasis.

I. INTRODUCTION

The anterior pituitary gland plays a central role in the maintenance of homeostasis. Recent reviews in the field highlight the important roles of this gland in the regulation of the different endocrine axis. In recent years it has become increasingly evident that in addition to the multiple positive and negative external stimuli, the regulation within the pituitary gland is based on local interactions among pituitary cells and the integration of downstream signaling network and transcription factors.

This review focuses on these important aspects of the integration of external and paracrine/autocrine pathways that contribute to the precise control of the functional outcome response and plasticity to environmental stimuli of the pituitary. Discussed herein is how these signals combine to regulate the anterior pituitary plasticity response to homeostatic and physiopathological conditions and highlight the molecular mechanisms involved to obtain an integrated and appropriate physiological response.

II. THE PITUITARY GLAND ANATOMY, FUNCTION, AND COMMUNICATION

A. Anatomy and Functions

The pituitary gland, a key regulator of body homeostasis during development, stress, and other physiological processes, is an intermediary organ for physiological signal exchanges between the hypothalamus and the peripheral organs. This small organ is localized in a tiny bony cavity called *sella turcica*, covered by a dural fold named *diaphragm sellae*. The pituitary fossa is a depression of the sphenoid bone structure at the base of the brain. It is functionally and anatomically connected to the hypothalamus by the median eminence via the infundibular stalk through where the hypothalamic factors reach the pituitary gland (261). It has two anatomically and functionally distinct lobes: adenohypophysis (or anterior pituitary) and neurohypophysis (or posterior pituitary).

1. The neurohypophysis

The axonal terminals of the hypothalamic supraoptic and paraventricular (PVN) nuclei (magnocellular neurons) compose mainly the posterior pituitary. Pituicytes, specialized glial cells, surround these axons and may also contribute toward regulation of neurohypophysial hormone output (339). Oxytocin and vasopressin are released from the posterior lobe.

2. The adenohypophysis

The adenohypophysis is divided into three anatomical regions: *1)* the pars tuberalis (also known as pars infundibularis), an extension of a few layers of cells surrounding the external region of the lower hypophysial stalk. It mediates the photoperiodic changes in prolactin (PRL) secretion by a factor called tuberalin, in seasonal mammals (270). *2)* The pars intermedia (also known as intermediate lobe) is located in the marginal area between the anterior pituitary and the posterior pituitary. In humans, the intermediate lobe is rudimentary and is the vestigial posterior limb of Ratchke's pouch. In lower vertebrates it has a single endocrine cell type, the melanotrophs, which secrete several bioactive peptides including endorphins and α-melanocyte-stimulating hormone (α-MSH), a cleaved product of proopiomelanocortin (POMC), that regulates the production and the distribution of melanin (217). In some species, the pars intermedia is nearly avascular, and melanotrophs are supported by nerve fibers originating from the hypothalamus. In mammalian species, different types of nerve terminals containing dopamine (DA), norepinephrine, GABA, and serotonin have been identified (217). Particularly in fish and amphibians, the pars intermedia is also innervated by peptidergic fibers, potentially involved in regulation of melanotroph secretory activity. *3)* The pars distalis is the largest portion of the adenohypophysis and is also known as the anterior lobe, comprising ~80% of the gland.

The adenohypophysis originates with the Rathke's pouch, which develops from an invagination of the oral ectoderm (see sect. IIC). The gland produces and releases endocrine hormones, growth factors, and cytokines by groups of cells that act as functional units. There are different types of specialized cells that primarily release adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), growth hormone (GH), PRL, the gonadotropins lutenizing hormone (LH), and follicle-stimulating hormone (FSH) (see sect. IIB). Hormone secretion is regulated mainly by factors through bloodstream input. The gland receives blood through the hypophysial portal circulation, which carries the hypothalamic hormones to the specialized adenohypophysial cells. In this way, hypothalamic stimulatory and inhibitory factors, together with feedback signals derived from target organs (which include hormones and nonhormonal neurotransmitting agents), converge with the auto- and paracrine factors, to induce transcriptional regulation, translation, and secretion of the pituitary hormones. Collectively, these regulatory mechanisms manage an accurate and dynamic gland homeostasic process.

In this review we focus primarily on the cellular and molecular aspects of anterior pituitary cells and their impact on the physiology of this key regulator of body homeostasis.

B. Hormone Producing Cells in the Anterior Pituitary

Hormones released by the anterior pituitary are produced by specialized cells **(TABLE 1)**. GH is produced by somatotroph cells, PRL by lactotrophs, ACTH by corticotrophs, TSH by thyrotrophs, and LH and FSH by gonadotrophs. As mentioned before, hormone secretion is mainly regulated by the hypothalamus; however, the function of the specialized cells is also greatly influenced by cell-cell interaction/communication as well as many systemic signals, as will be extensively discussed in this review.

Lactotrophs represent ~15% of the cell population in the anterior pituitary. These cells are distributed as scattered and/or dispersed cell populations throughout the anterior pituitary; however, a significant number are found in the posterior-medial portion of the gland.

An extensive range of factors affect PRL release, but its secretion is mainly regulated from the hypothalamus. DA represents the predominant inhibitory component of the hypothalamic regulation of PRL secretion in animals and humans (363). Thyrotropin-releasing hormone (TRH) is the main PRL hypothalamic releasing stimulatory factor (186), and estrogens and vasoactive intestinal polypeptide (VIP) are also stimulators of PRL (241, 253, 255, 319) (see sect. IIF3A).

Lactotroph tumoral cells produce elevated blood PRL levels and are responsible for prolactinomas.

Gonadotrophs constitute ~10% of the adenohypophysis. They are found throughout the pars distalis and include the major part of the pars tuberalis (24). These cells are in intimate contact with lactotrophs, facilitating paracrine interactions. Gonadotrophs produce LH and FSH mainly regulated by gonadotropin-releasing hormone (GnRH) (423) and feedback of gonadal factors (estradiol, testosterone, progesterone, and inhibin) (see sect. IIF3B).

Gonadotroph adenomas express the gonadotrophins (LH/FSH); however, they are usually clinically silent (316).

Table 1. *Hormone-producing cells in the anterior pituitary*

Cell	Hormone	% Cell	Pathology
Lactotrophs	PRL	15	Prolactinomas
Gonadotrophs	LH	10	Usually silent adenomas
	FSH		
Thyrotrophs	TSH	5	Plurihormonal
Somatotrophs	GH	40–50	Acromegaly
Corticotrophs	ACTH	15–20	Cushing's disease

PRL, prolactin; LH, luteinizing hormone; FSH, follicle-stimulating hormone; TSH, thyroid-stimulating hormone; GH, growth hormone.

Thyrotrophs represent ~5% of the total pituitary cell population and are commonly found in the anterior medial part of the gland.

As well as other pituitary hormones, TSH secretion depends on central and peripheral regulators. The dominant stimulatory hypothalamic effect on TSH secretion is TRH, while the dominant inhibitory action is exerted by the thyroid hormone feedback (271) (see sect. II*F3*C).

Thyrotrophs generate TSH-secreting tumors that have the particular characteristic of being plurihormonal, since they also produce α-subunits, PRL, LH, and FSH (358).

Somatotrophs constitute ~40–50% of the cell population in the anterior pituitary, located mostly at the lateral regions (261).

GH release is predominantly regulated by hypothalamic factors: it is regulated by GH releasing hormone (GHRH), and it is inhibited by somatostatin (SST), as well as an inhibitory feedback loop of the major target of GH, insulin-like growth factor-I (IGF-I). SST suppresses both basal and GHRH-stimulated GH release, without affecting GH bio-

synthesis (33). Many other regulators control GH synthesis and secretion such us ghrelin, thyroid hormone, glucocortocoids, and insulin (52, 430) **(FIG. 1)** (see sect. II*F3*D).

Somatotroph tumoral cells produce elevated blood GH levels and are responsible for acromegaly.

Corticotrophs represent 15–20% of the adenophypophysial cell population and are primarily found around the central mucoid wedge of the gland (109). Corticotrophs produce POMC and its proteolytic derivates, ACTH, MSH, lipotropic hormone (LPH), and endorphins (22, 371). With regard to ACTH secretion, the main releasing factors for these cells are corticotrophin-releasing-hormone (CRH) and vasopressin, while glucocorticoids (GC) are the major regulatory inhibitor (see sect. II*F3*E).

Corticotroph tumoral cells produce abnormal secretion of ACTH, which is responsible for or causal in the evolution of Cushing's disease (7).

Folliculostellate cells (FS) represent almost 5–10% of total pituitary cells. These cells are nonhormonal cells, but are the source of many agents that control the behavior of the
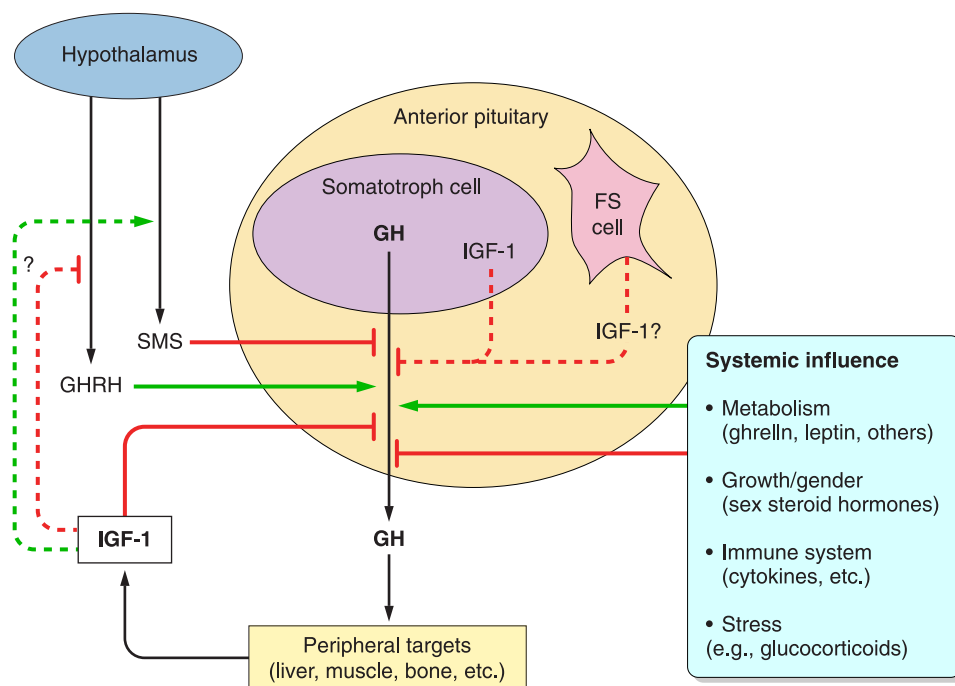
FIGURE 1. Somatotroph axis regulation. The somatotroph axis as an example of anterior pituitary hormone regulation. Somatotroph growth hormone (GH) synthesis and release is under hypothalamic control through stimulatory acting GH releasing hormone (GHRH) and inhibitory SMS. GH stimulates IGF-I production in various target organs, predominantly in liver, skeletal muscle, and bone. IGF-I downregulates through feedback inhibition the GH secretion by somatotrophs to keep the IGF-I level within the physiological range. Whether circulating IGF-I has a long-feedback influence (dotted lines) at hypothalamic level is still not clear. The somatotroph GH release is regulated in addition by an intrapituitary ultrashort-feedback mechanism involving somatotroph IGF-I. The role of FS-cell derived IGF-I in the GH regulation is not yet clear. The GH production is also under systemic stimulatory or inhibitory influence of a variety of other hormones (metabolic hormones, gender-dependent sex steroid hormones profiles, stress-induced glucococorticoids) and cytokines which are critically involved to adapt the somatotroph axis to altered physiological demands (e.g., during puberty) or physiopathological disturbances (e.g., infection/inflammation).

surrounding cells and the gland itself. They have an important role in the integration of information in the anterior pituitary auto/paracrine loops (30, 306), as discussed in section II*E*.

C. Factors Required for the Formation, Maintenance, and Expansion of the Rathke's Pouch

The infundibulum corresponds to a region of developing central nervous system (CNS) that forms in the midline of the ventral diencephalons, wherein the posterior lobe of the gland originates in all vertebrates. In contrast, the three compartments of the anterior lobe develop from the oral ectoderm (158). For the proper development of the pituitary gland, evidence points to the importance of intimate physical association between the anterior lobe primordium and the ventral diencephalon/infundibulum to promote Rathke's pouch development and all endocrine cell types in the anterior pituitary. At around day e9 in mouse, the Rathke's pouch is first to be detected, and around e12.5, after significant cell proliferation, the anterior pituitary development is completed. These developmental steps are similar in all vertebrate species studied (198, 295, 440).

During embryogenesis, important signaling molecules and transcription factors are expressed and are responsible for the anterior pituitary primordial development. These factors may in some cases act redundantly, but they usually have specific temporal/spatial expression patterns. Some of these factors are required in Rathke's pouch progenitor cells for their maintenance and proliferation. Some molecules involved in the pouch development are active within cells of the ventral diencephalon. Other factors involved for endocrine cell differentiation and hormone production will be discussed in the next section (201, 440).

Factors identified as being responsible for or involved in the formation of the primordial pituitary and its maintenance have been shown to be expressed within the Rathke's pouch itself and also by the ventral diencephalon **(TABLE 2)**. A first group of factors expressed at the primordium are as follows:

1) The SIX homeodomain proteins were identified and are expressed during pituitary development; most of the studies focused on *Six6* and *Six3* (152, 190).

2) The Paired-like homeodomain proteins include the transcription repressor factor *Hesx1* (51, 65, 94), which is one of the earliest markers of Rathke's pouch (175, 394). After 13.5 days post coitum (dpc), *Hesx1* downregulation is required for cell commitment, mostly leaving activator PROP1 to promote these events (421); *Otx2* which has been shown to be necessary for *Hesx1* expression (335);

Table 2. *Factors identified to be involved in the pituitary primordial formation and maintenance*

Factors	Genes
Factors expressed at the primordium	
The SIX homeodomain proteins	*Six6* and *Six3*
The Paired-like homeodomain proteins	*Hesx1*
	Otx2
	Pitx1
	Pitx2
LIM homeodomain	*Isl1*
	Lhx3
	Lhx4
SOX transcription factors	SOX2
WNT/β-catenin signaling	*Wnt4*
TCF/LEF family of transcription factors	*Tcf4*
Notch signaling	*Notch2, Notch3, Jagged1, Hes1*
Factors expressed at the ventral diencephalon	
The bone morphogenetic proteins	*Bmp-2, Bmp-4*
The fibroblast growth factors	*Fgf8, Fgf10* and *Fgf18*
The Sonic Hedgehog signaling	*Lhx3*
SOX transcription factors	*Sox2, Sox3*
WNT/β-catenin signaling	*Wnt5*
TCF/LEF family of transcription factors	*Tcf4*

Pitx1, the bicoid-related pituitary homeobox factor which is expressed earlier in the Rathke's pouch and also it is maintained throughout anterior pituitary development in all hormone-producing cell types (219); *Pitx2* which is structurally and functionally related to *Pitx1* (112, 147, 386, 398) and shows overlap expression with *Pitx1* suggesting a possible redundancy.

3) Three members of the LIM homeodomain genes include *Isl1*, the first LIM protein expressed during pituitary development and suggested to be necessary for proliferation/maintenance of pituitary progenitors (389); the expression of *Lhx3* is required not only for the survival of progenitor cells, but also for cell specification (28, 201, 365). In contrast, *Lhx4* expression has a more transient and restricted pattern (233).

4) SOX transcription factors are specifically expressed in the early ectoderm and maintained throughout the pouch during embryogenesis and in the adult gland. SOX2-positive cells have been identified in adult pituitary, and they might represent the gland's stem cells (134, 149, 159) (see sect. II*G*).

5) WNT/β-catenin signaling is also involved, and the expression of some of the ligands has been detected during early pituitary development such as *Wnt4* (291, 396). At a very early stage, TCF4 belonging to the TCF/LEF family of transcription factors is also expressed and might play a role as negative regulator of gland growth (53).

6) Notch signaling components such as *Notch2*, *Notch3*, *Jagged1,* and *Hes1* (e9. 5 dpc) are important for the maintenance of the pituitary progenitor's cells and for controlling the balance between proliferation and differentiation to allow the proper endocrine cell fate (268, 325, 441).

A second group of factors expressed by the ventral diencephalon and reported to be involved on Rathke's pouch development include the following:

1) The bone morphogenetic proteins (BMPs): in this family, *Bmp-4*, which is expressed very early in the emerging and/or developing infundibulum at e8.5 dpc, is responsible for the initial step of Rathke's pouch formation (119, 389, 396). Also, deletion of *Bmp-4* results in embryonic lethality around gastrulation. The ventral mesenchyme adjacent to Rathke's pouch was shown to have a critical role for the development of the primordium. For instance, *Bmp-2* is expressed in the mesenchymal at e10.5 dpc. Expression of *Isl1* is regulated by BMP-4 and BMP-2 (396).

2) The fibroblast growth factor (FGF) family members were shown to be important for organogenesis as well for anterior pituitary cell differentiation (see below). After the onset of BMP-4 expression, around e9.5 dpc, *Fgf8*, *Fgf10,* and *Fgf18* are expressed in the infundibulum (119, 396).

These factors induce progenitors cell proliferation within the Rathke's pouch (387, 389), and they antagonize BMP actions at both earlier stages and during terminal differentiation of the endocrine cells (396).

3) The Sonic Hedgehog signaling is also involved in the regulation of cell proliferation and cell type proliferation. SHH signaling controls progenitor proliferation mainly by the regulation of *Lhx3* and might contribute to cell determination by inducing *Bmp-2* expression (397).

4) *Sox3*, which is absent in the pouch, is expressed in the ventral diencephalon (427). *Sox2* is also expressed in the ventral diencephalon, and it was linked to its development (201). Deletion of *Sox3* causes hypopituitarism and craniofacial defects (337).

5) WNT/β-catenin signaling has a major role within the pouch as mentioned above, but is also important in the ventral diencephalon (53, 69, 396). Functional interactions between SOX and β-catenin have been suggested during pituitary organogenesis (201).

Interestingly, some of these key factors can act on more than one process during the gland development. For example, PITX proteins act at very early stages of organogenesis and also at much later stages when gonadotroph and thyrotroph lineage expansion occurs.

Others have been shown to play a role in the adult pituitary, as example SHH (415), or BMP-4, and these will be extensively discussed in this review.

D. Differentiation Factors That Control Cell Specification

Many transcription factors involved in pituitary development have been determined by studies on animal models as well as in mutations found in some of the pituitary transcription factors detected in human patients, validating their role in cell endocrine differentiation.

The Prophet of Pit-1 (PROP-1) induces Pit-1 expression (also known as POU1F1) (13) and is expressed during early stage of pituitary development. PROP-1 downregulates *Hesx-1* (374) and in conjunction with β-catenin complex (291) can regulate proliferation of progenitor cells. The mutation of PROP-1 causes *Pit-1* deficiency in Ames dwarf mice (374) and in humans a general pituitary hormone deficiency (429). *Pit-1* is essential for differentiation and/or maintenance of somatotroph, lactotroph, and thyrotroph linage (370). It is also required for GHRHR expression (14), and its mutations have been linked with hypoplasia of somatotrophs, lactotrophs, and thyrotrophs (229). In humans, it has been linked with hypopituitarism as well as GH, PRL, and TSH deficiency (229, 309, 324). In addition, it can act by inhibiting GATA2 transcriptional activity repressing gonadotroph development (95).

Tpit in cooperation with *Pitx1* specify ACTH-producing corticotrophs and melanotrophs. *Tpit* expression is first detected during the development of the gland and also later in the adult stage (218, 231). In POMC-expressing cells, TPIT promotes terminal cell differentiation by induction of POMC expression (200, 321). When *Tpit* expression is abolished by KO, reduced corticotrophs and melanotrophs were observed (320).

Timing of appearance for these specialized cells were accurately determined, through the use of cell type specific markers. The expression of the α-glycoprotein subunit (*Cga*), encoded by alpha-GSU gene, is the first cell marker expressed at the Rathke's pouch, giving place to a transitional thyrotroph population. In the adult gland, *Cga* is only expressed in thyrotrophs and gonadotrophs (370). Later, corticotrophs begin to differentiate by expressing POMC (218), giving place to the melanotrophs in the intermediate lobe as well.

As development progresses, thyrotrophs start to express the *Tshb* marker. In addition and concomitantly, somatotrophs and lactotrophs emerge expressing GH and PRL as their differentiation markers, respectively. The last type of cell to appear is the gonadotroph expressing *Lhb* followed by *Fshb 1*.

Many factors and signaling pathway components have relevant roles during pituitary development and cell commitment and specification. How these signals are integrated to regulate organ development and pituitary plasticity and function is still under extensive investigation.

E. Folliculostellate Cells

1. Lymphoid dendritic or microglia-like cell type?

Although detected nearly 60 years ago (336), it is only during the last 20 years that the diverse and important functional roles of this cell type in pituitary physiology has increasingly been recognized (12, 106, 184). FS cells have a star-shaped morphology and the ability to form colloid material containing intrapituitary follicles that increase both in number and in size during pituitary aging (195, 239, 288). Since FS cells are able to perform phagocytosis and in this way remove cell debris of apoptotic endocrine pituitary cells, it has been speculated that the follicles represent an intrapituitary deposit of cell residues (15, 382).

FS cells are positive for S100 protein and glial fibrillary acidic protein (GFAP), suggesting that this cell type may represent an astrocyte- or microglia-like cell type within the adenohypophysis (184). This idea is supported by their phagocytotic capabilities as well as their glia-like supportive functions within the pituitary involving ion homeostasis regulation, water transport (59, 184, 214, 312), and protection from damages caused by irradiation or free radicals (283, 437).

Whether subpopulations of FS cells also represent a dendritic, tissue-specific immune cell type is controversial (9, 10, 157, 174, 351, 405). Whereas some authors could detect dendritic MHC-class II markers like OX6 in a subset of S100-expressing FS cells, others have described OX6 and S100 expression in morphologically similar but different cell populations, suggesting that independent from FS cells, a small population of dendritic cells exists in the pituitary (351). In pituitary adenomas, S100 expressing FS were negative for markers of the monocyte/dendritic cell/macrophage lineage (HAM56, KP1, HLA-DR) (157). However, very recently, the dendritic character of a part of FS cells has been confirmed in transgenic mice expressing a suicide gene in the subpopulation of dendritic cells. Initiation of specific dendritic cell killing by ganciclovir was associated with a strong reduction of FS cells positive for S100 and MHC class II antigens in the anterior pituitary (11). It is speculated that a dendritic-like subpopulation of FS cells plays a specific role in the immune-endocrine cross-talk between FS cells and endocrine pituitary cells (12, 174).

2. Intrapituitary network formation

Immunohistochemical and ultrastructural studies have shown that FS cells form a network within the anterior pituitary in which the cellular extensions of FS cells are connected among each other mechanically and functionally through desmosomes and gap junctions, respectively (73, 132, 133, 380). Through the latter, FS cells are also in contact with neighboring endocrine pituitary cells (269, 372). Gap junctions are small pores that permit the intercellular exchange of molecules smaller than 1,000 Da including second messengers like cAMP, inositol phosphate, or calcium. Thus intercellular communication through these substances among FS cells as well as between FS and endocrine cells may be possible (132, 133). Indeed, in pituitary slices, the electric stimulation of a single FS cell led to an intracellular increase of calcium, which propagated to other FS cells through gap junctions (132). The membrane excitability of FS cells (comparable to glial cell types) is of interest because several reports have shown synaptic endings of nerve fibers close to FS cells, suggesting that these cells may be a target of not yet identified neuronal structures (240). Thus after neuronal FS stimulation and subsequent membrane depolarization, the increase in local intracellular calcium content may be distributed through gap junctions to other FS cells as well as to endocrine cells. In this way, long distance intercellular communication and coordinated response of FS and/or endocrine cells may be possible (133, 179, 380). Other factors acting on FS cells may induce through receptor-associated second messengers or through receptor regulated ion channels gap junction-mediated intercellular FS cell network activation (228, 381). Since the intercellular communication is dependent on rapid second messenger distribution and therefore on the density of intercellular gap junctions, it is of particular interest that hormones (GCs, sex steroid hormones) and other factors [tumor necrosis factor (TNF)-α, transforming growth factor (TGF)-$\beta3$, ciliary neurotrophic factor (CNTF), leptin] can regulate intrapituitary gap junction formation and density (146, 194, 213, 259, 343, 372). Regulated increase or decrease of gap junction number or their pore size could provide a mechanism to enhance or to suppress intercellular long-distance communication among FS cells or between FS and endocrine cells. However, the physiological role of the intrapituitary FS cell network for the regulation of the anterior pituitary homeostasis is still poorly understood.

F. Endocrine and Intrapituitary Communication

1. The importance of cell-to-cell communication in the anterior pituitary gland

Typically, anterior hormone serum levels change rapidly and strongly in response to physiological stimulation/inhibition by hypothalamic factors, as this is essential to exert maximum effects in the target glands or organs of pituitary hormones. Little is known about the molecular mecha-

nisms, and only recently first studies gave hints about the dynamic and the efficiency by which hypothalamic compounds might be transported to their hypophysial target cells (216, 353). These processes include delivery of hypothalamic factors through the portal vessel system to the anterior pituitary, transepithelial uptake by trans- and paracellular mechanisms into the pituitary, and subsequent diffusion of the hypothalamic compounds to their target cells (216, 353). There, the hypothalamic factors may act through specific receptors separately on individual target cells or may activate clusters of the same hormone producing cell types that are connected to each other. In fact, it has been shown that not only FS cells but also GH-producing somatotrophs form gap-junction connected networks within the pituitary (42, 176, 216, 420). Thus after GHRH or somatostatin binding, second messengers distributed through gap junctions would stimulate or inhibit GH release in clusters of cells (42, 420). This simultaneous stimulation/inhibition would allow a coordinated release of hormones into the bloodstream resulting in a rapid and robust rise in serum hormone levels (26, 346). However, because during the release of a certain hormone adaptive processes of other endocrine cell types may be necessary, it is thought that in addition to intracellular communication of cells of the same type interference with other pituitary cell types will take place. This intercellular communication will mainly be managed through soluble factors (105, 333), and FS cells may play a modulatory role as outlined in the following sections. All of the intrinsic auto-/paracrine acting factors (TABLE 3) regulating the communication between pituitary cells are also systemically delivered to the pituitary with the blood stream and thus represent also extrinsic factors. In most cases it is impossible to distinguish to which extent intrinsic and extrinsic proportions of a factor contribute to a distinct pituitary cell response.

2. Paracrine interactions between FS cells and intrapituitary endothelial cells

In addition to gap junction-mediated intercellular communication between FS and endocrine pituitary cells, crosstalk through soluble factors may also play an important role. FS cells represent both a target for and a source of multiple growth factors, cytokines, hormones, and peptides (TABLE 3), some of which are predominantly or even exclusively produced by FS cells within the anterior pituitary (105, 333). It is supposed that FS cell and endocrine cell-derived factors act through paracrine mechanisms to locally regulate endocrine cell function (105, 333) and thus participate in pituitary homeostasis control.

In 1989, an endothelial cell-specific growth factor was isolated from pituitary FS cells (138, 162). This vascular endothelial growth factor (VEGF or VEGF-A), which turned out to correspond to a previously detected vascular permeability factor (VPF) (361), was the first member of the VEGF protein family to be identified and has been shown to play a central role in blood vessel and lymph angiogenesis (64, 137, 139). Today, VEGFs and their receptors represent a major research focus in all diseases accompanied with aberrant vessel formation and represent a major target of corresponding therapeutic approaches (64, 137). In the normal pituitary, VEGF was identified in several endocrine cell types, but it seems that it is mainly produced by FS cells (89, 126, 138, 162). The two major receptors of VEGF, VEGFR-1 (Flt-1) and VEGFR-2 (Flk-1/KDR), are differently localized in the pituitary (32, 293, 414). VEGFR-1 is present in endocrine cells, whereas VEGFR-2 and its coreceptor neuropilin-1 (NRP-1) are mainly expressed in endothelial cells (293). During embryogenesis and postnatal development, VEGF may regulate in concert with other FS cell-derived angiogenic factors such as FGF-2 of PDGF the expansion of the intrapituitary vascular network in the growing pituitary (140, 278). In the adult pituitary, which is characterized by a considerable degree of plasticity, VEGF may play a role in the extension of the blood vessel system, for instance, during the transient pregnancy- and lactation-associated enlargement of the anterior pituitary (170, 292, 402).

The anterior pituitary is one of the most densely vascularized mammalian organs due to the fact that the previously described communication among hypothalamus, pituitary, and target organs is mediated predominantly through soluble substances transported within the bloodstream (402, 412, 413). Thus, to guarantee optimal function, VEGF may be needed not only to form but also to maintain this extremely dense intrapituitary vascular network (242). In this context, the recently detected sumoylation enhancer RSUME, which is highly expressed in the anterior pituitary (63), may play an important role. RSUME was shown to stabilize hypoxia-inducible factor-1α (HIF-1α) the regulated subunit of the transcription factor HIF-1 (63). The latter is induced by cellular hypoxia and induces multiple mechanisms to promote the survival of cells during transiently limited oxygen supply (360). The action of HIF-1 includes stimulation of angiogenic factors like VEGF-A to induce the formation of new vessels and, thus, to improve oxygen delivery under persistent hypoxic conditions (334). RSUME-supported, prolonged action of HIF-1 may be of relevance in rare cases of portal vessel ruptures (e.g., after severe traumatic brain injury) and subsequent anterior pituitary infarcts in which the oxygen supply of the pituitary cells is impaired.

Another putative intrahypophysial function of VEGF is given by its capability to stimulate vessel permeability through altering endothelial cell fenestration (242). In general, endocrine glands are characterized by a dense network of well-fenestrated capillaries with VEGF-producing cells in close juxtaposition to the fenestrated microvasculature (243). In the pituitary with their capillary sinusoids free of smooth muscle cells and rich in pericytes, the well-fenes-

Table 3. *Overview about intrapituitary sources and targets of peptides, growth factors, cytokines, and nonanterior pituitary hormones in normal anterior pituitary-specific endocrine and nonendocrine cell types*

Factor	Intrapituitary	
	Source	Target
Activin	G	G/L
Adrenomedullin	G	C/S
Angiopoietins	G	
Angiotensin(ogen)	G	C/FS/L
Annexin-1	FS	C/FS/G/L/S
Atrial natriuretic peptide (ANP)	C/G/L	C
Calcitonin	G	FS/L
Calcitonin gene-related peptide (CGRP)	G	C/S
Ciliary neurotrophic factor (CNTF)	FS	FS/G/L/S
Cocaine- and amphetamine-regulated transcript (CART)	C/G/L	G/L
C-type natriuretic peptide (CNP)	C/G	C/G
Endothelin-1	L/S	L/S
Endothelin-3	L/G	L/S
Epidermal growth factor (EGF)	C/G/S/T	C/FS/G/L/S/T
Fibroblast growth factor-2 (FGF2)	FS/G	FS/L
Follistatin	FS/G	G
Galanin	C/L/S/T	G/L
Gastrin-releasing peptide (GRP)	C/L/S	C/T
Ghrelin	L/S/T	S
Glial cell-derived neurotrophic factor (GDNF)	C/FS/S	S
Inhibin	G	G
Insulin-like growth factor I (IGF-I)	FS/S	FS/L
Interleukin-1	T	C/FS
Interleukin-6	FS	C/FS/L/S
Interleukin-11	FS	L/S
Intermedin	C	C/L/S
Leptin	C/FS/G/S/T	FS/G/S/T
Leukemia-inhibitory factor (LIF)	C/FS	C/G/L
Macrophage migration-inhibitory factor (MIF)	C/FS/T	C/FS
Nerve growth factor (NGF)	L	L
Neuromedin B	T	T
Neuromedin U	C	C
Neuropeptide Y	C/G/L/S/T	G/L/S
Neurotensin	G/T	L
Orexin A	L	C/S
Orexin B	C	C/S

Continued

Table 3.—Continued

Factor	Intrapituitary	
	Source	Target
Oxytocin	L	G
Pituitary adenylate cyclase-activating peptide (PACAP)	G	FS/G/L/S
Platelet-derived growth factor (PDGF)	FS	FS
Stromal cell-derived factor 1 (SDF1)	C/L/S	C/L/S
Substance P	S/T	L/T
Transforming growth factor-α (TGF-α)	C/G/L/S/T	C/FS/G/L/S/T
Transforming growth factor-β1 (TGF-β1)	FS/L	FS/L
Transforming growth factor-β3 (TGF-β3)	FS/L	FS/L
Urocortin	C/L/S	C/G
Urocortin II	C	C
Vascular endothelial growth factor (VEGF)	FS	
Vasoactive intestinal peptide (VIP)	L	FS/L/S
Vasopressin	C	C/T

C, corticotroph cells; FS, folliculostellate cells; G, gonadotroph cells; L, lactotroph cells; S, somatotroph cells; T, thyrotroph cells.

trated endothelial cells are in close contact to VEGF-producing folliculostellate cells (184, 372). This would enable both membrane-bound and secreted VEGF isoforms of FS cells to affect endothelial cell fenestration by juxtacrine and paracrine mechanisms, respectively. It is attractive to speculate that the modulation of endothelial cell fenestration may represent a mode of action to regulate the intrapituitary exchange of factors between blood and endocrine cells. For instance, the hypothalamic factor pituitary adenylate cyclase-activating polypeptide (PACAP), a strong stimulator of VEGF production in FS cells (160, 235), may in this way enhance capillary permeability and thus improve the action of hypophysiotropic hormones by facilitating their entry into the pituitary and by improving the release of pituitary hormones into the bloodstream. On the other hand, potent suppressors of VEGF like GC (235, 293) may impede these processes. However, clear data supporting the concept of endocrine modulation by vessel permeability regulation are still missing.

3. Endocrine, intrapituitary, and intercellular communication through soluble factors

In the next sections, illustrative examples on the role of intercellular communications in pituitary physiology are provided, highlighting the participation of FS in these circuits.

A) LACTOTROPH CELLS. The function and growth of lactotroph cells are predominantly regulated by the tonic inhibitory action of the dopaminergic system (34, 181). Among the different endocrine cell populations, lactotrophs are those with the highest degree of plasticity in particular in female mammalians, in which the lactotroph cell population strongly increases during pregnancy/lactation and rapidly declines to previous size after weaning (62, 289, 436). Moreover, lactotrophs represent the pituitary cell type with both the highest mitotic and apoptotic rate in particular in female mammals during the reproductive phase and varies during the menstrual cycle (62, 289, 436). Lactotroph proliferation peaks during estrus, while the apoptotic rate reaches its maximum in the afternoon of proestrus and ovariectomy abolishes these cyclic alterations (62, 289). These female- and cycle-specific changes have been found to be dependent on the action of estrogens, which regulates in concert with the dopaminergic system PRL production and lactotroph cell growth (34, 347).

Whereas estradiol predominantly stimulates PRL synthesis and release, this hormone was shown to differently affect lactotroph cell growth by acting either proliferative or apoptotically (347, 435). Several hypotheses have been developed to explain this phenomenon. Very recently, studies using cell membrane-impermeable estrogen derivatives have shown that these compounds induce apoptosis but not proliferation in lactotroph pituitary cells (435). It has been speculated that membrane-bound estrogen receptors (mbER) may induce apoptotic signals whereas classical intracellular estrogen receptors (ER) (predominantly ERα) are responsible for proliferative effects of estrogens (435).

Alternatively, estrogens may affect lactotroph growth and function through altering the dopaminergic control. It is well known that estradiol downregulates hypothalamic DA production and suppresses the activity of the D2 receptor (D2R) in lactotrophs by uncoupling the receptors from G$\alpha\alpha$/$\alpha\alpha$o G proteins (5, 34, 165, 348, 362). Estrogens also regulate the expression of the two D2R isoforms, D2RL (long isoform) and D2RS (short isoform), which differently interfering with G proteins (166, 266). As estradiol favors the production of D2RL over D2RS (5, 362), this may have consequences for D2R interaction with G proteins and thus for the action of DA on growth and function of lactotrophs.

Estrogen effects on lactotroph cell growth are mediated in part through estrogen-induced stimulatory or inhibitory acting growth factors like TGF-α, TGF-β, epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), IGF-I, IGF-II, interleukin (IL)-6, and others, which have been shown to stimulate or to inhibit PRL production and growth of lactotroph cells (62, 136, 172, 347). For instance, increasing estradiol concentrations reduce the intrapituitary production of TGF-β1 and stimulate the synthesis of TGF-β3 (347) **(FIG. 2)**. These two factors have opposite

effects on lactotroph cell growth, since TGF-β1 inhibits and TGF-β3 stimulates the proliferation of these cells (172, 349). Interestingly, these estradiol-induced changes are critically dependent on the presence of FS cells (294), which may be explained by the fact that these cells are a target of estrogens and a major intrapituitary production site of growth factors (TGF-β1, TGF-β3, bFGF, IL-6, and others) (104, 105). In particular, estradiol-induced TGF-β3 stimulates in FS cells the production of bFGF, which is a potent stimulator of PRL production and lactotroph cell proliferation and may thus regulate in a paracrine manner growth and function of lactotrophs (72, 104, 105). Regarding apoptosis, it has been demonstrated that estradiol upregulates the Fas/FasL apoptotic pathway in lactotrophs and induces the intrapituitary production of TNF-α, which acts apoptotic through the TNF receptor 1 (TNFR1) expressed on lactotrophs (61, 187). Thus, in female mammals, subtle changes of estradiol levels during cycling may induce through complex regulatory mechanisms changes in both proliferative and anti-proliferative growth factors as well as pro-apoptotic factors. Whether lactotrophs undergo proliferation or apoptosis will then depend on the actual dominance of the different factors during the cycle.

During pregnancy, upregulation of the estradiol levels may play a role in the enlargement of the lactotroph cell population by changing the intrapitpitary growth factor milieu towards maximal growth stimulation of lactotrophs (433). As estrogen levels decline rapidly after delivery, suckling-induced neuroendocrine mechanism may trigger the maintenance of the enlarged lactotroph cell population needed for continuous PRL production during the lactation period. After weaning, enhanced apoptosis restricted to lactotroph cells reduces the lactotroph cell population to normal state (15, 110, 314) involving an unusual, lactotroph-specific pro-apoptotic action of DA that is D2R independent (189). It has recently been demonstrated that rats in the postlactation period strongly and transiently overexpress tyrosine hydroxylase (TH) and the DA transporter (DAT) in lactotrophs. Lactotrophs themselves produce DA through TH, release it by exocytosis, and reuptake DA through the DAT (189). The accumulation of intracellular DA then induces mitochondrial membrane depolarization and thus initiates subsequent apoptotic mechanisms. This peculiar autocrine dopaminergic induction of apoptosis is restricted to lactotrophs during the postlactation period (189); the mechanisms initiating and terminating this process are not known.

The growth and PRL production of the lactotroph cell population is predominantly under dopaminergic but also under estrogenic (in females) and multiple growth factor control. These various endocrine and auto-/paracrine regulatory systems, which interfere among each other, generate a highly complex intrapituitary homeostasis of lactotroph regulation. Subtle shifts in the balance between positive and negative regulators may determine the function and fate of
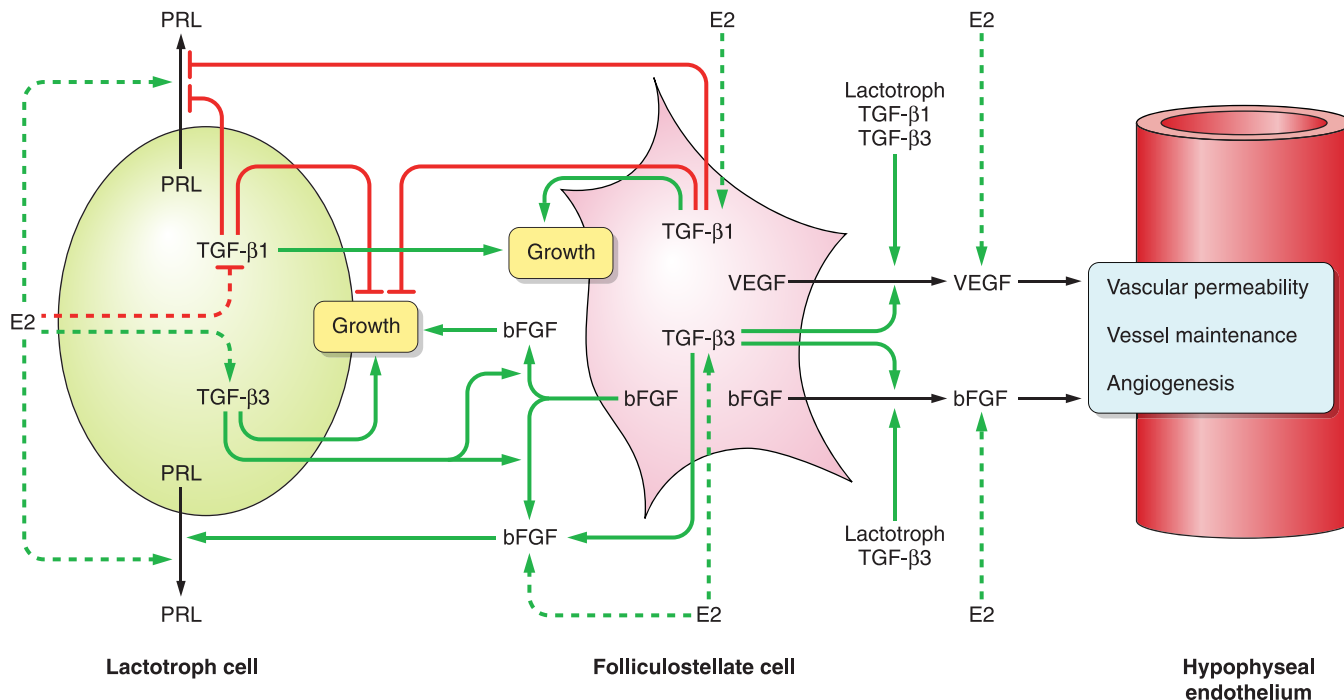
FIGURE 2. Scheme of stimulatory (+) and inhibitory (−) auto-paracrine interactions between lactotroph, folliculostellate, and endothelial cells in normal anterior pituitary. Subtle shifts in the balance between positive and negative autocrine/paracrine loops are integrated and contribute to determine the function and fate of pituitary cells, as illustrated in this example for lactotrophs, showing the interactions involving estrogen, transforming growth factor (TGF)-β, basic fibroblast growth factor (bFGF), and vascular endothelial growth factor (VEGF). bFGF, which is predominantly produced by FS cells, is not only an angiogenic factor but also a strong stimulator of lactotroph cell proliferation and prolactin release. TGF-β1 and TGF-β3 are produced by both FS and lactotroph cells and have direct contrary effects on both growth and prolactin prodution. In addition, through enhancing bFGF production, TGF-β3 indirectly stimulates lactotroph cell proliferation and prolactin secretion. TGF-β1 and TGF-β3 are also involved in the regulation of FS cell-derived angiogenic acting bFGF and VEGF, and consequently in hypophysial endothelial homeostasis. The auto-/paracrine action of all these factors is as well regulated by estrogens (E2, dotted lines), which in addition to their direct stimulatory effects on PRL production shift the TGF-β1 and -β3 balance and stimulate bFGF and VEGF.

lactotrophs. The integration of the signals at the PRL promoter and the crucial role of BMP-4 are discussed in section IV*B1*.

B) GONADOTROPH CELL REGULATION. Apart from the major regulation of gonadotrophin secretion through stimulating hypothalamic GnRH and feedback of gonadal factors (estradiol, testodterone, progesterone inhibin), the production of FSH and, to much lesser extent, of LH secretion is also under intrapituitary auto-/paracrine control of locally produced factors (82, 87, 121, 135, 164, 426). A putative candidate for an intrapituitary LH regulator is PACAP, a hypothalamic peptide that is also synthesized by gonadotroph and FS cells (411, 426). PACAP production and expression of its receptor (PAC1-R) was shown to be stimulated by GnRH and, in turn, PACAP was found to increase LH secretion directly and indirectly through supporting GnRH-receptor expression and enhancing GnRH-induced stimulation of LH (322, 411, 426).

Although LH and FSH are both stimulated through GnRH, the secretion characteristics and the levels of LH and FSH are different, and it is thought that divergent sensitivity to gonadal feedback mechanisms or variable intrapituitary implication in the production of the two types of gonadotropins are responsible for these differences (82, 121, 296, 426). Evidence for an LH-independent intrapituitary auto-/paracrine regulation of FSH production and release emerged from studies with GnRH disconnected pituitary fragments, in which LH secretion rapidly stopped, whereas FSH secretion continued in pulsatile fashion for a considerable time period (82, 121, 296). This points to intrapituitary FSH stimulatory mechanisms, in which locally produced inhibin, activin and follistatin play an outstanding role (163, 296, 425). Inhibin and activin belong to the TGF-β superfamily and are composed of in part common α- and β-subunits. Inhibin A and inhibin B are heterodimers of β_A-subunits and β_B-subunits, respectively (39, 58, 247, 379). Inhibin, as part of the peripheral feedback mechanisms in FSH regulation, is not only produced by gonads (Leydig cells, Sertoli cells) but also by endocrine pituitary cells, predominantly gonadotroph cells, and to lesser extent by somatotrophs, thyrotrophs, and FS cells (39, 403). In gonadotroph cells, the inhibin receptor TGF-βR3 (betagly-

can) mediates the inhibitory effect of both gonadal and intrapituitary inhibin on FSH production because inactivation or downregulation of the TGF-βR3 strongly reduces inhibin's suppressive action of FSH secretion (163, 425). Since the TGF-βR3 contains no intracellular signal domain, the FSH suppressing action of inhibin is still not well understood but may predominantly involve inibition of the FSH stimulatory action of the activin receptor system through interaction of TGF-β3 with the activin type II receptor, resulting in an inactive receptor heterodimer (120, 163, 247, 422).

Activin isoforms are composed only of β-subunits from which in addition to βA and βB, three other forms (βC-βE) are known (58, 251). The best-studied and probably most relevant FSH stimulating activins are activin A (βAβA) and activin B (βBβB) homodimers as well as the activin AB (βAβB) heterodimer (58). In mammalian pituitaries, activin βA and βB subunits are predominatly expressed in gonadotrophs (105, 403). The release of inhibin and activin isoforms from gonadotrophs may depend on the relative intracellular availability of the α- and β-subunits, and an excess of α- over β-subunits will lead to the predominant release of inhibin isoforms, whereas a high intracellular β:α subunit ratio will favor the formation and secretion of activin isoforms (58). This suggests that an intrapituitary inhibin/activin homeostasis may exist that is shifted by factors stimulating or inhibiting α- and β-subunit synthesis upon corresponding physiological demands.

Gonad-derived and intrapituitary activin is further regulated by follistatin, an activin-binding protein that is predominantly produced by gonadotrophs and FS cells but also by other endocrine cell types (thyrotrophs, lactotrophs, somatotrophs) (39, 197, 296, 426). Follistatin further complicates the multi-facetted, selective FSH regulation by binding activin with high affinity and thus neutralizing its FSH stimulatory action probably to prevent putative excessive action of elevated intra- or extrapituitary concentrations of activin (39, 296, 426). Since there is evidence that follistatin synthesis by FS cells is upregulated by various factors like IL-1, PACAP, GC, and testosterone (39, 221), these substances may indirectly and in paracrine manner suppress through the stimulation of follistatin the FSH production under distinct physiopathological circumstances, e.g., during inflammatory or infectious processes.

In general, FSH production is under complex hypothalamic, gonadal, and intrapituitary control. This regulatory complexity may explain why LH and FSH can be regulated differently despite production and regulation in the same cell and by the same hypothalamic releasing hormone, respectively. The physiological role of the intrapituitary activin/inhibin/follistatin system, which mainly involves gonadotroph and FS cells, is still poorly understood but may maintain the FSH secretion and pulsatility and thus gonadal function in situations of disturbed hypothalamic stimulation or impaired gonadal feedback inhibition of FSH production.

C) THYROTROPHIC AXIS REGULATION. TSH production and release within the hypothalamic-pituitary-thyroid (HPT) axis is regulated by two hypothalamic hormones, stimulatory acting TRH and inhibitory SST and through feedback inhibition by TSH-stimulated thyroid hormones T_3 and T_4 (143, 177, 258, 301). TRH exerts its TSH stimulatory effects through the G protein-coupled type 1 TRH receptor (TRH-R1) and by inducing the inositol phosphate/calcium/protein kinase C (PKC) signaling pathway (388). SST inhibits TSH predominantly through the inhibitory G protein-coupled SSTR2 by reducing intracellular calcium levels (35, 177). Bioactive T_3 mediates the inhibitory feedback through binding to the thyroid hormone (TH) receptor (THR), a transcription factor suppressing TRH and TSH synthesis at hypothalamic and hypophysial level, respectively (78). TSH shows a pulsatile release pattern and diurnal variations with a peak in the night and low levels during the day (169). SST inhibits not only TSH secretion but also GH release (see below), which may be due to the fact that the HPT and the somatotroph axis are important regulators of metabolic homeostasis, and coordinated suppression may be of physiological benefit (177). GCs and inflammatory cytokines also suppress TSH production both directly and indirectly (through inhibition of hypothalamic TRH) and may be responsible for the life-threatening low T_3/T_4 syndrome observed in sepsis (258).

Regarding intrapituitary control of TSH production, FS cells express TSH receptors (TSHR) (54, 317, 391) and other factors related to thyrotrophic axis regulation such as type 2 deiodinase (D2) and the thyroid hormone transporter monocarboxylate transporter 8 (MCT8) (144). FS cells are thought to play an important role in an intrapituitary ultra-short feedback loop, in which thyrotrophic TSH induces the secretion of a FS cell-derived putative inhibitor of TSH secretion, probably TGF-β2 (8, 301, 318). Moreover, the T_4/T_3 transporter MCT8 and T_4 to T_3 converting D2 are located exclusively in FS cells (144). Therefore, TSH may also regulate through TSHR the folliculostellate D2 activity and in this way the intrapituitary T3 production (144). These ultra-short feedback actions may be involved in TSH pulsatility by fine-tuning the oscillation of the thyrotroph axis by a local, FS cell-mediated, dampening of TSH action in anticipation of its action on T4 secretion (318).

D) SOMATOTROPH AXIS. At the pituitary level, GHRH stimulates and SST inhibits (mainly through the SST2 receptor) GH production through stimulatory or inhibitory G proteins and through enhancing or suppressing calcium influx and the cAMP messenger signal cascade (35, 153, 272). The feedback inhibition of IGF-I on GH production is mediated

11

through the IGF-I tyrosine kinase receptor (IGF-IR) that is linked to different signaling cascades (IRS-1/PI3 kinase pathway or SHC/GRB2/Sos-1/RAS/MAP kinase pathways) (272). Recently, it has been shown that somatotroph cells are organized as a gap-junction connected network (42, 420). Thus, after receptor activation in a single cell, small signaling molecules (cAMP, calcium, phosphoinositol etc.) can diffuse to neighboring cells and thus activate/inhibit clusters of somatotroph cells (26, 42). Like other pituitary hormones, GH is released in a pulsatile manner and shows a circadian rhythm with maximum GH secretion during sleeptime (169, 272, 366). With increasing age, GH bursts decline in magnitude and frequency, and in men over 50 and postmenopausal women, the circadian rhythm has largely disappeared (56, 127, 169, 366). With regard to intrapituitary GH regulation, an ultrashort intrapituitary feedback loop has been hypothesized in which GH regulates its own production locally, but the putative physiological impact of such a local feedback is not known (118). The role of FS cell-derived IGF-I (29) in GH regulation has not yet been studied, and GH-stimulating, FS-cell derived IL-6 may be involved in immunomodulatory changes of GH production during immune system activation (20, 105).

Playing a key role in body growth and in metabolic homeostasis, the somatotroph axis is regulated by many other hormones, neuropeptides, growth factors, and cytokines at hypothalamic, hypophysial, and peripheral levels (272) (FIG. 1). Key hormones of other endocrine axes such as GC, sex steroid hormones, or DA seem to affect the somatotroph axis predominantly at hypothalamic level by altering GHRH and/or SST release (108, 150, 151, 199). For instance, reduced GH levels and thus dwarfism in DA D2R knock-out mice seem to be a consequence of both failures of embryonic pituitary development (reduced somatotroph cell population) and impairments of the hypothalamic GH regulating factors GHRH and SST (150). Factors regulating food intake and energy expenditure all influence GH levels at least in part by acting directly at the somatotroph level (156, 210). In general, GH levels increase during fasting and decline in obesity (237). During reduced food intake, enhanced GH levels are needed for consumption of fat stores to maintain glucose levels high. In this process, the metabolic hormone ghrelin, predominantly produced in the stomach during food uptake, seems to play an important role in elevating GH levels because ghrelin is apart from GHRH the most potent stimulator of GH through GHS receptors expressed on somatotrophs (66, 220). However, as during fasting, the availability of food intake associated with circulating ghrelin is reduced; it is speculated that intrapituitary ghrelin production is enhanced to promote GH production under fasting conditions (237). The mechanisms responsible for GH suppression in obesity, in particular the disturbed interplay between leptin and GH, are less well understood (66, 80, 237). The adipokine leptin is produced by adipocytes and stimulates GH secretion through leptin receptors expressed on somatotrophs. In normal weight mammals, somatotrophs are thought to represent a metabolic sensor through which in states of nutrient excess leptin enhances the secretion of lipolytic-acting GH to prevent excessive fat accumulation (80). The disturbance of this control mechanism in obesity, where despite high leptin levels the GH production is reduced, may be explained by leptin resistance of somatotrophs (e.g., leptin receptor downregulation) which probably involve intrapituitary, auto-/paracrine acting leptin (237). However, other metabolic hormones, nutrients, or adipose tissue-derived factors (insulin, leptin, adiponectin, resistin, free fatty acids, etc.) also have different direct and indirect effects on GH production and secretion by somatotroph cells (307, 313, 338), leading finally to elevated GH levels in catabolic states (e.g., anorexia nervosa) or suppressed GH concentrations in obesity (156, 210). As part of these, anabolic and catabolic hormones are produced inside the pituitary (287); these factors may also locally contribute to the GH production and thus play a role in the multifaceted and complex regulatory loops controlling energy homeostasis under different physiological and physiopathological conditions.

E) CORTICOTROPH AXIS. Within the hypothalamo-pituitary-adrenal (HPA) axis, CRH stimulates ACTH through the CRH type 1 receptor (CRH-R1) coupled to a stimulatory G protein. CRH binding results, first in a rapid vesicular release of stored ACTH and, after prolonged CRH exposure, in de novo ACTH synthesis (31). It has been shown that subpopulations of corticotroph cells exist that differ in CRH-R1 expression (constitutive or inducible CRH-R1) and therefore, upon stimulation, only a proportion of the corticotroph cell population secrete ACTH, whereas other cells show a delayed response (79, 191, 250, 282). In this way, continuous release of ACTH is sustained under persistent CRH stimulation during chronic stress. Regarding GC-mediated feedback inhibition, rapid GR-mediated pulses of gene transcription are necessary to maintain the pulsatility of ACTH (341, 378). Diurnal changes in frequency and size of the ACTH pulses result in a circadian rhythm with a peak in the morning and lowest ACTH levels in the evening; both pulsatility and diurnal rhythmicity of ACTH are modulated by multiple factors (169, 359).

In addition to CRH, arginine vasopressin (AVP) is an important stimulator of ACTH production and is also involved in the maintenance of the corticotroph cell population (3). AVP is either transported from the posterior to the anterior pituitary (3) or is produced within the latter, predominantly by corticotroph cells (105). AVP stimulates the release of ACTH through the V1b receptor (3, 377) and augments the number of corticotrophs responsive to CRH; in turn, CRH increases the proportion of cells that respond to AVP (79, 191, 250, 282, 384). Interestingly, the AVP levels remain elevated during GC exposure and may therefore maintain ACTH production under chronic stress con-

ditions (3). In experimental CRH-R1 knock-out mice, AVP was able to compensate the chronic stress response during experimental inflammation (400).

During infection/inflammation, cytokines stimulate the hypophysial ACTH production as part of the mechanisms enhancing the production of anti-inflammatory acting GC (38). In this process, both immune cell-derived circulating cytokines (TNF-α, IL-1, IL-6) and intrapituitary, FS cell-derived gp130 cytokines (LIF, IL-6) play an important role (10, 20, 174, 410). These cytokines are potent stimulators of ACTH and thus contribute to the rise of anti-inflammatory GC, which protects the organism from self-destructing actions of the overactivated immune system (38). Intrapituitary IL-6 is released from FS cells by systemically activated cytokines (TNF-α, IL-1) but also by cell wall components of the pathogens (LPS, MDP, DAP, and others) for which receptors (Toll-like receptors 2 and 4, NOD receptors) are expressed in FS cells (50, 86, 236). These important components of the innate immune system induce after binding of bacterial cell wall components and through the involvement of NF-κB the production of IL-6 (236). In general, complex and multiple endocrine as well as auto-/paracrine mechanisms involving local and circulating cytokines as well as pathogen products mediate the regulation of ACTH during inflammatory or infectious processes, and the pathophysiology of this complexity is still under study. The crosstalk and integration of signals that regulate corticotroph physiology are detailed in section IV*B2*.

G. Current Knowledge About Adult Pituitary Stem Cells

The pituitary has a considerable degree of plasticity and self-renewal capacity. It has been speculated the adult anterior pituitary may contain a pool of stem cells, perhaps present as a side population able to differentiate upon physiological demand into the corresponding hormone-producing cell type.

Whereas embryonic pituitary stem cells are well characterized (see sect. II, *D* and *E*), the research on adult pituitary stem cell and progenitors has only escalated in the last 5 years (75, 111, 134, 149, 159, 224, 409) and has led to, in part, discrepant results with respect to intrapituitary stem cell distribution and stem cell marker expression.

Several cell types and populations, including chromophobe/ hormonally null cells, follicular cells, FS cells and poorly specified clonogenic cells have been considered to represent adult pituitary stem cells (180, 276, 408).

Pituitary stem cells seem to be located predominantly in the periluminal or marginal zone (MZ) placed at the margin between the anterior pituitary and the cleft (a rudimentary structure derived from Rathke's pouch invagination) (134,

408). In the human pituitary in which the intermediate lobe and cleft is lacking, stem cells are located around so-called Rathke's pouch cysts that are remnants of the cleft (408). It is thought that stem cells take place in the MZ niche and that upon demand, they migrate into the anterior pituitary to differentiate into hormone-producing cells. Moreover, one model proposes the presence of "multiples niches" of stem/progenitors cells in the pituitary gland that could switch from one cell type to another by responding to a particular body/organism requirement (159).

Recently, a niche of nonhormonal putative stem/progenitor cells was identified in rodents and humans (149). These cells were denominated GPS (GRFa2+, Prop1+, Stem) cells and express stem cell markers such as Sox2, Sox9, SSEA4 and Oct4, but they are negative for Nanog and Nestin and some adult stem cells markers. Interestingly, about half of the GPS cells were also positive for the FS cell marker S100 (149).

It was reported that two small populations called by the authors "side populations" (SP) could be sorted out in the adult pituitary by FACS analysis regarding the stem cell antigen-1 (Sca1) expression. These cells are located in the periluminal area, and they are also distributed as small clusters throughout the whole anterior gland, suggesting that different stem cell niches could exist that generate differentiated anterior pituitary cells. These cells were able to form pituispheres and under matrigel culture conditions generating all endocrine cell types (74). With the use of transgenic mice expressing green fluorescent protein (GFP) under Nestin promoter control, a small population of Nestin+ cells in the pituitary gland at 11.5 days into embryogenesis has been identified (159). These cells express Lhx3 and Sox2 and exhibit self-renew property as well as potential to differentiate into all six pituitary cell lineages. The pool of these cells increases up to 10-fold after postnatal spur; thus these cells might contribute to the self-renewal in the adult pituitary gland (159).

So far, considerable progress has been achieved in the detection and characterization of adult stem/progenitor cell populations, which show some degree of homology (evidence of self-renewal capacity, ability to differentiate into mature pituitary cell types). However, to explain differences in the characteristics and location of stem cells, further efforts are needed to isolate a homogeneous pool of adult pituitary stem cells, to explore how they contribute to the plasticity of the anterior pituitary, and to investigate the mechanisms by which distinct mature pituitary cell types are generated from pluripotent or multipotential stem cell precursors.

III. HOMEOSTATIC CONTROL OF PITUITARY CELL GROWTH

During the postnatal period, a considerable proliferative activity is observed in the developing anterior pituitary to generate the different endocrine and nonendocrine cell pop-

ulations in the gland. When the different cell populations have reached their various final sizes, the proliferative index declines to values around 0.1% with increasing age (227, 260, 289, 436). In parallel, an even smaller apoptotic index has been reported in pituitary tissue, suggesting that the anterior pituitary may represent a life-long, extremely slowly expanding gland (227, 284, 289). Alterations in both the proliferative and the apoptotic index, for instance, during the menstrual cycle, pregnancy, and postlactation period in females suggest that in distinct physiological states associated with altered endocrine demands, the pituitary cell populations vary in cell number, suggesting that proliferation or apoptosis becomes transiently activated, probably by specific or growth inhibitory factors (289, 436). The basically low proliferative and apoptotic rates are somewhat amazing because the pituitary cells are both the target and, in part, the source of multiple factors regulating cell proliferation and apoptosis **(TABLE 3)**. This would suggest that the overall net action of stimulatory and inhibitory factors affecting growth and apoptosis is well balanced, and mechanisms exist that keep cells largely quiescent and that are changed only under certain physiopathological conditions.

As will be detailed in the next section, pituitary cells synthesize and release numerous growth factors and cytokines and express their corresponding receptors (328, 333) **(TABLE 3)**. This has led to the knowledge that, as mentioned above, the anterior pituitary cells are not only regulated in an endocrine manner by hypothalamic factors and circulating peripheral hormones, but also by locally produced auto- or paracrine-acting factors. It has been speculated that intrapituitary factors could play a role in pituitary physiology by modulating the response of pituitary cells to extrapituitary stimulation. There is increasing evidence that intrinsic growth factor production could be stimulated or inhibited by extrapituitary factors, which suggests that the effects of the latter could partially be mediated, enhanced, or dampened by intrapituitary factors (328, 333).

A. Signals and Factors Involved

The spectrum of factors that impact on and influence pituitary cell proliferation ranges is extremely broad and covers all sorts of bioactive substance classes **(TABLE 3)**. The anti- or proliferative effects of these substances have been identified in pituitary tumor cell lines, in experimentally induced pituitary tumors in rodents, or in primary cell cultures of human pituitary adenomas (105, 328, 332). The growth regulating factors not only reach the pituitary or pituitary tumors through the systemic circulation and therefore act in an endocrine manner, but are also locally produced by normal or tumoral pituitary cells and thus must be considered as auto-/paracrine acting growth factors (105, 332). As pituitary growth factor receptors are very heterogeneous,

multiple pathways transduce signals affecting pituitary cell proliferation. Steroid hormones like estradiol or GC may affect proliferation through activating the transcriptional activity of ERs and GR and thus would directly act on genomic levels. In contrast, membrane-associated, G protein-coupled receptors would act through the cAMP/PKA or the phosphoinositol/PKC pathway. Tyrosine kinase or serine/threonine kinase receptors would modulate upon stimulation of mitogen-activated protein (MAP) kinase pathways, phosphatidylinositol 3-kinase/mTOR, Smad protein pathways, and others. Since the signaling cascades are often linked to each other and share common downstream targets (e.g., NF-κB) under physiological conditions where multiple factors act in parallel on pituitary cells, the different stimulatory and inhibitory signals may under certain conditions neutralize each other or may lead in appropriate combination to growth stimulation or inhibition.

In contrast to hormone secretion, which is changed by corresponding regulatory factors within minutes, proliferation of pituitary cells is altered only after long-term (hours, days) exposure to effective concentrations of substances regulating cell growth. This is due to the fact that the emergency of cells from the G_0 phase into the G_1/S phase of the cell cycle or the induction of cell cycle arrest takes much longer than the rapid release of vesicularly stored hormones. Thus, to stimulate or to inhibit proliferation, changes of growth factors have to remain at least for hours or even days, which may be the case only under fundamental physiological changes as experienced or evident during the menstrual cycling or pregnancy where estradiol and probably intrapituitary estradiol-induced growth factors induce transient or long-lasting proliferation of lactotroph cells leading to changes in the size of the lactoroph cell population (433, 436).

In most in vitro studies, the effective concentrations of pituitary cell growth stimulating or inhibiting factors were normally much higher than the basal serum concentrations of these factors, which may explain the low proliferative and apoptotic indexes in the anterior pituitary under normal physiological conditions. However, it is recognized, at least in some studies, that it is difficult to extrapolate from in vitro to in vivo findings. Therefore, it seems that in vivo only under certain conditions, under which growth factors are elevated in serum over a prolonged period, the factors may change growth of pituitary cells. This would be the case in females in estrus or during pregnancy when estradiol concentrations are very high and reach effective dosages for growth stimulation (62, 289, 433, 436). Alternatively, it has been speculated that in particular those factors that pituitary cells produce by themselves may act as auto-/paracrine growth factors within the pituitary in particular in context with pituitary tumor development (105). However, as no reliable techniques exist to determine the release and the resulting intrapituitary concentrations of growth fac-

tors in vivo, the auto-/paracrine concept is based on extrapolations from findings obtained with in vitro pituitary models including pituitary monolayer cell culture to generate conditioned medium, coculture of pituitary (tumor) cell types, pituitary aggregate, or pituitary tissue explant cell culture (30, 197, 331). To establish these models, disconnection from the blood supply and/or cellular dissociation of the pituitary (or pituitary tumors) is necessary, which per se may induce changes in the production and release of the putative auto-/paracrine acting factors. Therefore, although widely accepted, the auto-/paracrine concept of pituitary (tumor) growth regulation needs further exploration.

B. Studies in Normal and Adenomatous Pituitary Cells: Physiopathology of Abnormal Pituitary Cell Growth

1. Growth of normal adult anterior pituitary

Since normal pituitary cells grow extremely slowly, in vitro growth studies in primary anterior pituitary cell cultures (from rat or mouse pituitaries) are difficult to perform even with sensitive methods like [^{3}H]thymidine incorporation (17). Some information about normal pituitary cell growth regulation has been obtained from in vivo studies with animals, in which the expression of pituitary-specific factors had been modified. For instance, overexpression of GHRH or the knockout of D2Rs (23, 91, 238) led to pituitary hyperplasia, suggesting that these factors not only stimulate (GHRH) or inhibit (DA) hormone secretion but also favor the growth of the corresponding endocrine target cell population after prolonged action because GHRH stimulates somatotroph cell growth and dopamine tonically inhibits lactotroph cell proliferation (23). The growth regulatory effects of hypothalamic factors may be of no relevance under physiological conditions, under which short pulses of these hypothalamic factors act on pituitary cells, but may play a role only under specific, putative pathological conditions (e.g., CRH- or GHRH-producing ectopic tumors). The observation that hypothalamic factors induce pituitary hyperplasia has led to the hypothesis of a hypothalamic involvement in pituitary tumorigenesis, in which a transient state of overproduction of hypothalamic factors would induce pituitary hyperplasia and finally lead to the generation of pituitary adenomas.

The local expression and production of multiple growth factors and cytokines within the anterior pituitary is the basis of the hypothesis that an intrapituitary network of these factors may exist that could play a role in pituitary physiology (20, 328, 333). This idea is supported by the observation that the expression of intrapituitary factors and their receptors is a dynamic process as they fluctuate during embryogenesis and postnatal development, as well as during the menstrual cycle, pregnancy, stress, infectious, and other processes in which the gland adapts with plasticity

(20, 62, 289, 328, 333, 436). Thus the changes in intrapituitary factors/receptors may reflect local adaptive processes during general alterations in endocrine homeostasis. This is particularly evident in female pituitaries, which show alterations of growth factors during cycling, pregnancy, lactation, and weaning that are associated with alterations in the proliferative/apoptotic index of lactotroph cells and thus alterations in the size of the lactotroph cell population. In section II$F3$A, these aspects are extensively described and it is discussed how changes in estrogen-regulated stimulatory and inhibitory acting growth factors may contribute to plasticity of the lactotroph cell population (FIG. 2).

2. Abnormal growth of pituitary tumors

During the past two decades, considerable progress has been achieved in identifying mechanisms/factors that are involved in pituitary tumor inititation and progression (23, 262). Pituitary adenomas are monoclonal and thus arise from a single transformed cell (6). In contrast to many solid tumors, which start with hyperplasia, pass a state of benign adenoma, and end up with an aggressive carcinoma, such kind of progression seems not to occur in pituitary tumor development although this is still a matter of debate (23, 85, 130, 262). The majority of pituitary adenomas develop sporadically, and only a small proportion of pituitary adenomas have a hereditary background. Germ line (in pituitary adenomas associated with hereditary syndromes) and somatic mutations (in sporadic adenomas) in combination with loss of heterozygosity may lead to aberrant expression of oncogenes, tumor suppressors, cell cycle regulators, and components of intracellular signaling cascades (83, 85, 116, 129, 407). For instance, the cell cycle of pituitary cells is well controlled during embryogenesis and in adulthood by the coordinated action of cell cycle regulators such as cyclins or CDKs (111, 323). Correspondingly disturbed cell cycle regulator expression and action resulting in aberrant cell cycle control is often observed in pituitary tumors (323) like the recently reported upregulation of cyclin E and the loss-of-function of p27, which cooperatively contribute to corticotroph pituitary tumor development (340). Disturbances of these factors are mostly associated with activating/inactivating mutations (83, 116, 129, 248) or epigenetic modifications (e.g., altered methylation or histone tail modifications) (114, 122), respectively, and are critically involved in the genesis and progression of pituitary tumors. For example, very recently it has been shown that resistance to dopamine agonist treatment in prolactinomas may involve dopamine D2 receptors inactivation by methylation. As demethylation reactivates dopamine receptor function, epigenetic modification could provide a new treatment concept in dopamine agonist resistant prolactinomas (4).

A) ABERRANT GROWTH FACTOR/RECEPTOR EXPRESSION AND ACTION. Since normal pituitary cells are under endocrine as well as auto-/paracrine control of numerous growth factors,

it has been postulated that disturbances in the expression and/or action of these factors and their receptors might contribute to pituitary tumor development and progression. Indeed, an altered expression of cytokines/growth factors and their receptors has been observed (20, 23, 328, 332, 333) in pituitary tumors as summarized in the following sections and in **TABLE 4**.

I) TGF-β protein family. Among the more than 30 members of the TGF-β protein family (252), TGF-β1, TGF-β3, activin, inhibin, and BMP-4 have all been identified as candidates involved in pituitary tumor cell growth. After binding to different, specific type 1 and 2 receptor heterodimers, the TGF-β isoforms, activin, and BMP-4 predominantly induce the Smad protein signal cascade but also interfere with other signaling mechanisms (252).

TGF-β isoforms mostly inhibit normal epithelial cell functions and growth and act stimulatory in tumors (251). In the normal pituitary and in lactotroph tumors, TGF-β1 was found to inhibit lactotroph cell growth (88, 327, 350), whereas TGF-β3 stimulated lactotroph cell proliferation (172). It was hypothesized that the already described estrogen-induced shift in the intrapituitary TGF-β1/-β3 balance towards growth-promoting TGF-β3 contributes to prolactinoma formation (300). TGF-β3 also enhances the intratumoral production of FGF-2 and VEGF, which both

stimulate lactotroph tumor cell proliferation and angiogenesis, suggesting that TGF-β3 both directly and indirectly supports prolactinoma progression (330, 347) **(FIG. 2)**.

Activin (see sect. II*F3*B) normally suppresses the growth of pituitary tumor cells through ALK4 wild-type receptors (93); however, in a considerable proportion of nonfunctioning adenomas, truncated isoforms of ALK4 have been found which compete with wild-type ALK4 for dimerization with ActIIRA or ActIIRB (438). Since receptor heterodimers containing truncated ALK4 isoforms are not able to induce the suppressive effects of activin on cell growth, they may be implicated in tumor development in a subset of nonfunctioning adenomas (438). Moreover, disturbances in the intratumoral expression of activin, inhibin, and follistatin in rare functional gonadotroph adenomas underline their potential role in pituitary tumor development (93, 379).

BMP-2 and BMP-4 are important regulators of embryonic pituitary development (see sect. IIC) (96, 119, 389, 396), and low expression levels are found in adult pituitaries. Compared with normal pituitary, BMP-4 was strongly overexpressed in prolactinomas (lactotroph tumors from Drd2$^{-/-}$ mice and human prolactinomas) and adenomas (298). To some extent it is also present in human corticotroph adenomas, but at lower levels than normal corticoco-

Table 4. *Aberrant growth factor and growth factor receptor expression and action in pituitary tumors*

Growth Factors	Expression/Function in Pituitary Tumors
Activin/inhibin	Disturbed expression in human hormone-inactive and gonadotroph adenomas
BMP-4	Overexpression in mice,* rats,[+] and human prolactinomas and low expression in human corticotroph adenomas
FGF-2	Overexpression in rat prolactinomas[+]
FGF-4	Overexpression in human invasive prolactinomas
Follistatin	Reduced expression in human gonadotroph adenomas
IL-6	Enhanced production in all types of human adenomas
LIF	Reduced expression in human prolactinomas
NGF	Reduced expression in dopamine agonist-resistant human prolactinomas
SDF1	Overexpression in different human adenoma types
TGF-α	Overexpression in rat prolactinomas[+]
TGF-β1	Reduced expression in rat prolactinomas[+]
TGF-β3	Increased expression in rat prolactinomas[+]
Growth factor receptors	
Alk4, truncated	Truncated Alk4 activin receptor binds activin without inducing its antiproliferative effect; expressed in different adenoma types
EGFR	EGFR expression correlates with tumor aggressiveness
ErbB2 (Her2/neu)	Constitutively active oncogenic variant of EGFR; expressed in prolactinomas and pituitary carcinomas
ErbB3	Kinase-deficient EGFR subtype; expressed (with ErbB2) in prolactinomas and carcinomas
FGFR2-IIIb	Tumor suppressive-acting receptor; epigenetically silenced (hypermethylated) in different adenoma types
ptd-FGFR4	Pituitary tumor-derived truncated and constitutive active variant of the FGF type 4 receptor; expressed in different adenoma types
NGFRp75	Absent in dopamine agonist-resistant human prolactinomas

*Prolactinomas in dopamine D2 receptor knockout mice. [+]Estrogen-induced prolactinomas in Fischer rats.

trophs (155, 298). BMP-4 was found to be involved in prolactinoma pathogenesis via a cross-talk between Smad1, Smad4, and ER (298). Interestingly, BMP-4 inhibited the proliferation and ACTH production of corticotroph tumor cells by interfering with the inhibitory action of retinoic acid (155) and somatostatin (399). Thus the various growth-modulatory actions of overexpressed BMP-4 in pituitary adenomas are tumor-specific and dependent on the interference of BMP-4-induced signals with other intracellular signaling pathways, as we will show in detail in section IV, *B1* and *B2*.

II) TGF-α and EGF. The EGF tyrosine kinase receptor (EGFR) mediates proliferative signals of both TGF-α and EGF in embryogenic and adult pituitary. Overexpression of TGF-α experimentally induced by estrogens seems to play a role in prolactinoma development, an effect that could be prevented by the TGF-α suppressing DA agonist bromocriptin (141, 256). Although clearly involved in pituitary pathogenesis and physiopathology, reports reach different conclusions regarding EGFR receptor expression. Furthermore, since most studies are confined to the role of its oncogenic variants or its ligands in cell lines and animal models, it makes it difficult to draw final conclusions about the role of EGFR, its oncogenic variants, and its ligands in human pituitary tumors (225, 390, 417).

III) The FGF family. The FGF protein family consists of more than 20 members, which act through 4 tyrosine kinase receptors (FGFR1–4) (148). In the adult pituitary and in pituitary adenomas, FGF2 (also known as basic FGF or bFGF) is an important factor influencing hormone secretion, endocrine cell proliferation, and angiogenesis (123, 357). Upregulation of FGF2 expression (in particular the 18-kDa isoform) in estrogen-induced prolactinomas, accumulation of nuclear FGF2 in hyperplastic pituitaries of Drd2$^{-/-}$ mice, elevated FGF2 expression in pituitary tumor transforming gene (PTTG)-overexpressing pituitary adenomas all point to a role of FGF2 in pituitary tumor formation (70, 90, 171, 439). This is supported by the observation that FGF2 is enhanced over GFG (the antiproliferative-acting product of the FGF2 antisense mRNA) in pituitary tumors compared with normal pituitary (25). Downregulation of the tumor-suppressive acting FGFR2-IIIb receptor isoform and the aberrant expression of the truncated, pituitary tumor-specific and constitutive active ptd-FGFR4 receptor variant in human pituitary adenomas further underline the importance of FGF proteins and/or receptors in pituitary tumor formation (23, 124).

IV) Nerve growth factor and D2R. Nerve growth factor (NGF) that acts via its two receptors trkA and p75NGFR plays a critical role DA agonist-resistant prolactinomas in which NGF is able to restore DA agonist responsivness by inducing reexpression of D2R (264). DA agonist-resistant prolactinomas not only lack D2R, but are also devoid of NGF and p75NGFR and contain inactive p53 (264). Transient treatment of DA agonist-resistant prolactinomas with NGF reconstitutes active p53 and leads to p75NGFR expression, through which NGF could then induce reexpression of D2R, mediated by the activation of nuclear factor kappa B (NF-κB) (142, 264). It seems that an autocrine loop involving NGF, p75NGFR, and trkA participates in controling D2R and p53 expression in normal lactotrophs (265). Loss of this autocrine mechanism after tumoral transformation probably leads to the formation of DA agonist-resistant prolactinomas (267).

V) The gp130 cytokine family. IL-6, IL-11, leukemia inhibitory factor (LIF), CNTF, oncostatin M (OSM), and cardiotropin-1 (CT-1) belong to the family of gp130 cytokines that bind to different receptors, but act through the common gp130 signal-transducing protein (16, 20). The putative oncogenic role of the gp130 protein has been demonstrated in lactosomatotroph GH3 tumor cells, which could no longer form tumors in nude mice when gp130 was downregulated (68). This indicates that one or more of the gp130 cytokines may play a role in pituitary tumorigenesis (68). The expression of almost all of the gp130 cytokines and their corresponding receptors has been detected in pituitary or pituitary adenomas (168, 192, 305). IL-6 is produced by pituitary tumor cells themselves (168, 192, 393, 395) but may also be delivered to the adenoma cells through IL-6-producing FS cells, which surround or invade the pituitary tumors (128, 178, 404, 405). As we will discuss in section IIIC, the intratumoral production of tumor cell growth-stimulating IL-6 in the majority of pituitary adenomas makes this cytokine an attractive candidate as an auto-/paracrine stimulator of pituitary tumor development (17, 43, 192, 292, 303, 352, 393). LIF is involved in corticotroph tumor development (27, 206, 432) but might also play a role in the pathology of prolactinomas, in which LIF is not expressed but when added to prolactinoma cell cultures, inhibits PRL secretion (36). Interestingly, sulpiride, a D2R antagonist, reverted the suppressive effect of LIF on PRL. Therefore, it has been suggested that LIF might inhibit PRL secretion through an interaction between the gp130 pathway and the D2R (36). Loss of this suppressive autocrine loop may participate in prolactinoma development.

B) PITUITARY TUMOR NEOVASCULARIZATION. As in any solid tumor, neovascularization is essential for pituitary adenoma progression, as the expanding tumor cell population needs to be supported with nutrients and oxygen (101, 401, 402). Neovascularization is induced by angiogenesis, a complex process by which distinct tumor cell-derived soluble factors induce in vessels in the surrounding of the tumor the sprouting of new vessels and ingrowth into the developing tumor (64, 137, 226). The major trigger of tumor neovascularization is hypoxia, which through HIF-1 induces the expression of different angiogenic factors (334, 360), among them VEGF-A, bFGF, and PDGF, all of which are expressed both

in normal pituitary and pituitary tumors (23, 205, 209, 257, 293) (see also sect. II*F2*). In particular, angiogenic-acting VEGF-A, which also stimulates pituitary tumor cell growth (293), is thought to play a major role in pituitary tumor progression, as many studies show correlations between VEGF-A and pituitary adenoma characteristics such as vessel density, adenoma type, size, and invasiveness (92, 234, 235, 293, 412, 413). There is increasing evidence that hypophysial VEGF-A is under inhibitory control of the hypothalamic factors somatostatin and DA (89, 235). In $Drd2^{-/-}$ female mice (91, 202), the expression of the angiogenic protein VEGF-A is increased, and increased pituitary VEGF expression is mainly dependent on the lack of dopaminergic control (89). In agreement with this assumption, VEGF-A protein expression is higher in DA-resistant human prolactinomas compared with nonfunctioning as well as GH- and ACTH-secreting adenomas (92). The observation that not only hormone production and growth but also VEGF-A and as previously mentioned, FGF2 production is under inhibitory hypothalamic control (90), would contribute to explain the slow development of pituitary adenomas because not only tumor cell proliferation but also angiogenic factor-driven neovascularization are suppressed by inhibitory acting hypothalamic factors. This would be in agreement with earlier speculations by some authors that pituitary adenoma progression may accelerate after the tumors receive through angiogenesis direct arterial blood supply (356) and thus escape from the inhibitory hypothalamic control through the portal blood vessel system.

c) estradiol-induced prolactinomas: a tumor model of aberrant growth factor control? When the available data are summarized in the context of genetic and growth factor-related disturbances in pituitary tumors, it is evident that some of the disturbances are isolated events whereas others share common mechanisms. With regard to the latter, it is obvious that estradiol is a major trigger of changes of growth factors and their receptors in the pituitary finally leading to the development of prolactinomas (170, 171). The cross-talk with BMP-4 is detailed in section IV*B1*. The question arises whether estrogens could be a risk factor for prolactinoma development in humans (170). Actually, apart from an enhanced incidence of microprolactinomas in women (23), there is little evidence to support this hypothesis. For example, male-to-female transsexuals treated with excessive dosages of estradiol rarely develop prolactinomas (161, 207). Rodents treated with high concentrations of estrogens develop at best lactotroph hyperplasia but not prolactinomas with the exception of Fischer 344 rats, in which estrogens rapidly induce prolactinomas in both sexes (170, 171, 347). The induction of prolactinomas in these animals is associated with FS cell activation (294, 355) and E2-induced overexpression of FGF2, TGF-α, and TGF-β3 (347), all of which have growth-stimulating properties on lactotrophs, and suppression of TGF-β1, which inhibits lac-

totroph cell growth. Moreover, E2-induced VEGF (32, 170, 171, 292) could act in concert with FGF2 to induce tumor neovascularization in addition to tumor expansion. It is evident that E2-regulated mechanisms observed in the pituitaries of cycling and pregnant female mammalians contribute to prolactinoma formation in Fischer rats. However, it is still not known which additional, probably genetic alterations, make this particular rat strain extremely sensitive for E2-induced prolactinoma formation. An alternative hypothesis is that there is a species predilection toward tumor development that show differences between, in this case, rodent models and their human or mammalian counterparts.

C. Oncogene-Induced Senescence: The Pituitary Gland as a Model of Homeostatic Control of Cell Growth

Despite the high incidence of adenohypophysial adenomas, they very rarely undergo malignant transformation. Although these monoclonal adenomas are usually sharply demarcated benign lesions, they occasionally exhibit higher proliferation activity associated with invasive features and impinge on local structures. However, true pituitary carcinomas are exceedingly rare, and pituitary metastases have only been reported in isolated cases. Although oncogenes like H-ras and c-ErbB2 have been found in single carcinomas, they show no common characteristics with respect to chromosomal aberrations, oncogene overexpression, or tumor suppressor downregulation. Case reports have shown that they derive from different types of originally benign adenomas that became increasingly resistant to initially successful pharmacotherapy and radiotherapy and rapidly regrow after surgical debulking.

Cellular senescence appears to be an interesting model to further understand the protective role against malignant transformation and other environmental challenges. Cellular senescence involves more than dysfunctional telomeres and can be triggered by various cellular stresses. Observations made in cultured cells led to the principle that oncogene-induced senescence (OIS) is irreversible and involves activation of a set of well-known tumor suppressors that are often inactivated in human cancer.

PTTG was isolated in a pituitary tumor cell line and characterized as tumorigenic (302). Overexpression of PTTG in human pituitary adenomas is associated with increased angiogenesis and growth factor production. Pituitary-directed transgenic PTTG overexpression leads to development of focal hormone-secreting pituitary adenomas (1), and PTTG is also abundantly expressed in human pituitary adenomas (171). PTTG depletion results in pituitary hypoplasia, aneuploidy, genomic instability, and activation of DNA-damage signaling pathways (416). In PTTG-null mice, PTTG deletion also results in pituitary-specific senescent features,

including increased levels of p53 and Cdk inhibitors, p19 and p21, overexpression of cyclin D1, apoptosis block, and elevated senescence-associated β-galactosidase expression. In the $Rb^{+/-}$ mouse, PTTG depletion selectively rescues pituitary but not thyroid, tumor development and also enhances senescence in mouse embryonic fibroblasts (MEF), while deletion of p21 from $Rb^{+/-}$ $PTTG^{-/-}$ mice showed increased pituitary cell proliferation and decreased number of senescent MEFs (76, 77). Human GH-producing pituitary adenomas were shown to exhibit aneuploidy and senescence as evidenced by increased p21, ataxia-telangiectasia mutated, and senescence-associated β-galactosidase levels. In contrast, p21 was undetectable in the human pituitary carcinomas tested. The activation of DNA damage and p53/p21 senescence induced by the securin properties of PTTG may be thus involved in pituitary senescence. PTTG also behaves as protooncogene, and high PTTG as well as other oncogene levels can trigger OIS.

It is likely that in the pituitary, OIS may be mediated by IL-6. This cytokine is required for both induction and maintenance of OIS and acts in a cell-autonomous fashion to enable OIS (212). IL-6 acts in an autocrine manner to regulate OIS as this signaling cascade is blocked by si IL-6 mRNA and requires an intact IL-6R. Thus the results in human fibroblasts suggest that a cell-autonomous pool of IL-6 produced by senescent cells and acting in an autocrine and paracrine fashion mediates OIS (212).

As mentioned above, IL-6 (and IL-6R) and other members of the gp130 cytokine family are produced in the pituitary gland (20, 192) and regulate synthesis of anterior pituitary hormones, consistent with a paracrine or autocrine model. IL-6 directly regulates pituitary cell growth (16, 20). Intriguingly, although IL-6 stimulates DNA synthesis and cell number in GH3 pituitary cells, similar concentrations of IL-6 inhibit growth of normal rat pituitary cells (17). In several tumor types (ACTH-, PRL-, and GH-secreting as well as nonfunctioning adenomas), IL-6 exhibited either inhibitory or stimulatory effects not associated with tumor type or size, as described by blocking IL-6 intrapituitary action. Thus, in the normal pituitary, both paracrine and autocrine-derived IL-6 (16, 20, 192, 376) inhibit pituitary growth. In contrast, in tumoral GH3 cells, paracrine IL-6 further induces DNA synthesis and cell proliferation, suggesting that paracrine IL-6 is required for senescence bypass, while the autocrine IL-6 may have the opposite action. The new findings of the IL-6 role in OIS suggest that endogenous IL-6 could be involved in development of pituitary adenoma OIS, which, as well as its induction by aberrant intracellular PTTG levels, may explain the benign nature of these abundant tumors (18).

OIS response requires time to develop, allowing an initial proliferative phase, but resulting in a benign tumor with stable growth arrest, which is indeed the natural history of pituitary adenoma growth. A mechanism that in response to oncogenic stress restrains proliferation but allows the cell to remain viable and perform its physiological function favors vital functioning of the pituitary gland for homeostasis control.

IV. ANTERIOR PITUITARY GLAND INTEGRATIVE RESPONSE OF MULTIPLE SIGNAL PATHWAYS

A. Positive and Negative Signals That Control Hormone Secretion

As detailed extensively in this review, the anterior pituitary as a master gland of the endocrine system receives multiple regulatory inputs from both central and peripheral signals and intracellular signals, which need to be coordinated within the gland and adapted to a variety of physiological demands (FIG. 3). These signals modulate not only the trophic hormone secretion but also the reversible plastic changes in cell pituitary growth, and have an impact on pituitary hormone production leading to a precise control of body homeostasis. Pituitary specialized cells derive from a common progenitor/stem by pituitary-specific developmental factors and, from its origin, developmental, physiological and environmental inputs, determine the pituitary structure/organization and function. In this structure, the multiple signals received by the pituitary, including peripheral and hypothalamic signals and the autocrine/paracrine loops, are integrated. Cross-talk of downstream signal transduction pathways activated by specific receptors merge these signals into a set of transcriptions factors critical for the accurate control on hormone secretion.

As already outlined in this review, anterior pituitary hormone secretion by specialized cells are centrally regulated through stimulatory or inhibitory factors of the hypothalamus, which itself are under complex control of higher brain centers and under feedback control of hypophysial or peripheral hormones (34, 82, 177, 230, 272, 301) (FIG. 3). Some of the hypothalamic factors are released in a pulsatile manner, and the corresponding hypophysial target hormones also show a pulsatile release pattern (87, 169, 272). The principle of pulsatility may prevent target receptor desensitization, since all hypothalamic factors bind to specific transmembrane receptors on pituitary cells. In case constitutive stimulation occurs by hypothalamic factors, this would downregulate their corresponding target receptors and would induce reduced sensitivity to the hypothalamic stimuli (87, 169, 272). Pulsatility of stimulation thus represents a principle of mechanism allowing target receptor recovery and therefore optimal response to the next burst of hypothalamic factors.

Central hormones are mainly responsible not only for the overall diurnal variations of anterior hormone levels but
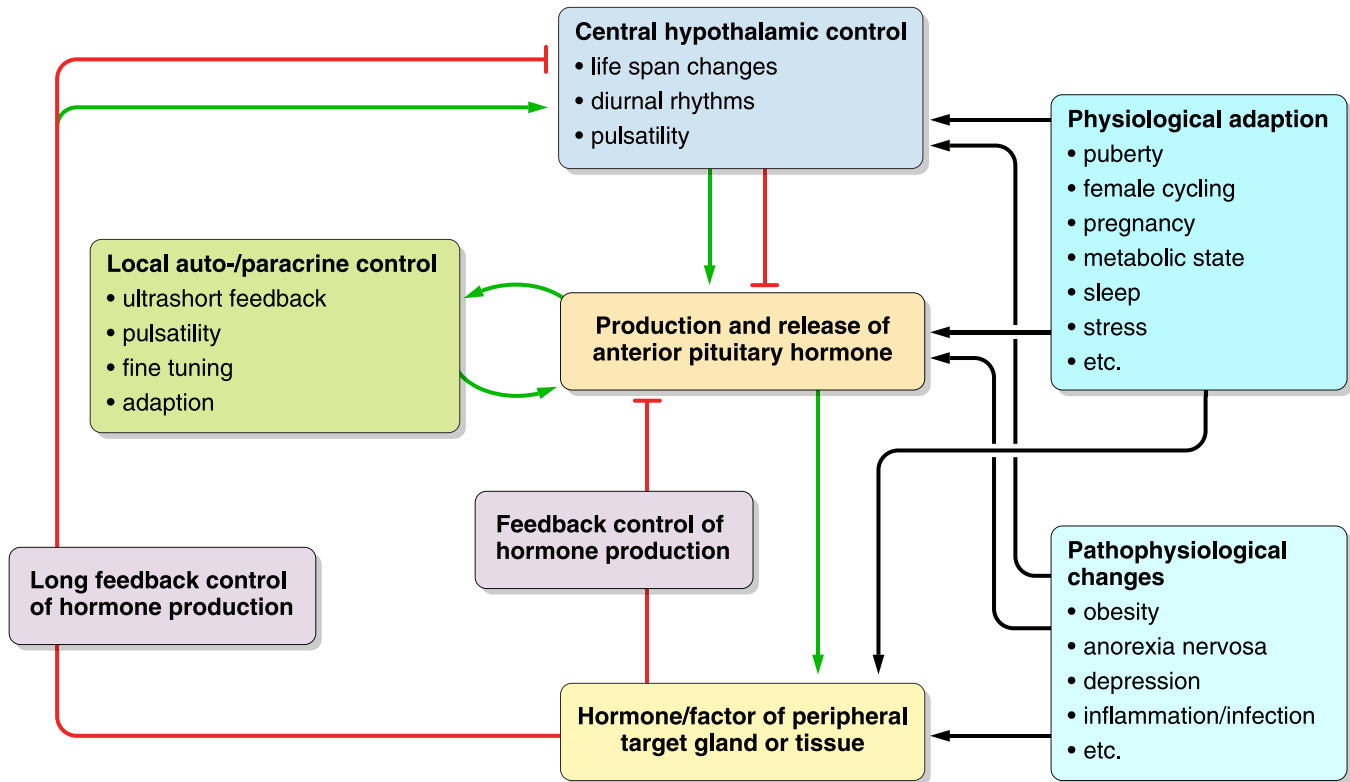
FIGURE 3. General regulatory principle. Scheme of major regulatory principles of anterior pituitary hormone production. Hormone synthesis and release are under stimulatory and/or inhibitory control of hypothalamic, hypophysiotropic hormones which critically trigger pulsatility, diurnal rhythms, and life-long changes of anterior hormone production. The target products of the anterior pituitary hormones control their production through feedback mechanisms at the level of the pituitary but also through long-feedback control at the hypothalamic level. For most anterior pituitary hormones, intrapituitary ultrashort-feedback mechanisms have been described that may play a role in adaptive processes or in the fine-tuning of anterior pituitary hormone production. To adapt the pituitary hormone production to altered physiological demands or to physiopathological disturbances, many factors have been identified, which modify the hormone production either by affecting the hormone synthesis and secretion directly at the hypophysial level or by modifying the hypothalamic control or the feedback inhibition of anterior pituitary hormone production. Green lines indicate stimulation, red lines indicate inhibition, and black lines indicate stimulation or inhibition.

also for variations observed during lifespan (127). Diurnal and lifespan-associated hormonal changes in mammalians are closely related and adapt hormonal/physiological demands in wakefulness/sleep and the physiological changes and demands in young, adult, and aged mammals (56, 169). This is particularly evident for the gonadotroph axis, which in mammalians is active in neonatals but then is silenced during childhood due to the absence of hypothalamic input. Only with the onset of puberty does the hypothalamic GnRH pulse generator become activated again to induce, through the action on gonadotroph pituitary hormones, the maturation of reproductive organs and maintenance/control of the reproductive phase (164). The gonadotrophs show morphological changes as a reflex of hormonal status in the pars distalis, but not in the pars tuberalis of the anterior pituitary. The 5' regulatory region of the gonadotropin-alpha gene promoter contains multiple transcriptional regulatory elements that control the tissue-specific gene expression of the alpha subunits (113). Thus it has been reported that CRE binding sites for CREB (188) and two distinct regulatory elements (URE-1 and URE-2) bind proteins that are restricted to placental cells. GnRH-induced transcription of the human is increased by estradiol (368). Estradiol decreases CREB phosphorylation, producing a decrease on basal alpha promoter activity, although at the same time increases its responsiveness to GnRH. LH beta subunit gene expression is also regulated by GnRH as well as by many other factors specifically within the gonadotrophs (125, 203, 367). Although different factors such as testosterone, estrogens, and members of the TGF-β family proteins participate in LH-β regulation, the precise molecular mechanism involved is under investigation. Pulsatile GnRH administration in vivo induces the transcription of LH beta and FSH beta gene expression (367), involving the activation of PKC signaling (55, 383) while, in contrast, constitutive stimulation by GnRH only enhances alpha genes transcription.

The age-associated somatotroph axis changes usually reach maximal activity during the pubertal growth spurt and

early adulthood and then decline with increasing age. This axis is also mainly triggered by changes in the pulsatile release of stimulatory (GHRH) and inhibitory (SMS) factors from the hypothalamus (56) **(FIG. 1)**. Accordingly, there is a decrease in both the number and amplitude of these factors with age (366). Repetitive GHRH stimulation eventually results in decreased GH release due to somatotroph desensitization (56, 153). The loss of GH sensitivity does not occur in somatotrophic tumor cells (375), which may reflect either abnormal signaling or a large intracellular pool of GH. GHRH regulates not only GH secretion, but also increase GH synthesis. Many factors are involved in the transcriptional regulation of the GHRH-GH axis, including Pit-1. Several putative and inferred binding sites for transcription factors are present on GH promoter regions [in addition to Pit1, glucocorticoid-responsive element (GRE), thyroid hormone responsive element (TRE), upstream stimulatory factor (USF), nuclear factor 1 (NF1), specificity protein 1 (SP1)] (41, 183, 223, 315). Although analysis of the of hGH promoter did not show consensus sequences for CRE, the presence of novel CRE elements upstream in the GH promoter have been reported (48), while CREB binding protein (CBP) is a cofactor for Pit-1-dependent human GH activation (84). In addition, it has been shown that a Pit-1β (a spliced isoform structure- and functionally different for Pit-1) is able to repress the expression of the GH promoter (as well as PRL promoter) in GH4 pituitary cells allowing a fine control of GH promoter expression in these cells (193).

Thyroid hormones are important regulators of GH expression and secretion. Stimulation of T_3 is mediated by a nuclear associate receptor that enhances GH expression (344). GH regulatory regions contain a thyroid responding element (TRE) that increases T_3 induction (49). As well, it has been shown in vivo that thyroid hormones levels alter the mRNA levels of GH as well as PRL and other pituitary hormones (345, 369). Indeed, levels of thyroid hormones are also very important during prenatal life, since neonatal hypothyroid lead to lower expression of GH mRNA in adult life (102). Hydrocortisone (HCT) has been also shown to induce GH secretion (364) and a synergistic stimulation of GH by T_3 and HCT in GH3 cells (263) was also observed. Moreover, insulin suppressed both the T_3 and HCT-induced GH secretion as well as the synergistic stimulation effect (263).

The peripheral hormones and other factors induced by the hypophysial hormones inhibit through membrane-associated (e.g., IGF-I receptor) or intracellular receptors (e.g., GR, ER) the synthesis and/or release of the corresponding anterior pituitary hormone. In this way, the peripheral products contribute to the regulation of their production and prevent an excessive level of these factors (34, 82, 177, 230, 272). In some cases, e.g., for IGF-I, the inhibitory control persists lifelong and contributes to the decline of GH during aging (56, 169). However, since steroid hor-

mones like estradiol and testosterone decline with age, they are no longer available to inhibit LH and FSH secretion, and therefore, the serum concentration of these hormones increases in postmenopausal females and in aging males (82, 121).

As detailed already, anterior pituitary cells do not only express receptors for hypothalamic hormones and feedback-mediating peripheral factors of the target organs, but also contain receptors for numerous growth factors, cytokines, neuropeptides, and gastroenteropancreatic hormones **(TABLE 3)**. As part of the precise control of hormone secretion regulated by hypothalamic factors, they interact with growth factors and peripheral hormones to regulate pituitary expression. In this intrapituitary signaling network, some factors can act quite uniquely, but for others it has been observed that some redundancy might occur to guarantee its ultimate control. In addition, intrapituitary factors may act in concert with others from the circulation being antagonized or synergized to integrate the responses and modify the hormone production. For instance, at the somatotroph axis level, intrapituitary ultrashort feedback inhibition of GH production by autocrine mechanisms would be possible, as somatotroph cells not only produce GH but also IGF-I and, moreover, express both GH and IGF-I receptors (21, 118) **(FIG. 1)**.

Changes of the hormonal input do not necessarily induce variation of corticotroph cell number; however, they can go through morphological changes when endocrine homeostasis varies (81). The CRH system is an excellent example of the concerted action of internal homeostasis and environmental stimuli that can act together with neuroanatomical signaling pathways to regulate pituitary functions in a receptor site-specific manner (31, 100). As described, at the level of the corticotroph, CRH activates CRH-R1 and constitutes a model of how specific hormone production is regulated. In this way, signaling pathways triggered by activation of specific ligand-receptor and their cross-talk with other pathways that ultimately determine the composition of transcriptional factors complex responsible for gene activation, and are described in detail in the next section (19, 44, 47, 310, 392).

Fundamental physiological or physiopathological changes affect endocrine homeostasis to adapt it to the altered physiopathological state. Changes in the levels of hormones, growth factors, or cytokines in serum play an important role and modify the endocrine homeostasis through their actions and consequences at hypothalamic, hypophysial, and peripheral levels. Transient or prolonged elevation of these factors to influence serum concentrations during physiopathological changes will allow them to affect the release of pituitary hormones. A classical example of a prolonged physiological change affecting hormone production is pregnancy and lactation in female mammal (433). Rising

estradiol levels during pregnancy induce a persistent elevation of PRL needed for the induction of milk production (433). After delivery, when estradiol levels rapidly decline, suckling of the pups keeps the PRL levels high (107, 419). During pregnancy/lactation, the inhibitory dopaminergic tone is reduced, and high concentrations of PRL inhibit the gonadotroph axis by reducing the activity of the GnRH pulse generator to suppress the onset cycling during the lactation phase (419). After weaning, PRL levels rapidly decline, and the normal regulatory endocrine circuits become active (189).

The anterior pituitary is instrumental in the systemic interactions that are important for the communication within the mammalian endocrine and body systems. As an example, most hormones of the gastroenteropancreatic system, adipokines, adipose hormones, and so on act directly on endocrine pituitary cells and may coordinate anabolic and catabolic processes (220, 313). In metabolic disorders like anorexia nervosa or obesity, dramatic changes in pituitary hormone levels are seen, suggesting that the aberrantly expressed metabolic hormones have important impact on endocrine hormone secretion and are in part responsible for the physiopathology of metabolic disorders (156, 210). The systemic control represents a regulatory principle that enables the communication between endocrine system with other important body systems, including also the immune system (16, 258), and vice versa, by soluble factors. If one of the systems undergoes physiological or physiopathological changes, bidirectional communication with the other systems through soluble factors will adapt the organisms to the altered physiopathological demands.

Other components can contribute to modulate the intrapituitary hormone regulation having not only an impact on the physiological regulation but also on tumorigenesis. In fact, it has been postulated that the extracellular matrix provides not only a structural support but also a role through specific receptors, not only on hormone secretion (e.g., PRL or ACTH secretion at the level of the POMC gene transcription) but also in many other events that regulate cell behavior and have an impact on hormone production, such us cell adhesion, migration, proliferation, differentiation, and survival of pituitary cells. Some matrix components like laminin, integrins, and cadherins have a differential expression during pituitary development in the embryo and during tumorigenesis in the adult (73, 211, 297).

An accurate balance on the bidirectional communication between the gland with the peripheral body system through soluble factors is required for the fine-tuning of hormone production and secretion. The intrapituitary organization and signaling network combine the peripheral and hypothalamic signals through specialized receptors signaling to end with a precise expression of differentiated gene products to adapt to body demands. In the following section we will illustrate in two promoters used as model examples how the anterior pituitary gland integrates multiple signals and comes out with a specific response at the molecular level to ensure a coordinated secretion adapted to the physiological needs.

B. Models for Signal Specific Integration

We will illustrate with the examples of the regulation of PRL and POMC promoters the integration of multiple signals by the anterior pituitary gland.

1. The PRL promoter

PRL expression is tightly regulated by several hormones, as already outlined in this review. All these signals integrate a coordinated transcription factor response that controls the expression of PRL within at least two distinct regions of the 5'-flanking sequence, a proximal promoter region, and a distal enhancer region located ~1.7 kb upstream from the transcription initiation site (98, 167, 204, 281) (**FIG. 4A**).

Estrogens bind to the PRL gene regulatory region at degenerate estrogen response elements (EREs). In humans, EREs are located at a distal enhancer region 1,189 bp upstream of the transcription start site and enhance PRL gene transcription due to estrogen stimulation. The rat ERE on PRL promoter is also located at the distal enhancer (2, 37, 273).

A key transcription factor that regulates PRL expression is Pit-1 (see sect. II*D*). Several binding sites for Pit-1 protein have been described on the PRL promoter both at distal and proximal regions (182, 280). Notably, estrogens regulate PRL transcription when Pit-1 is bound to PRL distal enhancer (354). Indeed, several studies have pointed out that the distal enhancer activity contributes mainly to the basal level of PRL gene expression and may be involved in pituitary cell specification (281, 370). Pit-1 interacts with many other proteins to mediate multiple signal transduction pathways on the PRL gene. A cooperative interaction between Pit-1 and estrogens is apparent and is required for enhancer activity and estrogen response. A physical interaction between the ER and Pit-1 was also described (285). This cooperative effect was abolished when a deletion of the POU-specific domain mutant version of Pit-1 was expressed (97). Also, mutations of Pit-1-binding sites in either the proximal or the distal region of PRL regulatory regions decrease estrogen action on PRL expression. The most important Pit-1-mediated biding site is located at the distal enhancer next to the estrogen receptor-binding site. Thus Pit-1 and estrogen are cooperative, and their synergic interactions are considered critical for lactotroph cell maturation, and also might have relevance for PRL-GH secreting tumor development.

The site known as 1P is the most proximal Pit-1 binding site on the PRL promoter. 1P responds to several signals such as

cAMP (185, 290, 326, 431), Ca^{2+}, and TRH (431). It also binds the PRL regulatory element-binding protein (PREB) (145), which participates in TRH-stimulated PRL expression (145, 434).

In addition to the inhibition of PRL secretion (mainly through regulation of Ca^{2+} levels), DA mediated D2R-dependent negative regulation of the PRL gene orchestrated by several signal transduction pathways, including intracellular cAMP levels, phosphatidylinositol turnover, and intracellular Ca^{2+} (115, 254, 406). A short proximal region of the PRL promoter (position −78 bp), which includes the TATAA box linked to heterologous binding sites for Pit-1, is sufficient for DA inhibition in GH4 cells (115). DA negatively regulates Pit-1 transcription (115), therefore affecting PRL transcription also in an indirect manner.

Repression of PRL expression by thyroid hormone is mediated by a strong inhibitory element located in the proximal promoter region (308). Interestingly, the thyroid receptor does not bind directly to the PRL promoter in either the human, or rat promoter. In the human PRL promoter, the AP-1 response element is also located in the same region, and PRL induction mediated by AP-1 binding is abolished in the presence of thyroid hormones, suggesting the cross-talk of both pathways (308).

GCs suppress human and rat PRL expression and lactotroph differentiation (373). The bovine PRL promoter has been shown to be a target of negative regulation by GCs (60). In these species, GC effects are mediated through a site initially described as a negative glucocorticoid responding element (nGRE) (342). This nGRE can increase PRL expression in the absence of GC or the GR (279, 385). Murine cells carrying a dimerization-defective GR ($GR^{dim/dim}$) showed an increase of PRL gene expression demonstrating the DNA-binding-dependent repression of PRL (329). Particularly in pituitary GH3 cells, transfected with the human PRL promoter, the enhanced expression of PRL in the absence of GC was suggested to be as a result of Pit-1 binding to nGRE and the repression by GC to be mediated by a GR displacement of this factor (279). Nevertheless, the precise mechanism of GCs on pituitary cells still needs to be further characterized.

As discussed in section II, the TGF-β family of proteins are key regulators of the pituitary function, in particular the lactotroph physiology (103, 173).
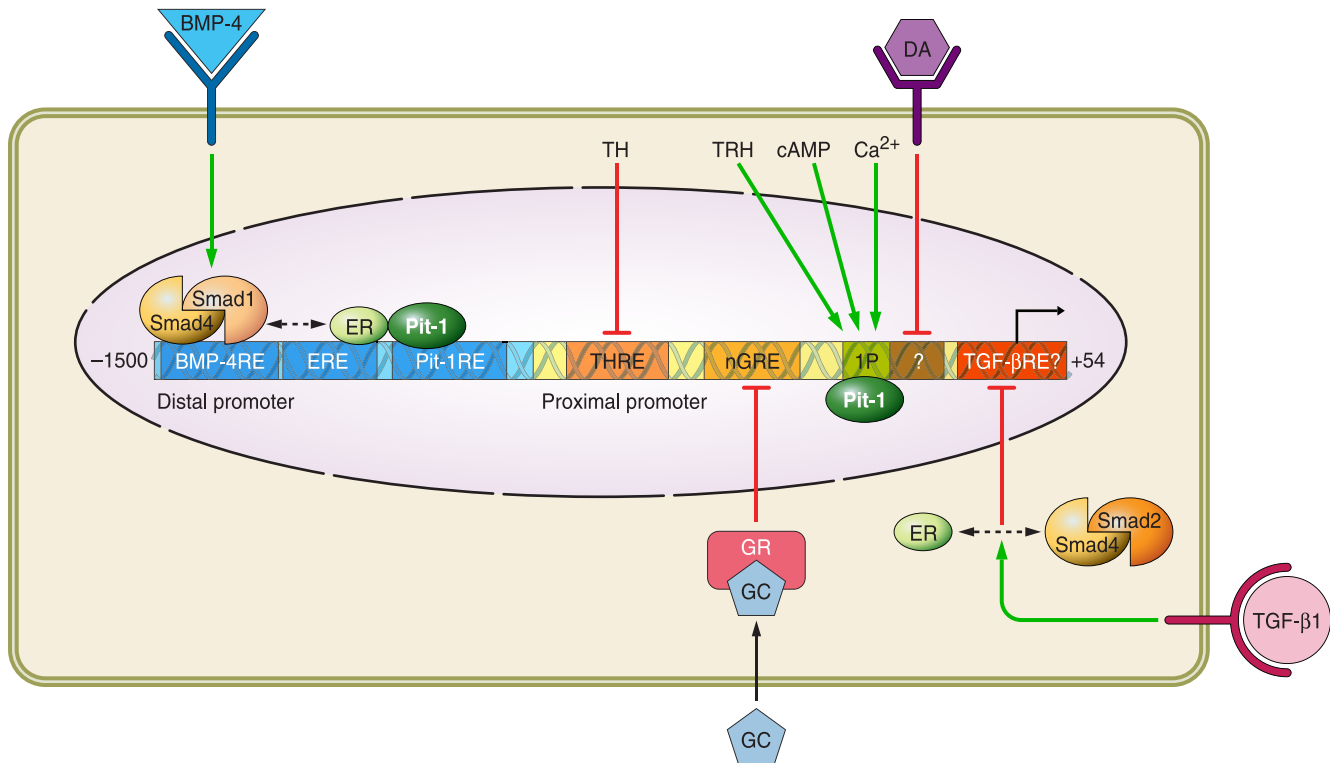
The described inhibitory action of TGF-β1 on PRL production is mainly through transcriptional regulation of the PRL gene. A region between −116 and 54 bp in the 5' rat PRL promoter was shown to be responsible for the TGF-β1 inhibitory transcriptional mechanisms (131). However, the sequencing analysis of this region did not shown any sequence homology to a classical inhibitory TGF-β response element, suggesting that TGF-β1 may act through a complex signaling pathway that involves multiple DNA elements within the PRL promoter (131). Although it was shown that Activin negatively regulates PRL expression by repressing the transcription and expression of Pit-1 (215), TGF-β would act without modifying Pit-1 gene expression (103, 131).
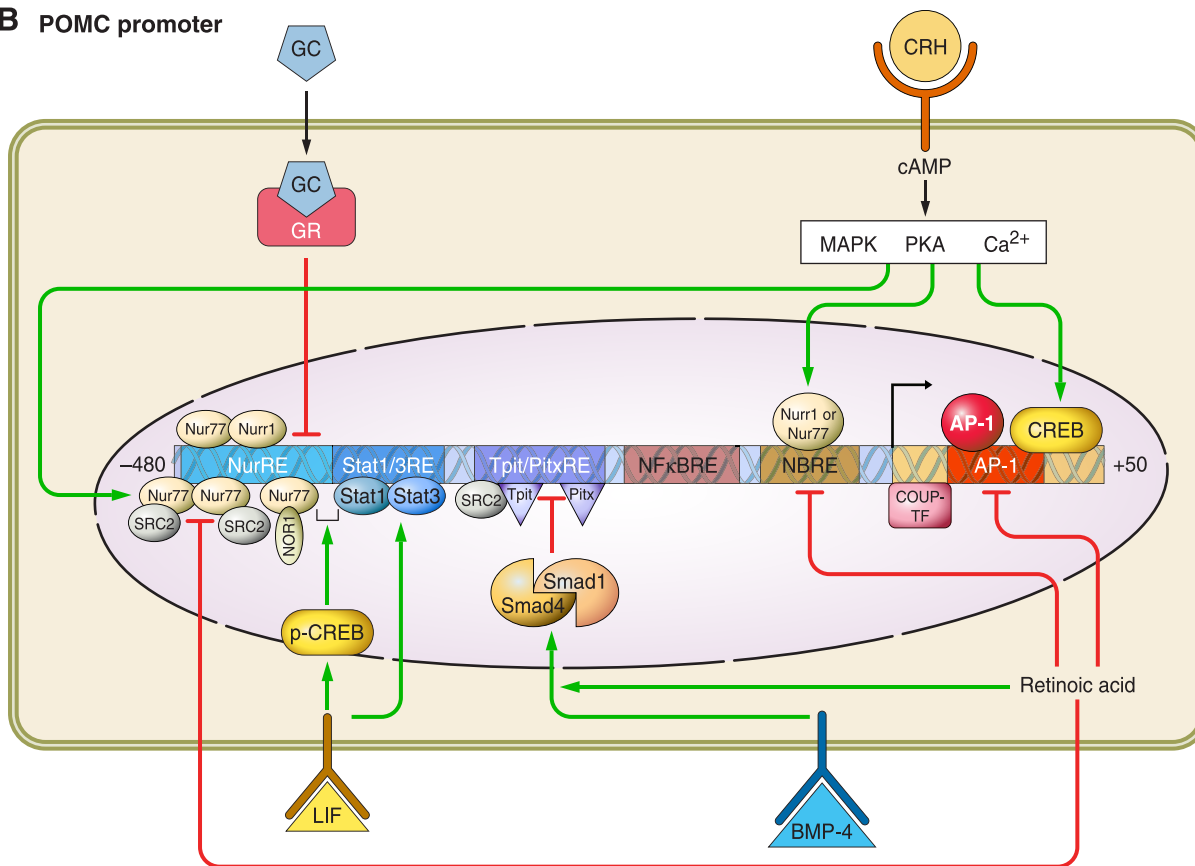
As already detailed, BMP-4 has opposite roles to TGF-β1 in lactotroph physiology. BMP-4 has a stimulatory action on PRL expression, secretion, and proliferation (154). The molecular basis of these actions has been established in recent years. BMP-4 stimulatory action on PRL expression is mediated by Smad1 proteins (154). In contrast, TGF-β1, which signals through Smad2/3, inhibits not only the basal PRL transcriptional activity (131), but also the PRL expression induced by BMP-4 (154). Thus PRL regulatory regions and the availability of cofactors determine the regulatory effects of TGF-β1 and BMP-4. An important partner of BMP-4 for regulating PRL expression, as well as for lactotroph cell proliferation, is the ER (154, 298). BMP-4 positive regulation of PRL synthesis depends on a BMP-4 response element within the promoter that cross-talks with the ER (154). In fact, this nonclassical consensus response element for BMP-4/Smad was found to be in close proximity with the ERE site on the PRL distal enhancer (154). In addition, the BMP-4/estrogen cross-talk was not inhibited by a point mutation of the ERE in the PRL promoter but was rather abolished when a Smad-1dn (dominant negative) was coexpressed in the cells. Coimmunoprecipitation studies also demonstrated a physical interaction between Smad proteins and ER (298), and this interaction depends on the previous stimuli received by cells. For example, BMP-4 or estrogen treatment induces a direct physical interaction between the ER and Smad-4/1 complex. In contrast, treatment with TGF-β1 induces a physical interaction between ER and Smad-4/2 complex, but not with Smad1 (298). Both ERα and ERβ have a similar association. Although estrogens have no effect on the transcriptional activity of the specific TGF-β1/Smad proteins, estrogens enhance BMP-4-specific Smad-induced transcriptional activity in the presence of BMP-4, but not under basal conditions (154). This reciprocal regulation between BMP-4 and estrogens contributes to the specific PRL regulation by BMP-4 in lactotrophs (**FIGS. 4A** and **5**).

Some of the factors that control PRL expression (and secretion) bind to the PRL gene regulatory regions, in combination with other partners, to have a precise control of PRL expression. In particular, TGF-β family proteins in combination with estrogens have a relevant consequence on lactotroph cell behavior and constitute an excellent model for understanding the tight regulation of lactotroph physiology at the molecular level. Smad proteins regulate PRL expression, and this depends on the type of ligand, the composition of the receptor complex, and availability of Smad in-

teractors. While the Smad 2/4 complex may be responsible for TGF-β1 inhibition, Smad 1/4 participates in the stimulatory action of BMP-4. This complex interaction on the PRL promoter determines the outcome of the lactotroph physiological response.

2. Corticotroph cells, the POMC promoter

ACTH biosynthesis is coordinately controlled by different transcription factors at the level of the POMC promoter (FIG. 4B) (44, 46, 310, 392). CRH induces transcriptional activity of AP-1 and CREB transcription factor, which have been proposed to be involved in POMC transcription at the level of the AP-1 site located in the first exon (45, 46). AP-1 regulates POMC transcription, but the main mediators of the stimulatory effects of CRH are the nuclear orphan receptors from the Nur family (46, 310). CRH exerts its effect in corticotrophs through the CRH-R1 (31, 100), which raises intracellular cAMP levels. CRH also elicits calcium entry through L-type voltage-dependent calcium channels, which in turn triggers the release of secretion vesicles anchored near the plasmatic membrane (222). While CRH receptors activate the cAMP pathway and calcium channels, the AVP receptor V1b activates the inositol phosphate pathway and calcium channels as well (46, 99). AVP potentiates CRH-induced ACTH synthesis and release through a mechanism that involves a molecular cross-talk between PKC (triggered by AVP) and cAMP-PKA activation (CRH mediated) (232).

In addition to its effect on the release of ACTH from vesicles, calcium is involved in the regulation of POMC mRNA (418) and is associated with the stimulation of c-*fos* expression by CRH (47). As mentioned, Nur factors are the main mediators of CRH and cAMP stimulation of POMC in corticotrophs (246, 274, 310). NGFI-B (Nur77), Nurr1, and NOR-1 are orphan nuclear receptors that belong to the Nur subfamily of transcription factors (117). They possess a highly conserved DNA binding domain (DBD) that allows them to interact with the same DNA sequences in promoters, although specific and independent actions have also

been described for these factors. Nur factors are particularly important in the regulation of the HPA axis, acting on the hypothalamus (274), pituitary (310), and adrenal glands (424). In the pituitary, Nur77 and Nurr1 are involved in CRH-dependent induction of POMC mRNA, acting at two sites in the promoter: the proximal binding sequence named Nur77-binding response element (NBRE) that can bind one of these proteins, Nur 77 or Nurr1, as a monomer, and the distal Nur response element (NurRE), which binds Nur77 homodimers or Nur77/Nurr1 heterodimers and plays a dominant role in mediating stimulation by CRH (246, 274, 310, 311). The POMC NurRE (gTGATATTTacctccAAATGCCA) is an inverted copy of two NBRE (AAAGGTCA) sites with two mutations each, separated by six base pairs. The POMC NurRE is more sensitive to CRH stimulation than the NBRE site and may be responsible for stimulation of the POMC promoter under physiological conditions (246, 310, 311). NOR-1, the third member of the Nur subfamily, although capable of interacting with the consensus NurRE and NBRE sites, can only bind the POMC NurRE site and activate transcription as heterodimer together with Nur77 (246). After dephosphorylation of the Nur DBD and formation of Nur factor dimers that recognize the POMC promoter, recruitment of the coactivator SRC-2 (TIF2) to the AF-1 domain of NGFI-B occurs (245).

The CRH/cAMP signaling that leads to Nur77/Nurr1 mRNA induction and transcriptional activation, and thus POMC expression, is dependent on PKA and involves calcium/CAMKII (Nur induction/activation) and MAPK calcium-dependent and -independent (Nur phosphorylation-activation) pathways (208). All these signaling pathways can be blocked by small molecules and result in a reduced transcriptional activity of Nur and consequently less POMC transcription and ACTH production. In cell types that express the kinase B-Raf, such as corticotrophs (208), receptor stimulation of intracellular PKA, and cAMP leads to B-Raf activation by Rap-1 and in turn activation of ERKs despite the inhibition of Raf-1. This pathway is an example

FIGURE 4. Fundamental factors in the regulation of the prolactin and pro-opiomelanocortin promoters: two models of signal integration. The most studied response elements, along with signaling cascades, are shown. Some response elements have been omitted for simplicity. The binding sites indicated are approximate, and their positions are relative among each other. Some of these sites have been reported to be in different relative positions in different species. *A*: the prolactin promoter is divided into two regulatory regions, the distal promoter and the proximal promoter. In the distal promoter, BMP-4, Pit-1, and estrogen response elements (ERE) have been identified, and physical interactions between estrogen and Smad-1 (indicated by dotted lines), which bind to the BMP-4RE, occur. Pit-1 also binds to estrogen (indicated by the direct physical contact in the figure). In the proximal promoter, there is an inhibitory region that responds to thyroid hormone (TH: T_3/T_4). Binding sites for AP-1 in the human promoter and for AP-2 in the rat promoter have been mapped in the proximal region (not shown in the figure). Other regulatory sites as nGRE, the 1P site and the TGF-βRE discussed in the text, are shown. The still not fully described sites for DA and TGF-βRE are indicated by a "?". *B*: the pro-opiomelanocortin (POMC) promoter is positively regulated by CRH, which initiates PKA, calcium, and MAPK signaling that lead to binding of the Nur transcription factors: Nurr1, Nur77, and NOR-1, which act on NurRE and NBRE sites. Other relevant regulatory sites discussed in the text, such as STAT1/3, NFκBRE, and COUP-TF binding sites, contribute to the integration of signals on this promoter. Two binding sites for COUP-TF have been mapped, one at -40 (not shown in the figure), and the other near the AP-1 element. Retinoic acid has a negative effect on the POMC promoter by inhibiting the transcriptional activity of AP-1 and Nur transcription factors. GCs inhibit POMC transcription by trans-repression of Nur transcription factors (in response to CRH on NurRE-dependent activity) and a negative nGRE described at $-70/-63$ (not shown in the figure).

of how intermediate cell specific kinases confer cell specificity to signals.

The inhibitory feedback of GC on the POMC promoter results, at least in part, from transrepression exerted by GR on the activity of Nur77 (311). Indeed, transcription elicited by Nur77, Nurr1, and NOR1 is subject to GR transrepression. In response to CRH signals, only NurRE-dependent activity is subject to GC repression (249). The molecular mechanism of transrepression between GR and Nur requires the chromatin remodeling protein Brg1 and its ATPase activity in this mechanism (40). Also nGREs (277, 392), mediating negative effects of GCs, have been described on the POMC promoter.

Studies provided evidence that, in corticotrophs, the inhibition of NFκ-κB binding at its consensus binding site on the POMC promoter is required for the transcriptional activation of the POMC gene by CRH (196). Additionally, a functional STAT1/3 (signal transducer and activator of transcription 1/3) low-affinity binding site overlapping in part with the NurRE was identified in the distal region of the POMC promoter and responds to LIF (44). A synergistic signaling by CRH and LIF (44), bridged by phosphorylated CREB at the NurRE-STAT element of the POMC promoter, has been described (275). It has been reported that BMP-4 represses POMC transcription by the activation of Smad1/4 transcription factors (286). CRH signals also act on the POMC promoter through SRC-2 coactivation of Tpit (244), a highly cell-restricted T-box transcription factor (218).

COUP-TF is an orphan receptor that belongs to the steroid/thyroid hormone receptor superfamily. COUP-TFI is expressed in mesenchymal cells, but is absent in terminally differentiated epithelium (304). COUP-TF1 is expressed in an ACTH-secreting subpopulation of normal pituitary cells. In ACTH-secreting tumors, however, no expression of COUP-TF1 was observed, indicating a possible role of this transcription factor in ACTH-secreting tumor development (57, 299). The presence of COUP-TF1 binding sites in the POMC promoter further supports the hypothesis that this transcription factor could have a role in the regulation of ACTH biosynthesis (392).
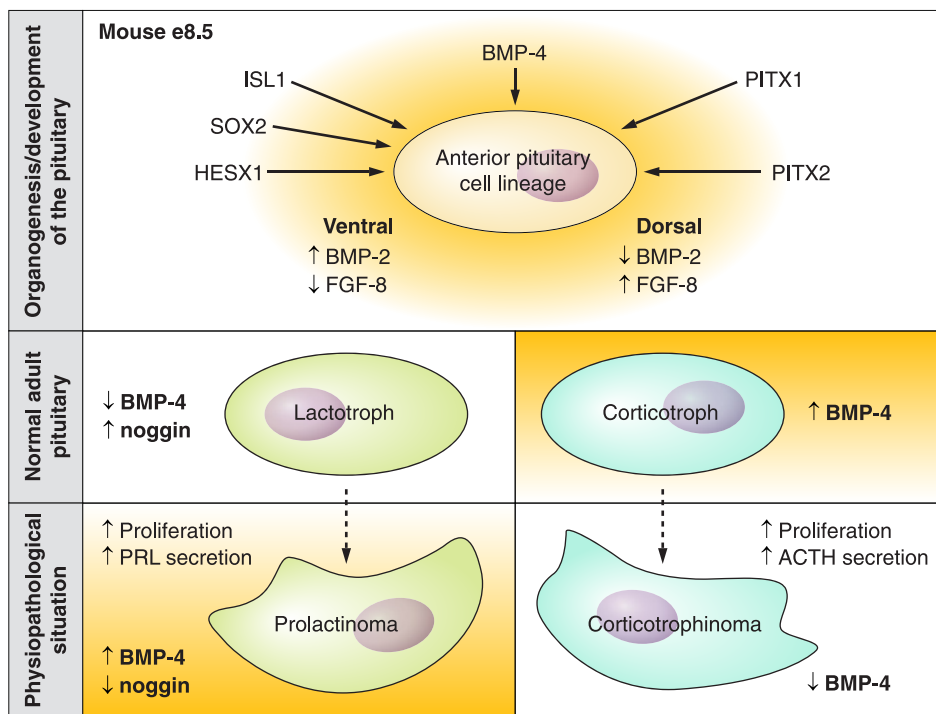
FIGURE 5. Contrary role of BMP-4 on lactotrophs and corticotrophs in normal and physiopathological situations: an example of signal plasticity. BMP-4 participates in the development of the anterior pituitary cell lineage, starting at embryonic day 8.5 (e8.5), along with other factors such as PITX1, PITX2, ISL1, SOX2, and HESX1. Shortly later on in development, a dorsal-ventral gradient of BMP-2 and FGF-8 in the primordial pituitary gland determines the fate of lactotrophs and corticotrophs. A high concentration of BMP-2 and a low concentration of FGF-8 in the ventral part of the hypophysial primordium determines lactotroph, while a low concentration of BMP-2 and a high concentration of FGF-8 in the dorsal part determines corticotroph development. In the adult pituitary gland, lactotrophs express low levels of BMP-4 and elevated levels of noggin (BMP receptor antagonist), while corticotrophs express high levels of BMP-4. In physiopathological situations, such as in prolactinomas or in corticotrophinomas, the former are characterized for having high expression levels of BMP-4 and low levels of noggin, while the latter have low levels of BMP-4. BMP-4 has a contrary role in corticotrophs and lactotrophs, and this also happens regarding the physiopathological situation of each cell type. The color intensity of the background in the figure denotes the importance of BMP-4 in each situation.

The importance of these regulatory pathways in the integrative control of POMC transcription is highlighted by the mechanism of action of a promising drug in controlling the hypersecretion of ACTH. Retinoids, comprising the native and synthetic derivatives of vitamin A, are promising agents for the prevention and treatment of human cancers, including those of breast and lung. The biological effects of retinoids are mainly mediated by their nuclear receptors, retinoic acid receptor (RAR) and retinoid X receptor (RXR) (71). Retinoic acid inhibits the transcriptional activity of AP-1 and Nur in ACTH-secreting cells (299). This inhibition results in reduced secretion of ACTH in ACTH-secreting tumor cells. However, normal ACTH-secreting cells and other normal pituitary cells are not affected by retinoic acid, demonstrating a specific effect of this drug on tumor cells, probably related to the degree of differentiation of normal versus tumor cells (299). Moreover, COUP-TF1 reverts the inhibitory effects of retinoic acid in ACTH-secreting tumor cells (299, 428). Retinoic acid also inhibits cell proliferation and induces apoptosis in ACTH-secreting tumor cells (299). In vivo treatment with retinoic acid completely inhibited the growth of tumors and ACTH and cortisol plasma levels in nude mice having ACTH-secreting tumors (299) and also in dogs with Cushing's disease (67).

Notably, the induction of BMP-4 mediates the retinoic acid-induced inhibition of POMC transcriptional activity (155). BMP-4 signaling negatively regulates endogenous POMC expression as well as POMC promoter activity in AtT-20 cells. This negative regulation is mediated by the classical BMP-4 signaling pathway involving ALK3/6 receptors and the Smad1/4 transcription factors. As mentioned in section II*D*, the transcription factors PITX1 and TPIT are critical for terminal differentiation and identification of corticotroph cells participating in synergistic interactions that are the basis of cell-specific POMC transcription. Upon BMP-4 stimulation of corticotroph AtT-20 cells, activated phospho-Smad1 is recruited to the POMC promoter, where it may act through interactions with the PITX and TPIT transcription factors and subsequently may disrupt transcriptional activity (286). BMP-4 inhibited ACTH secretion and cell proliferation in AtT-20 cells (155). In addition, AtT-20 cells stably transfected with a dominant-negative form of the BMP-4 signal cotransducer Smad-4 or the BMP-4 inhibitor noggin show increased tumorigenicity. Also SST analogs regulate ACTH synthesis through BMP-4 (399), pointing to the relevance of this pathway in the negative regulation of corticotrophs. BMP-4 opposite actions, negative regulation of the corticotroph, in contrast to its stimulatory action on the lactotroph constitute an excellent model of cell specific signaling outcome within the anterior pituitary gland (FIG. 5).

V. CONCLUSION

Our knowledge regarding hormone production, secretion, and their physiopathological relevance has been progressively increased during the last few years. Accordingly, we have begun to understand the fundamental properties of pituitary function, in particular those related to the cellular organization and plasticity. A question that we should perhaps ask and attempt to answer or address is: how does the anterior pituitary gland adapt to physiological needs through its integration of multiple input signals and thereby elicit precise and measured specific responses (FIG. 6). The answer might be the integration of intercellular signaling networks and hypothalamic, as well as feedback signals, through specialized receptors and downstream signaling that ultimately induce precise expression of differentiation gene products to adapt (gland plasticity) to body necessities. The pituitary gland's main characteristic is its plasticity,
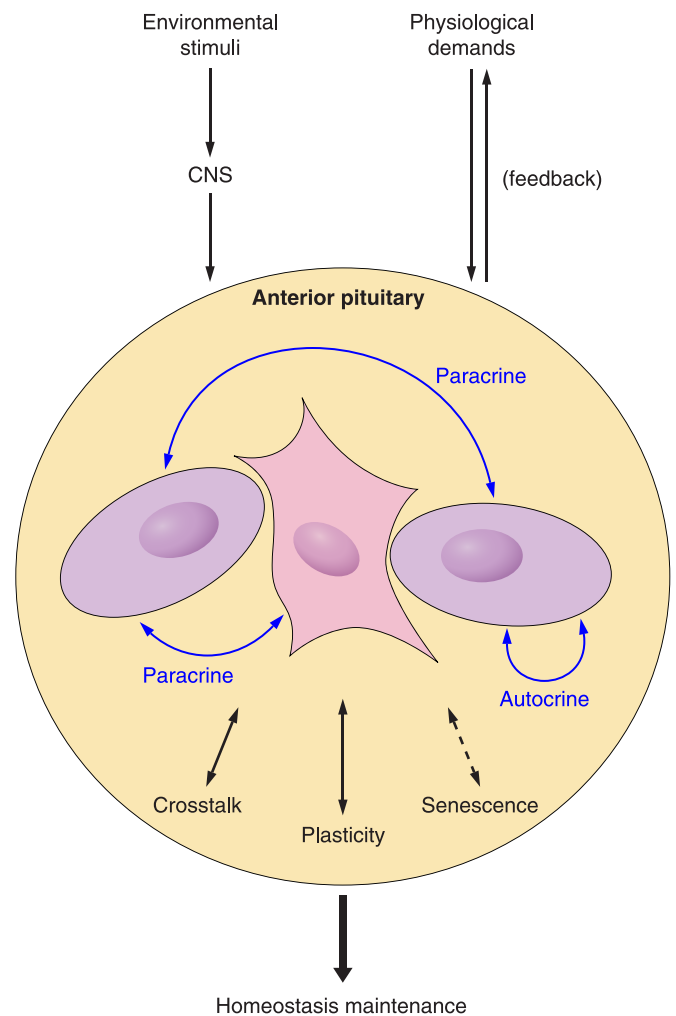

FIGURE 6. The pituitary gland in homeostasis maintenance. The pituitary gland is receptive of environmental stimuli, through the CNS, and of internal physiological demands. It has the ability to integrate these signals through different capacities such as crosstalk among the various cell types that form part of it, plasticity to adapt to the changing signals and the, still under study, ability to senesce (dashed lines), allowing the gland to continue with its functions under situations that alter its normal growth. These characteristics allow the pituitary to sense and respond to the external stimuli and internal physiological demands through the autocrine and paracrine stimuli that pituitary cells are able to produce and receive, and feedback at different levels to maintain homeostasis.

which allows it to adjust to distinct physiological states associated with different endocrine demands. This unique plasticity is based on the adjustment and maintenance of the pituitary cell number mediated by specific growth factors, and it is partially attributed to the presence of a stem/progenitor cell population in the adult pituitary gland, which may differentiate upon physiological demand into the corresponding required hormone-producing cell type. The plastic response of the anterior pituitary gland to environmental challenges and demands allows its different cells to perform their vital homeostatic control (FIG. 6).

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DISCLOSURES

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