0163-769X/00/$03.00/0
Endocrine Reviews 21(5): 488–513

Intercellular Communication in the Anterior Pituitary*

JEFFREY SCHWARTZ

Department of Physiology, University of Adelaide, Adelaide, SA 5005 Australia; and Departments of Obstetrics & Gynecology and Physiology and Pharmacology, Wake Forest University School of Medicine, Winston-Salem, North Carolina 27157

ABSTRACT

In addition to hypothalamic and feedback inputs, the secretory cells of the anterior pituitary are influenced by the activity of factors secreted within the gland. The list of putative intrapituitary factors has been expanding steadily over the past decade, although until recently much of the work was limited to descriptions of potential interactions. This took the form of evidence of production within the pituitary of factors already known to influence activity of secretory cells, or further descriptions of actions on pituitary cells by such factors when added exogenously. A new phase of discovery has been entered, with extensive efforts being made to delineate the control of the synthesis and secretion of the pituitary factors within the gland, regulation of the receptors and response mechanisms for the factors in pituitary cells, and measurements of the *endogenous* actions of the factors through the use of specific immunoneutralization, receptor blockade, tissue from transgenic animals, and other means. Taken together, these findings are producing blueprints of the intrapituitary interactions that influence each of the individual types of secretory cells, leading toward an understanding of the physiological significance of the interactions. The purpose of this article is to review the recent literature on many of the factors acting as intrapituitary signals and to present such finding in the context of the physiology of the secretory cells. (*Endocrine Reviews* **21:** 488–513, 2000)

Address reprint requests to: Jeff Schwartz, Ph.D., Department of Physiology, University of Adelaide, Adelaide, SA 5005 Australia. E-mail: jeff.schwartz@adelaide.edu.au

* Supported by NIH Grant HD-11210, Australian Research Council Large Grants, and Wake Forest and University of Adelaide intramural funding.

I. Introduction

THE SECRETORY cells of the anterior pituitary (AP) are influenced by a wide array of factors. Primary among these are the hypothalamic release and inhibitory factors, and feedback signals from the target organs of the pituitary hormones. In addition, there is an ever increasing catalogue of factors known to be produced, secreted, and to act within the AP to influence secretory cells. Much of the recent work in this area has come to emphasize the biochemical diversity of these factors, the extent to which the factors can alter secretory cell function, the sensitivity of the target cells to such influence, and the degree of control maintained over the secretion of the factors themselves. Indeed, given the potency of some factors and the virtual certainty of their being produced in cells adjacent to the target cell (in the case of autocrine interactions—within the target cell itself), it may be as physiologically relevant to ask what *prevents* these factors from acting locally as asking how they might act.

This review is a broad survey of recent literature relevant to physiological interactions that have been demonstrated to occur or are likely to occur within the AP. Emphasis will be placed on studies in the past 7 yr, and the observations will

be noted from two perspectives, in terms of the factor being studied and in terms of the cells involved. The aim is to produce a clear and worthwhile introduction to the subject and provide basic illustration of most of the best characterized interactions. Beyond that, this review is intended to provide a point of departure for further investigation of the literature about specific intrapituitary interactions. For important material published before 1992, the reader of the present review is often referred to an *Endocrine Reviews* article that appeared in that year (1). This has less to do with immodesty than a desire to keep the present review succinct. Since a number of topics relevant to intrapituitary interactions have also been reviewed recently, either as such or as part of a treatment of pituitary physiology from another perspective, reference to these has been cited in the present review. These include a number of other reviews on interactions in the AP, focused on the intrapituitary actions of peptides (2), components of the renin-angiotensin system (3), cytokines and growth factors (4), and activin and follistatin (5–9), and the use of reaggregate cultures to study intrapituitary interactions (10).

In this review there are two basic units. In the first unit the sections are delineated according to intrapituitary factor, and the discussion of each factor generally includes (in the following order): evidence of synthesis or secretion for the factor or its receptors within the AP; reports of how the genetic expression/biosynthesis/secretion of the factor or its receptors may be subject to physiological regulation; and description of the actions of the factor within the AP.

For many factors this circumstantial evidence provides a basis on which intercellular interactions may be presumed to occur; at least it demonstrates the *potential* for certain interactions. It does not prove or provide direct evidence that an interaction does occur or furnish support for any physiological role of the interaction.

In other cases the weight of currently available results provides more substantial evidence, justifying the presumption of an intrapituitary interaction. One example of such evidence is a change in the secretion rate for a hormone caused by specific immunoneutralization of an endogenous factor in a closed *in vitro* system. Addition of an antiserum with high affinity for galanin decreases secretion of PRL in a closed culture of dissociated AP cells, directly suggesting that galanin of AP origin normally acts to maintain secretion of PRL thorough an autocrine-paracrine mechanism (11). Other examples of such evidence include direct demonstration that such factors are secreted (as opposed to simply found or synthesized) by AP cells or altered behavior *in vitro* by AP cells of transgenic animals that over- or underexpress a putative paracrine factor. In cases of factors where such evidence exists, particularly coming from multiple approaches or multiple groups of investigators, a separate subsection is included to emphasize the high likelihood, even at this point, that the compound acts as a physiological intrapituitary factor. Figures 1, 2, 3, 4, and 5 illustrate a number of interactions for which substantial information exists that the locally produced factors are acting physiologically within the AP.

The second unit of this review covers interactions in which the intercellular factors involved are unidentified or incompletely characterized. This unit is indexed according to the various cell types of the AP, with the sections under each heading divided into explicit subsections, dealing with the cell as source and target of the unidentified factors.

A note on the concentration dependence of some effects: The concentration-response relationships of a number of factors covered in this review reveal effects on AP cells under varying conditions (as, for example, in *Section I*). These include 1) only at very high (*e.g.*, micromolar) concentrations; 2) with a biphasic response curve; and 3) with opposite effects, depending on concentration. Such observations are noteworthy in the context of local intercellular interactions. The concentrations of putative intercellular factors in the vicinity of the cells in which they are synthesized are likely to vary over an extremely wide range. This is particularly true of the systemic hormones, some of whose concentrations must be high enough within the AP to result in concentrations in the low nanomolar range in the peripheral circulation even after dilution in the blood, whereas at other times secretion by individual cells must be markedly suppressed. In all cases, concentrations within the AP will vary exponentially over time and as a function of distance from the source cell.

Because the pattern in which AP cells are exposed to paracrine factors is different to endocrine type exposure, a number of realizations should be noted in interpreting observations reported in this paper.

1. Effects observed to occur only at high concentrations may be physiologically relevant because of the levels encountered by target cells located adjacent to the source cells for a given factor.

2. AP cells may be chronically exposed to a factor secreted by an adjoining cell, and the normal response to that factor is thereby down- (or up-) regulated.

3. The "cocktail" of AP intercellular factors to which AP cells are normally exposed is likely quite different to that of peripheral cells. Thus, the media used for *in vitro* experiments may include or omit compounds, other than the factor(s) under study, that would normally modulate the activity of the cells *in vivo*. For this reason, observations, such as those differences observed in the behavior of cells in serum-free *vs.* serum-supplemented media, are quite interesting.

II. Factors That Are Potential Paracrine Messengers in the Anterior Pituitary (AP)

This unit describes the evidence that certain factors are synthesized, secreted, and act within the AP to influence the secretory cells. Some of the more recently described actions of these factors on pituitary cells are summarized in Table 1. Table 2 contains citations of recent observations that have localized the sites of origin and activity within the AP of these factors.

In most cases in the text a common name is used as the heading for a single factor, although it also might be known by another name (*e.g.*, GnRH *vs.* LRF). In some cases several biochemically related factors are described under a single heading (*e.g.*, POMC fragments) for efficiency. The use of

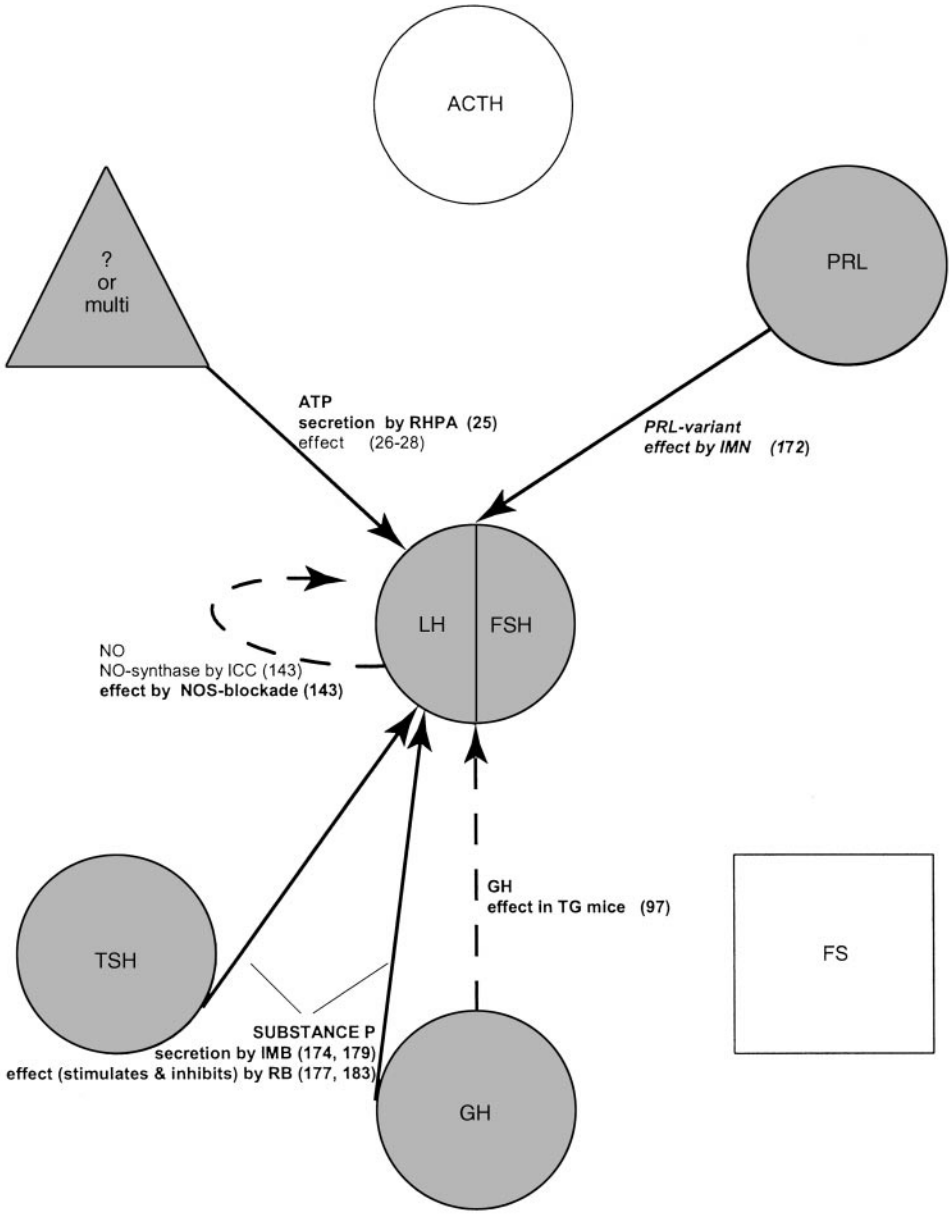

FIG. 1. Direct and corroborating evidence for some interactions involving gonadotrophs as the target cells for intrapituitary factors. *Arrows* are labeled with the names of the various factors and depicted as originating in the presumed source cell(s) of the factor. *Solid arrows* indicate stimulation of target cell; *dashed arrows* indicate inhibition; *reflex arrows* indicate autocrine stimulation or inhibition. *Arrows directed to either side* indicate effect on LH or FSH; *arrows directed at equator* indicate effect on both hormones or cellular function in general. *Numbers in parentheses* cite references in the text that provided evidence for the secretion of factor by AP cells (or localization/synthesis in type of AP cell), or evidence for the effect of the factor on the target cell. Direct evidence is cited in *bold*; corroborating evidence in *normal type*. For effect *roman type* indicates an action on hormone biosynthesis or secretion; *italic type* indicates an action on proliferation or differentiation of the target cell. The nature of the scientific evidence is indicated by the following abbreviations: IMB, cellular immunoblotting; BC, direct biochemical measurements; BA, bioassay; WB, Western blot; RHPA, reverse hemolytic plaque assay; ICC, immunocytochemistry; ISH, *in situ* hybridization; IMN, immunoneutralization experiments; TG, experiments with AP cells from transgenic animals; RB, pharmacological blockade of receptors; FS, folliculostellate cell; ? or multi, source cell is unidentified or includes most types of AP cells.

broader headings, however, was not used too frequently to avoid confusion (*e.g.*, what to include under Growth Factors).

A. α-MSH

α-MSH is most commonly characterized as a cleaved product of POMC, secreted by melanocytes of the intermediate lobe of the pituitary and acting systemically in certain species to increase skin coloring. The potential for AP cells to synthesize and secrete MSHs has been studied (reviewed in Refs. 1, 2, and 12), and α-MSH is known to stimulate PRL secretion.

A number of recent developments have been reported on lactotroph function and α-MSH. In addition to acting on its own, α-MSH has been found to increase the PRL-secretory responses to TRH or ATP (13). Two other reports have noted that α-MSH may act only on subsets of lactotrophs. In one, α-MSH was shown to increase calcium entry into a subset of lactotrophs; in the other, using immunocytochemistry and autoradiography, it was found that binding of α-MSH is also limited to a subset of PRL-positive cells (13, 14). In pituitaries of rats and sheep the effect of α-MSH is probably mediated by MC5 receptors; in mice it is likely MC3 (15).

A related peptide, γ_3-MSH, has also been found to influence lactotroph function. γ_3-MSH, whose amino acid sequence constitutes a segment of $POMC_{(1–74)}$, was found to have the same mitogenic effects as the larger peptide (see *Section II.X*, below), albeit with lower potency (16).

B. α-Subunit

The glycoproteins LH, FSH, and TSH are each composed of a common α-subunit and a specific β-subunit. Although the α-subunit is acknowledged to have no systemic endo-

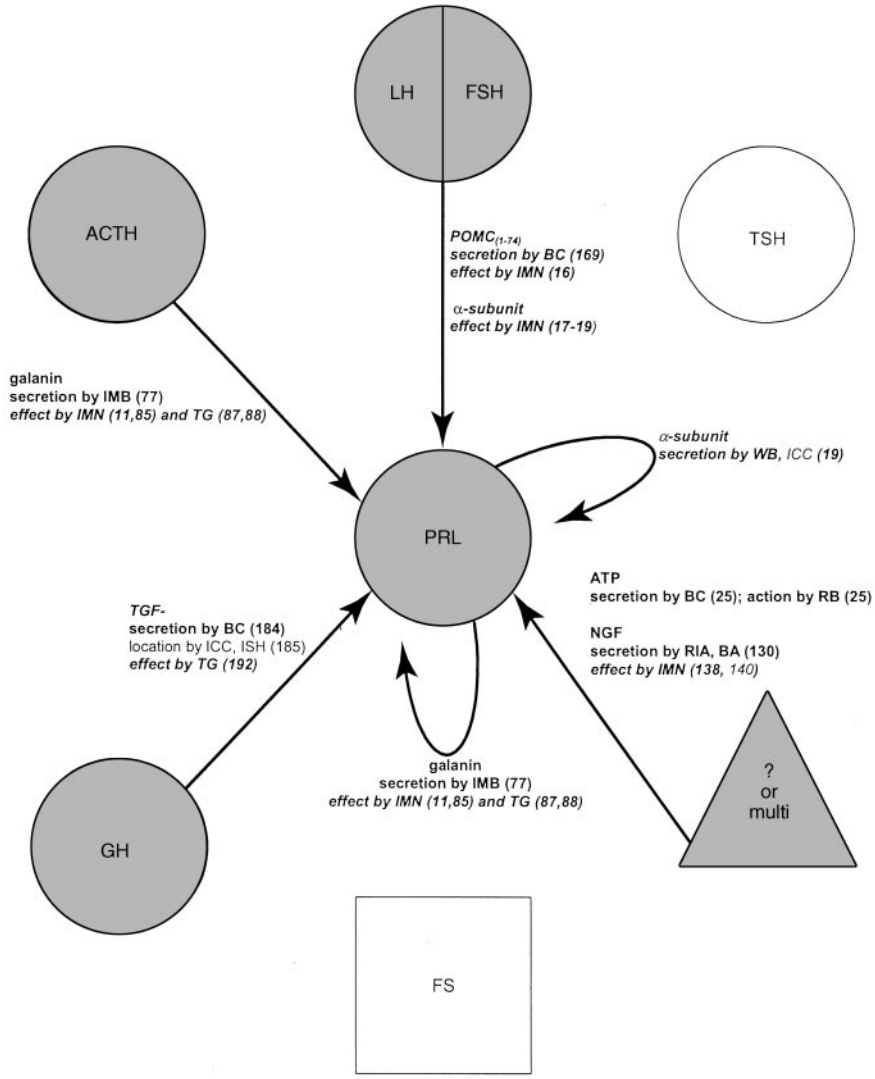

FIG. 2. Direct and corroborating evidence for some interactions involving lactotrophs as the target cells for intrapituitary factors. See legend to Fig. 1.

crine role by itself, it has been observed to stimulate the differentiation of lactotrophs (17, 18). In bullfrog pituitary cells there is direct evidence for secretion of α-subunit, and α-subunit stimulates secretion of PRL (19). Further evidence for an action of gonadotrophs or products of gonadotrophs on lactotrophs comes from recent studies with gonadotroph-deficient transgenic mice. In the absence of gonadotrophs, engineered by the expression of diphtheria toxin in cells with active α-subunit promoters, there is also a decrease in the number of lactotrophs (20). Although the lactotroph-deficient phenotype in the transgenic mice may be the result of diminished α-subunit, it may also involve other change associated with the presence of fewer gonadotrophs.

C. Activin

The actions on pituitary cells of activin and the control of activin biosynthesis and secretion within the AP are well described and have been reviewed recently (including Refs. 5–9). A few recent observations on activin are noteworthy in terms of the physiology of activin. Pituitary levels of activin B mRNA expression correlate with the plasma FSH levels characteristic of various breeds of swine (21). In *in vitro* studies of female rat AP cells, treatment with activin has been shown to increase both the numbers of cells secreting FSH as well as the amount of FSH secreted per cell, and to inhibit both the amount of PRL and numbers of cells secreting PRL (22). Biochemical interactions between follistatin and activin molecules have long been documented, forming the basis for the theoretical modulation of activin activity by follistatin. In a study of extracts of pituitary tissue, follistatin has been found bound to activin in the *in situ* condition (23). Local activin may play a key physiological role in the pituitaries of a wide range of vertebrates in addition to the more commonly studied species, as an immunoreactive activin/inhibin β_B chain has been detected in the gonadotrophs, thyrotrophs, and somatotrophs of *Xenopus* (24).

D. Adenosine, ATP

Adenosine and ATP are produced by virtually all cells, so the likelihood that either might act on neighboring cells is very high. Measurable quantities of ATP are secreted by AP

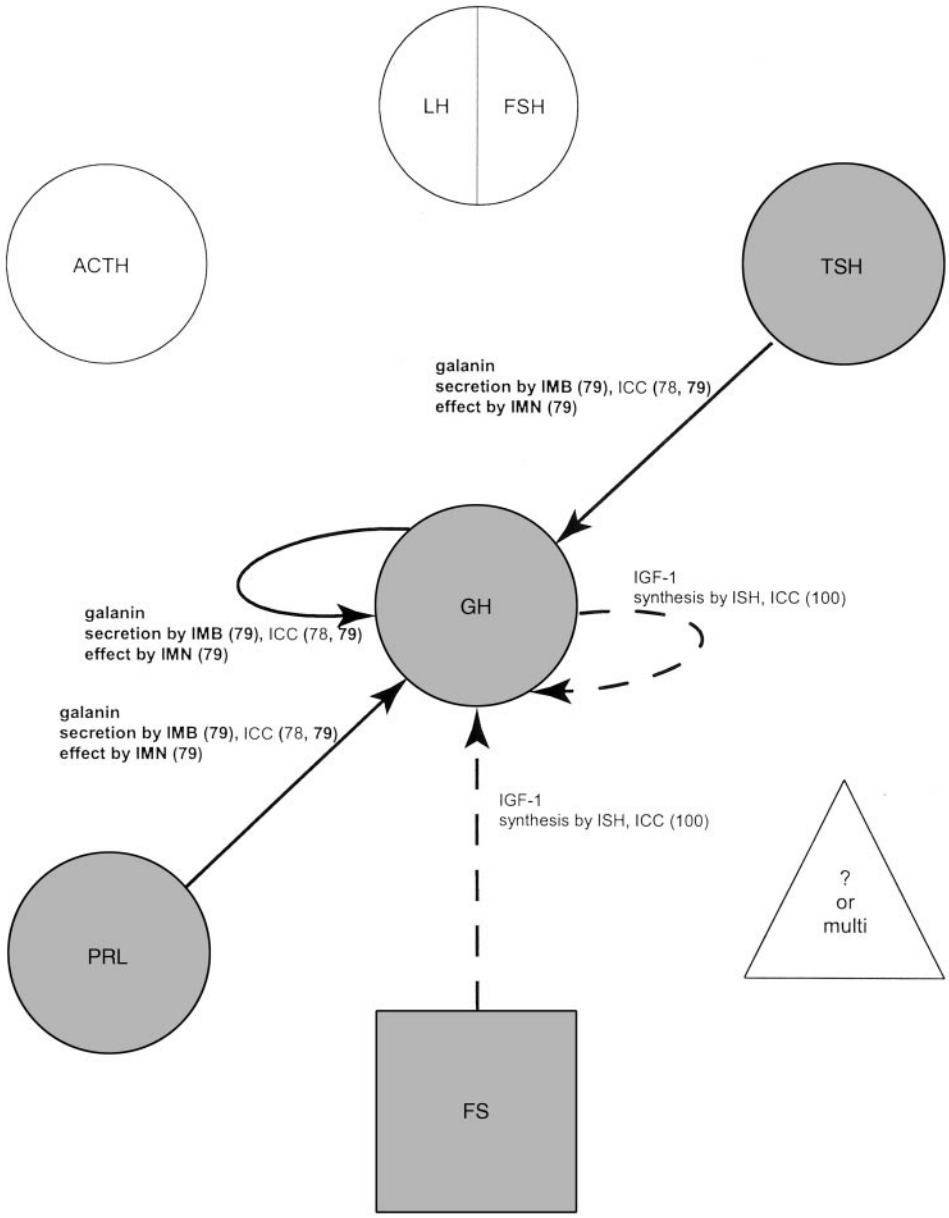

FIG. 3. Direct and corroborating evidence for some interactions involving somatotrophs as the target cells for intrapituitary factors. See legend to Fig. 1.

cells (25). In gonadotrophs, ATP has been shown to stimulate flux of calcium and increase LH secretion (26). Similarly, ATP and UTP were reported to increase secretion of LH by rat pituitary cells (27). Other studies have demonstrated an effect of ATP on calcium flux in all types of pituitary cells (28), and evidence for the presence of specific ATP receptors has been demonstrated in the rat pituitary by RT-PCR (29).

One mechanism of action of ATP in the pituitary involves specific, ATP-sensitive potassium channels, where ATP stimulates the closure of such channels (30). In contrast, in the absence of ATP, potassium efflux increases and the cells are thereby hyperpolarized (30). An extensive review of the literature on the molecular biology of these channels has been published recently (31). Whether this mechanism functions in the action of ATP on neighboring pituitary cells, or only within cells, remains to be elucidated.

In addition to the secretion of LH, ATP stimulates PRL secretion. Studies involving the reverse hemolytic plaque assay provide a potential physiological role in the pituitary for extracellular ATP (25). Secretory patterns for ATP parallel those of PRL in response to at least two factors: TRH increases, and bromocriptine decreases the secretion of both ATP and PRL. Although the parallel secretory responses could be the result of cosecretion from secretory vesicles, the observation that exogenous ATP stimulates PRL secretion would be consistent with the possibility of ATP action playing an intercellular role in the responses to TRH or dopamine.

Physiological activity of endogenous ATP. Evidence that endogenously produced ATP reaches neighboring cells at sufficient concentration to act physiologically comes from a number of different approaches. As noted above, ATP is secreted in measurable amounts by AP cells *in vitro* (25). In addition,

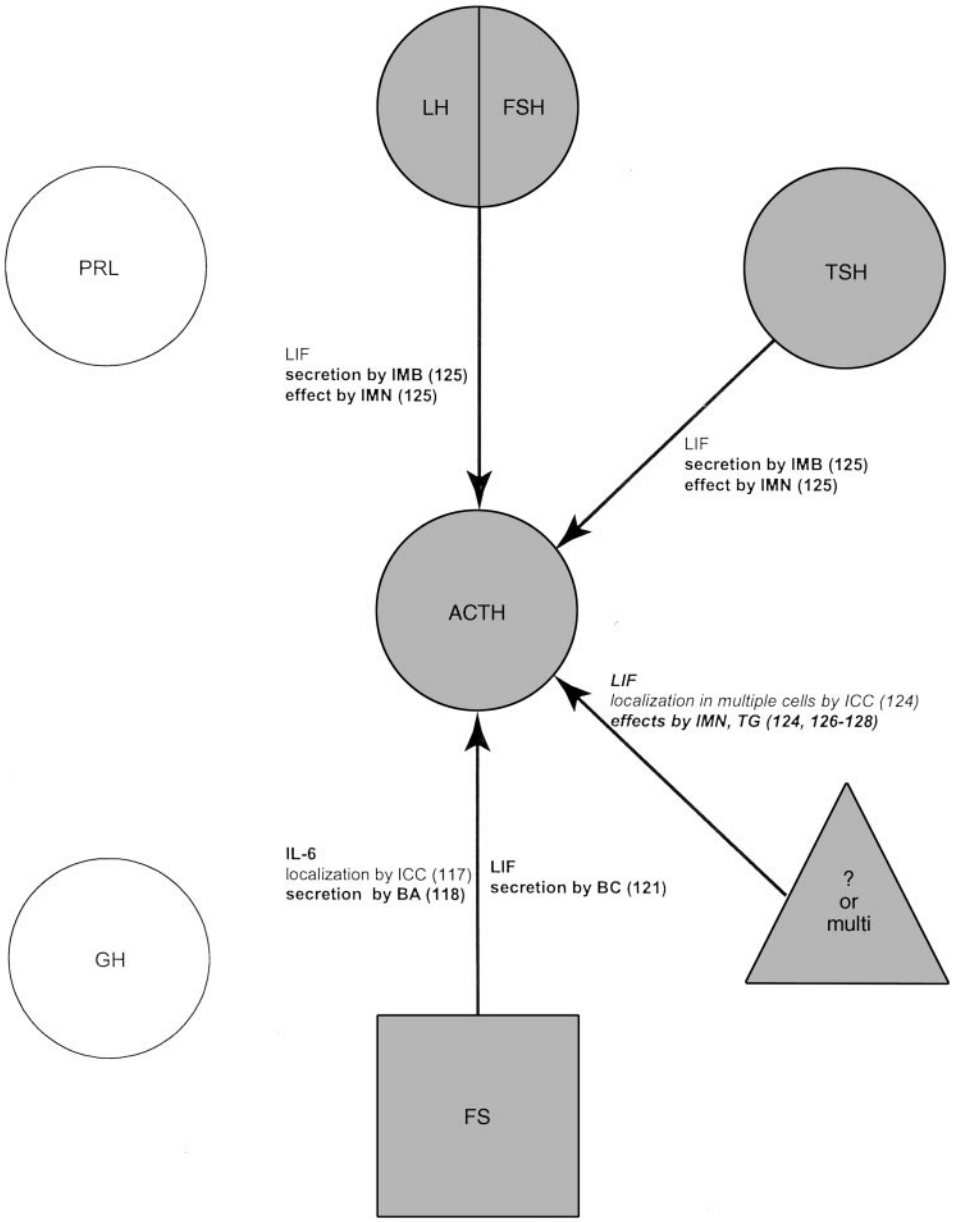

FIG. 4. Direct and corroborating evidence for some interactions involving corticotrophs as the target cells for intrapituitary factors. See legend to Fig. 1.

blockade of ATP receptors or accelerated enzymatic metabolism of endogenous extracellular ATP decreases PRL secretion by AP cells *in vitro* (25).

Adenosine also has been reported to stimulate secretion of PRL in an action mediated by A_1 type receptors (32). It also inhibits secretion of FSH (32). In another study, adenosine was reported to inhibit both LH and FSH secretion, under basal and GnRH-stimulated conditions (33).

E. Bombesin and gastrin-releasing peptide (GRP)

Bombesin and GRP are two structurally related peptides, known to be synthesized in the AP. In the rat AP, GRP mRNA has been detected by RT-PCR and Northern analysis (34). Bombesin and GRP protein have also been found in goldfish pituitaries, where bombesin increases the secretion of GH and the gonadotropin GtH-II (35). In rat APs GRP has also been localized by immunocytochemistry to the corticotrophs and lactotrophs (36). Binding sites for bombesin are present in rat AP, primarily on somatotrophs and lactotrophs (37).

Physiological activity of endogenous GRP. A number of recent observations are helping to delineate the physiology of this peptide. GRP is reported to inhibit basal and TRH-stimulated secretion of TSH in rat hemipituitaries; perhaps more significantly, treatment of the same tissue with GRP antagonists increases secretion of TSH, consistent with a role for endogenous local GRP (38). The related peptide neuromedin B appears to play a similar role (*Section II.T*, below).

F. Brain-derived neurotrophic factor (BDNF)

mRNA for BDNF and for trkB, a protein associated with its receptor, have been detected in rat AP by Northern anal-

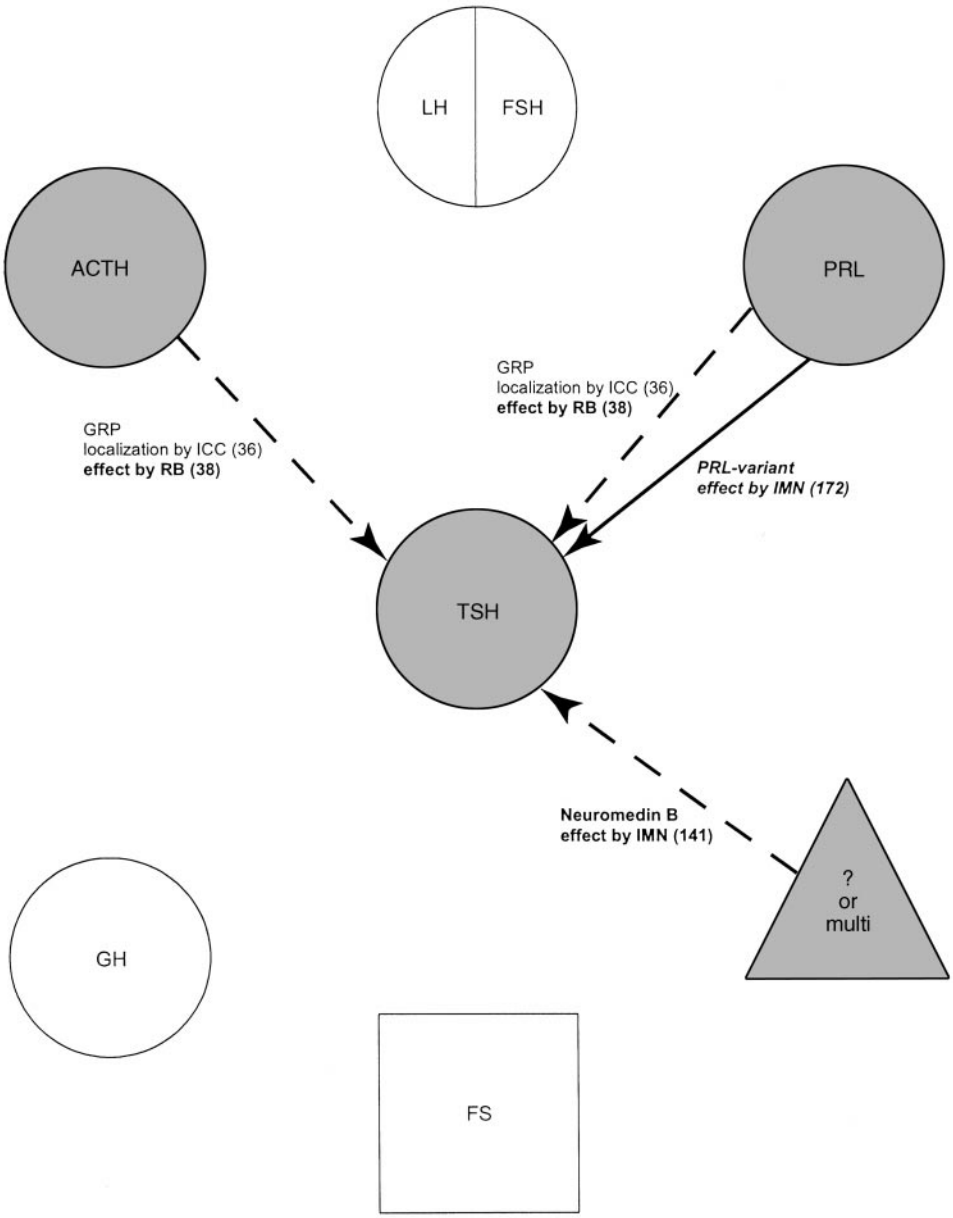

FIG. 5. Direct and corroborating evidence for some interactions involving thyrotrophs as the target cells for intrapituitary factors. See legend to Fig. 1.

ysis and *in situ* hybridization (39). Further studies have noted decreases in expression levels of trkB mRNA with aging (40) and increases in levels of BDNF mRNA in AP cells after stress of the animals (41). Immunocytochemical methods have been used to identify BDNF protein in pituitary cells and colocalize it with TSH (42, 43). The biological role of intrapituitary BDNF remains undelineated, although, given the role played by BDNF in development, it may be quite important.

G. Calcitonin gene-related peptide (CGRP)

CGRP immunoreactivity is present in AP cells (44, 45). More recently, attention has shifted to the actions of CGRP on pituitary cells. Some significant observations are those of stimulatory activity on ACTH (46) and interleukin-6 (IL-6) (47). Given the action of IL-6 itself on ACTH secretion (reviewed in Refs. 1 and 48), these observations may indicate the existence of a potentially very complex system, involving CGRP and interleukins, that influences ACTH secretion.

H. Eicosanoids

Defining the potential role of metabolites of arachidonic acid (eicosanoids) as intercellular signals is somewhat problematic. These molecules clearly act as *intra*cellular signals and it is difficult to distinguish *inter- vs. intra*cellular actions of the eicosanoids in AP cells. Indirect evidence for intercellular interactions of eicosanoids generally takes the form of an effect by a particular eicosanoid, exogenously added, at a concentration at which the compound has been observed to be present among AP cells in the same or similar *in vitro* conditions. One relevant question in such cases is whether the observed concentration is physiological or an artifact of the experimental system. Another problem in ascribing

*inter*cellular actions to eicosanoids is the difficulty of studying the effect of blockade of the actions of extracellular eicosanoids. Experiments in which the local biosynthesis of various metabolites of arachidonic acid is blocked have proven useful in studying the AP actions of eicosanoids. However, the most parsimonious interpretation of such data must be to ascribe the action of the inhibited eicosanoid to an *intra*cellular role. With this as a guideline, a number of observations on the activity of eicosanoids on AP cells will be described, as they may suggest involvement in intercellular actions.

A number of unidentified intercellular factors influence corticotrophs (1). Given the range of actions of metabolites of arachidonic acid in the AP, eicosanoids may play an intercellular role. Early studies with inhibitors of the various metabolic pathways suggested that lipoxygenase-generated metabolites stimulate, and cyclooxygenase products inhibit, ACTH secretion (49, 50). More recent studies suggest that metabolites of C_{450} enzymes also stimulate ACTH secretion (51).

Eicosanoids also alter the function of gonadotrophs. In the gonadotroph cell line αT3–1, treatment with arachidonic acid, 5-HETE, or leukotriene C_4 increases the levels of LH α-subunit mRNA, suggesting a stimulatory action (52).

I. Endothelins (ETs)

The ET family of peptides, including ET-1, ET-2, and ET-3, has been found to be produced and likely to act within the AP, primarily as an inhibitor of lactotrophs. Studies with reverse hemolytic plaque assays have demonstrated that lactotrophs also secrete ETs (53). A study that has updated these observations has provided further intriguing results, suggestive of multiple molecular interactions (54). ET-1 and ET-3 were observed to decrease PRL secretion by rat AP cells cultured in serum-supplemented medium. Similarly, at relatively low concentrations, the ETs decreased PRL secretion in cells cultured in serum-free medium. However, in cells cultured in serum-free conditions ET-1 and ET-3 *stimulated* PRL secretion, when present at relatively high concentrations. As noted in the *Introduction*, the changes in response of AP cells as a function of the concentration of ETs and the presence of serum factors may be highly relevant in terms of how the AP responds *in vivo*. Further elucidation of the interactions of the various factors involved in the responses to ETs will define their role in secretion of PRL.

Physiological activity of endogenous ET. One of the most elegant demonstrations of a likely physiological action of ETs within the AP is described in a recent study (53). As previously noted, the investigators were able to demonstrate secretion of immunoreactive ET-1 by AP with a plaque assay. An inhibitory effect of endogenous ET on PRL secretion was also demonstrated by increases in PRL in response to pharmacological blockade of ET_A, but not ET_B, receptors and by inhibition of local ET-convertase enzyme.

J. Epidermal growth factor (EGF)

As with many of the peptides termed growth factors, EGF was characterized chemically, and the actions of the peptide were first described several years ago. Since the discovery of evidence of its biosynthesis in pituitary cells, a measure of attention has been paid to potential activity of EGF within the pituitary. There is now abundant evidence of regulated production of EGF and its receptors in AP cells. The demonstrated actions of EGF on AP cells are consistent with the presence of both a direct role of EGF on secretory cells and an indirect role in which EGF influences the response of secretory cells to other factors. The demonstrated direct actions of EGF range from altering secretion rates of hormones to stimulation of mitosis and differentiation of cells. This subsection will describe the latest findings on the control of EGF in the AP and its role in the physiology of the AP.

All the components necessary for a local EGF system, including expression of mRNA and protein for EGF and EGF receptors, have been detected in the AP. EGF has been shown to be secreted by about 20% of AP cells (55–57). In lactating rats, a distribution has been described, wherein a substantial fraction of all secretory cells also secrete EGF (PRL, 27%; GH, 20%; LH, 18%; FSH, 14%; TSH, 14%; ACTH, 5%) (56). In contrast, in immature rats, the majority of EGF-secreting cells are LH-positive (57). Other groups have reported EGF mRNA in adult male rat AP in GH- and gonadotropin-positive cells (58), and EGF protein in all cell types in human pituitaries (59).

Receptors for EGF are also present on many AP cells. EGF receptors have been reported to be present on 48% of AP cells (55). In male rat AP, the distribution of cells with receptors for EGF apparently extends to subsets of all the secretory cells (58) and varies in female rats as a function of the estrous cycle (60). High and low affinity binding of radiolabeled EGF can be demonstrated in AP cells (61).

The synthesis and secretion of EGF and the functional expression of its receptors are subject to dynamic regulation. As noted above, EGF receptor populations vary with the estrous cycle (60). Other physiological changes also alter the pituitary EGF system. Exposure of adult male rats to cold stress or restraint stress, but not ether stress, increases levels of EGF mRNA in the pituitary (58, 62). In immature female rat AP cells, GnRH is reported to increase the amount of EGF secreted per cell (57). In sheep pituitary cells, exposure to any of the following: estrogen, T_3, cortisol, EGF itself, basic fibroblast growth factor (bFGF), transforming growth factor (TGF)-β, or phorbol ester, increases the affinity and decreases both the binding capacity for EGF and mRNA of the high-affinity EGF receptor (61). Estradiol can decrease the fraction of gonadotrophs with EGF receptors (63). Further evidence that EGF itself plays a role in regulating EGF receptors in FSH-expressing cells comes from studies with serum-supplemented incubation medium. While serum supplementation is associated with increases in the numbers of LH- and FSH-positive cells with EGF receptors, removal of serum or immunoneutralization of EGF in the serum will prevent the increase in FSH-positive cells with EGF receptors (63).

A number of actions of EGF on pituitary cells have been characterized. In rat AP cells, EGF increases the presence of receptors for GnRH and the LH-secretory response (64). Evidence that local EGF is responsible comes from the observation that the same effect can be caused by adding AP

TABLE 1. Factors that are potential paracrine signals in the AP

Factor	Action	Species/cell line	Reference
α-MSH	Increase PRL secretion; Ca^{++} entry (subset of lactotrophs)	Rat	13
α-Subunit	Stimulate differentiation of lactotrophs	Rat (fetal)	17
		Mouse (TG: gonadotroph-deficient)	20
	Increase PRL secretion	Bullfrog	19
		Rat	17
Activin	Increase number of cells secreting FSH, amount FSH/cell; Decreased number of cells secreting PRL, amount of PRL	Rat	22
Adenosine	Increase PRL; decrease FSH secretion	Rat	32
	Increase PRL; decrease LH, FSH secretion	Rat	33
ATP	Increase Ca^{++} entry; LH secretion	Rat	26
	Increase LH secretion	Rat	27
	Close ATP-sensitive K^+ channels	Rat	30
	Increase PRL secretion	Rat	25
Bombesin	Increase GH, GtH-II secretion	Goldfish	35
CGRP	Increase ACTH secretion	Rat	46
	Increase IL-6 synthesis	Rat	47
ETs	Decrease PRL secretion	Rat	53
ET1, ET3	Increase/decrease PRL secretion	Rat	54
EGF	Increase EGF receptors in gonadotrophs	Rat	63
	Increase TSH secretion	Rat	65
	Increase PRL synthesis and secretion	GH_4	66
	Increase expression of dopamine D_2 receptors	GH_4	67
	Increase adenosine A_1 receptors	GH_4	68
	Decrease TRH receptor mRNA	GH_4	69
	Increase BrDU uptake: corticotrophs	Rat	70
	Increase thymidine uptake: gonadotrophs	Sheep	71
	Increase GnRH binding, LH response to GnRH	Rat	64
	Increase number of cells, fraction secreting PRL only, PRL secretion	GH_3	72
Follistatin	Expression linked to attenuated FSH response to GnRH	Rat	76
Galanin	Increase PRL secretion and mitosis	235–1	79
	Increase GH secretion	Mouse (TG: hGHRH+)	79
	Increase PRL secretion	Rat	11,85
	Lactotroph hyperplasia	Mouse *in vivo* (TG: galanin KO)	88
		(TG: galanin + PRL promoter)	87
	Decrease ACTH secretion	Rat	77
GnRH	Increase differentiation: gonadotrophs, thyrotrophs	Rat (fetal day 11)	18
	Increase differentiation: lactotrophs	Rat (fetal day 12)	94
		(neonate)	168
GH	Increase LH, FSH secretion; Decrease FSHβ, LHβ, mRNA, FSH protein response to GnRH	Mouse *in vivo*, *in vitro* (TG: bGH+)	97
GRP	Decrease TSH secretion	Rat	38
5-HETE	Increase α-subunit mRNA	αT3-1	52
IGF-I	Decrease GH secretion	Sheep *in vivo*	111
	Increase BrDU uptake: corticotrophs, lactotrophs	Mouse	99,109
	Increase VIP synthesis, secretion, PRL secretion	Rat	112
	Inhibit apoptosis	Tilapia	101
	Increase GtH-II synthesis, secretion	Eel (juvenile)	114
IL-II	Increase ACTH secretion, POMC mRNA	AtT_{20}	120
LIF	Increase ACTH synthesis, secretion; POMC mRNA	AtT_{20}	124
	Increase ACTH secretion	Human (fetal)	124
		Sheep	125

TABLE 1. *Continued*

Factor	Action	Species/cell line	Reference
NGF	Decrease proliferation, GH secretion; increase PRL secretion, D_2 receptors	GH_3	139
	Increase thymidine uptake: lactotrophs, corticotrophs, lactotrophs	Rat (neonate)	140
			138
Neuromedin B	Decrease TSH secretion	Rat	141
NO	Increase LH secretion	Rat	143
	Increase/decrease PRL secretion	Rat	147, 148
NPY	Increase number of FSH-positive cells	Hamster	162
	Increase FSH secretion	Rat	158
	Increase LH secretion	Rat	154–158
	Increase GH, Gt-II secretion	Goldfish	159–161
	Decrease LH secretion	Rat	155
	Decrease PRL secretion	Rat	164
POMC (27–52)	Decrease PRL secretion	Rat	166
POMC (1–74)	Increase thymidine uptake in lactotrophs	Rat	16, 169
PRL	Increase proliferation	GH_3	171
PRL (cleaved variant)	Increase thymidine uptake in gonadotrophs, thyrotrophs	Rat (neonate)	172
SP	Increase LH secretion	Rat	183, 177
	Attenuate LH, FSH responses to GnRH	Hamster	180
TGF-α	Increase lactotroph proliferation	Mouse *in vivo* (TG: hTGF-α + PRL promoter)	192
TGF-β	Decrease PRL synthesis, secretion	Rat	186, 195–197
TRH	Increase thyrotroph, somatotroph proliferation	Rat *in vivo*	200
	Increase thyrotroph, gonadotroph, lactotroph differentiation	Rat (fetal day 11)	201
	Increase VIP activity	Rat	209
VIP	Increase galanin secretion	Rat	85

This table summarizes many of the most recent reports of the actions of the factors, specifying the type of AP tissue in which the observations were made and citing the specific reports. Species abbreviations: TG, transgenic, + indicates insertion of the gene preceded by the symbol (if the inserted gene is targeted to specific AP tissue, the promoter to which it was linked follows the symbol); KO, knock out of the preceding gene. Unless indicated as *in vivo*, all cited experiments were performed *in vitro* on cell lines or pituitary tissue. Note that where a factor may be of local or extrapituitary origin, the table includes only studies that are likely to reflect the actions of locally produced factors.

cell-conditioned medium to a second population of AP cells, and that this effect is eliminated by specific immunoprecipitation of EGF from the conditioned medium. EGF stimulates TSH secretion by fragments of rat pituitary (65). In the cell line GH_4, which secretes PRL and very much less GH, EGF increases synthesis and secretion of PRL (66). Interestingly, in the same cell line EGF also induces the functional expression of dopamine D_2 receptors, which they normally lack, and these receptors are active in terms of coupling to potassium channels (67). In other experiments with GH_4 cells, EGF increases adenosine A_1 receptors and mRNA for TRH receptors (68, 69).

Other reported actions of EGF in the pituitary are related to growth and differentiation. In an enriched population of corticotrophs from male rats, EGF increases uptake of bromodeoxyuridine (BrDU) (70). After a 1-h exposure to CRH and EGF, 47% of corticotrophs are BrDU positive. In sheep pituitary cells, treatment with EGF increases the uptake of radiolabeled thymidine, with the majority of labeled cells being gonadotrophs or cells that did not stain for any of the pituitary hormones (71). Exposure of GH_3 cells, which secrete both PRL and GH, to EGF for 6 days in culture increases the fraction of the cells that exclusively secrete PRL from 0.5 to 8.0% (72). Similar changes occur when normal rat AP cells are cultured 2 days with EGF; in addition, PRL secretion is increased in these cells (72).

Physiological activity of endogenous EGF. As noted above, at least one of the recently described actions of EGF can be associated with endogenous local peptide. The action of EGF on the response of AP cells to GnRH can be eliminated by immunoprecipitating EGF from the AP cell-conditioned medium (64).

TABLE 2. Involvement of the various types of AP cells in intrapituitary interactions

Factor	Source					Target					Species/cell line	Reference
	G	L	S	C	T	G	L	S	C	T		
α-MSH							L				Rat	13, 14
α-Subunit							L				Bullfrog	19
											Rat	17
Activin	G		S		T						*Xenopus*	24
						G	L				Rat	22
Adenosine						G	L				Rat	32
							L				Rat	33
ATP						G					Rat	26, 27
							L				Rat	25
BDNF					T						Rat	42, 43
Bombesin							Lb	Sb			Rat	37
						G		S			Goldfish	35
CGRP									C		Rat	46
							Folliculostellate cells				Mice	117
ETs		L					L				Rat	253
							L				Rat	54
EGF	G	L	S	C	T						Rat (lactating)	56
											Human	59
	G										Rat (immature female)	57
	G		S			Gb	Lb	Sb	Cb	Tb	Rat (adult male)	58
						G					Sheep	71
											Rat	64
						Gb					Rat	63
EGF										T	Rat	65
							L				GH_3	72
											GH_4	66, 67
									C		Rat	70
							L				Rat (neonatal)	72
Galanin		Ls					L				Rat	11, 85
		L		C							Rat	77
								S			Mouse (TG: hGHRH+)	79
				C							Human (adenoma)	80
		L	S		T						Mouse (wt and TG: hGHRH+)	78, 79
							L				Mouse (TG: galanin + PRL promoter)	87
											(TG: galanin KO)	88
GnRH						G				Ti	Rat (fetal day 11)	18
		Rathke's pouch									Rat (fetal day 12)	94
	G										Human	91, 92
GH						G					Mouse (TG: bGH+)	97
						G	L				Mouse (TG: hGH variant B+)	98
						Gb		Sb			Rat	96
						Gb	Lb	Sb			Human	95
GRP										T	Rat	38
		L		C							Rat	36
5-HETE						G					αT3-1	52
IGF-1			S					Sb	Cb		Mouse	99
							L		C		Mouse	99, 109
	G							S			Tilapia	101
		Folliculostellate cells									Rat	100
								S			Sheep (*in vivo*)	111
							L				Rat	112
						G					Eel	114
IL-6		Folliculostellate cells									Mouse	117

TABLE 2. *Continued*

Factor	Source					Target					Species/cell line	Reference
	G	L	S	C	T	G	L	S	C	T		
IL-II									C		AtT_{20}	120
LIF	Folliculostellate cells										Cow	121
LIF	Gs	Ls	Ss	Cs	Ts				C		Mouse	124
									C		Mouse	127
	G				T				C		Sheep	125
NGF		L									Rat	131
					T						Rat	132, 133
	Gs	Ls	Ss	Cs	Ts						Rat	134
							L				Rat	188
							L		C		Rat	140
	Nonsecreting cells										Macaque	135
Neuromedin B										T	Rat	141
NO							L				Rat	147, 148
	G	Folliculostellate				G					Rat	143
	Folliculostellate cells										Human	144
NPY						G		S			Goldfish	159–161
						G					Rat	154, 156–158
											Hamster	162
							L				Rat	164
OT							Lb				Rat	165
$POMC_{(27–52)}$							L				Rat	166
$POMC_{(1–74)}$	G						L				Rat (neonate)	16, 169
PRL						Gb	Lb	Sb	Cb	Tb	Rat	170
							L	S			GH_3	171
PRL (cleaved variant)						G				T	Rat (neonate)	172
SP			S		T						Rat	174
					T						Guinea pig	179
						G					Rat	177, 180, 183
											Hamster	180
TGF-α			S								Human	185
							L				Mouse (TG: TGF-α + PRL promoter)	192
TGF-β							L				Rat	186, 195–197
	G	L			T						Rat	187
						G					Rat	193
TGF-β		L									Rat	188
TRH	G										Rat	198
								S		T	Rat (*in vivo*)	200
						G	L			T	Rat	201
Urocortin									C		Rat	203, 204
			S								Human	202
VIP		L									Rat	206

This table summarizes many of the most recent reports of the factors according to their source and target cells within the AP, specifying the tissue in which observations were made and citing the specific reports. *Uppercase letters* in the appropriate column indicated recently published evidence that the factor in the *column on the left* is either secreted by or acts on the listed type of cell: G, gonadotroph; L, lactotroph; S, somatotroph; C, corticotroph; T, thyrotroph. Other abbreviations: If only a limited subset of a given type of AP cell is described as being the source or target for a factor, then a *lowercase s* is appended to the designating letter. In a report, if there is only evidence of potential binding of a factor to a target cell (for example, via radioreceptor binding assays or the presence of receptor mRNA or protein) but no evidence of a physiological effect on the cell, then a *lower case b* is appended to the designating letter. If an effect on a target might be indirect, possibly mediated by a second cell, then a *lowercase i* is appended to the designating letter. Species abbreviations: TG, transgenic; + indicates insertion of the gene preceded by the symbol (if the inserted gene is targeted to specific AP tissue, the promoter to which it was linked follows the symbol); KO, knock out of the preceding gene. Unless indicated as *in vivo* all cited experiments were performed *in vitro* on cell lines or pituitary tissue.

K. Follistatin

As with activin, the reader is directed to specialized reviews for broad discussions in this area (including Refs. 6–9). The present review will be limited to recent developments that add physiological perspective to the actions of follistatin in the AP. In castrated male monkeys *in vivo*, intravenous infusion of follistatin was found to inhibit the FSH response to activin, but not to GnRH, consistent with a modulatory role for follistatin acting only as an activin-binding protein (73). Along the same lines, the reduction of FSH β mRNA associated with exposure to another factor, pituitary adenylyl cyclase-activating peptide (PACAP), is also associated with increased follistatin gene expression (74). Interleukin-(IL)-1β, which was shown to stimulate follistatin secretion, was also observed to attenuate the FSH response to activin A (75). The stimulatory effect of GnRH on FSH β mRNA was studied in perifused male rat AP cells, using various pulse patterns of GnRH (76). Treatment of the cells with GnRH at a frequency of one pulse per hour stimulated FSH β mRNA and not follistatin mRNA. In contrast, when the frequency of the GnRH pulses was increased, so were the levels of follistatin mRNA, and the increase in levels of FSH β mRNA was attenuated. When treatment with follistatin was included during hourly pulse treatments with GnRH, the increase in FSH β mRNA observed earlier was blocked. Taken together, these data are consistent with activin playing a mediating role in the response to GnRH, and with endogenous follistatin being an increasingly important intrapituitary modulator of the action of GnRH on expression levels of FSH β mRNA as pulse frequency increases.

L. Galanin

In terms of its potential physiological activity, galanin is one of the better characterized paracrine factors in the pituitary. Much recent work has focused on galanin actions relative to the activity of corticotrophs and lactotrophs.

Because of the known physiological relevance of galanin, it is important to determine the pituitary cells that produce it (12). As yet, there is no clear picture of the localization of galanin in the pituitary. A number of studies have colocalized galanin with PRL in, at least, a fraction of the lactotrophs (11, 77, 78). These and other studies have reported colocalization in other cells in addition to or instead of lactotrophs. One study, employing cellular immunoblotting technology with rat AP cells, localized galanin with PRL or ACTH (77). In the normal and transgenic (human GHRF-expressing) mouse AP, immunocytochemical techniques were used to demonstrate the colocalization of galanin with GH, PRL, or TSH (78, 79). In humans galanin secretion has been measured in cultures of ACTH-secreting tumors (80). Recently, using immunocytochemical techniques, galanin also has been reported to be present in nerve fibers in monkey and canine pituitaries in close proximity to all types of secretory cells (81).

The regulation of galanin synthesis and secretion in AP cells is also an area of ongoing investigation. *In vivo* administration of the synthetic glucocorticoid dexamethasone increases galanin mRNA in rat AP (82). Pituitary cells obtained from transgenic mice that overexpress human GHRH secrete more galanin than those obtained from control mice, as demonstrated by cellular immunoblotting (79). A number of studies have also established a role for the thyroid in maintaining pituitary galanin content (83, 84). Vasoactive intestinal peptide (VIP) increases galanin secretion by pituitary cells (85). PRL has been reported to decrease levels of galanin and VIP mRNAs (86). Arguably, estrogens exert the most important influence on galanin activity in the pituitary, where estradiol positively regulates galanin-expressing cells in a number of ways, including the amount of galanin protein and mRNA in pituitaries and the number of galanin-secreting cells (85, 86).

The local pituitary action of galanin is most closely associated with the secretion of PRL. Transgenic mice that overexpress galanin have larger pituitaries (females) with a higher fraction of lactotrophs and greater expression levels of PRL mRNA per lactotroph (87). Taken one physiological step further, pituitaries of transgenic mice that do not express galanin have decreased PRL protein and mRNA, and the females do not lactate (88). In normal rat AP cells and the rat lactotroph cell line 235–1, inhibition of endogenous galanin by immunoneutralization decreases PRL secretion and the mitogenic effects of estradiol (11, 85). In the interaction between VIP and galanin, it was found that VIP increases secretion of galanin; and the attenuation of PRL secretion by immunoneutralization of VIP does not occur in populations of separated lactotrophs [indicating that VIP comes from other cells (85)].

Galanin has also been associated with secretion of GH (1). An interesting finding is that immunoneutralization of endogenous galanin decreases GH secretion from pituitary cells obtained from mice genetically engineered to express human GHRH (79).

In a study addressing the role of galanin in ACTH secretion, it was reported that treatment *in vitro* with either galanin or estradiol inhibits ACTH secretion by rat AP cells (77). In addition, immunoneutralization of galanin reverses the inhibitory action of estradiol, suggesting that endogenous galanin plays a role in mediating the effects of estrogens on ACTH secretion (77).

Locally produced galanin appears to inhibit GnRH-stimulated gonadotropin secretion in rat pituitary cells, as immunoprecipitation of endogenous galanin potentiates GnRH-stimulated LH secretion (89).

Physiological activity of endogenous galanin. The extensive studies of the actions of galanin in the AP provide strong evidence that galanin operates as an intrapituitary intercellular factor. As described above, a preponderance of evidence, including measurements of galanin protein and mRNA within AP cells and cellular immunoblotting of galanin secretion by AP cells (77), indicates that galanin is synthesized and secreted by AP cells, and the activity of galanin in the AP is tightly regulated. The potential physiological role of galanin is emphasized by the studies in which endogenous galanin was physically or functionally removed: the APs of galanin-deficient transgenic mice contain less PRL protein and mRNA, and females do not lactate (88); and in wild-type AP cells, immunoneutralization of endogenous galanin decreases PRL and GH

secretion, increases GnRH-stimulated LH secretion, and reverses the action of estrogens on ACTH (11, 77, 79, 89).

M. GnRH

Several of the hypophysiotropic releasing and inhibitory factors and hormones, originally thought to be synthesized only in the hypothalamus, have been reported to be synthesized and secreted by pituitary cells (12, 90). GnRH has been reported to be produced by AP cells, and recently GnRH mRNA was found in human pituitary tumors (91, 92).

Studies of the action of GnRH on gonadotrophs have been reviewed in depth (93). The implications of local production of these potent factors are self-evident. Among the most recent developments in the area of pituitary production of GnRH is the observation that GnRH induces differentiation of gonadotrophs and thyrotrophs among fetal rat AP cells (18). Although the effect *in vivo* may be due to hypothalamic GnRH, the uneven distribution of the cells suggests involvement of some local factors.

Physiological activity of endogenous GnRH. As evidence that local GnRH mediates actions within the AP and further to the role of GnRH in development, it is noteworthy that GnRH mRNA has been detected in extracts of Rathke's pouch of rat fetuses at 12 days of gestation by RT-PCR (94). In explants of Rathke's pouch, pharmacological blockade of GnRH receptors during culture decreases the area of PRL staining (94).

N. GH

If there is any class of compounds about which there is no doubt as to the synthesis and secretion in pituitary cells, it is the pituitary hormones. Aside from their systemic actions, recent work has been directed at delineating activity of the pituitary hormones within the pituitary. An inhibitory action of GH on somatotrophs has been known for some time. Recently, receptors for GH have been localized within the pituitary by immunocytochemistry and *in situ* hybridization to somatotrophs, lactotrophs, and gonadotrophs (95). Radiolabeled GH is taken up by somatotrophs and gonadotrophs (96).

Transgenic mice, engineered to overexpress GH, have altered pituitary function. The excess GH in these animal models is not necessarily produced in the pituitary and thus may be acting indirectly; nevertheless, the effects of elevated GH, regardless of its origin, are worth noting as they may mimic concentrations normally encountered only by AP cells adjacent to GH-secreting cells. Compared with controls, transgenic mice, expressing the bovine GH gene, produce pituitaries with less FSHβ and LHβ mRNAs, less FSH protein, higher unstimulated LH and FSH secretion in perifusion *in vitro,* and a decreased gonadotropin response to GnRH (97). Interestingly, mice expressing the human GH-variant B produce pituitaries that have a decreased rate of unstimulated PRL secretion and an increased LH-secretory response to GnRH *in vitro* (98).

O. Insulin-like growth factor-I (IGF-I)

The discovery within the AP of the biosynthesis and activity of IGFs has led to further research aimed at defining the potential role of an intrapituitary IGF system. An expanding number of observations provide evidence for multiple actions of IGFs in the APs of a variety of species. These include direct effects of IGFs on the proliferation of secretory cells and the synthesis and secretion of pituitary hormones. There are also reports of a stimulatory effect of IGF-I on VIP, which may mediate further intercellular interactions. As more becomes understood about the actions of IGFs and the control of secretion of IGF in the AP, the potential physiological roles of intrapituitary IGFs is becoming clearer. The purpose of this section is to describe recent findings on the expression and actions of IGF-I in the AP.

IGF-I is synthesized in AP cells. In mice, IGF-I protein and mRNA have been localized to somatotrophs, and IGF-I receptor mRNA has been localized to corticotrophs and somatotrophs by *in situ* hybridization (99). In rat pituitaries, IGF-I mRNA was found by *in situ* hybridization to be distributed throughout the pituitary, primarily in cells thought to be typical of folliculostellate cells (100). Interestingly, the authors of the latter study interpret the sum of the data to suggest that although some cells produce both GH and IGF-I, there is no particular correlation of IGF synthesis with somatotrophs. In the fish species *tilapia* in further contrast, IGF-I has been colocalized in cells with gonadotropin GtH-II (101).

Evidence for the synthesis of IGFs has also been found in fetal APs. In the pituitaries of fetal rats of 14–15 days gestation, IGF-II mRNA, but not IGF-I mRNA, was detected by *in situ* hybridization (102). In the fetal sheep pituitary, mRNA for IGF-II is also detectable by Northern blot analysis, and IGF-I and IGF-II protein have been detected by immunocytochemistry (103).

In terms of the regulation of expression of mRNA for IGF-I and IGF receptors, and the synthesis of the factor in the AP, several interesting findings have been reported. In rats, streptozotocin-induced diabetes increases levels of IGF-I protein and mRNA in the pituitary (104). Binding of labeled IGF-I in rat AP slices varies as a function of exposure to estrogens and or the phase of the estrous cycle although, as the authors note, this may reflect changes in IGF-binding proteins as well as receptors (105). Also, in rats *in vivo* administration of IL-1 is associated with a decrease in pituitary IGF-I content (106). Along these lines it may be noteworthy that IGF-I is also reported to decrease GH secretion (see below), and IL-I has been reported to increase GH secretion (107, 108), all of which fits a scenario in which IGF-I mediates the action of IL-1 on GH secretion.

The actions of IGFs in the pituitary are varied. IGF-I has been reported to increase the proliferation rate for corticotrophs and lactotrophs (99, 109). On the other hand, IGFs were known to inhibit GH secretion even before they were called IGFs. In this regard, the inhibitory effect of IGF-I has been shown recently to increase in terms of sensitivity between the fetal and neonatal periods in swine pituitary (110). Another study has demonstrated *in vivo* that the GH-inhibitory action of IGF-I is direct on the pituitary (111).

A recent study in rat AP cells further elucidates IGF-I actions in the pituitary (112). Three-hour incubations with IGF-I result in increases in VIP content and secretion of PRL; after 48 h, mRNA for VIP is also elevated as is PRL secretion

and content, but not PRL mRNA. In the same studies, concomitant immunoneutralization of VIP blocked the action of IGF-I on PRL, but not (inhibition of) GH, suggesting that IGF-I stimulates lactotrophs indirectly via an increase in VIP. Another illustration of potential multifactorial intrapituitary influences is in the observation that in the PRL-secreting cell line GH_4 estradiol stimulates IGF-I production, when the cells are plated at low density (10,500 cells/cm^2) but not at high density (42,000 cells/cm^2) (113).

In other species local IGF-I may play different roles. In *tilapia* pituitary cell cultures enriched in somatotrophs, local IGF-I is reported to inhibit apoptosis that would otherwise occur (101). In the AP of juvenile female eels, IGF-I stimulates the production and secretion of gonadotropin GtH-II (114).

P. Interleukin-6 (IL-6)

Intrapituitary generation and action of cytokines has been the subject of investigation for several years, and a number of cytokines have been identified as potential intercellular mediators. The actions of cytokines in the AP are also described in a number of recent reviews. Two are particularly relevant to paracrine interactions (4, 48).

This review will focus on developments concerning three cytokines, IL-6, IL-11, and leukemia inhibitory factor (LIF). Since the three cytokines have been implicated in the secretion of ACTH, thereby activating adrenal steroidogenesis, intrapituitary actions of cytokines may represent one aspect of the endocrine-immune interactions that are believed to be a key physiological regulatory mechanism (115).

IL-6 now has been detected in the APs of a number of species, including swine (116). Immunocytochemical studies in murine AP have produced evidence of IL-6 localization in folliculostellate cells (117). IL-6 mRNA has now been detected by RT-PCR, and exposure of pituitary cells to endotoxin increases both IL-6 mRNA and IL-6 secretion. IL-6 has also been found to be secreted by cells of the rat intermediate lobe, which may also contribute to local control of ACTH, if transported via the short portal vessels (118).

Regulation of IL-6 secretion by AP cells has been investigated. Exposure of AP cells to IL-1 stimulates secretion of IL-6 by pituitary cells (1), an interaction that may be important in regulating ACTH responses. Lysophosphatidylcholine, a second messenger involved in responses to IL-1, also stimulates secretion of IL-6 by rat AP cells directly (119). Other factors that might interact with cytokines involved in the secretion of ACTH include PACAP and CGRP, which stimulate IL-6 production in rat AP cells (47). CGRP also increases ACTH secretion, which raises the possibility that IL-6 mediates the action of CGRP on corticotrophs (46).

Q. Interleukin-11 (IL-11)

IL-11 has also been found to be part of an intrapituitary regulatory system (120). IL-11 mRNA has been detected in AP tissue by RT-PCR. IL-11 receptor mRNA has been found by Northern analysis in the corticotrophic cell line AtT_{20} cells as well as in normal human and murine pituitary tissue. Exogenous IL-11 increases ACTH secretion and levels of POMC mRNA in AtT_{20} cells.

R. Leukemia inhibitory factor (LIF)

Since evidence of production of LIF by pituitary cells was found several years ago (121), the potential for LIF to act locally in the pituitary has been investigated by a number of groups. In rat AP, dexamethasone down-regulates LIF mRNA (122). Subsequently, LIF and LIF receptor mRNA were found to be up-regulated by exposure of animals to endotoxin (123). Originally localized to folliculostellate cells in bovine AP (121), LIF has been localized in later studies to subsets of all secretory cells in human fetal AP (124) or to gonadotrophs and thyrotrophs in ovine AP (125).

Physiological activity of endogenous LIF. LIF stimulates ACTH secretion by AtT_{20} and normal ovine pituitary cells (124, 125), and ACTH secretion *in vitro* is decreased under certain conditions by immunoneutralization of endogenous LIF (124, 125). Physiological relevance has been added to the actions of LIF by experiments in which an attenuated hormonal response to stress or IL-1 has been observed in genetically LIF-deficient mice (126–128). In contrast, transgenic mice that overexpress LIF in the AP have retarded development of the AP and increased numbers of corticotrophs (129).

S. Nerve growth factor (NGF)

The study of the physiology of NGF has been expanded by assessing its biosynthesis and actions within the AP. There is an accumulating body of literature describing the localization and regulation of NGF expression within the pituitary as well as its actions and potential roles.

NGF is produced in and secreted by cells of the AP. Immunoreactive and bioactive NGF has been measured in medium exposed to pituitary cells (130), and NGF mRNA has been detected in pituitary cells (42). Some investigators have reported colocalization of NGF with PRL (131). Others have reported colocalization with TSH (132), an association that persists in pituitary cells in culture (133). Another group (134) has found a broader distribution of NGF immunoreactivity (10% of corticotrophs, 64% of thyrotrophs, 75% of LH gonadotrophs, 51% of somatotrophs, and 42% of lactotrophs), while a fourth group (135) using adult male macaque pituitaries and acknowledging the presence of NGF in the pars distalis, reported colocalization in cells that stain negatively for the six pituitary hormones.

Secretion of NGF appears to be influenced by numerous factors. In rat AP cells in culture, IL-1β was reported to stimulate, and GHRF, tumor necrosis factor-α, and bFGF to inhibit, NGF secretion (130). Pituitaries from hyperthyroid rats have been observed to contain more NGF than those of control rats (136).

It is very likely that NGF acts physiologically on pituitary cells also. Receptors for NGF and NGF receptor mRNA have been found in pituitary cells. *In situ* hybridization studies have shown the low-affinity neutrophin receptor p75 mRNA in the developing rat AP, with a positive signal in all cells of Rathke's pouch at day 13 of gestation and in declining numbers thereafter (137). Similarly, in the monkey, pituitary cells with NGF and NGF receptor (p75) are more numerous in fetal than postnatal life (135).

NGF receptor immunoreactivity was found in postnatal

rat pituitaries (134). Consistent with the studies cited above, these investigators observed no p75 NGF receptor, but, significantly, did detect the high-affinity, physiological NGF receptor gp140trkA, localized to corticotrophs (33%), thyrotrophs (45%), gonadotrophs (44%), somatotrophs (23%), and lactotrophs (41%).

Studies have provided evidence that NGF plays a key role in mitosis and differentiation of AP cells, which is relevant to the appearance of NGF and its receptor in fetal life. One series of studies has provided evidence that NGF is involved in the differentiation of cells into lactotrophs. NGF increases, and immunoneutralization of endogenous NGF decreases, the proportion of lactotrophs in cultured neonatal rat pituitary cells (138). NGF also inhibits proliferation of GH_3 cells, while increasing PRL secretion, decreasing GH secretion, and causing the lactotroph-specific D_2 dopamine receptor to be expressed (139). Another study has demonstrated an increase in mitotic activity in neonatal rat pituitary reaggregates *in vitro* by lactotrophs and other cells in response to NGF (140).

T. Neuromedin B

This peptide belongs to the bombesin/GRP family. It is synthesized in AP cells (34). Neuromedin B inhibits secretion of TSH, when added exogenously *in vitro*, whereas immunoneutralization of locally produced neuromedin B increases TSH secretion (141). Similar experiments and results have been described for GRP (see *Section II.E*). As a part of studies to establish the local role of neuromedin B, recent experiments have demonstrated in rats that fasting is associated with decreased, and diabetes associated with increased, levels of neuromedin B in the pituitary (142).

U. Nitric oxide (NO)

Since the discovery of NO as a signal molecule, efforts have been directed at assessing its potential as a local mediator in the pituitary. Because of the short half-life of NO, the presence of the enzyme nitric oxide synthase (NOS) has been used to localize the site of synthesis of NO. Numerous studies have provided evidence for the presence of NOS in pituitary cells. Gonadotrophs and folliculostellate cells have been reported to contain NOS (143). The neuronal isoform of NOS and its mRNA were found in pituitary adenomas and in lower quantities in normal human pituitaries, localized by immunocytochemistry and *in situ* hybridization to secretory as well as folliculostellate cells (144, 145). The endothelial isoform of NOS was also detected in human pituitaries (144).

The presence and activity of NOS in the AP is also subject to extrapituitary influence. In cultures of rat AP cells, interferon (IFN)-γ increases the number of cells with identifiable quantities of the inducible isoform of NOS (146). Morphological criteria and experiments with separated populations of cells are consistent with the NOS-containing cells being a subpopulation of folliculostellate cells and some nonhormone-secreting cells (146). IFN also increases NO production as measured by increases in the concentration of nitrates in the incubation media (146).

Additional actions of NO in the pituitary have been studied by measuring changes associated with the addition of NO, NO donor molecules, or inhibitors of NOS (12). Among recent reports, blockade of NO synthesis was demonstrated to potentiate the LH-secretory response to GnRH (143). Interestingly, in these studies the NOS inhibitor *N*-methyl-l-arginine had no effect on LH in the absence of GnRH. This suggests that NO may play a role as a signal to terminate release of LH in response to GnRH, and that the NO involved in LH secretion either originates in gonadotrophs or requires the participation of gonadotrophs. NO may also influence secretion of PRL, although there are inconsistencies in some results. In two similar studies with rat hemipituitaries or dissociated AP cells, and treatments with NO donor molecules, NOS inhibitors, or the NO scavenger hemoglobin, the results were internally consistent for endogenous NO either to stimulate (147) or inhibit (148) secretion of PRL.

V. Neuropeptide Y (NPY)

NPY is another substance that is synthesized within the AP and has been shown to alter the function of pituitary cells. NPY protein and NPY mRNA are present in cells of the AP, and studies have extended the identification to human pituitary cells (149). From studies in rats it is known that the activity of NPY varies as a function of the estrous cycle, and expression levels also change according to the steroid environment (150). Compared with the pituitaries of immature female rats receiving estradiol only for 2 days, those of female rats that received an additional injection of progesterone on the third day have elevated NPY protein and the same levels of NPY mRNA (150). Thyroidectomy is also associated with increased NPY protein and mRNA (151). Measurable quantities of binding sites for NPY are present in human AP (152) as is NPY-Y1 receptor mRNA in sheep (153).

Other work in the past 7–8 yr has more fully defined the actions of NPY in the pituitary, although it is worth bearing in mind that these actions might not reflect the physiological actions of locally produced NPY, since NPY from the hypothalamus reaches the AP as well. Most studies on the effect of NPY on LH secretion are consistent with NPY having no effect by itself, but a potentiating action on the LH-secretory response to GnRH (154–157). On the other hand, some studies have demonstrated stimulation of secretion of gonadotropin in response to NPY alone. In rat AP cells, LH secretion was reported to be stimulated by NPY at 10^{-6} M (158). Interestingly, effects in AP cells at high concentration are more likely to reflect actions of locally produced NPY on cells adjacent to the source cells, rather than NPY from the hypothalamus, which is subject to dilution in the blood. In goldfish pituitaries NPY (at nanomolar concentrations) stimulates gonadotropin II (GtH-II) secretion, an action that is potentiated in pituitaries from sexually immature fish by prior *in vivo* treatment with testosterone or estradiol (159–161). In terms of potentiation of the LH-secretory action of GnRH, the action of NPY was found to be prevented by inhibition of protein kinase C (154). In contrast, NPY was also found to *attenuate* the action of progesterone plus GnRH on LH secretion from rat pituitaries obtained at metestrus (155).

NPY also has a positive effect on FSH. In autotransplanted neonatal hamster pituitaries 7 days post surgery, the number

of FSH-immunopositive cells is higher in glands from host animals that had been pulse-infused with NPY plus GnRH than from hosts that had been infused with either peptide alone or saline (162). NPY was also reported to potentiate the FSH-secretory action of GnRH in rat pituitary cell cultures (158). One potential mechanism by which NPY might potentiate the action of GnRH on gonadotrophs is by increasing the number of functional GnRH receptors (163).

NPY also stimulates GH secretion, as reported in studies with goldfish (159–161). PRL secretion is also influenced by NPY. The peptide inhibits PRL secretion and attenuates both the PRL-secretory and intracellular calcium flux responses to TRH in rat AP cells (164).

W. Oxytocin

More than a decade ago this peptide was discovered to be synthesized in the pituitary; among its actions are stimulation of secretion of PRL and LH. In recent years, oxytocin receptor mRNA has been localized to lactotrophs (165). This reinforces the concept that oxytocin of hypothalamic or local origin acts on the pituitary via specific receptors; it also suggests that the action of oxytocin on LH secretion (90) involves production of another local factor secreted by lactotrophs.

X. POMC fragments

POMC, the biosynthetic precursor of ACTH, β-endorphin, and a number of other peptides, is synthesized in the AP. One fragment of POMC, α-MSH, was discussed above. A number of recent studies have focused on the actions of other segments of the POMC molecule on pituitary cells. $POMC_{(27–52)}$, originally isolated from hypothalamic extracts, was found recently to be a potent inhibitor of PRL secretion (166).

The mitogenic activity of locally produced $POMC_{(1–76)}$ on AP lactotrophs has been carefully established in a series of studies with AP cells from 14-day-old female rats, in which observations on the effects of the presence or absence of other cell types on thymidine uptake in lactotrophs led to the isolation of an active compound from medium conditioned by exposure to AP cells. In an early study with reaggregates of dissociated AP cells, enriched in gonadotrophs, it was found these latter cells secrete a factor that increases thymidine uptake into DNA of lactotrophs and corticotrophs and decreases uptake in somatotrophs (167). In the same study, it was found that mixed cultures of all AP cells also produced the factor in response to NPY or GnRH, whereas gonadotroph-deprived cultures did not (167). Similarly, GnRH increased the total area of cytoplasm and the number of cells containing PRL mRNA (168). In a subsequent study, $POMC_{(1–74)}$ was found to be the likely factor that stimulates the uptake of labeled thymidine into the DNA of lactotrophs (169). Thus, in that study it was interesting that the POMC fragment was initially isolated as an active fragment of culture medium conditioned by exposure to reaggregates of enriched gonadotrophs, rather than the cells that express POMC mRNA in adulthood, the corticotrophs. In AP cells from 14-day-old rats exogenous $POMC_{(1–76)}$ and γ_3-MSH were also found to stimulate the number of lactotrophs incorporating labeled thymidine.

Physiological activity of endogenous $POMC_{(1–76)}$. In the above cited series of studies it was established that specific immunoneutralization of endogenous $POMC_{(1–76)}$ decreased thymidine uptake in lactotrophs of mixed cultures of AP cells (16).

Y. PRL

The full range of local actions of PRL within the AP are only beginning to be understood. Receptors for PRL have been detected by immunocytochemistry on all types of pituitary cells, with the highest frequency of labeling being associated with somatotrophs (170). GH_3 cells are a cell line that secretes both PRL and GH. Exogenous PRL increases the rate of proliferation, and immunoneutralization of endogenous PRL decreases the rate of proliferation of GH_3 cells in culture, suggesting a physiological role for endogenous PRL (171).

Physiological activity of endogenous PRL variant. A cleaved variant of PRL was reported to be mitogenic in rat AP cells (172). Immunoneutralization of the endogenous PRL variant decreases uptake of labeled thymidine into the DNA of gonadotrophs and thyrotrophs in reaggregates of pituitary cells of 14-day-old rats (172).

Z. Substance P (SP) and neurokinin A (NKA)

The synthesis by AP cells of SP, a tachykinin, has been known since at least 1982 (173). Consideration of its role as a local factor in the pituitary has been enhanced by studies that demonstrated its secretion by pituitary cells (174). SP is a good molecule to use as a model for local activity. It is secreted by a number of different pituitary cells, it acts on a number of different cells, its secretion is subject to regulation, and pharmacological blockade of endogenous SP has a measurable effect—all of which suggest a role for locally produced SP (174–178).

Immunocytochemical localization studies have placed SP in thyrotrophs [guinea pig (179)] or thyrotrophs and somatotrophs [rat (174)]. In rat pituitary cells, it is also thyrotrophs and somatotrophs that have been demonstrated to secrete SP (174). The association with thyrotrophs assumes further relevance in light of the observation that prior thyroidectomy increases the number of SP-secreting cells and the total amount of SP secreted but decreases the average amount of SP secreted per cell (178).

The Siberian hamster, a species noted for gonadal responses to changes in photoperiod, has more SP in the AP than the rat, and the abundance of SP varies inversely with the length of photoperiod (180). Changes in SP are mirrored in those of the related peptide NKA. The latter peptide is also involved in intrapituitary interactions, as blockade of NK_2 receptors alters FSH and LH secretion, and immunoneutralization of endogenous NKA decreases secretion of gonadotropins by AP cells from Siberian hamsters (180).

SP has long been associated with secretion of GH and PRL (175). More recently, SP and VIP have been found to interact

at the level of signal transduction mechanisms in enriched populations of lactotrophs (181, 182).

Physiological activity of endogenous SP. SP also influences LH secretion, both positively and negatively, as demonstrated in rat AP cells (177, 183). The results of the more recent study suggest that the estrogen/progesterone environment is a factor in determining the action of SP on LH secretion; and effects of blockade of the SP receptors (neurokinin NK_1) by RP 67580 in the presence and absence of SP are consistent with SP acting via NK_1 receptors and endogenous local SP playing a role in influencing LH secretion (177). In pituitaries of female Siberian hamsters, blockade of NK_2 receptors, for which the presumed endogenous ligand is the related peptide NKA, results in increased secretion of FSH and an attenuated LH or FSH response to GnRH (177, 180). An intriguing consistency between the two studies with NK_1 and NK_2 receptor antagonists in rats and hamsters is the apparent dual nature of the endogenous tachykinin signal, being either stimulatory or inhibitory of gonadotropin secretion, dependent either upon the simultaneous presence of GnRH or SP. Taken together, the preponderance of evidence indicates that locally produced SP influences the secretion of gonadotropins and probably other hormones by neighboring cells.

AA. Transforming growth factors (TGFs)

These proteins were named initially for the ability to stimulate phenotypic transformation and have since been found to act positively and negatively on cellular growth and transformation. Thus, a number of studies have focused on potential actions in neoplastic tissues. In addition, an ever expanding repertoire of actions is being described for these factors in neoplastic and normal AP cells, suggesting potential activity.

TGFα, previously found in, and determined to be secreted by, bovine AP cells (184), was recently found in human pituitary somatotrophs (185). TGFα, it is worth noting, acts via EGF receptor pathways.

Evidence has been found that TGFβ is synthesized in the AP (186), with TGFβ_1 mRNA recently localized to 80% of rat lactotrophs and lesser fractions of other AP cells (187). It has been reported that 60% of TGFβ cells are lactotrophs and that treatment with estradiol *in vivo* decreases the number of TGFβ-positive cells (188). In addition to TGFs, recent studies have provided evidence for TGF receptors in pituitary. Cells of the tumor line GH_3 have receptors for TGFβ as do many human pituitary adenomas (189–191).

TGFα likely plays a role in regulation of lactotrophs. Transgenic mice that are engineered to overexpress the peptide in lactotrophs have pituitaries with increased proliferation of lactotrophs and often have prolactinomas (192).

Although first associated with FSH secretion, TGFβ can also influence secretion of PRL (193). Lactotrophs express receptors for and respond to TGFβ (194), and in rat AP cells TGFβ decreases PRL secretion by itself and in response to TRH (186, 195). Recently, it was found that the inhibition of PRL synthesis, secretion, and mRNA levels by TGFβ declines with age and occurs at physiologically relevant concentrations (196, 197). TGFβ has also been reported to stimulate labeled thymidine uptake into sheep AP cells in culture (71).

BB. TRH and prepro-TRH

The discovery of the synthesis of prepro-RH and the secretion of TRH by AP cells added a local regulatory perspective to the physiological actions of the products of prepro-TRH (1). Regulation of the synthesis and processing of prepro-TRH appears to be tightly controlled. In monolayers of cultured dissociated cells, immunoreactive TRH and mRNA for the precursor increase slowly over 3 weeks, and the increase is even slower in reaggregates of cells, suggesting a cell-cell inhibition (198). Immunocytochemical and *in situ* hybridization studies place the site of TRH synthesis in LH-positive cells, an observation that is consistent with a stimulatory effect of GnRH on TRH secretion (198). Inhibition of peptidyl amide monooxygenase, thereby blocking processing of prepro-TRH to TRH, increases levels of mRNA for the precursor (199). This observation is consistent with the presence of feedback inhibition of the gene expression by its product and the decreased rates of production of TRH, cited above, in cell aggregates.

Aside from known actions on TSH and PRL secretion, TRH influences cell division and differentiation in the pituitary. These actions may tie in with intracellular regulation of prepro-TRH gene expression. They also might be critical in development, as distribution of cell types in the pituitary is more specific than would be expected if TRH, acting as a differentiation factor, were available solely via the hypophysial portal circulation. *In vivo* TRH has a mitogenic effect on thyrotrophs and somatotrophs (200). In fetal rat pituitary cells *in vitro* it has been shown that TRH influences the differentiation of thyrotrophs, gonadotrophs, and lactotrophs (201).

CC. Urocortin

This peptide would appear to be a likely regulator of ACTH secretion. It is synthesized in abundance in human pituitary cells (primarily somatotrophs) and adenomas (202), and recent work has confirmed that it is more potent than CRH in stimulating ACTH secretion by AP cells (203, 204). Given its distribution and potency, retention within the cells in which it is synthesized would be physiologically critical, lest it flood CRH-R_1 receptors in the AP. Secretion, if it occurs, would need to be tightly regulated and this appears to be the case. One reported study *in vivo* would argue against a physiological role for urocortin in a response to stress. Immunoneutralization of urocortin during an ACTH-associated stress had a negligible effect, whereas immunoneutralization of CRH decreased the ACTH response to the same stress (205).

DD. Vasoactive intestinal peptide (VIP)

This peptide has long been characterized as a likely local factor influencing function of lactotrophs (1). A number of recent observations on the expression and actions of VIP in the pituitary are noteworthy from the perspective of delineating the physiological role of VIP. VIP mRNA has been localized to a subpopulation of lactotrophs (206). Changes in osmolality in rats *in vivo* were found to influence levels of pituitary PRL mRNA and inversely influence VIP mRNA

(207). Also *in vivo,* VIP mRNA levels in autotransplanted pituitaries were found to be inhibited by the ensuing increase of PRL (86). The PACAP/VIP receptor is the subject of a recent review (208). In rat AP cells *in vitro,* TRH increases VIP and PRL secretion (209).

Physiological activity of endogenous VIP. Pharmacological blockade of VIP receptors attenuates the PRL response to TRH, consistent with TRH acting, at least partially, via local production of VIP (209). Although, as noted above, VIP is apparently synthesized in lactotrophs, the actions of VIP on PRL secretion may involve other cells, as the effect on PRL of immunoneutralization of VIP in mixed populations of pituitary cells is lost in lactotroph-exclusive populations (85). In this regard it is worth noting that VIP increases secretion of galanin (85) and that VIP interacts with SP in lactotrophs (181, 182). Immunoneutralization of VIP also blocks the stimulation of PRL secretion by IGF-I (112).

III. Intrapituitary Interactions Involving Unidentified Factors

This unit examines intrapituitary actions of unidentified and unsubstantiated factors, according to the cells from which the factors are apparently secreted and the cells in which the actions occur.

A. Gonadotrophs

1. Gonadotrophs as source cells. Several lines of evidence suggest that gonadotrophs are a critical source of mitogenic and/or differentiation factors during development. The pituitaries of gonadotroph-deficient transgenic mice (the result of expression of diphtheria toxin in cells in which the α-subunit promoter is active) contain fewer lactotrophs than controls, implying a role for the products of gonadotrophs in the differentiation of lactotrophs (20). As noted earlier, the α-subunit itself may be the active factor here, but other gonadotroph-derived compounds may operate as well. Another line of evidence comes from observations that there is no effect of GnRH in reaggregates of 14-day-old rat lactotrophs, corticotrophs, and somatotrophs, whereas in similar reaggregates that also contain gonadotrophs, GnRH increases the number of lactotrophs and corticotrophs and decreases the number of somatotrophs labeled with radioactive thymidine (167). Similar effects are seen on PRL and GH secretion by reaggregates of lactotrophs and somatotrophs in the absence and presence of the gonadotroph cell line αT3–1 (210). Fragments of the POMC molecule, which appear to be secreted by gonadotrophs during development, may be one class of mitogenic factors (16, 169). Other, unidentified compounds are also involved. Although the effects of gonadotrophs on lactotrophs are mimicked by POMC fragments, the effects on somatotrophs and corticotrophs are not (16, 169).

Evidence for the existence of a factor secreted from gonadotrophs that may prevent apoptosis comes from studies in fish (101). Somatotrophs thrive in mixed cultures of all pituitary cells from tilapia. In contrast, somatotrophs cultured alone undergo apoptosis. The apoptosis can be prevented by treatment with medium conditioned by exposure to mixed cultures of AP cells or with IGF-I, which is a product of gonadotrophs in tilapia. It remains to be established whether IGF-I is the intrapituitary factor in the mixed cultures that prevents the apoptosis.

A number of other factors that influence pituitary cells have also been reported to be present or synthesized in gonadotrophs. Among those mentioned above are NO (NOS is present in gonadotrophs and its abundance is modulated by gonadal steroids, as it increases with gonadectomy), EGF, TGFβ, and activin β_B. C-type natriuretic peptide (CNP) is also colocalized with LH; evidence for synthesis in the pituitary comes from the presence of CNP mRNA in extracts (211).

2. Gonadotrophs as target cells. A number of excellent recent reviews cover the subject of the control of gonadotroph function; among which are those that include discussion of local factors (Ref. 90, for example). Among the most extensively characterized intrapituitary interactions are those involving activin and follistatin, full discussion of which will not be done here, since this area has been the intensive subject of several excellent recent reviews (including Refs. 5–9).

The differential distribution of morphologically distinct gonadotrophs (distribution of factors such as chromogranin and secretogranin) suggests local influences on differentiation (212). In this regard, it may be worth reexamining the potential of the so-called hypothalamic factors as intrapituitary factors. One distinction of local GnRH or TRH, as opposed to that produced by hypothalamus and distributed throughout the pituitary via the capillary beds, is the directionality of effect, which may be important in development. GnRH has recently been reported to induce differentiation of gonadotrophs in fetal pituitary cells *in vitro* (18). TRH, recently discovered to be secreted by pituitary cells, may also play a developmental role, as demonstrated by the effect of TRH on increasing the area of fetal rat AP immunologically identified as gonadotrophs *in vitro* (201).

Among the more intricate paracrine actions involving gonadotrophs is that of oxytocin-stimulated gonadotropin secretion. Since oxytocin receptor mRNA is present only in lactotrophs, the effect of oxytocin on LH secretion must involve another, as yet unidentified, intercellular interaction (165).

B. Lactotrophs

1. Lactotrophs as source cells. In addition to known factors, there are as yet unidentified paracrine factors synthesized in lactotrophs whose existence can be shown by the effects of lactotroph cells being in close proximity to target cells. For example, it was found that mean intracellular calcium and the calcium flux profiles of lactotrophs were modulated by interactions with neighboring cells. In doublets of dissociated cells (*i.e.*, two adjacent cells not completely dissociated) a greater decrease in activity of lactotrophs was noted when the accompanying cell was another lactotroph, suggesting the transmission of a signal from one lactotroph that dampens calcium oscillations in neighboring lactotrophs (213).

Lactotrophs may also produce a factor that influences gonadotrophs in response to OT (see *Section III.A.2* above).

An interesting observation in bullfrog pituitaries is that lactotrophs can synthesize and secrete the α-subunit of the glycoprotein hormones (19), the effects of which are described above. It is not known whether this observation is unique to this species or is more common.

2. Lactotrophs as target cells. As noted above, there is an element of ambiguity with regard to local factors that influence the proliferation or differentiation of lactotrophs. Gonadotroph-lactotroph interactions appear to be critical, as the pituitaries of gonadotroph-deficient transgenic mice also contain fewer lactotrophs than those of intact mice (20). The α-subunit of glycoprotein hormones and $POMC_{(1–76)}$ are believed to play a role in this effect, but other factors may also be involved. GnRH was found to increase the number of lactotrophs (168) and to induce differentiation of lactotrophs in fetal rat cells. At least part of this effect is due to locally produced GnRH, because in explants of Rathke's pouches, obtained at day 12 of gestation from rat fetuses, treatment of explants with an antagonist of GnRH decreases the area that stains immunocytochemically for PRL (94).

As noted above, lactotrophs secrete some factor that decreases calcium flux in neighboring lactotrophs (213). Another unidentified factor that influences PRL secretion may come from gonadotrophs. As determined by the behavior of cells in reaggregate culture, αT3–1 gonadotrophs secrete some factor in response to GnRH that decreases PRL secretion (210).

TRH was known to stimulate secretion of PRL before secretion of TRH by pituitary cells was discovered. Recent work has shed light on the potential physiological role of TRH on lactotroph function. In pituitary cells from intact male rats, TRH, but not angiotensin II—another potential locally acting agent, stimulates PRL; both peptides do so in AP cells from male rats that have been castrated and treated with estrogens (214).

C. Somatotrophs

1. Somatotrophs as source cells. Somatotrophs are arguably the pituitary cells for which there is the most compelling evidence that the primary systemic secretory product, in this case GH, influences the function of the secreting cell itself. The local actions of GH in the AP are only now being more fully elucidated. Similarly, there is new evidence for the synthesis of bFGF in the somatotrophs of the AP (215). Its local actions have not been elucidated but may be quite complex (2). The intrapituitary actions of GH and other factors that originate in somatotrophs are described in the first unit.

2. Somatotrophs as target cells. Several recent reviews (including Ref. 216) of the control of GH secretion contain valuable discussion of local factors that act within the AP. As described above, somatotrophs are target cells for intrapituitary interactions, and this extends to being a target for GH itself.

An as yet unidentified factor (possibly IGF-I) has the novel function of inhibiting apoptosis in tilapia somatotrophs, as described in *Section III.A.1* above (101).

Evidence for other unidentified factors from gonadotrophs that decrease thymidine uptake in somatotrophs come from studies with reaggregate cultures of pituitary cells from 14-day-old female rats, and is also covered in *Section III.A.1* above (16, 167, 169).

D. Corticotrophs

1. Corticotrophs as source cells. Recent work on potential paracrine factors from corticotrophs appears to have focused more on new properties of products already known to come from corticotrophs rather than discovery of new factors. In one such study an unidentified factor(s) from CRH-target corticotrophs, previously found to inhibit ACTH secretion in other corticotrophs, was found to suppress levels of POMC mRNA as well (217).

2. Corticotrophs as target cells. Recent reviews of the literature on the control of ACTH secretion include discussion of intrapituitary interactions; this includes a timely review on the inhibition of ACTH secretion (218). One unidentified factor that acts on corticotrophs is secreted from gonadotrophs (see *Section III.A.1* above) that increases thymidine uptake (16, 167, 169).

As with corticotrophs as source cells, most of the recent work on corticotrophs as the target of intrapituitary factors involves characterization of the actions of already identified actors, and this is described in the first unit. An intriguing exception is the recent report of CRH biosynthesis and secretion by AP cells (219), the action of which is well known, although the significance of the discovery within the AP remains to be elucidated.

E. Thyrotrophs

1. Thyrotrophs as source cells. A number of factors, which are known to alter the function of pituitary cells when added exogenously, have been found to be synthesized in thyrotrophs. These have been described above and include TGFβ, SP, galanin, and the β_B chain of activin/inhibin (21).

2. Thyrotrophs as target cells. Thyrotrophs are subject to influence in various forms by neighboring cells. Among the factors not yet identified, GnRH acts on gonadotrophs to produce a factor that induces thyrotroph differentiation (18). This factor may be TRH, because prepro-TRH mRNA has been colocalized with LH and is stimulated by GnRH (198). *In vivo* TRH has been found to have a mitogenic effect on thyrotrophs (200), and in fetal rat cells *in vitro* TRH influences differentiation of thyrotrophs as well as other cells (201). Although on this basis it is tempting to speculate that TRH from gonadotrophs plays a role in the differentiation of other pituitary cells and the proliferation of thyrotrophs, such a scenario remains to be tested.

IV. Conclusion

The identification and characterization of a growing number of intercellular interactions within the AP represents a new dimension to our understanding of the physiological function of this gland. Although likely to be of a subtle nature, these influences almost certainly temper or potentiate the responses to extrapituitary signals. For example, intra-

pituitary galanin appears to play a key role in the effect of estrogens on lactotrophs. It also seems to be part of the response of lactotrophs to VIP.

Although the contribution of any given intrapituitary interaction to the overall secretion of the pituitary hormones may seem insignificant, it may be critical in terms of the integrated physiological response. Along with the innovative approaches afforded by novel technology, recognition of such roles has likely provided the basis for many of the studies and projects described above. Aside from the simple challenge of describing exchanges of information that might occur only between adjacent cells and involve hundreds of individual molecules, attention will, no doubt, be focused in the future on assessing the real impact of these interactions on the physiology of the whole organism.

Acknowledgments

The composition of this review was assisted immeasurably by the research and editorial efforts of Ms. Peta Gil and the redaction of Dr. Cathie Coulter. The comments of Drs. Jim Rose and Michael Roberts were also most valuable.

References

1. **Schwartz J, Cherny R** 1992 Intercellular communication within the anterior pituitary influencing the secretion of hypophysial hormones. Endocr Rev 13:453–475
2. **Houben H, Denef C** 1994 Bioactive peptides in anterior pituitary cells. Peptides 15:547–582
3. **Ganong WF** 1993 Blood, pituitary, and brain renin-angiotensin systems and regulation of secretion of anterior pituitary gland. Front Neuroendocrinol 14:233–249
4. **Ray D, Melmed S** 1997 Pituitary cytokine and growth factor expression and action. Endocr Rev 18:206–228
5. **McCann SM, Kimura M, Walczewska A, Karanth S, Rettori V, Yu WH** 1998 Hypothalamic control of gonadotropin secretion by LHRH, FSHRF, NO, cytokines, and leptin. Domest Anim Endocrinol 15:333–344
6. **Phillips DJ, De Krester DM** 1998 Follistatin: a multifunctional regulatory protein. Front Neuroendocrinol 19:287–322
7. **Woodruff TK** 1998 Regulation of cellular and system function by activin. Biochem Pharmacol 55:953–963
8. **Sugino H, Sugino K, Hashimoto O, Shoji H, Makamura T** 1997 Follistatin and its role as an activin-binding protein. J Med Invest 44:1–14
9. **Knight PG** 1996 Roles of inhibins, activins, and follistatins in the female reproductive system. Front Neuroendocrinol 17:476–509
10. **Vankelecom H, Denef C** 1997 Paracrine communication in the anterior pituitary as studied in reaggregate cell cultures. Microsc Res Tech 39:150–156
11. **Cai A, Bowers RC, Moore Jr JP, Hyde JF** 1998 Function of galanin in the anterior pituitary of estrogen-treated Fischer 344 rats: autocrine and paracrine regulation of prolactin secretion. Endocrinology 139:2452–2458
12. **Schwartz J, Perez FM** 1994 Intercellular interactions in the anterior pituitary. J Endocrinol Invest 17:459–470
13. **Nunez L, Frawley LS** 1998 α-MSH potentiates the responsiveness of mammotropes by increasing calcium entry. Am J Physiol 274: E971–E977
14. **Zheng T, Villalobos C, Nusser KD, Gettys TW, Faught WJ, Castano JP, Frawley LS** 1997 Phenotypic characterisation and functional correlation of α-MSH binding to pituitary cells. Am J Physiol 272:E282–E287
15. **Morooka Y, Oomizu S, Takeuchi S, Takahashi S** 1998 Augmentation of prolactin release by α-melanocyte stimulating hormone is possibly mediated by melanocortin 3-receptors in the mouse anterior pituitary cells. Zool Sci 15:567–572
16. **Tilemans D, Ramaekers D, Andries M, Denef C** 1997 Effect of $POMC_{(1–76)}$, its C-terminal fragment γ3-MSH and anti-POMC(1–76) antibodies on DNA replication in lactotrophs in aggregate cell cultures of immature rat pituitary. J Neuroendocrinol 9:627–637
17. **Begeot M, Hemming FJ, DuBois PM** 1984 Induction of pituitary lactotrope differentiation by luteinizing hormone α subunit. Science 226:566–568
18. **Heritier AG, DuBois PM** 1994 Re-evaluation of gonadotropin-releasing hormone (GnRH) action on pituitary cell differentiation with special regard to its effect on LH and TSH cell types. J Neuroendocrinol 6:33–37
19. **Oguchi A, Tanaka S, Yamamoto K, Kikuyama S** 1996 Release of α-subunit of glycoprotein hormones from the bullfrog pituitary: possible effect of α-subunit on prolactin cell function. Gen Comp Endocrinol 102:141–146
20. **Seuntjens E, Vankelecom H, Quaegebeur A, Vande-Vijver V, Denef C** 1999 Targeted ablation of gonadotrophs in transgenic mice affects embryonic development of lactotrophs. Mol Cell Endocrinol 150:129–139
21. **Li MD, MacDonald GJ, Ford JJ** 1997 Breed differences in expression of inhibin/activin subunits in porcine anterior pituitary glands. Endocrinology 138:712–718
22. **Miyamoto S, Irahara M, Ushigoe K, Kuwahara A, Sugino H, Aono T** 1999 Effects of activin on hormone secretion by single female rat pituitary cells: analysis by cell immunoblot assay. J Endocrinol 161:375–382
23. **Wang EY, Draper LB, Lee. E, Polak A, Sluss P, Weiss J, Woodruff TK** 1999 Identification of naturally occurring follistatin complexes in human biological fluids. Biol Reprod 60:8–13
24. **Uchiyama H, Komazaki S, Asashima M, Kikuyama S** 1996 Occurrence of immunoreactive activin/inhibin βB in gonadotrophs, thyrotrophs, and somatotrophs of the *Xenopus* pituitary. Gen Comp Endocrinol 102:1–10
25. **Nunez L, Villalobos C, Frawley LS** 1997 Extracellular ATP as an autocrine/paracrine regulator of prolactin release. Am J Physiol 272:E1117–E1123
26. **Tomic M, Jobin RM, Vergara LA, Stojilkovic SS** 1996 Expression of purinergic receptor channels and their role in calcium signalling and hormone release in pituitary gonadotrophs. J Biol Chem 271: 21200–21208
27. **Chen Z-P, Kratzmeier M, Levy A, McArdle CA, Poch A, Day A, Mukhopadhyay AK, Lightman SL** 1995 Evidence for a role of pituitary ATP receptors in the regulation of pituitary function. Proc Natl Acad Sci USA 92:5219–5223
28. **Villalobos C, Alonso-Torre SR, Nunez L, Garcia-Sancho J** 1997 Functional ATP receptors in rat anterior pituitary cells. Am J Physiol 273:C1963–C1971
29. **Housley GD, Greenwood D, Bennett T, Ryan AF** 1995 Identification of a short form of the P2xR1-purinoceptor subunit produced by alternative splicing in the pituitary and cochlea. Biochem Biophys Res Commun 212:501–508
30. **Bernardi H, De Weille JR, Epelbaum J, Mourre C, Amoroso S, Slama A, Fosset M, Lazdunski M** 1993 ATP-modulated K^+ channels sensitive to antidiabetic sulfonylureas are present in adenohypophysis and are involved in growth hormone release. Proc Natl Acad Sci USA 90:1340–1344
31. **Aguilar-Bryan L, Bryan J** 1999 Molecular biology of adenosine triphosphate-sensitive potassium channels. Endocr Rev 20:101–135
32. **Yu WH, Kimura M, Walczewska A, Porter JC, McCann SM** 1998 Adenosine acts by A1 receptors to stimulate release of prolactin from anterior pituitaries *in vitro*. Proc Natl Acad Sci USA 95:7795–7798
33. **Picano-Diniz DLW, Favaretto ALV, Antunes-Rodrigues J** 1996 On the purinergic regulation of hormonal secretion from the anterior pituitary gland. Rev Bras Biol 56:369–372
34. **Houben H, Vandenbroucke A-T, Verheyden A-M, Denef C** 1993 Expression of the genes encoding bombesin-related peptides and their receptors in anterior pituitary tissue. Mol Cell Endocrinol 97:159–164
35. **Himick BA, Peter RE** 1995 Bombesin-like immunoreactivity in the forebrain and pituitary and regulation of anterior pituitary hormone release by bombesin in goldfish. Neuroendcrinology 61:365–376

36. **Houben H, Denef C** 1991 Evidence for the presence of gastrin-releasing peptide immunoreactivity in rat anterior pituitary corticotrophs and lactotrophs, AtT_{20} cells, and GH3 cells: failure to demonstrate participation in local control of hormone release. Endocrinology 128:3208–3218
37. **Houben H, Andries M, Denef C** 1994 Autoradiographic demonstration of ^{125}I-Tyr4-bombesin binding sites on rat anterior pituitary cells. Peptides 15:1289–1295
38. **Santos CV, Pazos-Moura CC, Moura EG** 1995 Effect of gastrin-related peptide (GRP) and GRP antagonists on TSH secretion from rat isolated pituitaries. Life Sci 57:911–915
39. **Kononen J, Soinila S, Persson H, Honkaniemi J, Hokfelt T, Pelto-Huikko M** 1995 Neurotrophins and their receptors in the rat pituitary gland: regulation of BDNF and trk B mRNA levels by adrenal hormones. Mol Brain Res 27:347–354
40. **Kononen J, Hokfelt T, Pelto-Huikko M** 1995 Effects of aging on the expression of neurotrophins and their receptors in the rat pituitary gland. Neuroreport 6:2429–2434
41. **Smith MA, Makino S, Kim SY, Kvetnansky R** 1995 Stress increases brain-derived neurotropic factor messenger ribonucleic acid in the hypothalamus and pituitary. Endocrinology 136:3743–3750
42. **Hopker VH, Amoureux MC, Varon S** 1997 NGF and BDNF in the anterior pituitary lobe of adult rats. J Neurosci Res 49:355–363
43. **Conner JM, Yan Q, Varon S** 1996 Distribution of brain-derived neurotrophic factor in the rat pituitary gland. Neuroreport 7:1937–1940
44. **Bloom SR, Steel JH, Gon G, Giaid A, O'Halloran DJ, Emson MA, Van Noorden S, Ghatei MA, Jones PM, Amara SG, Ishikawa H** 1992 Localization of calcitonin gene-related peptide in the rat and human pituitary gland using immunocytochemistry and *in situ* hybridization. CGRP expression during ontogeny and after endocrine manipulations. Ann NY Acad Sci 657:135–154
45. **Ju G, Liu S-J, Ma D** 1993 Calcitonin gene-related peptide and substance immunoreactive innervation of the anterior pituitary in the rat. Neuroscience 54:981–989
46. **Iino K, Oki Y, Tominaga T, Iwabuchi M, Ozawa M, Watanabe F, Yoshimi T** 1998 Stimulatory effect of calcitonin gene-related peptide on adrenocorticotropin release from rat anterior pituitary cells. J Neuroendocrinol 10:325–329
47. **Tatsuno I, Somogyvari-Vigh A, Mizuno K, Gottschall PE, Hidaka H, Arimura A** 1991 Neuropeptide regulation of interleukin-6 production from the pituitary: stimulation by pituitary adenylate cyclase activating polypeptide and calcitonin gene-related peptide. Endocrinology 129:1797–1804
48. **Spangelo BL, Gorospe WC** 1995 Role of the cytokines in the neuroendocrine-immune system axis. Front Neuroendocrinol 16:1–22
49. **Vlaskovska M, Knepel W** 1984 β-Endorphin and adrenocorticotropin release from rat adenohypophysis *in vitro*: evidence for local modulation by arachidonic acid metabolites of the cyclooxygenase and lipoxygenase pathway. Neuroendocrinology 39:334–342
50. **Abou-Samra A-B, Catt KJ, Aguilera G** 1986 Role of arachidonic acid in the regulation of adrenocorticotropin release from rat anterior pituitary cell cultures. Endocrinology 119:1427–1431
51. **Cowell AM, Flower RJ, Buckingham JC** 1991 Studies on the roles of phospholipase A2 and eicosanoids in the regulation of corticotrophin secretion by rat pituitary cells *in vitro*. J Endocrinol 130: 21–32
52. **Ben-Menahem D, Shraga-Levine Z, Limor R, Naor Z** 1994 Arachidonic acid and lipoxygenase products stimulate gonadotropin α-subunit mRNA levels in pituitary αT3–1 cell line: role in gonadotropin releasing hormone action. Biochemistry 33:12795–12799
53. **Kanyicska B, Lerant A, Freeman ME** 1998 Endothelin is an autocrine regulator of prolactin secretion. Endocrinology 139:5164–517354.
54. **Dymshitz J, Laudon M, Ben-Jonathan N** 1992 Endothelin-induced biphasic response of lactotrophs cultured under different conditions. Neuroendocrinology 55:724–729
55. **Mouihate A, Lestage J** 1995 Epidermal growth factor: a potential paracrine and autocrine system within the pituitary. Neuroreport 6:1401–1404
56. **Mouihate A, Verrier D, Lestage J** 1996 Identification of epidermal growth factor-secreting cells in the anterior pituitary of lactating female rats. J Endocrinol 148:319–324
57. **Mouite A, Verrier D, Lestage J** 1996 EGF release by rat gonadotroph cells: characteristics and effects of LHRH. Life Sci 58:107–114
58. **Fan X, Childs GV** 1995 Epidermal growth factor and transforming growth factor-α messenger ribonucleic acids and their receptors in the rat anterior pituitary: localization and regulation. Endocrinology 136:2284–2293
59. **LeRiche VK, Asa SL, Ezzat S** 1996 Epidermal growth factor and its receptor (EGF-R) in human pituitary adenomas: EGF-R correlates with tumor aggressiveness. J Clin Endocrinol Metab 81:656–662
60. **Armstrong J, Childs GV** 1997 Changes in expression of epidermal growth factor receptors by anterior pituitary cells during the estrous cycle: cyclic expression by gonadotropes. Endocrinology 138: 1903–1908
61. **Chaidarun SS, Eggo MC, Stewart PM, Sheppard MC** 1994 Modulation of epidermal growth factor binding and receptor gene expression by hormones and growth factors in sheep pituitary cells. J Endocrinol 143:489–496
62. **Fan X, Nagle GT, Collins TJ, Childs GV** 1995 Differential regulation of epidermal growth factor and transforming growth factor-α messenger ribonucleic acid in the rat anterior pituitary and hypothalamus induced by stresses. Endocrinology 136:873–880
63. **Armstrong JL, Childs GV** 1997 Regulation of expression of epidermal growth factor receptors in gonadotropes by epidermal growth factor and estradiol: studies in cycling female rats. Endocrinology 138:5434–5441
64. **Leblanc P, L'Heritier A, Kordon C** 1997 Cryptic gonadotropin-releasing hormone receptors of rat pituitary cells in culture are unmasked by epidermal growth factor. Endocrinology 138:574–579
65. **Altschuler LR, Parisi MN, Cageao LF, Chiocchio SR, Fernandez-Pol JA, Zaninovich AA** 1993 Epidermal growth factor stimulates thyrotropin secretion in the rat. Neuroendocrinology 57:23–27
66. **Aanestad M, Rotnes JS, Torjesen PA, Haug E, Sand O, Bjoro T** 1993 Epidermal growth factor stimulates the prolactin synthesis and secretion in rat pituitary cells in culture (GH4C1 cells) by increasing the intracellular concentration of free calcium. Acta Endocrinol (Copenh) 128:361–366
67. **Gardette R, Rasolonjanahary R, Kordon C, Enjalbert A** 1994 Epidermal growth factor treatment induces D2 dopamine receptors functionally coupled to delayed outward potassium current (IK) in GH4C1 anterior pituitary cells. Neuroendocrinology 59:1–9
68. **Navarro A, Zapata R, Canela EI, Mallol J, Lluis C, Franco R** 1999 Epidermal growth factor (EGF)-induced up-regulation and agonist- and antagonist-induced desensitization and internalization of A1 adenosine receptors in a pituitary-derived cell line. Brain Res 816:47–57
69. **Monden T, Yamada M, Konaka S, Satoh T, Ezawa H, Iwasaki T, Mori M** 1995 Transcriptional down-regulation by epidermal growth factor of TRH receptor mRNA in rat pituitary cells. J Mol Endocrinol 15:73–79
70. **Childs GV, Rougeau D, Unabia G** 1995 Corticotropin-releasing hormone and epidermal growth factor: mitogens for anterior pituitary corticotropes. Endocrinology 136:1595–1602
71. **Chaidarun SS, Eggo MC, Stewart PM, Barber PC, Sheppard MC** 1994 Role of growth factors and estrogen as modulators of growth, differentiation, and expression of gonadotropin subunit genes in primary cultured sheep pituitary cells. Endocrinology 134:935–944
72. **Felix R, Meza U, Cota G** 1995 Induction of classical lactotropes by epidermal growth factor in rat pituitary cell cultures. Endocrinology 136:939–946
73. **Merrigiola MC, Dahl KD, Mather JP, Bremner WJ** 1994 Follistatin decreases activin-stimulated FSH secretion with no effect on GnRH-stimulated FSH secretion in prepubertal male monkeys. Endocrinology 134:1967–1970
74. **Winters SJ, Dalkin AC, Tsuji T** 1997 Evidence that pituitary adenylate cyclase activating polypeptide suppresses follicle-stimulating hormone-β messenger ribonucleic acid levels by stimulating follistatin gene transcription. Endocrinology 138:4324–4329
75. **Bilezikjian LM, Turnbull AV, Corrigan AZ, Blount AL, Rivier CL, Vale WW** 1998 Interleukin -Iβ regulates pituitary follistatin and inhibin/activin β_B mRNA levels and attenuates FSH secretion in response to activin A. Endocrinology 139:3361–3364

76. **Besecke LM, Guendner MJ, Schneyer AL, Bauer-Dantoin AC, Jameson JL, Weiss J** 1996 Gonadotropin-releasing hormone regulates follicle-stimulating-hormone-β gene expression through an activin/follistatin autocrine or paracrine loop. Endocrinology 137: 3667–3673
77. **Cimini V** 1996 Galanin inhibits ACTH release *in vitro* and can be demonstrated immunocytochemically in dispersed corticotrophs. Exp Cell Res 228:212–215
78. **Hyde JF, Moore Jr JP, Cai A** 1998 Galanin in normal and hyperplastic anterior pituitary cells. Ann NY Acad Sci 863:48–55
79. **Moore Jr JP, Cai A, Maley BE, Jennes L, Hyde JF** 1999 Galanin within the normal and hyperplastic anterior pituitary gland: localization, secretion, and functional analysis in normal and human growth hormone-releasing hormone transgenic mice. Endocrinology 140:1789–1799
80. **Invitti C, Giraldi FP, Dubini A, Moroni P, Losa M, Piccoletti R, Cavagnini F** 1999 Galanin is released by adrenocorticotropin-secreting pituitary adenomas *in vitro* and *in vivo*. J Clin Endocrinol Metab 84:1351–1356
81. **Liu S, Gao J** 1998 The relationship of galanin immunoreactive nerve fibres to glandular cells in the anterior pituitary in the monkey. Brain Res 781:114–120
82. **Vrontakis M, Torsello A, Leite V, Vuille J-C, Zhang H** 1996 Regulation of galanin by dexamethasone in the rat anterior pituitary and the uterus. Neuroendocrinology 64:20–24
83. **Hooi SC, Koenig JI, Gabriel SM, Maiter D, Martin JB** 1990 Influence of thyroid hormone on the concentration of galanin in the rat brain and pituitary. Neuroendocrinology 51:351–356
84. **Hyde JF, Moore Jr JP, Drake KW, Morrison DG** 1996 Galanin gene expression in radiothyroidectomy-induced thyrotroph adenomas. Am J Physiol 271:E24–E30
85. **Wynick D, Hammond PJ, Akinsanya KO, Bloom SR** 1993 Galanin regulates basal and oestrogen-stimulated lactotroph function. Nature 364:529–532
86. **Hammond PJ, Khandan-Nia N, Withers DJ, Jones PM, Ghatei MA, Bloom SR** 1997 Regulation of anterior pituitary galanin and VIP by oestrogen and prolactin status. J Endocrinol 152:211–219
87. **Cai A, Hayes D, Patel N, Hyde JF** 1999 Targeted overexpression of galanin in lactotrophs of transgenic mice induces hyperprolactinaemia and pituitary hyperplasia. Endocrinology 140:4955–4964
88. **Wynick D, Small CJ, Bacon A, Holmes FE, Norman M, Ormandy CJ, Kilic E, Kerr NCH, Ghatei M, Talamantes F, Bloom SR, Pachnis V** 1998 Galanin regulates prolactin release and lactotroph proliferation. Proc Natl Acad Sci USA 95:12671–12676
89. **Todd JF, Small CJ, Akinsanya KO, Stanley SA, Smith DM, Bloom SR** 1998 Galanin is a paracrine inhibitor of gonadotroph function in the female rat. Endocrinology 139:4222–4229
90. **Evans JJ** 1999 Modulation of gonadotropin levels by peptides acting at the anterior pituitary gland. Endocr Rev 20:46–67
91. **Miller GM, Alexander JM, Klibanski A** 1996 Gonadotropin-releasing hormone messenger RNA expression in gonadotroph tumors and normal human pituitary. J Clin Endocrinol Metab 81:80–83
92. **Sanno N, Jin L, Qian X, Osamura RY, Scheithauer BW, Kovacs K, Lloyd RV** 1997 Gonadotropin-releasing hormone and gonadotropin-releasing hormone receptor mRNA expression in nontumorous and neoplastic pituitaries. J Clin Endocrinol Metab 82:1974–1982
93. **Kaiser UB, Conn M, Chin WW** 1997 Studies of gonadotropin-releasing hormone (GnRH) action using GnRH receptor-expressing pituitary cell lines. Endocr Rev 18:46–70
94. **Van Bael A, Seuntjens E, Proesmans M, Denef C** 1998 Presence of gonadotropin-releasing hormone (GnRH) mRNA in Rathke's pouch and effect of the GnRH-antagonist ORG 30276 on lactotroph development *in vitro*. J Neuroendocrinol 10:437–445
95. **Mertani HC, Pechoux C, Garcia-Caballero T, Waters MJ, Morel G** 1995 Cellular localization of the growth hormone receptor/binding protein in the human anterior pituitary gland. J Clin Endocrinol Metab 80:3361–3367
96. **Mertani HC, Waters MJ, Morel G** 1996 Cellular trafficking of exogenous growth hormone in dwarf rat pituitary. Neuroendocrinology 63:257–268
97. **Tang K, Bartke A, Gardiner CS, Wagner TE, Yun JS** 1993 Gonadotropin secretion, synthesis, and gene expression in two types of bovine growth hormone transgenic mice. Biol Reprod 49:346–353
98. **Steger RW, Bartke A, Parkening TA, Collins T, Buonomo FC, Tang K, Wagner TE, Yun JS** 1991 Effects of heterologous growth hormones on hypothalamic and pituitary function in transgenic mice. Neuroendocrinology 53:365–372
99. **Takahashi S, Oomizu S, Honda J, Takeuchi S** 1997 Insulin-like growth factor I system in the mouse pituitary. In: Kawashima S, Kikuyama S (eds) Advances in Comparative Endocrinology. Proceedings of the XIII International Congress of Comparative Endocrinology. Monduzzi Editore, Bologna, pp 1123–1126
100. **Bach MA, Bondy CA** 1992 Anatomy of the pituitary insulin-like growth factor system. Endocrinology 131:2588 2594
101. **Melamed P, Gur G, Rosenfeld H, Elizur A, Yaron Z** 1999 Possible interactions between gonadotrophs and somatotrophs in the pituitary of tilapia: apparent roles for insulin-like growth factor I and estradiol. Endocrinology 140:1183–1191
102. **Bondy CA, Werner H, Roberts Jr CT, LeRoith D** 1990 Cellular pattern of insulin-like growth factor I (IGF I) and type I IGF receptor gene expression in early organogenesis: comparison with IGF II gene expression. Mol Endocrinol 4:1386–1398
103. **Lu F, Yang K, Han VKM, Challis JRG** 1995 Expression, distribution, regulation and function of IGFs in the ovine fetal pituitary. J Mol Endocrinol 14:323–336
104. **Olchovsky D, Bruno JF, Gelato MC, Song J, Berelowitz M** 1991 Pituitary insulin-like growth factor I content and gene expression in the streptozotocin-diabetic rat: evidence for tissue-specific regulation. Endocrinology 128:923–928
105. **Michels KM, Lee W-H, Seltzer A, Saavedra JM, Bondy CA** 1993 Up-regulation of pituitary [^{125}I] insulin-like growth factor-I (IGF-I) binding and IGF binding protein II and IGF-I gene expression by estrogen. Endocrinology 132:23–29
106. **Fan J, Wojnar MM, Theodorakis M, Lang CH** 1996 Regulation of insulin-like growth factor (IGF)-I mRNA and peptide and IGF-binding proteins by interleukin-1. Am J Physiol 270:R621–R629
107. **Bernton EW, Beach JE, Holaday JW, Smallridge RC, Fein HG** 1987 Release of multiple hormones by a direct action of interleukin-1 on pituitary cells. Science 238:519–521
108. **Beach JE, Smallridge RC, Kinzer CA, Bernton EW, Holaday JW, Fein HG** 1989 Rapid release of multiple hormones from rat pituitaries perifused with recombinant interleukin-1. Life Sci 44:1–7
109. **Oomizu S, Takeuchi S, Takahashi S** 1998 Stimulatory effect of insulin-like growth factor I on proliferation of mouse pituitary cells in serum-free culture. J Endocrinol 157:53–62
110. **Torronteras R, Gracia-Navarro F, Elsaesser F** 1997 Control of growth hormone secretion from porcine fetal and neonatal pituitary tissue *in vitro* by growth hormone-releasing hormone, somatostatin, and insulin-like growth factor. Neuroendocrinology 65: 117–128
111. **Fletcher TP, Thomas GB, Dunshea FR, Moore LG, Clarke IJ** 1995 IGF feedback effects on growth hormone secretion in ewes: evidence for action at the pituitary but not the hypothalamic level. J Endocrinol 144:323–331
112. **Lara JI, Lorenzo MJ, Cacicedo L, Tolon RM, Balsa JA, Lopez-Fernandez J, Sanchez-Franco F** 1994 Induction of vasoactive intestinal peptide gene expression and prolactin secretion by insulin-like growth factor I in rat pituitary cells: evidence for an autoparacrine regulatory system. Endocrinology 135:2526–2532
113. **Gilchrist CA, Park JHY, MacDonald RG, Shull JD** 1995 Estradiol and triiodothyronine increase production of insulin-like growth factor I (IGF-I) and insulin-like growth factor binding protein-3 (IGFBP-3) by GH4C1 rat pituitary tumour cells. Mol Cell Endocrinol 114:147–156
114. **Huang Y-S, Rousseau K, Le Belle N, Vidal B, Burzawa-Gerard E, Marchelidon J, Dufour S** 1998 Insulin-like growth factor-I stimulates gonadotrophin production from eel pituitary cells: a possible metabolic signal for induction of puberty. J Endocrinol 159:43–52
115. **Reichlin S** 1993 Neuroendocrine-immune interactions. N Engl J Med 329:1246–1253
116. **Abraham EJ, Minton JE** 1997 Cytokines in the hypophysis: a comparative look at interleukin-6 in the porcine anterior pituitary gland. Comp Biochem Physiol 116:203–207

117. **Vankelecom H, Matthys P, Van Damme J, Heremans H, Billiau A, Denef C** 1993 Immunocytochemical evidence that S-100-positive cells of the mouse anterior pituitary contain interleukin-6 immunoreactivity. J Histochem Cytochem 41:151–156
118. **Spangelo BL, DeHoll PD, Kalabay L, Bond BR, Arnaud P** 1994 Neurointermediate pituitary lobe cells synthesize and release interleukin-6 *in vitro*: effects of lipopolysaccharide and interleukin-1β. Endocrinology 135:556–563
119. **Spangelo BL, Jarvis WD** 1996 Lysophosphatidylcholine stimulates interleukin-6 release from rat anterior pituitary cells *in vitro*. Endocrinology 137:4419–4426
120. **Auernhammer CJ, Melmed S** 1999 Interleukin-11 stimulates proopiomelanocortin gene expression and adrenocorticotropin secretion in corticotroph cells: evidence for a redundant cytokine network in the hypothalamo-pituitary-adrenal axis. Endocrinology 140:1559–1566
121. **Ferrara N, Winer J, Henzel WJ** 1992 Pituitary follicular cells secrete an inhibitor of aortic endothelial cell growth: identification as leukemia inhibitory factor. Proc Natl Acad Sci USA 89:698–702
122. **Carter DA** 1995 Leukaemia inhibitory factor gene expression in cultured rat anterior pituitary is regulated by glucocorticoids. J Neuroendocrinol 7:623–628
123. **Wang Z, Ren S-G, Melmed S** 1996 Hypothalamic and pituitary leukemia inhibitory factor gene expression *in vivo*: a novel endotoxin-inducible neuro-endocrine interface. Endocrinology 137: 2947–2953
124. **Akita S, Webster J, Ren SG, Takino H, Said J, Zand O, Melmed S** 1995 Human and murine pituitary expression of leukemia inhibitory factor. Novel intrapituitary regulation adrenocorticotropin hormone synthesis and secretion. J Clin Invest 95:1288–1298
125. **Schwartz J, Ray DW, Perez FM** 1999 Leukemia inhibitory factor as an intrapituitary mediator of ACTH secretion. Neuroendocrinology 69:34–43
126. **Chesnokova V, Auernhammer CJ, Melmed S** 1998 Murine leukemia inhibitory factor gene disruption attenuates the hypothalamo-pituitary-adrenal axis stress response. Endocrinology 139: 2209–2216
127. **Akita S, Malkin J, Melmed S** 1996 Disrupted leukemia inhibitory factor gene attenuates adrenocorticotropin secretion. Endocrinology 137:3140–3143
128. **Auernhammer CJ, Chesnokova V, Melmed S** 1998 Leukemia inhibitory factor modulates interleukin 1β-induced activation of the hypothalamo-pituitary adrenal axis. Endocrinology 139:2201–2208
129. **Akita S, Readhead C, Stefaneanu L, Fine J, Tampanaru-Sarmesiu A, Kovacs K, Melmed S** 1997 Pituitary-directed leukemia inhibitory factor transgene forms Rathke's cleft cysts and impairs pituitary function. A model for human pituitary Rathke's cycts. J Clin Invest 99:2462–2469
130. **Patterson JC, Childs GV** 1994 Nerve growth factor in the anterior pituitary: regulation of secretion. Endocrinology 135:1697–1704
131. **Missale CS, Boroni F, Sigala S, Buriani A, Fabris M, Leon A, Dal Toso R, Spano P** 1996 Nerve growth factor in the anterior pituitary: localization in mammotroph cells and cosecretion with prolactin by a dopamine-regulated mechanism. Proc Natl Acad Sci USA 93: 4240–4245
132. **Conner JM, Varon S** 1993 Nerve growth factor immunoreactivity in the anterior pituitary of the rat. Neuroreport 4:395–398
133. **Burnham P, Conner JM, Varon S** 1995 Colocalization of NGF and TSH-Like immunoreactivity in cultures of adult rat anterior pituitary cells. J Neurosci Res 41:73–78
134. **Patterson JC, Childs GV** 1994 Nerve growth factor and its receptor in the anterior pituitary. Endocrinology 135:1689–1696
135. **Borson S, Schatteman G, Claude P, Bothwell M** 1994 Neurotrophins in the developing and adult primate adenohypophysis: a new pituitary hormone system? Neuroendocrinology 59:466–476
136. **Calza L, Giardino L, Aloe L** 1997 NGF content and expression in the rat pituitary gland and regulation by thyroid hormone. Brain Res 51:60–68
137. **Ramaekers D, Proesmans M, Denef C** 1997 Expression of the low affinity p75 nerve growth factor receptor in the developing rat pituitary. Neurochem Res 22:1353–1357
138. **Missale C, Boroni F, Frassine M, Caruso A, Spano P** 1995 Nerve growth factor promotes the differentiation of pituitary mammotroph cells *in vitro*. Endocrinology 136:1205–1213
139. **Missale C, Boroni F, Sigala S, Zanellato A, Dal-Toso R, Balsari A, Spano P** 1994 Nerve growth factor directs differentiation of the bipotential cell line GH-3 into the mammotroph phenotype. Endocrinology 135:290–298
140. **Proesmans M, Van Bael A, Andries M, Denef C** 1997 Mitogenic effects of nerve growth factor on different cell types in reaggregate cell cultures of immature rat pituitary. Mol Cell Endocrinol 134: 119–127
141. **Pazos-Moura CC, Moura EG, Rettori V, Polak J, McCann SM** 1996 Role of neuromedin B in the *in vitro* thyrotropin release in response to thyrotropin-releasing hormone from anterior pituitaries of eu-, hypo- and hyperthyroid rats. Proc Soc Exp Biol Med 211:353–358
142. **Ortiga-Carvalho TM, Curty FH, Nascimento-Saba CC, Moura EG, Polak J, Pazos-Moura CC** 1997 Pituitary neuromedin B content in experimental fasting and diabetes mellitus and correlation with thyrotropin secretion. Metabolism 46:149–153
143. **Ceccatelli S, Hulting A-L, Zhang X, Gustafsson L, Villar M, Hokfelt T** 1993 Nitric oxide synthase in the rat anterior pituitary gland and the role of nitric oxide in regulation of LH secretion. Proc Natl Acad Sci USA 90:11292–11296
144. **Lloyd RV, Jin L, Qian X, Zhang S, Scheithauer BW** 1995 Nitric oxide synthase in the human pituitary gland. Am J Pathol 146: 86–94
145. **Ueta Y, Levy A, Powell MP, Lightman SL, Kinoshita Y, Yokota A, Shibuya I, Yamashita H** 1998 Neuronal nitric oxide synthase gene expression in human pituitary tumours: a possible association with somatotroph adenomas and growth hormone-releasing hormone gene expression. Clin Endocrinol (Oxf) 49:29–38
146. **Vankelecom H, Matthys P, Denef C** 1997 Inducible nitric oxide synthase in the anterior pituitary gland: induction by interferon-γ in a subpopulation of folliculostellate cells and in an unidentifiable population of non-hormone-secreting cells. J Histochem Cytochem 45:847–857
147. **Brunetti L, Ragazzoni E, Preziosi P, Vacca M** 1995 A possible role for nitric oxide but not for prostaglandin E2 in basal and interleukin-1-β-induced prolactin release *in vitro*. Pharmacol Lett 56:277–283
148. **Duvilanski BH, Zambruno C, Seilicovich A, Pisera D, Lasaga M, Diaz M-C, Belova N, Rettori V, McCann SM** 1995 Role of nitric oxide in control of prolactin release by the adenohypophysis. Proc Natl Acad Sci USA 92:170–174
149. **Grouzmann E, Deruaz JP, Gomez F, Waeber G** 1998 Immunolocalization of neuropeptide Y in human pituitary tumours. Regul Pept 76:89–92
150. **O'Conner JL, Wade MF, Brann DW, Mahesh VB** 1995 Evidence that progesterone modulates anterior pituitary neuropeptide Y levels during the progesterone-induced gonadotropin surge in the estrogen-primed intact immature female rat. J Steroid Biochem Mol Biol 52:497–504
151. **Jones PM, Ghatei MA, Wallis SC, Bloom SR** 1994 Differential response of neuropeptide Y, substance P and vasoactive intestinal polypeptide in the rat anterior pituitary gland to alterations in thyroid hormone status. J Endocrinol 143:393–397
152. **Gehlert DR, Gackenheimer SL, Millington WR, Manning AB, Chronwall BM** 1994 Localization of neuropeptide Y immunoreactivity and [^{125}I] peptide YY binding sites in the human pituitary. Peptides 15:651–656
153. **Dyer CJ, Simmons JM, Matteri RL, Keiser DH** 1997 cDNA cloning and tissue-specific gene expression of ovine leptin, NPY-Y1 receptor, and NPY-Y2 receptor. Domest Anim Endocrinol 14:295–303
154. **Leupen SM, Levine JE** 1999 Role of protein kinase C in facilitation of luteinizing hormone (LH)-releasing hormone-induced LH surges by neuropeptide Y. Endocrinology 140:3682–3687
155. **Knox KL, Bauer-Dantoin AC, Levine JE, Schwartz NB** 1995 Unmasking of neuropeptide Y inhibitory effects on *in vitro* gonadotropin secretion from pituitaries of metestrous, but not proestrous, rats. Endocrinology 136:187–194
156. **Leiva LA, Croxatto HB** 1994 Comparison of the effect of hypothalamic neuropeptides upon luteinizing hormone secretion by cultured rat anterior pituitary cells. Biol Res 27:113–121
157. **Bauer-Dantoin AC, Knox KL, Schwartz NB, Levine JE** 1993 Es-

trous cycle stage-dependent effects of neuropeptide Y on luteinizing hormone (LH)-releasing hormone-stimulated LH and follicle-stimulating hormone secretion from anterior pituitary fragments *in vitro*. Endocrinology 133:2413–2417
158. **O'Conner JL, Wade MF, Brann DW, Mahesh VB** 1993 Direct anterior pituitary modulation of gonadotropin secretion by neuropeptide Y: role of gonadal steroids. Neuroendocrinology 58:129–135
159. **Peng C, Humphries S, Peter RE, Rivier JE, Blomqvist AG, Larhammar D** 1993 Actions of goldfish neuropeptide Y on the secretion of growth hormone and gonadotropin-II in female goldfish. Gen Comp Endocrinol 90:306–317
160. **Peng C, Trudeau VL, Peter RE** 1993 Seasonal variation of neuropeptide Y actions on growth hormone and gonadotropin-II secretion in the goldfish: effects of sex steroids. J Neuroendocrinol 5:273–280
161. **Peng C, Chang JP, Yu KL, Wong AO, Van Goor F, Peter RE, Rivier JE** 1993 Neuropeptide Y stimulates growth hormone and gonadotropin-II secretion in the goldfish pituitary: involvement of both presynaptic and pituitary cell actions. Endocrinology 132:1820–1829
162. **Woller MJ, Campbell GT, Blake CA** 1995 Neuropeptide Y and luteinizing hormone releasing hormone synergize to stimulate the development of cellular follicle-stimulating hormone in the hamster adenohypophysis. J Neuroendocrinol 7:733–736
163. **LeBlanc P, L'Heritier A, Rasolonjanahary R, Kordon C** 1994 Neuropeptide Y enhances LHRH binding to rat gonadotrophs in primary culture. Neuropeptides 26:87–92
164. **Wang J, Ciofi P, Crowley WR** 1996 Neuropeptide Y suppresses prolactin secretion from rat anterior pituitary cells: evidence for interactions with dopamine through inhibitory coupling to calcium entry. Endocrinology 137:587–594
165. **Breton C, Pechoux C, Morel G, Zingg HH** 1995 Oxytocin receptor messenger ribonucleic acid: characterisation, regulation, and cellular localisation in the rat anterior pituitary gland. Endocrinology 136:2928–2936
166. **Schally AV, Guoth JG, Redding TW, Groot K, Rodriguez H, Szonyi E, Stults J, Nikolics K** 1991 Isolation and characterisation of two peptides with prolactin release-inhibiting activity from porcine hypothalami. Proc Natl Acad Sci USA 88:3540–3544
167. **Tilemans D, Andries M, Denef C, Straetemans L** 1991 Luteinizing hormone-releasing hormone and neuropeptide Y influence deoxyribonucleic acid replication in three anterior pituitary cell types. Evidence for mediation by growth factors released from gonadotrophs. Endocrinology 130:882–894
168. **Van Bael A, Huygen R, Himpens B, Denef C** 1994 *In vitro* evidence that LHRH stimulates the recruitment of prolactin mRNA-expressing cells during the postnatal period in the rat. J Mol Endocrinol 12:107–118
169. **Tilemans D, Andries M, Proost P, Devreese B, Van Beeumen J, Denef C** 1994 *In vitro* evidence that an 11-kilodalton N-terminal fragment of proopiomelanocortin is a growth factor specifically stimulating the development of lactotrophs in rat pituitary during postnatal life. Endocrinology 135:168–174
170. **Morel G, Ouhtit A, Kelly PA** 1994 Prolactin receptor immunoreactivity in rat anterior pituitary. Neuroendocrinology 59:78–84
171. **Krown K, Wang Y-F, Ho TWC, Kelly PA, Walker AM** 1992 Prolactin isoform 2 as an autocrine growth factor for GH_3 cells. Endocrinology 131:595–602
172. **Andries M, Jacobs GFM, Tilemans D, Denef C** 1996 *In vitro* immunoneutralization of a cleaved prolactin variant: evidence for local paracrine action of cleaved prolactin in the development of gonadotrophs and thyrotrophs in the rat pituitary. J Neuroendocrinol 8:123–127
173. **Morel G, Chayvialle JA, Kerdelhue B, Dubois PM** 1982 Ultrastructural evidence for endogenous substance P-like immunoreactivity in the rat pituitary gland. Neuroendocrinology 35:86–82
174. **Arita J, Kojima Y, Yamamoto I, Mazawa S, Kimura F** 1994 Somatotropes and thyrotropes in the rat anterior pituitary gland cosecrete substance P: analysis by the sandwich cell immunoblot assay. Neuroendocrinology 60:567–574
175. **Kato Y, Chihara K, Ohgo S, Iwasaki Y, Abe H, Imura H** 1976 Growth hormone and prolactin release by substance P in rats. Life Sci 19:441–446
176. **Ma D, Zhao C, Mayhew TM, Ju G** 1997 Response of substance P-immunoreactive nerve fibres in the anterior pituitary to plasma oestrogen levels in the rat. J Neuroendocrinol 9:735–740
177. **Duval P, Lenoir V, Kerdelhue B** 1998 The *in vitro* effect of substance P on the GnRH-induced LH release depends on the steroidal environment and is reverted by a NK1 receptor antagonist (RP 67580) in the cycling female rat. Neuropeptides 32:97–101
178. **Arita J, Kojima Y, Kimura F** 1993 Measurement of the secretion of a small peptide at the single cell level by the cell immunoblot assay: thyroidectomy increases the number of substance P anterior pituitary cells. Endocrinology 132:2682–2688
179. **DePalatis LR, Fiorindo RP, Ho RH** 1982 Substance P immunoreactivity in the anterior pituitary gland of the guinea pig. Endocrinology 110:282–284
180. **Debeljuk L, Bartke A** 1994 Immunoreactive substance P and neurokinin A in the hypothalamus and anterior pituitary gland of Siberian and Syrian hamsters and of rats. J Reprod Fertil 101:427–434
181. **Mau SE, Saermark T, Vilhardt H** 1997 Cross-talk between cellular signalling pathways activated by substance P and vasoactive intestinal peptide in rat lactotroph-enriched pituitary cell cultures. Endocrinology 138:1704–1711
182. **Mau SE, Vilhardt H** 1997 Cross talk between substance P and melittin-activated cellular signalling pathways in rat lactotroph-enriched cell cultures. J Neurochem 69:762–772
183. **Shamgochian MD, Leeman SE** 1992 Substance P stimulates luteinizing hormone secretion from anterior pituitary cells in culture. Endocrinology 131:871–875184
184. **Samsoondar J, Kobrin MS, Kudlow JE** 1986 α-Transforming growth factor secreted by untransformed bovine anterior pituitary cells in culture. I. Purification from conditioned medium. J Biol Chem 261:14408–14413
185. **Finley EL, King JS, Ramsdell JS** 1994 Human pituitary somatotropes express transforming growth factor-α and its receptor. J Endocrinol 141:547–554
186. **Sarkar DK, Kim KH, Minami S** 1992 Transforming growth factor β 1 messenger RNA and protein expression in the pituitary gland: its actions on prolactin secretion and lactotropic growth. Mol Endocrinol 6:1825–1833
187. **Qian X, Lin L, Grande JP, Lloyd RV** 1996 Transforming growth factor-β and p27 expression in pituitary cells. Endocrinology 137:3051–3060
188. **Burns G, Sarkar DK** 1993 Transforming growth factor-β 1-like immunoreactivity in the pituitary gland of the rat: effect of estrogen. Endocrinology 133:1444–1449
189. **Moustakas A, Takumi T, Lin HY, Lodish HF** 1995 GH3 pituitary tumor cells contain heteromeric type I and type II receptor complexes for TGFβ and activin A. J Biol Chem 270:765–769
190. **Yamishita H, Okadome T, Franzen P, Ten Dijke P, Heldin C-H, Miyazono K** 1995 A rat pituitary tumor cell line (GH_3) expresses type I and type II receptors and other cell surface binding protein(s) for TGFβ. J Biol Chem 270:770–774
191. **Fujiwara K, Ikeda H, Yoshimoto T** 1995 Immunohistochemical demonstration of TGFβ-receptor type II in human pituitary adenomas. Acta Histochem 97:445–454
192. **Mc Andrew J, Paterson AJ, Asa SL, McCarthy KJ, Kudlow JE** 1995 Targeting of transforming growth factor α expression to pituitary lactotrophs in transgenic mice results in selective lactotroph proliferation and adenomas. Endocrinology 136:4479–4488
193. **Ying S-Y, Becker A, Baird A, Ling N, Ueno N, Esch F, Guillemin R** 1986 Type β transforming growth factor (TGFβ) is a potent stimulator of the basal secretion of follicle stimulating hormone (FSH) in a pituitary monolayer system. Biochem Biophys Res Commun 135:950–956
194. **De A, Morgan TE, Speth RC, Boyadjieva N, Sarkar DK** 1996 Pituitary lactotrope expresses transforming growth factor β type II receptor mRNA and protein and contains ^{125}I-TGF1 binding sites. J Endocrinol 149:19–27
195. **Murata T, Ying S-Y** 1991 Transforming growth factor-β and activin inhibit basal secretion of prolactin in a pituitary monolayer culture system. Proc Soc Exp Biol Med 198:599–605

196. **Tan S-K, Wang F-F, Pu H-F, Liu T-C** 1997 Differential effect of age on transforming growth factor-β_1 inhibition of prolactin gene expression *vs.* secretion in rat anterior pituitary cells. Endocrinology 138:878–885
197. **Abraham EJ, Faught WJ, Frawley LS** 1998 Transforming growth factor 1 is a paracrine inhibitor of prolactin gene expression. Endocrinology 139:5174–5181
198. **Peters A, Heuer H, Schomberg L, De Greef WJ, Visser TJ, Bauer K** 1997 Thyrotropin-releasing hormone gene expression by anterior pituitary cells in long-term cultures is influenced by the culture conditions and cell-to-cell interactions. Endocrinology 138:2807–2812
199. **Bruhn TO, Rondeel JMM, Jackson IMD** 1998 Thyrotropin-releasing hormone gene expression in the anterior pituitary. IV. Evidence for paracrine and autocrine regulation. Endocrinology 139:3416–3422
200. **Quintanar-Stephano A, Valverde C** 1997 Mitogenic effects of thyroxine and TRH on thyrotrophs and somatotrophs of the anterior pituitary gland in thyroidectomized rats. J Endocrinol 154:149–153
201. **Heritier AG, DuBois PM** 1993 Influence of thyroliberin on the rat pituitary cell type differentiation: an *in vitro* study. Endocrinology 132:634–639
202. **Iino K, Sasano H, Oki Y, Andoh N, Shin R-W, Kitamoto T, Totsune K, Takahashi K, Suzuki H, Nagura H, Yoshimi T** 1997 Urocortin expression in human pituitary gland and pituitary adenoma. J Clin Endocrinol Metab 82:3842–3850
203. **Asaba K, Makino S, Hashimoto K** 1998 Effect of urocortin on ACTH secretion from rat anterior pituitary *in vitro* and *in vivo*: comparison with corticotropin-releasing hormone. Brain Res 806: 95–103
204. **Vaughan J, Donaldson C, Bittencourt J, Perrin MH, Lewis K, Sutton S, Chan R, Turnbull AV, Lovejoy R, Rivier C** 1995 Urocortin, a mammalian neuropeptide related to fish urotensin 1 and to corticotropin-releasing factor. Nature 378:287–292
205. **Turnbull AV, Vaughan J, Rivier JE, Vale WW, Rivier C** 1999 Urocortin is not a significant regulator of intermittent electrofootshock-induced adrenocorticotropin secretion in the intact male rat. Endocrinology 140:71–78
206. **Chew L-J, Seah V, Murphy D, Carter D** 1996 Anterior pituitary vasoactive intestinal peptide mRNA is colocalised with prolactin mRNA in hyperoestrigenised rats. J Mol Endocrinol 16:211–220
207. **Chew L-J, Pardy K, Murphy D, Carter DA** 1993 Osmotic stimuli attenuate vasoactive intestinal peptide gene expression in the rat anterior pituitary gland. Mol Cell Endocrinol 92:9–14
208. **Rawlings SR, Hezareh M** 1996 Pituitary adenylate cyclase-activating polypeptide (PACAP) and PACAP/vasoactive intestinal polypeptide receptors: actions on the anterior pituitary gland. Endocr Rev 17:4–29
209. **Balsa JA, Cacicedo L, Lara JI, Lorenzo MJ, Pazos F, Sanchez-Franco F** 1996 Autocrine and/or paracrine action of vasoactive intestinal peptide on thyrotropin-releasing hormone-induced prolactin release. Endocrinology 137:144–150
210. **Andries M, Vijver VV, Tilemans D, Bert C, Denef C** 1995 Interaction of αT3–1 cells with lactotropes and somatotropes of normal pituitary *in vitro*. Neuroendocrinology 61:326–336
211. **McArdle CA, Olcese J, Schmidt C, Poch A, Kratzmeier M, Middendorf R** 1994 C-type natriuretic peptide (CNP) in the pituitary: is CNP an autocrine regulator of gonadotropes? Endocrinology 135:2794–2801
212. **Jeziorowski T, Watanabe T, Bargsten G, Grube D** 1997 Heterogeneity of pituitary gonadotrope cells in male rats. Arch Histol Cytol 60:355–370
213. **Abraham EJ, Villalobos C, Frawley LS** 1998 Effects of cellular interactions on calcium dynamics in prolactin-secreting cells. Endocrinology 139:2988–2993
214. **DePaul A, Pons P, Aoki A, Torres A** 1997 Different behaviour of lactotroph cell subpopulations in response to angiotensin II and thyrotrophin-releasing hormone. Cell Mol Neurobiol 17:245–258
215. **Marin F, Boya J** 1995 Immunocytochemical localization of basic fibroblast growth factor in the human pituitary gland. Neuroendocrinology 62:523–529
216. **Bluet-Pagot M-T, Epelbaum J, Gourdji D, Hammond C, Kordon C** 1998 Hypothalamic and hypophyseal regulation of growth hormone secretion. Cell Mol Neurobiol 18:101–123
217. **Van de Pavert SA, Clarke IJ, Rao A, Vrana KE, Schwartz J** 1997 Effects of vasopressin and elimination of CRH-target cells on proopiomelanocortin mRNA levels and adrenocorticotropin secretion in ovine anterior pituitary cells. J Endocrinol 154:2249–2258
218. **Engler D, Redei E, Kola I** 1999 The corticotropin-release inhibitory factor hypothesis: a review of the evidence for the existence of inhibitory as well as stimulatory hypophysiotropic regulation of adrenocorticotropin secretion and biosynthesis. Endocr Rev 20: 460–500
219. **Pecori Giraldi F, Cavagnini F** 1998 Corticotropin-releasing hormone is produced by rat corticotropes and modulates ACTH secretion in a paracrine/autocrine fashion. J Clin Invest 101:2478–2484

New Address for the *Endocrine Reviews* Editorial Office

As of **November 1st,** all correspondence with *Endocrine Reviews* and *Recent Progress in Hormone Research* should be directed to the following address:

Endocrine Reviews
The University of Texas Medical Branch
Room 111C, Basic Science Building
Galveston, TX 77555-0629
Phone: 409-747-4710
Fax: 409-747-4711
E-mail: endoreviews@endo-society.org