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Pituitary Cytokine and Growth Factor Expression and Action

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I. Introduction

THE anterior pituitary gland is the source of six classic trophic hormones including ACTH, GH, PRL, TSH, FSH, and LH. Each of these polypeptide hormones is expressed by unique highly differentiated anterior pituitary cell types. These specific cells originate from a common stem cell whose ultimate phenotypic development is determined by pituitary-specific developmental factors including transcription factors, surface receptors, and peripheral and hypothalamic signals (1–4). Developmental and physiological control of pituitary cell proliferation and specific gene expression is controlled by hypothalamic peptides and their receptors. Although the pituitary gland itself regulates somatic growth, a wealth of evidence supports the notion that intrapituitary chemical mediators themselves act as regulators of pituitary function. Furthermore, because of the expression of a readily measurable differentiated gene product, *i.e.* a polypeptide hormone, the pituitary has lent itself to being a convenient cell model for studying mechanisms of growth factor actions.

It has become increasingly evident that locally produced pituitary proteins mediate development, mature function, and cellular organization of the anterior pituitary. These growth factors and cytokines, in addition to mediating cell division, also directly regulate specific pituitary trophic hormone gene expression. Therefore, this intrapituitary signaling network provides a further level of control, integrating with central and peripheral signals to modulate pituitary trophic hormone secretion and cell proliferation.

This review describes pituitary expression and action of cytokines and growth factors and proposes integrated hypotheses for paracrine control of anterior pituitary function, mediation of the stress response, and pituitary tumorigenesis. Although the ensuing discussion describes the known pituitary paracrine factors, those which have been compellingly characterized in terms of their relevance to pituitary function are highlighted. As recent major advances in understanding the inhibin-activin axis have been extensively reviewed (5–6), this review therefore focuses predominantly on intrapituitary factors regulating ACTH, GH, PRL, and TSH expression.

A. Hormone secretion

Three tiers of control subserve the regulation of anterior pituitary hormone secretion (Fig. 1).

1. Tier 1. Tier 1 comprises central signals from the brain and hypothalamus. These include the now classic hypothalamic release and inhibiting hormones, neurotransmitters, and brain peptides. These molecules traverse the portal venous system in classic endocrine fashion to impinge upon their respective distal receptors located on the pituitary trophic hormone cell surface (7–15). These highly differentiated receptors transduce their signals to the cell nucleus, thereby

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determining biosynthesis and ultimate secretion of the anterior pituitary hormones. The hypothalamic hormones may also determine pituitary cell mitotic activity; GHRH induces somatotroph DNA synthesis (16) and also induces c-*fos* mRNA expression (17). Clinically, pathological GHRH oversecretion results in somatotroph hyperplasia and adenoma formation (15).

2. Tier II. The second tier of pituitary control comprises the intrapituitary network of cytokines and growth factors reviewed here (Table 1). These molecules provide highly specific unique signals to the pituicyte (*e.g.* EGF regulation of PRL) or an overlapping redundancy (*e.g.* interleukin regulation of ACTH). Furthermore, they may often synergize with hypothalamic hormones [*e.g.* fibroblast growth factor (FGF) and TRH; leukemia inhibitory factor (LIF) and CRH] or even antagonize their actions [*e.g.* insulin-like growth factor-I (IGF-I) and GHRH]. In addition, some growth factors interact with peripheral hormones to regulate pitutiary expression (*e.g.* galanin and estradiol).

A hallmark of autocrine function is in fact the demonstration of endogenous production of the specific growth factor. Because of the paucity of tissue and the failure of human pituitary cells to proliferate *in vitro*, many descriptive studies in human pituitary tumors do not provide compelling subcellular regulatory information required to establish a physiological function for intrapituitary growth factors. It has only recently been possible to begin evaluating the true cytogenesis of the pituitary growth factors, and most of them do indeed appear to be synthesized by trophic hormone cells (18, 19). The role of the folliculostellate or other nonendocrine cells as paracrine sources of pituitary growth factors remains controversial. Clearly, this cell is the source of growth factors with important extrapituitary or nonendocrine functions (*e.g.* vascular endothelial growth factor), but its role as a paracrine determinant of pituitary function remains unproven. In man, the existence of such a cell and its distinction from macrophages is also currently being debated.

The pituitary growth factors invariably have dual functions — regulating cell development and replication and controlling differentiated gene expression. These two functions are often subserved independently and may in fact be discordant (*e.g.* LIF induces POMC transcription while blocking S phase entry; EGF slows cell replication while inducing PRL transcription).

3. Tier III. The third tier of pituitary control is the peripheral target hormone. Classic pituitary tumors were generated in the past by ablation of thyroid, adrenal, or gonadal tissue. Clinically, loss of negative feedback inhibition by target hormones results in pituitary trophic hormone hypersecretion, hyperplasia, and sometimes adenoma formation, as may be encountered in severe hypothyroidism or hypoadrenalism. Peripheral hormones may also directly induce pituitary hormone genes (*e.g.* estradiol induction of PRL; T_3 induction of GH).

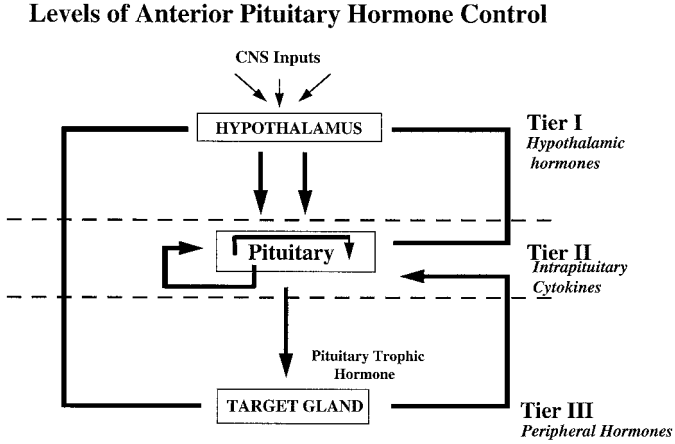


FIG. 1. Levels of anterior pituitary control. Depiction of the three tiers controlling pituitary trophic hormone secretion.

II. Cytokines and Growth Factors

Cytokines and growth factors are soluble peptide mediators of cell growth and differentiation. Although cytokines generally act on hematopoietic or inflammatory cells, they also serve as growth and differentiation factors for other cell types. They are secreted or expressed directly on the cell membrane or may accumulate in the extracellular matrix. Cytokine cell surface receptors are linked to intracellular signal transduction pathways that ultimately impact on nuclear transcriptional events. These receptors may also be alternatively spliced to yield secreted forms lacking the residues anchoring the transmembrane protein. Soluble receptor molecules may behave as natural antagonists and can also serve as transport carrier proteins to distant sites of cytokine action.

Several cytokine receptors exhibit two distinct affinity

TABLE 1. Confirmed physiological pituitary cytokine families

Group	Factors	Receptor
4α Helix bundle	IL-2	Heterotrimer-JAK/STAT
	IL-6	gp130 subunit-JAK/STAT
	LIF	gp130 subunit-JAK/STAT
Epidermal growth factor	EGF	c-Erb B tyrosine kinase
	TGFα	c-Erb B tyrosine kinase
Fibroblast growth factors	FGF-2	Tyrosine kinase
	FGF-4	Tyrosine kinase
Insulin-like growth factors	IGF-I	Tyrosine kinase (type I)
	IGF-II	Tyrosine kinase (type I)
Nerve growth factor	NGF	gp140TrkA
TGFβ	Activin	Serine-threonine kinase
	Inhibins	Serine-threonine kinase

binding sites. These usually comprise high (10–100 pM) and lower (1–10 nM) affinity components attributable to distinct receptor subunits. These latter molecules behave as affinity converters and may be shared by more than one cytokine. For example, the receptors for interleukin-6 (IL-6), LIF, and Oncostatin M share the common gp130-signaling subunit. The gp130 may form homodimers in their association with the high-affinity receptor molecule (*e.g.* IL-6R) or may form heterodimers with the receptor molecule itself (*e.g.* LIFR). Ligand activation of cytokine receptor-signaling units may result in tyrosine phosphorylation and subsequent intracellular signaling to the nucleus (*e.g.* interleukins). Growth factor receptors, however, typically possess intrinsic tyrosine kinase activity.

Cytokine gene expression. Cellular cytokine reservoirs are available for rapid constitutive release in response to stimulation. They may be presynthesized and stored in cytoplasmic granules (*e.g.* EGF) or in the adjacent extracellular matrix (*e.g.* TGFβ). Regulated cytokine expression usually is induced by infectious agents, toxic stress, or other stress-induced molecules and may occur both transcriptionally as well as by precursor processing. Molecular mechanisms subserving transcription of cytokine genes are as yet poorly understood and may involve both 5′- and 3′-regulatory elements. In general, cytokine expression appears to be antagonized by glucocorticoids.

Cytokines may be grouped structurally (and often functionally) into superfamilies. The confirmed physiological pituitary-derived cytokines and growth factors are depicted in Table 2. In terms of regulation of endocrine cell growth and function, it would appear that much fortuitous overlap exists between the semantic distinction of cytokines and growth factors.

A. Interleukins

Several of the interleukins, although classically involved with hematopoeitic and inflammatory cell function, are also expressed in the pituitary and exert specific hormonal and proliferative functions.

1. IL-1, α and β. IL-1α [159 amino acids (a.a.)] and -β (153 a.a.) are endogenous pyrogenic proteins induced by bacterial endotoxin. The two forms are derived from two different genes and, in the human, only display 20% homology. Nevertheless, they bind to the same receptor and display identical biological activities. The IL-1 receptor is expressed in most cells and tissues, although often at very low levels (<100 binding sites per cell) (20). IL-1β is released by several cell types including activated macrophages and monocytes as a precursor molecule that is cleaved to the active cytokine by a specific IL-1β-converting enzyme. In addition to these modes of control, an additional secreted molecule, the IL-1 receptor antagonist, acts to oppose IL- I action at the receptor level (21). Activation of IL-1 receptor induces sphingomyelinase in the cell membrane and generation of ceramide, which may link activation of all three characterized mitogen-activated protein kinase cascades, resulting in tyrosine phosphorylation of a number of substrates, including transcription factors (22).

Pituitary IL-1 expression. In the rat, IL-1β mRNA has been identified in pituicytes, particularly thyrotrophs (23), and pituitary IL-1 gene expression is induced by endotoxin administration *in vivo* (23). In a series of human pituitary adenomas, IL-1β expression was demonstrated using RT-PCR (24).

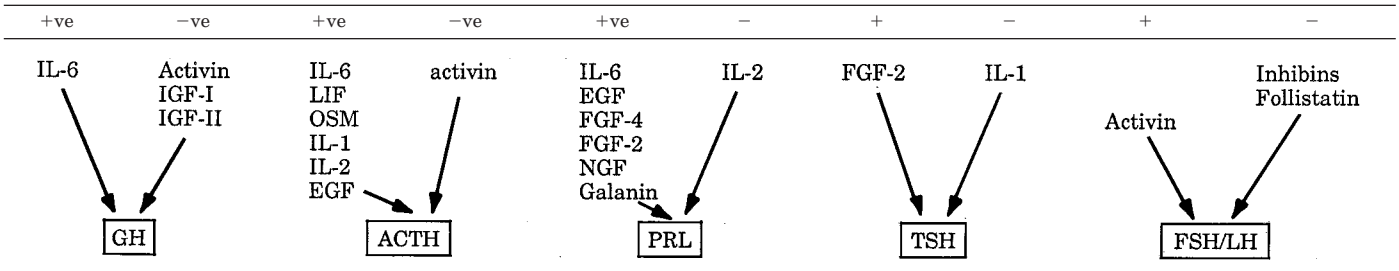
Pituitary receptors. Binding of IL-1α to the adenohypophysis has been detected using radioligand autoradiography, and specific mRNA for both receptor types have also been identified within the pituitary (25–28). IL-1 receptors, as measured by radioligand studies, have been detected in the murine AtT20 cell line (29), and receptor number was upregulated by CRH treatment and by other cAMP inducers including forskolin and isoproterenol. This induction is inhibited by both dexamethasone and somatostatin, agents that may also inhibit POMC expression (30).

Although these studies have shown the presence of both the signal-transducing type I receptor and the non-signal-transducing type II receptors in the pituitary (31), it is not clear which cell types express the receptors. Recent work, using specific antibodies directed against the two receptor isoforms, have shown receptor expression in the murine adenohypophysis and that both receptor types are expressed predominantly on the somatotroph cells (32).

In addition to the IL-1 receptor and ligand, the naturally occurring IL-1 receptor antagonist (33–35) binds competitively to the IL-1 receptor and neutralizes the biological action of IL-1 during acute inflammatory shock (36). Transcription of this "antagonist" gene and expression of its protein product have both been described in a variety of human pituitary adenomas, further underlying the complex network of potential IL-1 interactions within the human pituitary (37).

Pituitary action. The action of IL-1 on anterior pituitary hormone release is controversial. Primary cultures of rat pituitary cells responded to IL-1β by increasing secretion of ACTH, LH, GH, and TSH (38). In contrast, IL-1β has been

TABLE 2. Summary of principal intrapituitary cytokine signals



shown recently to inhibit pituitary TSH secretion directly, within 4 h, but not to alter TRH-induced TSH release (39). The reasons for these discrepant results are unknown. However, in the intact rat, although infusion of human IL-1 induced circulating levels of ACTH, this effect appeared to be due to action of the cytokine at the hypothalamus by stimulating CRH release. This was inferred from immunoneutralization studies showing that antiserum to CRH blocked IL-1 action (40). In another study using primary rat pituitary cultures, no effects of acute IL-1 administration on POMC gene transcription or ACTH peptide release were observed. Interestingly, chronic treatment of these cultures with either IL-1α or -β exerted a weak induction of ACTH release with no effect on POMC mRNA accumulation (41). An explanation for these divergent results may be that IL-1 modulates actions of other ACTH secretogogs, including catecholamines. In fact, over time in culture, β-adrenergic responses of ACTH decline and α-adrenergic responses supervene. This *in vitro* time-dependent effect on ACTH is blocked by coincubation of pituitary cells with IL-1 (42). Interestingly, IL-1β may also act as a proinflammatory cytokine by inducing pituitary NGF expression (43).

2. IL-2. IL-2 (133 a.a.) is a potent immunoregulatory T cell-derived cytokine important for T cell growth and differentiation (44) and acts through a specific transmembrane receptor complex consisting of three distinct polypeptide chains, α, β, and γ (45). A heterodimer of β- and γ-chains is required for signal transduction, and the γ-chain is shared with a number of other cytokines including IL-4. Mice homozygous for an IL-2 null gene mutation had normal thymocyte development, indicating some redundancy in the actions of this cytokine (46). This may reflect the fact that IL-4, IL-7, and IL-9 share the common γ-chain of the receptor complex, and IL-15 shares both the common γ- and β-chain (47, 48).

Pituitary expression. Expression of IL-2 mRNA was detected in human corticotroph adenoma cells and in mouse pituitary AtT20 cells (49). The pituitary IL-2 transcript was identical in size to that expected in stimulated lymphocytes. IL-2 mRNA and peptide secretion by these pituitary cells were induced by protein kinase C agonists such as phorbol esters (49), which may also stimulate ACTH release.

Pituitary receptors. Both human pituitary adenoma cells and AtT20 cells express IL-2 receptor mRNA, and membrane expression of the receptor could also be detected in these cells by binding studies. Further studies in the rat showed colocalization of the IL-2 receptor with ACTH in primary pituitary cultures (49).

Pituitary action. IL-2 enhances POMC gene expression in the pituitary (49) and also enhances ACTH secretion in AtT20 cells and in primary rat pituitary cultures (49, 50). IL-2, when administered to human subjects during cancer therapy trials, was found to increase circulating β-endorphin and ACTH levels (51, 52), demonstrating a role for IL-2 in activating the hypothalamic-pituitary-adrenal (HPA) axis *in vivo*.

3. IL-6. Interleukin 6 (IL-6) (183 a.a.) is involved in the terminal differentiation of B cells to antibody-secreting plasma cells, the activation of T cells, and the hepatic synthesis of acute phase proteins (53, 54). It acts through a specific IL-6 receptor but requires heterotrimerization between the IL-6 receptor subunit and two molecules of a signal transduction molecule gp130. The IL-6 receptor is membrane anchored but can also function as a soluble molecule. IL-6 and its receptor appear to form a complex that is recognized by gp130, which dimerizes to trigger subsequent signal transduction (55).

Pituitary expression. IL-6 is synthesized and secreted by the bovine pituitary folliculostellate cell, which does not express pituitary trophic hormones or their precursors *in vitro* (56). In addition, cultured primary rat pituitary cells release IL-6 relatively abundantly (57), and IL-6 is synthesized by both normal human and neoplastic anterior pituitary tissue (58–60).

Pituitary IL-6 expression is induced in a cell-specific manner by agents that act through induction of cAMP, such as forskolin. For example, VIP exerts a dose-dependent induction of IL-6 release from primary cultures of rat anterior pituitary, but GHRH, which also signals through cAMP but is presumably acting on the somatotroph cell, has no such effect (61). These observations are difficult to reconcile with the observed production of IL-6 by the folliculo-stellate cell. Another key regulator of pituitary IL-6 production is bacterial endotoxin. Primary cultures of rat pituitary respond to direct treatment with lipopolysaccharide by an increase in IL-6 accumulation in conditioned medium (62). IL-1, which rises in response to acute inflammatory shock, also exerts a direct effect on primary rat pituitary cultures to induce IL-6 expression (63). This effect appears to be due to an eicosanoid-dependent mechanism regulating biosynthesis of IL-6 (63). Further indirect evidence for the role of IL-1β in stimulating pituitary IL-6 expression is derived from second messenger studies using the lysophospholipid lysophosphatidylcholine. This predicted product of IL-1β induced phospholipase A2 action on membrane phosphatidylcholine to induce IL-6 production (64).

In vivo, pituitary IL-6 expression is induced by lipopolysaccharide as well. Within 2 h of intraperitoneal bacterial lipopolysaccharide (LPS) injection, a massive induction of rat pituitary IL-6 mRNA expression occurs, coinciding with a 30-fold induction of circulating ACTH concentrations (65). Induction of pituitary IL-6 was accompanied by a concomitant induction of splenic and hypothalamic IL-6 mRNA transcripts.

Receptor expression. High-affinity IL-6 receptors are formed by noncovalent heterodimeric bonding of an α-chain subunit and two gp130 signal transducer subunits (66, 67). IL-6 receptor expression has not been extensively studied in pituitary tissue, but the clonal rat pituitary cell line MtT/E, a transplantable prolactinoma, expresses approximately 1000 high-affinity IL-6 binding sites per cell (68), and binding sites have been detected in anterior pituitary tissue (69).

Pituitary action. IL-6 stimulates PRL, GH, FSH, and LH release from cultured rat pituicytes (70, 71). The opposing effects of TRH and dopamine on PRL secretion are respectively modified by IL-6 (51). *In vivo*, IL-6 is a potent stimulus of the HPA axis in man, probably acting at the hypothalamus to stimulate arginine vasopressin (AVP) release and subsequent ACTH induction (72) (Fig. 2). As IL-6 is also present in the circulation, especially during inflammatory stress, the

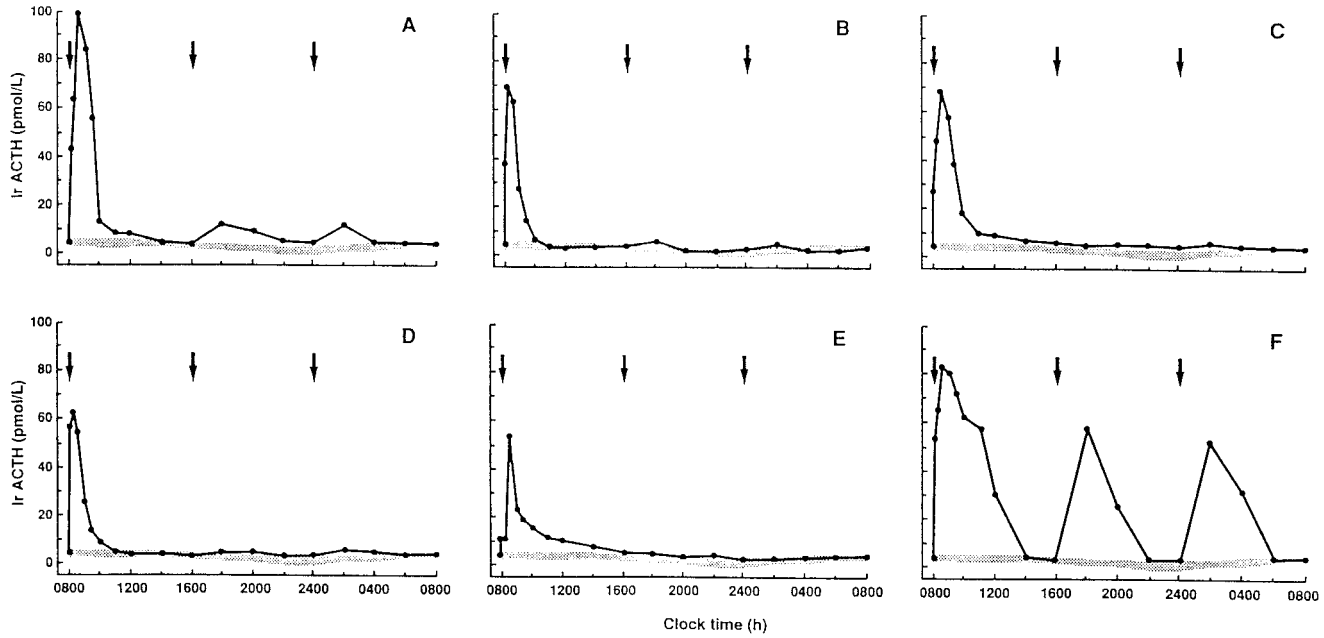


FIG. 2. IL-6 induces ACTH *in vivo* in human subjects. IL-6 was injected intravenously into six cancer patients, indicated by *arrows*, and circulating ACTH was measured. [Reproduced with permission from G. Mastorakas *et al. J Clin Endocrinol Metab* 79:934, 1994 (72). © The Endocrine Society.]

relative importance of locally derived *vs.* systemically available IL-6 on pituitary function remains to be determined (73). The potent induction of ACTH by IL-6 may in fact be of future utility as a diagnostic test for HPA axis function.

Effects of IL-6 on pituitary cell proliferation have also been examined. The clonal MtT/E rat pituitary cell line responds to IL-6 by increasing its rate of cell division (68), but other workers using primary pituitary culture methods have found IL-6 to, in fact, be antiproliferative, although specific pituitary cell types affected were not clearly defined (74). Isotopic DNA synthesis experiments in primary rat pituitary cultures are fraught with the pitfalls of studying a heterogenous cell population including endothelial and other support cells. It is therefore difficult to interpret cytokine effects on pituitary trophic hormone cell growth from these experiments.

B. Leukemia-inhibitory factor (LIF)

LIF (1053 a.a.) is a single-chain glycoprotein classed as a four-α-helical bundle structure. LIF was originally isolated as a factor inducing differentiation and suppressing proliferation of a murine monocytic leukemia cell line, M1 (75). Overexpression of LIF in a murine model leads to a lethal syndrome characterized by weight loss, behavioral changes, ectopic calcification, bone abnormalities, and thymic atrophy (76). In contrast, the LIF knockout mouse has a mild phenotype with modestly impaired growth and decreased numbers of hematopoeitic cells in the bone marrow and spleen (77). Female knockout mice are infertile, due to failure of uterine blastocyst implantation (78). Pituitary function in the LIF-knockout mouse is discussed below.

Pituitary expression. This pleiotropic cytokine is secreted by primary bovine pituitary cultures and was shown to regulate

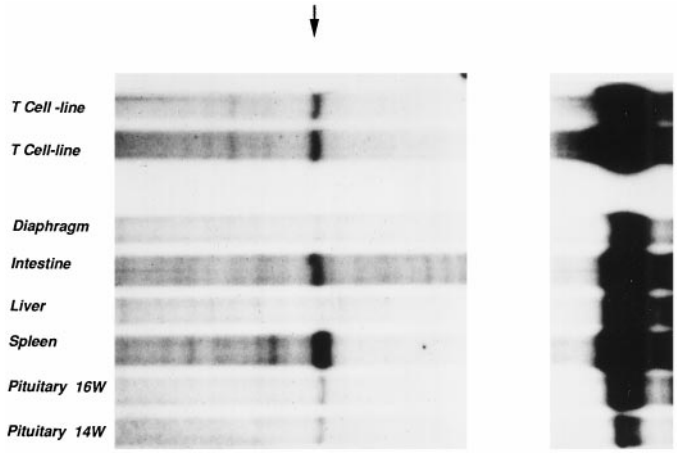


FIG. 3. LIF mRNA expression in human fetal tissues. Rnase protection assay of human fetal tissues derived at 14 (14W) or 16 (16W) wk. RNA extracts (20 μg per lane) were hybridized with 32^P-labeled LIF cRNA ($\sim 10^5$ cpm) and subjected to Rnase digestion. Protected fragments (*arrow*) were 400 bp in size. The *right panel* depicts β-actin mRNA-protected transcripts, which served as internal standards. [Reproduced with permission from A. Akita *et al.*: *J Clin Invest* 95: 1288–1298, 1995 (80) by copyright permission of The American Society for Clinical Investigation.]

blood vessel endothelial cell proliferation (79). LIF gene and protein expression were detected in human fetal (predominantly corticotrophs and somatotrophs) and normal adult pituitary tissue, as well as in functional human pituitary adenomas (80). A protected 400-kb LIF mRNA transcript measured by RNase protection assay was expressed in 14-week human fetal pituitary and was identical to that found in spleen and gastrointestinal tract (Fig. 3). LIF mRNA is also present in the rat and murine anterior pituitary gland as evidenced by both Northern analysis and *in situ* hybridiza-

tion (81). In pituitary explant cultures, protein synthesis inhibitors induced LIF mRNA levels, an effect probably indicating posttranscriptional LIF mRNA regulation (81).

There are two RNA splice variants of murine LIF mRNA, one of which encodes a matrix-associated and the other a diffusible form (82). Using quantitative RT-PCR, mouse pituitary LIF mRNA was induced dose-dependently by intraperitoneal injection of LPS *in vivo* (83). Interestingly, the diffusible form of the LIF mRNA splice variant, barely detectable in the unstimulated pituitary, was markedly induced by LPS, comprising most of the observed induction of pituitary LIF in the stressed animal (83) (Fig. 4). As this diffusible LIF isoform is presumably the molecule capable of acting at a distant site, these observations support a paracrine function for LIF in mediating the immuno-neuroendocrine interface within the pituitary.

Pituitary receptor. Specific binding sites for LIF are present in murine AtT20 pituicytes, as assessed by fluorescent activated cell sorting (FACS) (80). Presumably, these binding sites comprise heterodimers between the specific, low-affinity LIF receptor and the shared affinity converter gp130 common to IL-6, oncostatin, LIF, and ciliary nerve neurotrophic factor (CNTNF) (84). LIF surface receptors, measured by labeled ligand immunostaining, are present in human fetal pituitary cells, predominantly in fetal corticotrophs and somatotrophs, but also in other functional hormone-producing cells (80). LIFR mRNA expression is also found in normal mouse pituitary glands and hypothalami as assessed by RT-PCR immediately after postmortem resection (83). Pituitary LIFR mRNA was induced by LPS *in vivo*, although the changes were less pronounced than those observed for LIF mRNA (83).

Pituitary action. LIF action appears to occur principally on the pituitary corticotroph. Primary cultures of mouse pituitary cells respond to added LIF by enhanced ACTH secretion (85), as do AtT20 murine corticotroph cells (80, 86). In addition, LIF potentiates the action of CRH to induce ACTH secretion in AtT20 cells (86). Oncostatin M, a related cytokine with similar receptor signaling, also induces ACTH (86). LIF action on the corticotroph is blocked by antibodies directed against the gp130 receptor subunit and also is attenuated by dexamethasone. As addition of either LIF antiserum, gp130 antiserum, or LIFR antiserum to AtT20 cultures all attenuate endogenous ACTH secretion in the absence of added LIF, it would appear that autocrine or paracrine LIF regulates ACTH expression (86).

LIF stimulates the JAK/STAT pathway (86), induces transcription of the POMC gene, and synergizes very potently with CRH to enhance POMC expression (86) (Fig. 5). Unlike CRH, LIF does not induce cAMP or c-*fos*; thus it is likely that their synergy occurs distally. It is as yet unclear where the CRH and LIF intracellular signaling pathways interact. Both signaling cascades involve distal POMC promoter response elements apposed between −190 and −130 bp upstream from the POMC transcription start site (87). Deletion studies of the POMC promoter and specific competitive gel shift assays confirm that the two POMC inducers interact directly on the POMC gene (87).

As LIF promotes differentiated cell function in other systems, its effects on proliferating AtT20 cells were examined. LIF, in contrast to CRH, inhibits indices of cell proliferation, including cell number, viable mitochondria number, bromodeoxyuridine incorporation, and S phase entry as assessed by FACS. These inhibitory effects were coincident with induction of secreted ACTH. CRH and LIF, therefore, synergize at the level of hormone production, but exert opposing effects on cell proliferation (85). Thus, LIF appears to induce a neuroendocrine "switch" from a proliferative to a secretory phenotype.

Studies of the HPA axis in mice harboring a disrupted LIF transgene (LIF knockout) revealed a defect in activation of the axis in response to stress. Circulating ACTH levels are attenuated after fasting in the knockout animals, and chronic

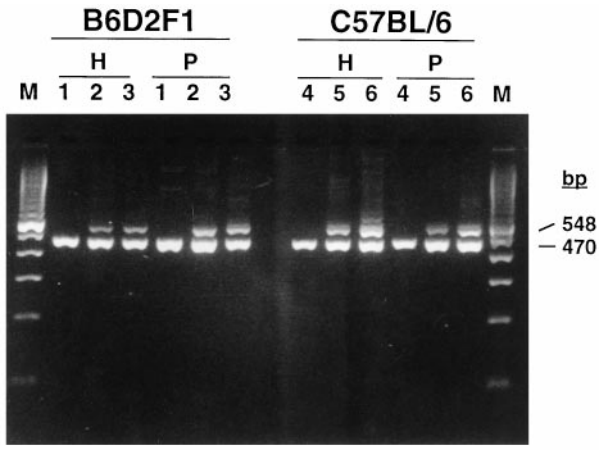


FIG. 4. LPS-induced pituitary LIF-diffusible transcripts. Diffusible (548 bp) and matrix (470 bp) forms of LIF in mouse hypothalamus (H) and pituitary (P) before and after LPS injection. PCR followed reverse transcription of tissue RNA extracted immediately after sacrifice. Lanes 1 and 4, Control mice; lanes 2 and 5, 25 μg LPS; lanes 3 and 6, 80 μg LPS. [Reproduced with permission from Z. Wang *et al.*: *Endocrinology* 137:2947–2953, 1996 (83). © The Endocrine Society.]

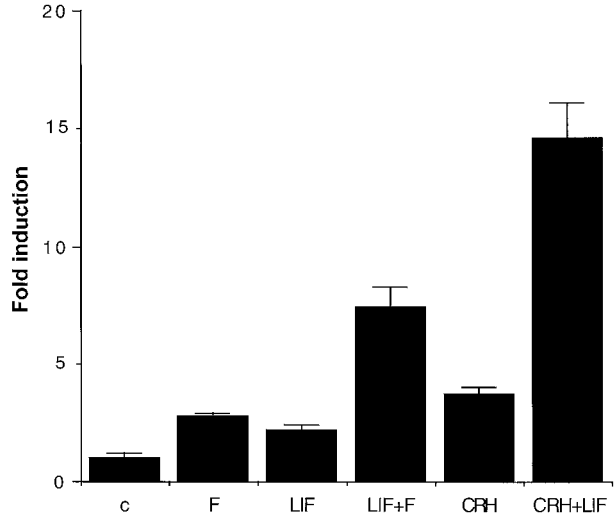


FIG. 5. LIF induces POMC transcription. AtT20 cells were transiently transfected with −706/+64 rat POMC.luc and treated as indicated. Each point represents mean ± SEM (n = 3). [Adapted from D. W. Ray *et al.*: *J Clin Invest* 97:1852–1859, 1996 (86) by copyright permission of The American Society for Clinical Investigation.]

replacement with LIF infusions restores HPA responses to levels seen in wild-type littermates (88).

C. Macrophage migration inhibitory factor (MIF)

This protein (115 a.a. precursor) originally identified as a T-lymphocyte-derived factor (89, 90) is a proinflammatory cytokine recently characterized in LPS-stimulated pituitary cells (91). The receptor for MIF has not yet been cloned, and there is little information on its expression. MIF acts directly on mononuclear cells to oppose the action of glucocorticoid (92–94), but no data are as yet available on a specific pituitary action for the cytokine. Current evidence would suggest that MIF is released by the pituitary to act as a peripheral proinflammatory cytokine.

D. Epidermal growth factor (EGF)

EGF (53 a.a.) a single-chained polypeptide, is a widely expressed growth factor exhibiting both potent mitogenic (95–99) as well as growth-inhibitory effects (100) on diverse cell types. EGF is a cleavage product of a large (1207 a.a.) membrane-associated precursor protein. EGF shares a transmembrane receptor with TGFα, which has intrinsic intracellular tyrosine kinase activity and is activated when two receptor molecules dimerize by interaction with extracellular ligand (101).

Pituitary expression. EGF secretion was detected in conditioned medium of cultured bovine pituitary cells (102), and subsequently both the immunoreactive protein and EGF mRNA were described in the rat pituitary (103).

Pituitary receptors. The product of the c-*erb*-B oncogene has extensive sequence homology with the EGF receptor and is a receptor tyrosine kinase. This receptor also recognizes TGFα (102). Utilizing ligand-binding assays, saturable, specific, high-affinity receptors for EGF were demonstrated in rat pituitary tumor cells (103, 104), as well as in normal adult rat pituitary (105). In contrast to the abundant EGF receptors found in clonal rat pituitary cell lines, and in both rat and normal human pituitary tissue, EGF receptors were not detected in human pituitary adenomas utilizing radiolabeled binding techniques (106). The significance of this finding is unclear in the light of known potent effects of EGF in inducing PRL transcription. More recent work utilizing both immunoreactive and RT-PCR techniques has, in fact, described both EGF and EGF receptors in most functional and nonfunctional human pituitary adenomas (107).

Pituitary action. Several studies have been performed to test the pituitary action of EGF both on cell replication and hormone secretion. EGF was shown to inhibit growth of pituitary cell lines GH3/D6 and GH4C1, and, suprisingly, this inhibitory effect was associated with enhanced PRL synthesis and GH inhibition. Other studies, employing different culture conditions, reported either enhanced or attenuated pituitary tumor cell proliferation (108–110). In neonatal rat pituitary cultures, EGF induces PRL secretion by enhancing the number of functional lactotrophs as well as the amount of PRL produced per cell (111).

The strong action of EGF on PRL transcription is mediated by specific 5′-flanking regions of the PRL gene (112, 113). In addition to these actions of EGF on PRL and GH, EGF has also been reported to stimulate ACTH secretion and corticotroph proliferation *in vitro* (114, 115). In larger doses, EGF also enhanced ACTH secretion in adult sheep *in vivo* (116). Further work has suggested a role for EGF in fetal ovine ACTH production, possibly explaining high circulating ACTH concentrations found in the latter part of pregnancy (117). Others have suggested that corticotroph stimulation by EGF with resultant ACTH induction may be indirect, as *in vivo* EGF is a potent stimulator of hypothalamic CRH synthesis (118). The interpretation of EGF action studied *in vivo* has been hampered by use of very large amounts of peptide causing cardiovascular changes. Thus, these nonendocrine effects may also have influenced pituitary function (117).

An interesting observation in GH_3 cells suggests that EGF may have a more generalized role in pituitary cell differentiation. EGF induces dopamine receptor expression, thus apparently conferring dopamine responsiveness to these tumor cells, which are usually dopamine resistant (119). As a minority of prolactinomas are dopamine resistant, these observations may imply defective EGF action in a subset of these tumors.

E. Transforming growth factor-α (TGFα)

TGF shares a receptor with EGF; thus the two peptides have overlapping activities. TGFα is implicated as a growth factor in a number of malignancies (101), and indeed it has been shown that expression of TGFα is sufficient to transform fibroblasts in culture (120). Mature TGFα is a 6-kDa molecule, apparently cleaved from a larger, secreted precursor of 17–19 kDa. The membrane-associated precursor peptide is capable of receptor activation and can also activate receptors on adjacent cells (121–123). Cleavage of precursor and release of soluble pro-TGFα peptide occurs when the precursor is membrane bound and depends on a signal sequence situated within the C terminus of the protein (124).

Pituitary expression. Conditioned medium from bovine calf pituitary cells in culture was found to contain a growth factor distinct from EGF, but one that required the EGF receptor for its action (102, 125). This factor was subsequently identified as TGFα (50 a.a.), with 44% homology to EGF. Extracts of porcine pituitary were found to contain a 15-kDa growth factor with characteristics of pro-TGFα (126). Furthermore, untransformed pituitary cells in primary culture were shown to secrete a 6-kDa form of TGFα, which is the expected size of the mature molecule. This suggests that cleavage of the membrane-bound form of the peptide is followed by cleavage of pro-TGF in conditioned medium to the mature peptide (123, 127, 128). Expression of pro-TGFα may, in some circumstances, lead to cell transformation even when addition of mature TGFα is devoid of transforming activity (129).

Intrapituitary TGFα gene expression was confirmed as the expected 4.8-kb mRNA species. Immunoreactive TGFα was also found in pituitary tissue sections, confirming the expression of this growth factor in a physiological context (130–134). These studies also demonstrated expression of TGFα to occur predominantly in lactotroph cells. Further work has identified the membrane-bound pro-TGFα in normal pituitary tissue, with specific binding sites. Immunohistochem-

istry studies have also colocalized TGFα with GH immunoreactivity (135). Others have detected TGFα in both normal and tumorous pituitary, where the majority of immunoreactive TGFα was membrane-associated pro-TGFα. There does not appear to be a correlation between functional tumor type and TGFα expression (136, 137).

Estrogen treatment of castrated female mice results in marked up-regulation of pituitary TGFα gene expression as measured by *in situ* hybridization (134, 138). This induction was blocked by cotreatment of mice with the D2 receptor agonist bromocriptine (138). This effect may be mediated by increased transcription rate of the TGFα gene, as transfection studies in breast cancer cells have shown estrogen to increase activity of a TGFα-chloramphenicol acetyltransferase reporter gene (139). Although EGF stimulates TGFα expression, accumulation of TGFα in conditioned pituitary culture medium inhibits this effect because TGFα presumably acts through the EGF receptor (140). As EGF is thought to act in part through protein kinase C, the effects of phorbol esters on TGFα gene expression were examined. Indeed, phorbol esters stimulated, and protein kinase C inhibitors suppressed, TGFα expression (140). TGFβ, which inhibits lactotroph proliferation, was also found to inhibit TGFα gene expression in bovine pituitary primary cultures (141).

Pituitary action. The rat pituitary cell line GH4C1 responded to TGFα with reduced proliferation, mainly caused by accumulation of cells in G0/G1, and reduced numbers of cells entering S phase (142). These cells were shown to express the EGF receptor. Interestingly, an intact TGFα pathway was found to be important in tumor growth of GH4CI cells when transplanted into Wistar-Furth rats (143). In support of an important role for TGFα in pituitary tumor progression is a lactotroph-targeted TGFα-overexpressing transgenic mouse. This transgenic mouse demonstrates selective pituitary lactotroph hyperplasia and PRL-containing adenoma formation (144). Interestingly, only female animals expressing the transgene developed adenomas. Therefore this animal may serve as a model for growth factor-induced prolactinoma pathogenesis. The apparent discordancy whereby TGFα inhibits proliferation *in vitro*, but is required for tumor growth *in vivo*, is intriguing. It is possible that TGFα requires an additional, cell matrix-derived factor to permit mitogenesis, and that this is lacking *in vitro*, or *in vivo* TGFα expression may lead to enhanced microvascular formation facilitating tumor progression.

F. Fibroblast growth factors (FGFs)

This family of growth factors consists of at least nine structurally related peptides that share the capacity for binding to heparin (145). FGF-1 or acidic FGF (155 a.a.), and FGF-2 or basic FGF (bFGF) (155 a.a.) have a 55% amino acid identity. These two peptides share similar biological functions and do not possess a signal peptide sequence (146) and so are presumably not secreted via the regulated pathway. FGF-4, however, a 206 a.a. polypeptide, does contain a signal peptide and therefore may enter the regulated secretory pathway.

As the evidence for pituitary FGF-1 expression is controversial (147, 148), this discussion is restricted to FGF-2 and FGF-4, both of which are significant regulators of pituitary function.

1. FGF-2.

Pituitary expression. Basic FGF (bFGF) is found in abundance within normal pituitary tissue, from where it was originally purified (148–150). Although pituitary FGF-2 mRNA is barely detectable, immunoreactive FGF-2 protein is expressed diffusely in pituitary endocrine cells where FGF-2 appears localized mainly to basement membranes and extracellular matrix. Human pituitary adenomas also contain bFGF, predominantly the 24-kDa form rather than the processed 18-kDa form (151–154). Gonadotroph FGF-2 expression is induced by estradiol, thus suggesting FGF-2 mediation of estrogen-induced pituitary vascularization (155). Within the rat anterior pituitary, bFGF was thought to be expressed predominantly within folliculostellate cells, which costain with S-100, as evidenced by immunohistochemistry (150). Nevertheless, the recent studies cited provide strong evidence for the expression of FGF-2 in pituitary endocrine cells (148, 156).

Multiple endocrine neoplasia-1 (MEN-1), a hereditary syndrome of pituitary, pancreatic, and parathyroid neoplasia is associated with loss of heterozygosity on chromosome 11q13 (157–160). Although this syndrome may therefore be caused by loss of a putative tumor suppressor gene, several interesting recent observations imply an additional abnormality of disordered pituitary FGF synthesis or function. In 40% of patients with MEN-I, bFGF is detectable in the peripheral circulation as measured by RIA (161). Despite the absence of a signal peptide sequence (146), bFGF therefore clearly gains extracellular access (162). Circulating FGF-like autoantibodies have also been detected in two of these patients (163). Because pituitary tumor resection or medical treatment was followed by lowering of circulating bFGF immunoreactivity in eight patients with MEN-I, it would appear that the pituitary is the source of the circulating bFGF. Alternatively, another pituitary factor could be inducing peripheral production of bFGF with resultant elevated growth factor levels. This appears less likely as the observation is restricted to patients with MEN-I, rather than sporadic pituitary tumors. These results suggest a role for bFGF in stimulating pituitary cell proliferation, but there is also evidence that bFGF acts to inhibit proliferation of adenoma cells *in vitro* or not to alter cell growth, either in pituitary adenomas or in rat pituitary cell lines (164–168).

Pituitary receptors. FGF binds to both low- and high-affinity receptors that possess an intrinsic tyrosine kinase domain. FGF receptor (FGFR1) mRNA is detectable by both *in situ* hybridization and immunostaining in rat pituitary endocrine cells (169), and human pituitary adenomas also express FGF receptor mRNA (151).

Pituitary action. Basic FGF has a direct effect on differentiated cell function within the anterior pituitary gland. Primary cultures of rat anterior pituitary respond to bFGF with a specific enhancement of PRL and TSH responses to hypothalamic TRH (166); however, at concentrations of up to 100 pM, bFGF had no effect on basal PRL secretion. Others have tested bFGF effects on human pituitary adenoma hormone production, and bFGF also apparently enhances PRL secre-

tion in the majority (12 of 14) of lactotroph tumors (165). However, others have shown that acute incubation of primary rat pituicytes with bFGF reduces PRL secretion per cell as measured by reverse phase hemolytic plaque assay, suggesting a complex role for bFGF *in vivo* (170). The role of bFGF on PRL production from cell lines has also been assessed. bFGF enhances PRL secretion from both $GH4_{C1}$ cells (110) and GH_3 cells (167, 168). bFGF also selectively increases PRL mRNA accumulation, but not GH mRNA, in GH_3 cells (167, 168).

2. Chondrocyte growth factor (CGF). During purification of GH, pituitary side fractions were shown to exhibit proliferative activity on plated chondrocytes. The factor causing this effect was termed CGF (171). The pituitary appeared to be the source of this factor as serum from pituitary surgery operative fields was rich in the factor, and pituitary explants also secreted the factor when cultured *in vitro* (172). Further purification and characterization of pituitary CGF showed it to bind to heparin and to exhibit cross-reactivity with antibodies to bFGF. It seems likely therefore that the CGF activity isolated from human pituitary tissue was, in fact, bFGF and therefore was the initial description of this factor in the human pituitary.

3. FGF-4. FGF-4 is the protein product of the *hst* gene (173). Its expression is restricted to embryonic tissue and, in the adult, this growth factor is only expressed in neoplastic tissue (174). FGF-4, the gene product for *hst* is glycosylated and secreted in the medium of producer cells. FGF-4 is a potent *in vitro* and *in vivo* mitogen for PRL-secreting cells.

FGF-4 stimulates rat PRL secretion in primary rat pituitary cultures and also induces PRL gene transcription while attenuating GH biosynthesis (175). Overexpression of FGF-4 cDNA in pituicytes results in markedly enhanced PRL secretion. Subcutaneous rat pituitary tumors (175) derived from *hst* stable transfectants were larger, secreted more PRL, and exhibited aggressive growth features including vascular invasion and increased proliferating cell nuclear antigen.

Human prolactinomas express *hst* gene sequences possessing transforming activity in an NIH3T3 transformation assay (176). Sixty percent of invasive prolactinomas immunostain positively for FGF-4, while less than 10% of other pituitary adenomas express the immunoreactive protein (I. Shimon, D. Hinton, M. Weiss, and S. Melmed, manuscript submitted). Vascular invasion and tumor aggression as assessed by proliferating cell nuclear antigen staining correlate highly with tumor *hst* expression (our unpublished data). These results indicate that, in addition to its mitogenic activity in promoting pituicyte proliferation *in vitro* and *in vivo*, FGF-4 selectively induces PRL gene transcription (our unpublished data). Therefore, the unrestrained PRL secretion characterizing these adenomas may not necessarily reflect an increased mass of hormone-secreting cells but, in addition, a growth factor-specific induction of polypeptide hormone transcription.

G. Nerve growth factor (NGF)

The neurotrophic NGF family includes NGF, brain-derived neurotrophic factor (BDNF), and neurotrophin-3 and 4. The prototype of this family NGF (120 a.a.) was identified as an activity that promoted neuronal survival, neurite growth, and sympathetic neuron neurotransmitter production. NGF is produced by target cells and is bound and internalized by sympathetic neurons. Thereafter it is transported by retrograde axonal movement to the cell soma where it acts via its cotransported receptor (177). A family of related molecules, the neurotrophins, were subsequently identified and these are thought to act similarly (178). Although NGF was originally identified as a survival and differentiation factor for sensory and sympathetic neurons, it is now known to exert a far wider ranger of biological actions. In inflammatory disease, NGF expression modulates pain perception, causing a hyperalgesic phenomenon. It also functions to prime and recruit local and systemic stress responses in conditions of physiological stress (179).

NGF action is primarily mediated by the Trk family of tyrosine kinase receptors, which are closely related to the transforming *trk* oncogenes (180). In addition to the three related tyrosine kinase-containing receptors Trk A, B, and C, there is also a low-affinity, p75 receptor. The p75 receptor functions as an enhancer of Trk receptor activity (181, 182), but use of selective Trk kinase inhibitors has shown the critical importance of this receptor for mediating NGF effects (183). Furthermore, disruption of the *trk* gene leads to a lethal phenotype in the mouse, with severe sensory and sympathetic neuropathies (184). The three Trk kinase receptors are expressed in a developmentally regulated fashion throughout the central nervous system, but their expression remains detectable in mature neurons throughout the central nervous system, suggesting that these neurons retain neurotrophin responsiveness (185). However, it seems that the p75 receptor is capable of generating the putative second messenger ceramide in response to NGF by activation of the sphingomyelin cycle (186). The cell response to NGF may also be mediated in part by induction of nitric oxide synthase. In PC12 cells NGF causes an initial proliferation, followed by growth arrest and phenotypic differentiation. This later action is mediated by nitric oxide (187).

Pituitary expression. Low levels of NGF mRNA and NGF-like immunoreactivity are present in the rat pituitary (188). Using a sensitive bioassay of neurite outgrowth in PC12 cells, as well as a specific ELISA, NGF was detected in cultured anterior pituitary cells (43). Further, rat intermediate lobe pituitary was found to express NGF immunoactivity *in vivo*, and secrete NGF in primary culture (189, 190). IL-1β induces *in vitro* NGF production, suggesting that NGF may be a mediator of trophic hormone responses to stress (43). Immunolabeling studies indicate that about 30% of anterior pituitary cells express NGF as well as the high-affinity gp140trkA receptors. These cell types include most of the trophic hormone cells, especially gonadotrophs and somatotrophs (188). In fact, GHRH inhibits NGF secretion, thereby further implicating the somatotroph as a source for NGF (43). However, others have found NGF to be specifically localized to the thyrotroph lineage; presumably, these differences reflect methodological variations (191, 192). NGF mRNA has also been identified in pituitary lactotroph cells, and indeed there is some evidence to suggest the pituitary as a source of circulating NGF. Lactotroph NGF expression appears to be

dopamine responsive, in parallel with changes in PRL itself (193).

Pituitary action. Several experimental models indicate a permissive role for NGF in promoting lactotroph development. In early postnatal rat pituitary cultures, NGF induces PRL secretion and doubled the number of lactotroph cells. Conversely, using an NGF immunoneutralizing antibody the appearance of mature lactotrophs *in vitro* was attenuated (194). Lactotroph hyperplasia also develops in mice overexpressing a pituitary-directly NGF transgene (195). Bromocriptine-resistant human pituitary tumor cells secreting PRL had dopamine responsiveness restored by pretreatment with NGF, presumably by inducing D2-receptor availability (196). In addition to these effects of NGF on the lactotroph lineage, NGF can act on the hypothalamic-pituitary-adrenal axis to increase secretion of ACTH, and so induce adrenal glucocorticoid production (197). This is a potential mechanism whereby the role of NGF as a modulator of the inflammatory response may be mediated. However, this effect is probably mediated by induction of hypothalamic AVP rather than a direct action of NGF on the pituitary corticotroph (198–200).

Curiously, exposure of human prolactinoma cells *in vitro* to NGF results in their assuming a less aggressive growth phenotype (201). Abrogation of NGF expression in prolactinoma cells by antisense oligonucleotides results in loss of dopamine D-2 receptor expression and an increase in cell proliferation rate (202). Although suggesting that an NGF-mediated autocrine loop inhibits lactotroph cell proliferation and tumor progression (202), these observations are at variance with the demonstrated stimulation of rodent lactotroph development and function by NGF. As human prolactinoma cells do not proliferate *in vitro*, these results may reflect measurements of nonendocrine pituitary cell growth.

H. Galanin

Galanin is a 29-amino acid peptide with limited sequence homology to other characterized peptides (203). It was originally isolated from intestine, but has a wide distribution within the central nervous system (204, 205), and other tissues. The highest concentrations of galanin have been identified within the hypothalamus and median eminence (206).

Pituitary expression. Galanin-like immunoreactivity has been detected in both normal human pituitary and adenomatous pituitary tissue (207). Galanin immunoreactivity was particularly prominent in corticotroph adenoma cells (208), whereas in other clinically nonfunctioning adenomas weaker immunoreactivity was present (207). Galanin also colocalizes with PRL in normal pituitary (209) but not in lactotroph adenoma tissue (207, 208).

Pituitary action. Central immunoneutralization studies in the rat have implicated galanin in the control of spontaneous, pulsatile secretion of GH, but not of PRL (210). Evidence has also accumulated suggesting that galanin action occurs primarily at the hypothalamus, stimulating GHRH secretion (211), but additional work showing galanin to potentiate maximal doses of GHRH in man suggests a further role for galanin in inhibiting hypothalamic somatostatin (212).

In marked contrast to the apparently hypothalamic site of galanin action on GH, galanin acts directly on the pituitary lactotroph mediating cell proliferation and PRL expression (213). Galanin is released from a subset of lactotrophs, both basally and in response to estradiol, a potent lactotroph stimulant, and also acts on other low level secreting lactotrophs to stimulate proliferation and PRL secretion. As estrogens stimulate lactotroph hyperplasia and ultimately adenoma formation in rats, and as this effect thus appears mediated by galanin, galanin may be a significant factor in human prolactinoma development.

Galanin increases circulating GH levels in healthy male volunteers (214) but in contrast, rather surprisingly, suppresses GH levels in acromegalic subjects (215). There also appears to be a permissive effect of circulating estradiol on galanin action, as young women have enhanced GH responses compared with postmenopausal women and men (216).

I. Insulin-like growth factors

1. Insulin-like growth factor-I. IGF-I, the peripheral growth mediator of GH is a 70 a.a. polypeptide structurally related to proinsulin and IGF-II (217). IGF-I is secreted predominantly by the liver, but the gene is also expressed in multiple extrahepatic tissues (218).

Pituitary expression. IGF-I is expressed in the rat and human pituitary (219–224). Rat pituitary tissue explants were shown to be a source of IGF-I in culture (219). Normal rat anterior pituitary, as well as rat pituitary GH_3 cell lines express IGF-I, as evidenced by the demonstration of IGF-I mRNA transcripts, immunohistochemical staining and accumulation of IGF-I peptide immunoreactivity in conditioned culture medium (220–222). Pituitary GH mediates most of its growth-promoting activity by inducing peripheral IGF-I production (225). Several lines of evidence support the notion that pituitary IGF-I is also, in fact, regulated by GH. When grown in thyronine-depleted medium to decrease GH synthesis, GH_3 cell and primary rat anterior pituitary cell IGF-I mRNA content is markedly diminished (226). Addition of T_3 or GH induces IGF-I mRNA transcripts and peptide in a time- and dose-dependent fashion (226). *In vivo*, administration of T_3 or GH to thyroidectomized rats also enhanced expression of pituitary IGF-I (227). Finally, in rats harboring GH-secreting tumors with high levels of circulating GH, pituitary IGF-I mRNA was also induced (221). Thus, there is a considerable body of *in vitro* and *in vivo* evidence that GH regulates pituitary IGF-I synthesis, similarly to its induction of IGF-I in peripheral tissues.

Although rat pituitary IGF-I mRNA localizes in nonendocrine interstitial cells, IGF-I receptor mRNA appears to be expressed on pituitary endocrine cells (224). In contrast, in human pituitary tumors, IGF-I immunoreactivity was detected in all trophic hormone-secreting cells (228). The concordant expression of pituitary GH and IGF-I may therefore reflect a mutual paracrine or autocrine feedback regulation occurring directly at the level of the somatotroph. Additionally, negative feedback of IGF-I on GH gene expression may be mediated via blood-borne (endocrine) delivery of the peptide from peripheral tissues (Fig. 6).

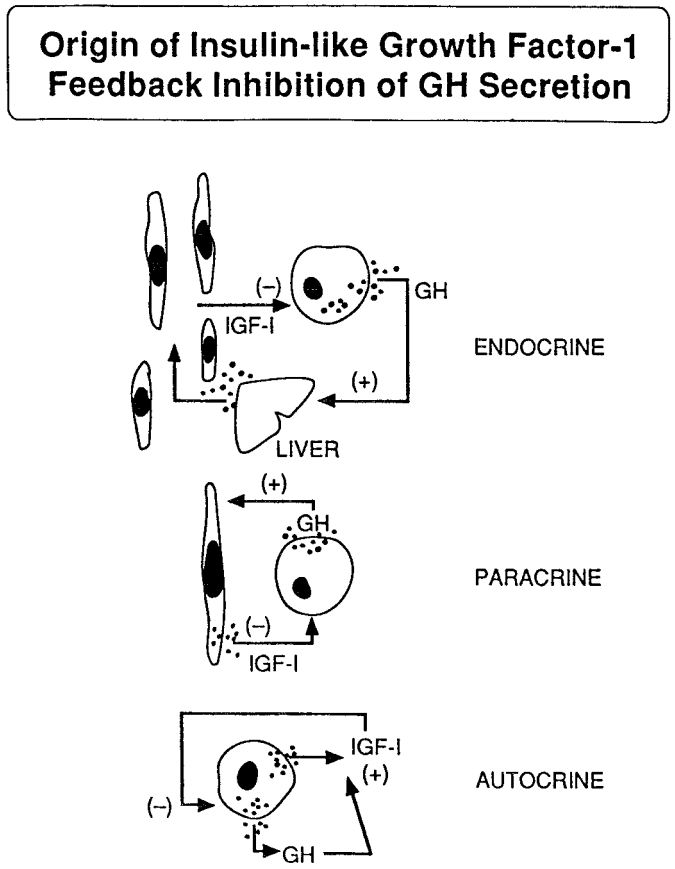


FIG. 6. IGF-I negative feedback. Cellular origins of IGF-I contributing to endocrine, paracrine, or autocrine regulation of the somatotroph. IGF-I synthesized either in the periphery, pituitary endothelial cells, or within the somatotroph itself may regulate GH gene expression. [Reproduced with permission from S. Melmed *et al.*: *Recent Prog Horm Res* 51:189–216, 1996 (251). © The Endocrine Society.]

Pituitary action. As IGF-I is the peripheral target hormone for GH action, regulation of pituitary GH synthesis and secretion by IGF-I may represent a classic negative feedback loop, analogous to that operative for thyroid and adrenal hormone feedback regulation of their respective pituitary trophic hormones.

In primary rat pituitary cultures, a partially purified somatomedin C preparation was shown to suppress cAMP-induced GH secretion (229, 230). Interestingly, using hypothalamic cultures, somatomedin C was also shown to stimulate accumulation of somatostatin (SRIF), thus adding a further level of negative control of GH expression by IGF-I (229). *In vivo*, central administration of somatomedin C also attenuated rat GH secretion (231).

Subsequently, the availability of synthetic recombinant IGF-I analogs allowed further delineation of pituitary IGF-I action. IGF-I was shown to attenuate GH secretion and mRNA accumulation *in vitro*, both in the basal state, as well as after GH induction by hydrocortisones T_3, cAMP, 12-*O*-tetradecanoylphorbol 13-acetate, and GHRH (232–234). The suppression of GH synthesis occurs directly at the level of GH transcription, as evidenced directly by run-off studies utilizing isolated pituitary nuclei (235) (Fig. 7) as well as by

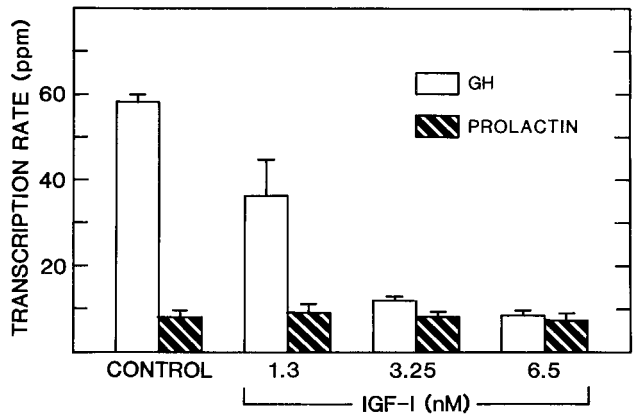


FIG. 7. IGF-I suppresses GH transcription. IGF-I effects on GH and PRL gene transcription. Primary cultures of rat anterior pituitary cells were incubated with or without added IGF-I. Nascent GH mRNA and PRL mRNA were measured by transcriptional runoff assay with ^{32}P-labeled GTP and hybridization against immoblized GH and PRL cDNA. [Reproduced with permission from S. Yamashita and S. Melmed: *J Clin Invest* 79:449–452, 1987 (235) by copyright permission of The American Society for Clinical Investigation.]

showing attenuation of GH-driven chloramphenicol acetyltransferase reporter gene activity in response to IGF-I (236). In addition to these direct nuclear effects of IGF-I, the growth factor also blocks acute GH secretion from perfused rat pituitary cells (237). The above lines of evidence therefore point to a potent inhibition of GH gene expression by IGF-I occurring at multiple levels within the somatotroph and acting additively with SRIF (238).

Although the above actions of IGF-I are clearly distinct from those of insulin based directly upon immunoneutralization and dose-response evidence, insulin itself also modestly suppresses GH expression and transcription (239, 240).

Pituitary receptors. The IGF-I receptor is a tyrosine kinase heterotetramer composed of two α- and two β-chains (241). The rat anterior pituitary gland as well as GC cell lines contain receptors for insulin, IGF-I, and IGF-II (242–245). In the rat pituitary, the relative abundance of these receptors is IGF-II > IGF-I > insulin, whereas the converse appears true for rat pituitary tumor cell lines. Pituitary IGF-I cell surface receptors are down-regulated by translocation to the intracellular pool, while ligand removal is followed by recycling and subsequent reexpression of surface receptors (246). Overexpression of IGF-I receptors in pituicytes markedly enhances somatotroph sensitivity to IGF-I without changing receptor affinity (247). Thus, structure-function analysis of the human-IGF-I receptor showed that IGF-I regulation of GH was clearly receptor-mediated and dependent on receptor mass. By studying human IGF-I receptor mutants transfected into GH cells, it was apparent that ^{950}Tyr situated in the transmembrane receptor domain was critical for transmission of the ligand-mediated signal to the somatotroph nucleus (248). Despite adequate autophosphorylation, the ^{950}Tyr mutant is unable to phosphorylate somatotroph cytoplasmic substrate, while a kinase-deficient mutant (^{952}STOP) also exhibited dominant negative inhibition of endogenous IGF-I receptor function, probably by forming heterodimeric hybrids with endogenous hemireceptors (249). Postreceptor IGF-I signaling in the somatotroph is also me-

diated by a rapid induction of mitogen-activated protein kinase, which appears to be clearly IGF-I receptor mediated (250).

The well defined negative feedback of IGF-I on GH secretion has several clinical implications involving the metabolic homeostasis of the GH axis (251).

Acromegaly. The structural integrity of the submembrane domain of the IGF-I receptor, as determined by PCR-SSCP analysis and direct sequencing, appears intact in GH cell tumors (252). This would explain the apparently intact *in vitro* IGF-I regulation of GH in cultured acromegaly tumor cells (253). In GH cell adenomas, therefore, unrestrained GH secretion characteristic of acromegaly (233) is not associated with defective IGF-I receptor structure. As IGF-I receptor numbers are clearly down-regulated by IGF-I in rat pituicytes (246), the elevated circulating IGF-I levels characteristic of acromegaly may presumably decrease GH responses by down-regulating pituitary IGF-I receptor mass.

Pituitary IGF-I action in the human. Several recent studies have confirmed that exogenously administered IGF-I to healthy subjects suppresses GH-secretory activity (254–256). When IGF-I was administered by continuous subcutaneous injection (7–21 μg/kg/h) GH levels were attenuated by more than 50% (254). IGF-I suppresses the number of GH pulses as well as the mass of GH secreted per pulse (255). *In vivo* IGF-I action on the human pituitary requires continuous infusion, and rapid GH recovery occurs within 3 h of IGF-I cessation (256). As fasting and malnutrition are associated with elevated GH and concomitantly lower IGF-I levels, pituitary IGF-I feedback regulation may, in fact, function to counteract catabolic effects of malnutrition by allowing unrestrained secretion of anabolically active GH (257). Pituitary IGF-I receptors may also be regulated during metabolic derangements such as thyroid dysfunction or diabetes (227). Diabetic rat pituitary glands contain markedly elevated IGF-I content, suppressed GH concentrations, and low peripheral tissue IGF-I levels (222). Therefore, intrapituitary GH suppression by IGF-I may also serve as a compensatory mechanism for hyperglycemia.

2. IGF-II. IGF-II binding sites are abundantly expressed in the rat anterior pituitary (242). Although competition studies have indicated that IGF-I affinity for the IGF-I receptor was 14-fold greater than that of IGF-II for the IGF-I receptor, similar to their ED_{50} differences in attenuating GH secretion, it would appear from several models that somatotroph IGF-II action is mediated by the IGF-I receptor (258). For example, mutant IGF-II ligands selectively binding to the IGF-II receptor do not alter GH, while cells exclusively overexpressing IGF-I receptor exhibit enhanced sensitivity to IGF-II attenuation of GH (258). *In vivo*, IGF-II also appears to be critical for IGF-I inhibition of GH (259). The true function, therefore, of the pituitary IGF-II receptor remains elusive.

J. TGFβ

TGFβ (112 a.a.) is distinct from TGFα, does not support rat fibroblast colony formation in soft agar, and acts predominantly to inhibit cell growth (260). There are five forms of TGFβ, all of which are inititally synthesized as part of a larger precursor molecule (261–265). After cleavage by a subtilisin-like protease, mature TGFβ is secreted noncovalently bound to the latency-associated peptide, a precursor remnant (263). The physiological step leading to activation of the latent complex is uncertain, but this step is critical in the regulation of TGFβ. Mature TGFβ is a homodimer of two identical 112 aa chains (266).

The 2.4-kb transcript of TGFβ I was detected in rat pituitary and immunoreactive peptide was also identified (267). Specifically, expression of TGFβ I, the predominant isoform, was detected in pituitary gonadotroph and lactotroph cells, with lower expression in somatotroph and corticotroph cells (268). Pituitary expression of TGFβ is inhibited by estradiol treatment, coincident with lactotroph hyperplasia (269, 270), and in those tumor cell lines that are inhibited by estradiol (MtTF4 and F4P), estradiol also induced TGFβ expression (271). These reports suggest a complex role for TGFβ in mediation of estradiol actions. In the normal pituitary, estradiol inhibits TGFβ expression, coincident with promotion of lactotroph proliferation, but in some transformed lactotrophs estradiol inhibits proliferation, and this inhibition appears to be mediated by TGFβ.

The actions of TGFβ are mediated by three cell surface receptor types. Types I (53 kDa) and II (70–85 kDa) interact with each other and are capable of transducing a signal (272, 273). The type III receptor (250–350 kDa) betaglycan exists in both membrane-bound and soluble forms and is incapable of transmitting a signal (273). The proposed model for TGFβ interaction with its receptors suggests TGFβ binding to betaglycan (type III receptor) followed by the complex interacting with the type II receptor. The betaglycan is then expelled from the complex by the type I receptor to leave a high-affinity complex of TGFβ with type I and type II receptors, which initiates signal transduction. In cells lacking betaglycan expression, the high-affinity complex forms directly (274, 275). In addition pituitary cells have been proposed to express a type IV receptor (60 kDa), which binds activin, inhibin, and TGFβ (276). These receptors have been identified in nonfunctioning and somatotroph cell adenomas (277). It seems likely that TGFβ action is modulated by tissue-specific expression of receptor subtypes with different affinities for the different TGF molecules.

There is much interest in the role of TGFβ as an inhibitor of tumor cell proliferation (278). The molecular mechanisms of this inhibition, at least in epithelial cells, appear to involve Rb induction, inhibition of N-myc expression, and induction of the three cyclin-dependent kinase inhibitors p21, $p27^{KIP1}$, and $p15^{ink4B}$ (279–283). In the pituitary, TGFβ results in significant decreases in both cellular $p27^{KIP1}$ protein levels and $p27^{KIP1}$ mRNA (284). TGFβ also inhibits cell proliferation, probably by introducing a "brake" to G1/S cell cycle phase transition (285). The decrease in cell proliferation is accompanied by a decrease in expression of TGFα in primary bovine pituitary cell cultures (141). Studies using enriched pituitary lactotroph cells show that TGFβ reduces estradiol-stimulated PRL release, and in these cultures TGFβ also had an antimitogenic effect (286). TGFβ also acts to reduce both basal and calcium ionophore-stimulated PRL production from clonal rat pituitary tumor cell lines (287).

TGFβ receptor splice variants are also present in nonfunc-

tioning and GH-cell human tumors (277), presumably mediating activin action (277). $p27^{KIPI}$, a cyclin-dependent kinase inhibitor, acts to suppress cell cycle progression (284), and studies in other cell systems have implicated $p27^{KIPI}$ as a target protein for TGFβ (288). Interestingly, disruption of $p27^{KIPI}$ results in gigantism and neurointermediate lobe hyperplasia with normal GH levels in transgenic mice (289–291). The lack of anterior pituitary abnormalities in these knockout mice suggests that $p27^{KIPI}$ is not important for mediating TGFβ effects on pituitary function.

K. Activin, follistatin, and inhibin

Activin and inhibin are heterodimeric proteins, members of the TGFβ family and have been extensively studied as regulators of the pituitary gonadotroph (5, 6). Briefly, activin is expressed in the pituitary gonadotroph cell, and follistatin is probably expressed principally by the folliculostellate cell (292) but also by the somatotroph and gonadotroph (293, 294). The importance of pituitary-produced inhibin *vs.* peripherally derived peptide is as yet uncertain. In addition to their actions on gonadotroph cells, which have been well reviewed elsewhere (5, 6), activin suppresses GH (295) and POMC expression (296, 297).

L. Miscellaneous

Pituitary expression of many growth factors or cytokines has been demonstrated, mainly by immunostaining techniques. Nevertheless, much of their physiological or pathological significance is as yet undetermined or controversial. Evidence for the pituitary relevance of some of these factors is provided and underscores the need for further work to substantiate their pituitary function.

1. PTH related peptide (PTHRP). PTHRP was originally identified as the causal factor in humoral hypercalcemia of malignancy. The N-terminal portion of PTHRP shares close homology with the N-terminal sequence of PTH, and the two hormones share a common receptor. Although, PTHRP has been implicated in several developmental and cell cycle-related actions (298–300), its physiological function remains enigmatic.

Immunoreactive PTHRP is found in normal human pituitary tissue obtained at autopsy (301), and immunoreactivity is strong in GH-secreting adenomas and to a lesser and variable degree in other adenoma types (301). Overall, 50% of human pituitary adenomas exhibit PTHRP immunoreactivity (301). A variant GH_3 pituitary cell line with malignant characteristics has been subcloned and shown to exhibit marked overexpression of PTHRP (302).

2. TNFα. TNFα, also known as cachectin, plays a key role in the initiation of the inflammatory response, and its expression has been shown to exert many adverse effects seen in the septic shock syndrome (303). There is no direct evidence for intrapituitary synthesis of TNFα (157 a.a.). Exogenous TNFα reduced TSH (39) secretion in primary rat pituitary cultures, had no effect on TRH-stimulated TSH release, and induced PRL release (304, 305). In this regard the effects of TNFα were similar to those observed for IL-1β. However, others have found acute TNF treatment to enhance release of ACTH, TSH, and GH without altering PRL (306). Another study demonstrates TNF to inhibit PRL, the CRH induction of ACTH, the GHRH induction of GH, and the LHRH induction of LH (307). Clearly, these variant results are difficult to interpret and do not suggest a mechanistic role for TNF in the pituitary. *In vivo* TNFα stimulates circulating ACTH levels in rats, but this effect was suggested to be due in part to stimulation of hypothalamic CRH synthesis, based on explant cultures and immunoneutralization studies (308).

3. Hypothalamic factors. Although GHRH, SRIF, CRH, GnRH, and TRH are synthesized in the hypothalamic nuclei, these hypothalamic hormones are also expressed in normal and tumorous pituitary tissue, as evidenced by *in situ* hybridization and immunochemical techniques (309–315). The contribution of locally produced hypothalamic peptides to paracrine control may be significant as pituitary cells possess high-affinity receptors for these peptides. Physiologically, it may be difficult to distinguish hypothalamic from paracrine sources of these peptides. This may be significant for these patients harboring functional gangliocytomas, which impinge anatomically on the anterior pituitary resulting in hypersecretion of GH, ACTH, or gonadotropins.

4. Endothelin. Endothelins are potent vasoactive peptides produced by endothelial cells. They act to induce vasoconstriction in smooth muscle and are important regulators of vascular tone (316). There are three endothelin molecules, ET-1, ET-2, and ET-3, which act through three receptors, ETA, ETB, and ETC. The ETA receptor is found principally on the arterial side of the circulation and mediates vasoconstriction, whereas the ETB receptor is found on the venous side and mediates vasodilation. The ETC receptor is of uncertain physiological significance. Intracellular signaling events triggered by ETA receptor involve activation of phospholipase C and subsequent mobilization of calcium stores (316). Infusion of endothelin 1 into healthy men suppressed GHRH-stimulated GH and PRL. It also potentiates the CRH-stimulated rise in ACTH secretion (317). These effects are only partially modulated by cotreatment with calcium channel antagonists, suggesting more diverse intracellular pituitary signaling for endothelin 1. Endothelin 3 stimulates GH, TSH, FSH, and LH and suppresses PRL (318–321). Long-term dopamine exposure *in vitro* reverses the PRL-inhibitory action of endothelin (322). The specific cellular source of pituitary endothelin 3 is as yet undetermined. The endothelins appear to be synthesized in the rat and human anterior pituitary (323, 324), and there is clear evidence for ETA receptor (325) expression in normal pituitary tissue. Therefore, there is clear evidence that these molecules exert diverse *in vivo* and *in vitro* effects on pituitary trophic cell function. Nevertheless, the physiological or pathophysiological role of this pathway remains to be determined.

5. Angiotensin. Angiotensin II (AII) has variously been reported to be expressed in gonadotrophs (326) and lactotrophs (326). AII may increase production of TSH (327) and either increase or decrease GH and ACTH (328–330). These results, however, do not substantiate physiological relevance, as the

prevalent use of pharmacological AII antagonists does not alter pituitary function.

III. Integrated Role of Intrapituitary Cytokines and Growth Factors

A. Cytokines and pituitary tumorigenesis

Although the ability of the pituitary cell to both produce and respond to an intrapituitary growth factor or cytokine is now well established, mechanisms for subsequent mitogenesis and cell transformation to a pituitary adenoma are still unknown. The observation that pituitary tumors are monoclonal in origin provides compelling support for an intrinsic pituitary mutation leading to tumorigenesis (331, 332).

Several of the pituitary-derived growth factors described above may in fact be potentially oncogenic as they possess the capacity to transform cells. Although overexpression of FGF-2 fails to induce cell transformation, the addition of chimeric secretory leader sequences converts FGF-2 into an oncogene (333). By structurally altering FGF-2, its gene product was able to undergo regulated secretion and to result in transformation similar to that induced by FGF-4 (334). Constitutive overexpression of TGFα also induces cell transformation and development of solid tumors in transgenic mice (144). NGF overexpression in the pituitary results in a curious phenomenon of pituitary hyperplasia, but comprises postmitotic, normal lactotrophs. Thus, these data are compatible with NGF acting on lactotroph progenitor cells, which are therefore expanded, and which subsequently mature and differentiate, rather than become transformed (195). These data are compatible with those discussed above showing NGF to exert a slowing effect on lactotroph proliferation. Interleukins may also behave as activated oncogenes either after a retroviral-induced promoter insertion or by constitutive overexpression (335). To date, true growth factor-mediated pituitary cell transformation has been best exemplified by studies of TGFα overexpression (144).

Although protooncogenic products may in fact be detectable in the pituitary, to date few pituitary oncogene mutations have been encountered. The *gsp* missense mutation in Gsα leads to constitutive cAMP activation and GH hypersecretion in a subset of GH cell adenomas (336). Activating *ras* mutations have been reported in isolated highly invasive or truly metastatic pituitary tumors (337, 338). Conversely, loss of heterozygosity on chromosomes 11q13 (339, 160) and 13 (340) may also indicate loss of a pituitary tumor suppressor gene in up to 20% of sporadic pituitary adenomas.

Indices of total DNA synthesis in intact or cultured primary pituitary tissue in response to growth factors may in fact provide mitogenic information on nontrophic pituitary cells and should not be interpreted as evidence in favor of true endocrine cell mitogenesis. Furthermore, merely demonstrating the presence of an immunoreactive growth factor in a pituitary tumor is insufficient evidence with which to ascribe a pathogenetic role for that factor. Functional transformation studies employing pituitary-specific transfected growth factor and receptor genes *in vitro* and *in vivo* are the ultimate test for a definitive growth factor role in pituitary tumor pathogenesis. Few such studies have been reported, although the transgenic models of pituitary-directed NGF and TGF animals are superb examples of the power of this methodology.

Multifactorial mechanisms appear to subserve the pathogenesis of pituitary adenomas (341). Dysregulation of early pituitary transcription factors (*e.g.* Pit-1) or chromosomal mutations (*e.g.* MEN-1) may in fact cause DNA-altering events in an early stem cell. Subsequently, multiple endocrine and paracrine growth factor signals may impinge on the previously "initiated" cell and determine clonal expansion. These include overstimulation by hypothalamic hormones or disordered hypothalamic-hormone signaling (*e.g. gsp*); disordered cytokine action on cell replication (*e.g.* interleukins) and or growth factor regulation of hormone transcription (*e.g.* LIF; FGF); disordered pituicyte signal transduction (*e.g.* cAMP response element binding protein); altered adenohypophyseal angiogenesis (*e.g.* vascular endothelial growth factor); loss of negative feedback inhibition (*e.g.* hypothyroidism or hypoadrenalism). The ultimate biological behavior and growth characteristics of the resultant transformed neoplasm are then determined by permissive growth factor action (*e.g.* FGF) or oncogene activation or inactivation (*e.g. ras*; chromosome 13).

B. Intrapituitary cytokine role in septic shock response

Cytokines are critical in the acute response to septic shock and may contribute to the catastrophic cascade of events leading to death (342). The pituitary integrates peripheral and central signals to modulate adrenal glucocoticoid production that accompanies host stress responses. Several lines of evidence may be integrated to suggest a unifying hypothesis linking activation of peripheral cytokine cascades, hypothalamic releasing factors, and intrapituitary cytokine expression with pituitary-mediated modulation of the systemic inflammatory response.

Acute septic insult provokes a local inflammatory response, with coordinated and sequential activation of a series of proinflammatory cytokines (73, 343, 344), neural and bacterial toxin signals that impinge on the hypothalamus and pituitary, activating the hypothalamic-pituitary-adrenal axis (345). Initially, peripheral activation of local and distal TNF expression is followed by IL-1, IL-6, and LIF (73). Interestingly, the hypothalamus and pituitary are also sites of *de novo* cytokine synthesis. Pituitary IL-1β and LIF are up-regulated by LPS (23, 28, 83), a model for gram-negative septic shock, and MIF is acutely released from pituicytes *in vitro* and *in vivo* in response to LPS (91). As discussed earlier, intrapituitary IL-6 is up-regulated by IL-1 (71, 73), and therefore an intrapituitary network of cytokines is established in the acute phase of septic shock, in addition to the circulating, peripherally derived cytokines. A number of the proinflammatory cytokines exert most, if not all, their activities at the hypothalamus, notably IL-6 acting on hypothalamic AVP (72), and IL-1 and TNF acting on CRH (40, 308). Others clearly act at the pituitary, notably LIF (86, 87).

The pituitary responses to septic shock can be divided into two functional groups. The first are those that suppress inflammation (IL-6 and LIF) (345) and are typically associated with activation of the HPA axis with increased adrenal glu-

cocorticoid production, thus limiting the extent of the inflammatory response, and protecting against lethality. The second group of reponses are associated with enhanced release of proinflammatory factors and enhance the lethality of experimental endotoxemia. The recent description of pituitary MIF is the first comprehensive description of such a pituitary factor (91).

At the hypothalamic level, both circulating and locally derived cytokines enhance expression of the powerful corticotropin releasing factors CRH and AVP. Hypothalamic LIF mRNA is also up-regulated by LPS treatment, especially the diffusible isoform (83), suggesting regulation of corticotroph function by a "typical" hypothalamically released factor. The relative importance of hypothalamic *vs.* pituitary *vs.* peripheral LIF has yet to be determined.

During acute inflammatory shock, cytokines are both synthesized acutely within the pituitary in response to peripherally derived stimuli and also reach the pituitary from peripheral sites of synthesis. The net result is an acute rise in the intrapituitary concentration of proinflammatory cytokines including LIF, which stimulates POMC expression and potently potentiates CRH action on the corticotroph (86), and IL-1, TNF, and IL-6, all three of which have been shown by some, but not all, studies to exert direct effects on pituitary ACTH secretion (38, 70, 308, 306) leading to increased glucocorticoid levels. Thus the rise in intrapituitary cytokines accompanies an increase in hypothalamic releasing factor tone. Thus central activation of the HPA axis by proinflammatory cytokines may be regarded as a classic long negative feedback loop.

Glucocorticoids suppress the HPA axis at several levels, including the hypothalamic synthesis of CRH and the pituitary production of POMC. The pattern of acute proinflammatory cytokines induced by septic shock opposes effective glucocorticoid signaling (346, 347), in part by activation of the NFkβ transcription factor, which antagonizes the glucocorticoid receptor action (348–350). Thus a further level of action of the cytokines is to antagonize the negative feedback loop of adrenal glucocorticoids on hypothalamic CRH expression and pituitary POMC secretion (345).

It is notable that some cytokines are associated with adverse mortality associated with septic shock. Pituitary MIF contributes significantly to circulating MIF levels in septic shock, and immunoneutralization of this cytokine leads to full protection against endotoxin lethality (91). Conversely, LIF administration confers protection against death from experimental gram-negative shock independent of bacterial killing (351). Further work using the LIF knockout mouse has demonstrated defective activation of the HPA axis in response to stress (88). It is tempting to speculate that the protective action of LIF may be in part mediated by activation of the HPA axis. The key role of HPA activation in conferring resistance to the lethal effects of unrestrained activation of sequential proinflammatory cytokine cascades is underscored by the poor performance of the CRH knockout mouse exposed to endotoxin (352) and by the beneficial effects of exogenous glucocorticoid administration to animals in septic shock (91).

There is undoubtedly a degree of fortuitous overlap in some activities of the proinflammatory cytokines. For example, the IL-6 knockout mouse does not express a striking phenotype (353–356). However, lifelong loss of a single cytokine may encourage atypical adaptive responses that mask an obvious deficiency of HPA axis activity. It may be more appropriate to consider integrated networks of cytokine activation in response to septic stress rather than ascribing functions to discrete actions of individual players.

C. Summary

The complex range of pituitary regulatory mechanisms reviewed here underlies the critical function of the pituitary in sustaining all higher life forms. Thus, the ultimate net secretion of pituitary hormones is determined by signal integration from all three tiers of pituitary control. It is clear from our current knowledge that the trophic hormone cells of the anterior pituitary are uniquely specialized to respond to these signals. Unravelling their diversity and complexity will shed light upon the normal function of the master gland. Understanding these control mechanisms will lead to novel diagnosis and therapy of disordered pituitary function (357).

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