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Review

Growth Hormone

A Paracrine Growth Factor?

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A number of tissues, including the brain, pituitary, immune system, placenta, mammary gland, and testis, may be self-contained units of GH regulation, production, and action. The production of GH and GH-releasing factors outside the hypothalamo-pituitary axis complements, rather than replaces, the traditional endocrine interactions between GH-releasing factors, GH, and its target tissues.

Key Words: Growth hormone; growth hormone receptors; paracrinology; CNS; immune; reproduction.

Introduction

It is well-established that growth hormone (GH) in systemic circulation is derived from the pituitary gland, because it is virtually undetectable following pituitary ablation *(1)* or when somatotroph differentiation is impaired *(2)*. Moreover, since growth is normally impaired by hypopituitarism or hyposomatotropism *(3)*, pituitary-derived GH in systemic circulation is classically considered to be an endocrine, with actions distant to its site of production. Circulating GH is not, however, obligatory for growth and pathological (sellar, suprasellar and hypothalamic disorders, acromegaly, and obesity) and physiological (fetal life) syndromes of "growth without GH" have been recognized *(4)*. In these syndromes, "paradoxical" growth has been considered to be a result of other GH variants, other GH-like moieties (placental GH, placental lactogen, prolactin), insulin, insulin-like growth factors (IGFs), and unidentified serum factors. It is, however, possible that growth in some of these syndromes may be a result of autocrine or paracrine actions of extrapituitary GH, because it is now known that GH gene expression is not restricted to the pituitary gland. Indeed, the widespread tissue localization of GH immunoreactivity and GH mRNA (Table 1) suggests an almost ubiquitous transcription of the GH gene or closely-related genes. This may reflect widespread expression of the pit-1 gene. Although pit-1 was originally thought to be a pituitary-specific transcription factor required for somatotroph proliferation and GH gene expression, it has now been found in pituitary thyrotrophs and lactotrophs *(5)*, immune system *(6)*, and placenta *(7)*. Most of these tissues also possess GH receptors (GHRs) and are responsive to GH stimulation (Table 2). It is therefore possible that GH may have paracrine or autocrine actions within some of its sites of synthesis. This possibility will be considered in this review.

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Growth Hormone: A Pituitary Autocrine/Paracrine?

Pituitary somatotrophs are primarily responsible for the synthesis of GH within the pituitary gland, although GH synthesis also occurs within prolactin- (mammosomatotrophs) and thyrotropin- (thyrosomatotrophs) secreting cells *(5)*. These and other adenohypophyseal cells may also be GH-target sites, since GHR gene expression occurs within the pituitary gland *(8–15)*.

Pituitary GH Receptors

Double *in situ* hybridization has established that GHR mRNA is located in some, but not all, GH-secreting cells of the rat pituitary gland *(9)*, although its abundance and wide distribution in the rat and rabbit pituitary gland *(8)* suggests it is present in other pituitary cell types. Indeed, GHR mRNA is abundantly present in the cephalic lobe of the chicken adenohypophysis, whereas somatotrophs are largely confined to the caudal lobe *(10)*. GHR transcripts are also present in the neural and intermediate lobes of the rat pituitary gland *(8)*. The abundance of GHR transcripts in the pituitary is comparable with that in many GH-responsive peripheral tissues *(16,17)* suggesting that it is also a target site for GH action. The presence of immunoreactive GHRs and binding proteins (GHBPs) in most, if not all, pituitary cell types *(8,18,19)* and the presence of GH-binding sites on pituitary membranes *(9,10,20)* supports this view, especially because GH-binding is to proteins comparable in mass to those present in hepatocytes and other traditional

Table 1
The Distribution of Growth Hormone (GH)-Like Proteins and mRNA in Extrapituitary Sites

Tissue	Species	GH	GHmRNA
Posterior pituitary	Rat	(58)	
	Sea lamprey	(61)	
	African freshwater fish	(60)	
Brain	Rat	(65)	(55)
	Frog	(251)	
	Chicken	(56)	(56)
	African freshwater fish	(60)	
Pineal	Sheep	(57)	
Spinal cord	Rat	(58)	
Placenta	Human	(130)	(130)
	Sheep	(131)	(131)
	Rat	(134)	
	Monkey		(133)
Mammary gland	Dog	(154)	(154)
	Cat	(154)	(154)
	Human	(152)	(152)
Testis	Human		(160)
Wolffian duct	Rat	(159)	
Mullerian duct	Chicken	(253)	
Kidney	Rat	(252)	
Lung	Rat	(252)	
Muscle	Human	(252)	(100)
GIT	Rat	(252)	
Skin	Human		(174)
Thymus	Human	(128)	(100)
Spleen	Chicken	(99)	(99)
	Human		(100)
Lymphocytes	Human	(96)	(100)
	Rat	(95)	
Tonsils	Human		(100)
Lymph node	Human		(100)

targets of GH action. The binding of GH to these sites is, furthermore, also blocked by a monoclonal antibody (mAb 263) that binds to epitopes in the ligand-binding domain of the rat liver GHR. The binding sites for GH on pituitary membranes are, however, of low abundance, low capacity or low affinity, and specifically bind < 2–3% of labeled tracer *(8)*. This may, however, merely reflect saturation by high concentrations of endogenous ligand, especially because GH-dependent pituitary function has been demonstrated.

Pituitary GH Actions

Paracrine communication between pituitary cells is now a well-established concept *(21–25)* and factors produced in corticotroph, gonadotropin, thyrotroph, lactotroph, and folliculo-stellate cells appear to locally regulate GH release *(26,27)*. Somatotrophs, in turn, appear to regulate the activity of these cells and may autoregulate their own secretion *(28,29)*. Exogenous GH has, for instance, been shown to suppress basal GH release from bovine pituitary cells *(30,31)* and to induce the expression of the IGF-I gene in rat pituitary glands *(32)*. Therefore, local paracrine or autocrine actions of GH may be involved in the autoregulation of GH secretion *(33,34)*, especially because IGF gene expression occurs in the dorsal-lateral wings of the rat anterior pituitary in which GH secreting cells are clustered *(35)*. Intracrine actions of GH may also contribute to GH autoregulation, since GH-binding sites are not restricted to the plasma membrane and are present within cytosol and nuclear membranes *(10)*.

Local paracrine actions of GH within the pituitary may also affect the function or differentiation of other pituitary cell types that express GHR proteins. Indeed, a pivotal role for GH in the development of the pituitary gland is suggested by the reversible pituitary endocrine abnormalities and impaired pituitary growth in neonatal rats injected with GH antibodies *(36)*. Growth hormone may, therefore, have a facilitory role in regulating the actions of thyrotrophs, gonadotrophs and corticotrophs, and in the maintenance of pituitary size. This possibility is supported by the increased number and size of corticotrophs and gonadotrophs in the pituitaries of mice transgenically expressing the GH gene

Table 2
The Distribution of Growth Hormone Receptor (GHR)-Like Proteins and mRNA in Sites of GH Synthesis

Tissue	Species	GHR	GHRmRNA
Brain	Human	(139)[a],(219)	
	Rat	(161)[a],(220)	(72,74,221)
	Mouse		(222)
	Sheep		(223)[a]
	Cow		(224)[a]
	Pig		(225)
	Rabbit	(226)	(226)
	Guinea pig		(14)
	Chicken	(66,226)	(226)
	Fish	(68,227)	
Anterior pituitary	Human	(219)	(8)
	Rat	(161)[a](9,19)	(8,9,16,221)
	Cow		(15)
	Rabbit		(8)
	Guinea pig		(14)
	Chicken	(10)	(10)
Spinal cord	Rat	(161)[a]	
Lens	Rat	(161)[a]	
Muscle	Human		(177),(228)[a]
	Rat	(161)[a]	(16,221,229)
	Mouse		(222)
	Sheep	(223)[a]	(221,230)
	Pig		(221)
	Rabbit		(231)[a],(231)
	Chicken		(232,233)
	Fish	(227)	
Adipose	Human	(176)	(177)
	Mouse		(222)
	Rat		(221,229)
	Cow		(15)
	Guinea pig		(14)
	Chicken		(233)
	Fish	(227)	
Chondrocyte Progenitors	Rat	(161)[a]	
Chondrocytes	Rat	(161)[a]	
	Human	(234)	(180)[a]
	Rabbit	(235)	
Head kidney	Fish	(109)	
Monocytes	Fish	(109)	
Lymphocytes	Human	(116,236)	
	Fish	(109)	
Granulocytes	Fish	(109)	
Gastrointestinal tract	Human		(237,238)
	Rat	(239),(161)[a]	(229,238),(238)[a]
	Cow		(224)
	Fish	(240,241)	
Spleen	Human		(228)[a]
	Rat		(16,221)
	Cow		(224)[a]
	Pig		(221)
	Chicken	(108)	(108)}
	Fish	(227)	

(continued on following page)

Table 2 *(continued)*

Tissue	Species	GHR	GHRmRNA
Thymus	Human	(139)[a]	(177)
	Rat		(16,221)
	Mouse	(115)	
	Cow		(224)[a]
	Pig		(221)
	Rabbit		(231)
	Chicken	(108)	(108,242)
Lung	Human	(139)[a](228)[a]	
	Rat	(161)[a]	(221)
	Mouse		(222)
	Sheep		(230)
	Chicken		(232)
Kidney	Human	(139)[a]	(177)
	Rat	(161)[a]	(16,221,229)
	Cow		(15),(224)[a]
	Sheep		(221,230)
	Pig		(221)
	Mouse		(222)
	Rabbit		(231),(231)[a]
	Chicken		(232)
	Fish	(227,240,243)	
Ovary	Human	(244)	(177)
	Rabbit		(231,245)
	Rat	(162),(161)[a]	(221,229,246)
	Mouse		(222)
	Fish	(227,240)	
Testis	Human		(177)
	Rat	(161)[a]	(247)
	Fish	(227,248)	
Placenta	Human	(139)	(137,228)
	Rat	(161)	
	Sheep		(223)
	Cow		(224)
Reproductive tract	Rat	(162),(161)[a]	
	Rabbit		(231)
Mammary gland	Human		(177)
	Rat		(221,229)
	Mouse		(222)
	Pig		(245)
	Cow		(224)
	Sheep		(245)
	Rabbit		(245)
Skin	human	(176),(139)[a]	(175,177),(180)[a]
	Rat	(176)	(16,246)
	Rabbit	(176)	
	Fish	(227,249)	
Skin fibroblasts	Human	(175,250)	(175,180)
	Rat	(161)[a]	

[a]In fetal tissues.

(37), in which plasma and pituitary LH levels and stimulated LH release are increased *(38–41)*. Similarly, mutations in the pit-1 gene, responsible for the development of somatotrophs, lactotrophs, and thyrotrophs, results in multiple endocrine deficiencies *(42)*. In contrast, lactotroph cells are scarce and immature in mice transgenically expressing the GH gene *(37,43)*, reflecting the decrease in size and abundance of somatotrophs *(44,45)*. Most prolactin cells are thought to be derived from GH-secreting cells and extinction of GH gene expression. The complete abla-

tion of somatotrophs, by expression of GH-diptheria toxin and GH-thymidine fusion genes (following their insertion into the germ line of transgenic mice), therefore results in an 80–90% loss of lactotroph cells *(46,47)*. Similarly, the loss of GH-secreting cells by GH immunoneutralization results in a correlated loss of lactotrophs *(48)*. Paracrine actions of GH within the pituitary may therefore regulate the differentiation and activity of most pituitary cell types.

The predominance of somatotrophs in the pituitary gland, the spatial relationships between pituitary cells and the diversity of pituitary cell types *(23)* facilitates paracrine regulation by GH. The extracellular concentration of GH in the pituitary gland may, however, be so pervasive that these paracrine actions are normally attenuated by GH-binding proteins to prevent pathological overstimulation. GH-binding proteins (GHBPs), with sequence identity with the extracellular binding domain of the GHR, can result from proteolytic degradation of the full-length receptor or from differential gene transcription *(49,50)*. Since GHBPs are not linked to signal-transduction systems, the competitive binding of GH to GHBPs provides a mechanism to attenuate GH action *(51,52)*. It is therefore pertinent that GHBP mRNA transcripts are abundantly present in the rat pituitary gland *(16)*, and that pituitary tissue may thus be a source of circulating GHBP.

Growth Hormone: A Neural Paracrine/Autocrine?

Neural GH

It is now well-established that the brain is an extrapituitary site of GH synthesis (*see* Harvey et al. *[53]* for review). The GH gene is expressed in the rat telencephalon, diencephalon, midbrain and metencephalon *(54,55)*, and in the chicken the cDNA of the neural GH gene is homologous to pituitary GHcDNA *(56)*.

Proteins immunologically identical to pituitary GH and of identical mass and bioactivity have also been identified in brain homogenates, although at concentrations <1% of those in the anterior pituitary gland of adult rats. Growth hormone moieties of smaller and larger molecular size and different immunological characteristics have, however, also been observed, suggesting a number of GH-like proteins may be expressed in the brain *(57–59)*.

Within the brain, GH immunoreactivity is widespread and located in perikarya, fibers, and axon terminals and in granular secretory vesicles. In rats, it is most abundant in amygdaloid and hypothalamic nuclei, in association with somatostatin (SRIF) and thyrotropin-releasing hormone (TRH) neurons *(58,59)*. These septohypothalamic and tuberoinfundibular tracts suggest roles for GH in limbic modulation and the neuroendocrine control of the pituitary gland. In fish, GH-containing fibers originating in the preoptic hypothalamus (POA) project to the adenohypophysis, through the infundibulum to the posterior pituitary gland, or through the wall of the preoptic recess to touch the wall of the third ventricle *(60)*. In contrast, the terminals of GH-immunoreactive fibers in sea lampreys terminate within the brain and none terminate in the CSF or pituitary gland *(61)*. Within the brain, neurons producing GH may thus have paracrine or autocrine actions on neighboring cells, especially because GH mRNA is not a rare transcript and as the GH concentration in discrete brain tissues (e.g., the chicken hypothalamus) may be almost 25% of that in the pituitary gland *(56)*.

In addition to the brain, the gray matter, ventral horns of the thoracic and lumbar spinal cord, and the posterior pituitary gland also contain GH immunoreactivity *(59)*. GH-like moieties, crossreacting with mammalian GH antibodies, are also present in the sensory ganglia of invertebrates lacking pituitary glands (i.e., locusts *[62]*, prawns *[63]*, and molluscs *[64]*), indicating that neural GH is phylogenetically more ancient than pituitary GH. Indeed, GH is present in the brains of primitive vertebrates lacking pituitary somatotrophs *(61)* and appears during ontogeny in the brain of fetal rats prior to its appearance in the pituitary gland *(65)*.

Neural GH Receptors

The possibility that neural GH may act in a paracrine or autocrine manner is supported by the occurrence of GH-binding sites *(66,67)* or GHR mRNA within the brain. GHR mRNA has been detected in the brains of fish *(68)*, birds *(69)*, and mammals *(70)*, in regions that overlap those of GH gene expression (reviewed by Harvey et al. *[71]*). Transcripts for the GHR gene are, for instance, present in the hippocampus and in the paraventricular nucleus (PVN), perventricular nucleus (PeVN), and arcuate nucleus of the rat hypothalamus *(72)*. Within these tissues, identified neurons expressing the GHR gene include 60% of SRIF neurons in the PEVN *(73,74)* and neuropeptide Y and GH-releasing factor (GRF) neurons in the arcuate nucleus *(75,76)*.

Neural GH Actions

In recent years, the brain has been recognized as a GH target tissue (*see* refs. *71,77,78* for reviews). Neuronal and glial growth and differentiation have been shown to be GH-dependent and severe deficits occur in GH-deficient states *(79)*. Neuromodulatory actions of GH in regulating catecholamine, indoleamine, cholinergic, and opioidergic pathways have also been described *(80,81)*, as have regulatory roles of GH in motor activity, breathing, learning, memory, sleep, feeding, and other central behaviors *(82,83)*. These roles have, however, largely been deduced as pathological correlates of pituitary GH deficiency or excess. It is therefore uncertain if they reflect local actions of GH synthesized within the brain, especially as GH in systemic circulation can access neural tissues and cerebrospinal fluid via retrograde hypophyseal portal blood flow *(84)*, and passage through the blood–brain barrier via

receptor-mediated transport *(85–89)*. Nevertheless, the localization of GH in the brain provides a morphological basis for possible paracrine or autocrine actions. The occurrence of GH in the ventromedial nucleus (VMN) of the hypothalamus *(90)*, for instance, suggests paracrine GH is involved in feeding, because the VMN is the primary regulator for appetite control. Similarly, the close association of GH-containing neurons within GHR-expressing SRIF neurons may indicate a local regulatory role. This possibility is also supported by the decrease in hypothalamic SRIF expression when GHR synthesis is blocked by the central administration of a GHR mRNA antisense oligodeoxynucleotide *(91)*. Similarly, the transgenic production of the hGH gene in the hypothalamus of the mouse is associated with a reduction in the expression of the hypothalamic GRF gene *(43)*.

Growth Hormone: An Immune Autocrine/Paracrine?

Immune GH

Rat and human lymphocytes secrete GH-like proteins in vitro *(92-96)*, as do leukocytes in vivo *(97)*. GH mRNA is also present in human and rat peripheral blood leukocytes *(93)* and in the spleen, thymus, and bone marrow, in which about 10% of mononuclear cells are GH immunoreactive *(93,98)*. Although the concentration of GH in mammalian immune cells is uncertain, in chickens GH immunoreactivity in the spleen thymus and bursa is 10, 2, and 1%, respectively, of that in the pituitary gland *(99)*.

The translation of the GH transcript in immune tissues is indicated by the incorporation of ^{3}H-labeled amino acids into immunoreactive GH *(93)*. In addition to lymphoid cells, translation of GH mRNA may also occur in other cell types, because epithelial and reticular cells in the human thymus and endothelial and smooth muscle cells in the human spleen also possess GH mRNA *(100)*.

Some GH-like and GH mRNA-like moities in immune tissues appear to be structurally different from those in the pituitary gland *(101,102)*, but sequence homology between immune and pituitary GH mRNA has been indicated by the presence of common restriction endonuclease cleavage sites *(100,103,104)*. Furthermore, GH cDNAs derived from the spleen, Bursa of Fabricius, and thymus of chickens have nucleotide sequences completely homologous with pituitary GH cDNA *(99)*.

The production of GH in spleen, thymus, and bone marrow is reduced in rats following hypophysectomy, although it is increased in peripheral blood leukocytes *(105)*. The secretion of GH by immune cells is, however, likely to be closely regulated in a paracrine or autocrine way by a variety of immune regulators. The production of GH by leukocytes from spleen, thymus, and the peritoneum is increased during immune challenge, provoked by intraperitoneal injections of lipopolysaccharide (LPS), and Fruend's Complete Adjuvant *(97)*. The expression of the GH gene by myeloid cell lines is similarly increased in actively proliferating cells *(106)*. The number of GH-secreting cells (principally T-helper and T-suppressor cells) and the release of immunoreactive GH from human lymphocytes is also stimulated by T-cell mitogens PHA *(97)* and concavalin A *(94,96)*. These mitogens do not, however, increase the number of GH-secreting B-cells, which are also unaffected by LPS, a B-cell mitogen *(94,96)*. The production of GH by peripheral mononuclear leukocytes is also directly stimulated by interleukin-2 (IL-2), which also increases the percentage of GH-secreting cells *(96)*.

Immune GH Receptors

It has long been known that immune cells are targets for GH action *(107)*. The GHR gene is expressed in the thymus and spleen *(16)* and in the Bursa of Fabricius of birds *(108)* and the head kidney of fish *(109)*. Lymphocytes and thymocytes have membrane-binding sites for ^{125}labeled GH *(110–115)*, and GHR immunoreactivity has been shown to be present on the membrane surface of circulating immune cells and immortalized lymphocyte cell lines *(116,117)*. These receptors are present in subpopulations of B- and T-lymphocytes and natural killer cells, and are most abundant in in B-cells of mammals. In contrast, in birds, the splenic, thymic, and bursal GHR/GHBP immunoreactivity is largely associated with macrophages and other large mononuclear nonlymphoid cells and is particularly present in the nucleus *(109)*. GHR/GHBP immunoreactivity is only occasionally present in avian lymphocytes and is similarly of low abundance in fish lymphocytes *(109)*. In the chicken, GHR/GHBP immunoreactivity is also present in thymic medullary cells, antigen-presenting interdigitating cells, and in ellipsoid-associated cells, and in all cases it is present in both nuclear and cytoplasmic compartments *(108)*. This widespread distribution of GHR/GHBP immunoreactivity therefore suggests roles (direct and indirect) for GH in regulating immune function, although it is uncertain how much of the immunoreactivity determined reflects the presence of GHBPs, which are likely to antagonize GHR-mediated GH action.

Immune GH Actions

It is well-established that GH plays an integral role in the maintenance of the immune system. Indeed, immune function is impaired by pituitary GH deficiency *(118–121)* and restored by exogenous GH therapy *(122–124)*. Hemopoietic and lymphoid actions of exogenous GH include increased thymic size, thymocyte proliferation and differentiation, proliferation of thymic epithelial cells and their secretion of thymulin, activation and proliferation of lymphocytes, increased production of cytokines, and the activation of monocytes, macrophages, phagocytosis, the generation of superoxide anions, and the intravascular migration of immune cells *(125)*. Although some of these actions may reflect endocrine roles of GH, at least some of these actions are likely to be mediated in a paracrine or

autocrine manner by the local production of GH and possibly by its induction of IGF-I gene expression *(125)*.

The physiological importance of immune GH in the induction of leukocyte function is demonstrated by the reduced in vitro proliferation of rat lymphocytes following the blockade of GH synthesis by the addition of a GH antisense oligonucleotide *(126)*. Autocrine actions of GH within leukocytes have also been indicated by their suppression of IGF-I when GH action is blocked by GH antibodies *(127)*. The immunoneutralization of endogenous GH similarly blocks the proliferation of rat thymic epithelial cells *(128)* and T lymphocyte proliferation *(129)*.

Placental GH: An Autocrine/Paracrine?

Placental GH

Pituitary GH is expressed in humans by the hGH-N gene, a member of the GH-chorionic somatomammotropin (hCS) gene family that includes five similar genes (hGH-N, hCS-L, hCSA, hGH-V, and hCS-B) *(130)*. The hGH-V gene, which is at least 92% homologous to the hGH-N gene, is primarily expressed in synctiotrophoblasts and epithelial cells, resulting in the production of placental GH *(130)*. The expression of this gene is largely restricted to the placenta by proteins that are almost ubiquitous in other tissues and function to repress the hGH-V promoter *(130)*. The hGH-V gene may, however, also be weakly expressed in the pituitary gland *(131)*; conversely, the pituitary GH gene may be minimally expressed in human and ovine placental tissues *(132)*.

Placental GH is a 191 amino acid, 22-kDa protein that differs from pituitary GH by 13 amino acid residues *(132)*. It is more basic and contains a unique N-linked glycosylation site, which when glycosylated results in a protein with a molecular mass of 25 kDa *(132)*. The hGH-V gene can also be alternatively spliced, resulting in a third placental GH protein with a molecular mass of 26 kDa, as are two GH-like proteins (GHP2 and GHP3) in the ovine placenta *(132)*. A placental GH (mGH-V) is also expressed in the rhesus monkey *(133)*, and the placenta of rodents expresses a novel family of GH-like proteins *(134)*. During early pregnancy, pituitary GH is the only measurable GH in maternal serum, although from 15 to 17 weeks of gestation until term, pituitary GH in serum is progressively replaced by increasing levels of placental GH that are directly related to the size of the fetoplacental unit.

Placental GH Receptors

Placental GH binds to GHRs and GHBPs, which are present in the placenta *(135,136)* are likely to mediate some of the binding of placental GH to placental membranes *(137)*. hGH-V and hGH-N cannot completely displace each other from placental membranes, suggesting separate binding sites for the placental GH variant *(138)*. An hGHR gene isoform (hGHRd3), lacking sequences encoded by exon 3, is also present in the chorion, amnion, and decidua of the placenta. The binding characteristics of this isoform are, however, identical to the full-length receptor *(130)*. The placental syncytium is rich in GH receptors, assessed by immunohistochemistry, from at least 10–12 wk gestation *(139)*, suggesting possible paracrine or autocrine actions of locally-produced placental GH, perhaps mediated through IGF-I production *(131)*. The trophoblast may also be a particular site of autocrine GH actions, because GHR mRNA and GH-V are especially abundant *(138)*.

Placental GH Actions

In addition to its well-established roles in regulating maternal IGF-I and metabolism, placental GH may exert local actions in the placenta. The lack of placental GH in fetal circulation *(140)* suggests that placental GH does not directly affect fetal growth, despite the finding that intrauterine growth retardation is associated with a signficant decrease in placental GH-producing cells per placental area *(141,142)*. Placental GH would therefore appear to affect fetal growth indirectly, perhaps via autocrine or paracrine actions. Although placental GH has not yet been shown to directly stimulate placental growth in vitro, placental GH has extensive mitogenic activity *(143,144)*, enhances placental IGF-I production *(145)*, and stimulates endometrial cell growth *(146)*. Placental GH may also alter the endocrine activity of the placenta, because hGH stimulates production of placental lactogens, estradiol, and progesterone in vitro *(147,148)*.

Mammary GH: An Autocrine/Paracrine?

Growth hormone-like moities have been detected in hyperplastic ductular epithelial elements and the neoplastic epithelium of dog mammary tumors and homogenates of normal mammary tissue *(149)*. The mammary gland in dogs has also been shown to be responsible for the pathophysiologically elevated levels of circulating GH that occur following progestin stimulation *(150)*. The hypophysectomy of dogs with progestin-induced GH excess does not reduce circulating concentrations *(151)*. The production of GH within the dog mammary gland has been shown by the ateriovenous GH gradient across the mammary gland *(149)* and by the presence of GH mRNA in the mammary gland that is indistinguishable from single-strand porcine and human pituitary GH cDNA *(152–154)*.

The synthesis of mammary GH in cats and dogs is inducible by progestins and is correlated with the hyperplasia and proliferation of mammary gland cells *(154)*. Growth hormone also has growth-promoting effects on human mammary cancer cells in vitro *(155)*. Furthermore, the normal and neoplastic growth of mammary glands is similarly induced in mice transgenically expressing the hGH gene *(156,157)*. These actions of GH are, however, thought to be mediated by the local production of IGF-I.

The induction of cell growth and differentiation within the mammary gland has been suggested to result from

paracrine interactions between GH- and IGF-I- secreting cells *(153)*. The local production of GH is thought to result in the recruitment and hyperplasia of stem cells, which differentiate into ductular epithelium by clonal expansion *(153)*. The proliferation and differentiation of these cells is, however, thought to result partly from the paracrine actions of IGFs released from mammary fibroblasts in response to GH produced in neighboring cells *(153,158)*.

Gonadal GH: An Autocrine/Paracrine?

Other reproductive organs may similarly be a site of GH production, because GH-immunoreactive proteins have been detected in the reproductive tract of 18-d fetal male mice *(159)* and GH mRNA has been detected in the human testis *(160)*.

In the fetal rat, GHR immunoreactivity is abundantly present in the Wolffian/Müllerian duct, ureter, epididymis, vas deferens, seminal vesicles, and gonads *(161)*. GHR immunoreactivity is similarly widespread in the reproductive tract of the adult rat, because it has been detected in the vas deferens, epididymis, prostate gland, Leydig and Sertoli cells, and, to a lesser extent, spermatozoa precursors in the seminiferous tubules *(162,163)*. The analogous female structures also contain GHR immunoreactivity, including the oviduct, fimbrae, uterine linings, oocytes, granulosa cells, and thecal cells *(162)*.

The abundance of GH- and GHR-immunoreactivity in the fetal reproductive tract is indicative of paracrine or autocrine interactions, especially because pituitary GH production is low prenatally. This possibility is strongly suggested by the ability of GH antiserum to block Wolffian duct differentiation in vitro in mice *(159)*. Exogenous GH also stabilizes the Wolffian duct in female fetuses in vitro *(159)*. Although GH production has not been demonstrated in the adult reproductive tract, locally produced GH could conceivably mediate demonstrated GH effects on spermatozoa motility *(164)*, spermatogenesis *(165)*, granulosa cell *(166)*, Sertoli cell *(165)* and Leydig cell proliferation *(167)*, steroid production *(167)*, hydrolytic enzymes in the prostate, seminal vesicle, and testis *(168)*, and androgen binding protein in the prostate and reproductive tract *(159,163)*. These effects may be mediated, at least in part, by local production of IGF-I, as GH increases IGF-I production in the testis, prostate, and seminal vesicles *(163,164,169)*.

Autocrine/Paracrine GH: A Growth/Differentiation Factor?

It is axiomatic that pituitary GH is obligatory for normal body growth. It is also well-established that exogenous GH can promote the growth and development of discrete organs and tissues *(170)*. Cellular proliferation and differentiation might therefore partly reflect autocrine/paracrine actions of locally produced GH rather than the endocrine actions of pituitary GH. GH may thus belong to a family of "autocoids" (e.g., IGFs and other growth factors, cytokines and PTHrP) that act as paracrine growth factors.

The possibility that GH may stimulate cellular differentiation has rarely been considered, although the limited data available supports this view. Indeed, the differentiation of the pituitary, mammary gland, male internal genitalia, and lymphoid elements *(36,126,159,171)* has been shown to be GH-dependent. The differentiation of several fibroblast cell lines (including 3T3-F442A, 3T3-L1, and Ob 1771) into adipocytes is similarly GH-dependent *(172)* as is the terminal differentiation of preadipocytes in vitro *(173)*. Since GH mRNA has been detected in human skin fibroblasts *(174)* and as GHRs and GHR mRNA are present in fibroblasts *(175)* and neighboring adipocytes *(176,177)*, these actions may reflect paracrine/autocrine signalling by locally produced GH. Furthermore, while hepatic IGFs have historically been thought to mediate the endocrine actions of pituitary GH on bone, it is now known that GH directly alters bone growth and differentiation; particularly, the differentiation of growth plate prechondrocytes into chondrocytes *(178)*. Since GH-like proteins *(179)* and GHR mRNA and/or proteins are also abundantly present in growth plate prechondrocytes *(161,180)*, locally produced GH may normally induce the differentiation of these cells.

The Minihypophysis Hypothesis

The secretion of pituitary GH is not autonomous and is dependent upon hypothalamic-releasing factors, particularly GH-releasing hormone (GHRH) and somatostatin (somatotropic release-inhibiting factor, SRIF), for stimulatory and inhibitory tone (*see* Harvey, refs. *181,182* for reviews). The activation of this hypothalamo-hypophyseal axis is modulated in a feedback way by GH-responsive peripheral endocrines (particularly IGF-I) and cellular metabolites (*see* Harvey *[183]* for review). The same stimuli may similarly regulate the synthesis and release of extrapituitary GH, although in a paracrine/autocrine manner.

Immune System

It is now well-established that a functional minihypophysis is present within the immune system. GHRH and GHRH mRNA are, for instance, abundantly present in rat and human lymphocytes *(103,184)* and rat spleen *(185)*, and GHRH receptors are present in rat thymocytes and splenocytes *(185,186)*. At least in rat leukocytes, GHRH would appear to affect GH synthesis by an autocrine or intracrine mechanism, as GHRH antisense oligonucleotides, but not GHRH antibodies, block GHRH-induced leukocyte GH synthesis *(186,187)*. GHRH of hypothalamic or leukocyte origin has similarly been shown to increase GH production by IM-9 cells *(188)*, and human lymphocytes *(184)*, respectively, although Hattori et al. *(95)* failed

to observe any affect of GHRH on GH production from human peripheral blood leukocytes.

SRIF mRNA has similarly been detected in human lymphocytes *(189)* and in some splenic B cells and thymic T cells of the rat *(190)*, but other studies failed to observe SRIF mRNA or immunoreactivity in any human mature lymphoid cell *(191)*. Although Hattori et al. *(95)* failed to observe any effect of SRIF on lymphocyte GH production, SRIF receptors are present on lymphoid cells *(190)* and effects of SRIF on macrophage and immune function have been demonstrated *(192,193)*. The role of SRIF in regulating immune GH thus remains to be established.

Immune GH may also regulated by feedback from GH-induced local factors. For instance, both pituitary and rat leukocyte GH mRNA and peptide are reduced by exogenous IGF-I in vitro *(107)*. However, unlike pituitary GH, human lymphocyte GH synthesis is unaffected by exogenous IGF-I and is upregulated by hGH *(194)*.

Placenta

A functional minihypophysis may similarly be present in the placenta, as GHRH mRNA and peptide are readily detectable in the human *(195)*, mouse *(196,197)*, and rat *(185)*, placenta and SRIF receptors are present in the rat placenta *(198)*. However, a link between this placental GHRH and placental GH remains to be established, as GHRH receptor mRNA was not detected in the rat placenta by the very sensitive RT-PCR/Southern blotting technique *(185)*, and placental GH production in the rat *(140)*, or human *(199)*, has not been shown to respond to GHRH *(140)*. The cDNA and molecular size of placental GHRH are, moreover, larger than their hypothalamic counterparts *(200–202)* and are differentially regulated by GH deficiency *(201)*.

Mammary Gland

GHRH and SRIF are present in the mammary gland (155). However, mammary GH secretion is not thought be affected by either peptide *(178)*. Alternatively, progesterone may be the primary regulator of mammary GH release *(178)*.

Testis

GHRH mRNA and peptide is present in human *(195,203, 204)* and rat testis *(185,205)*, and rat epididymis *(185)* and SRIF peptide *(206)* is present in rat testis. However, testicular GHRH more closely resembles placental GHRH than hypothalamic GHRH in cDNA sequence and HPLC characteristics *(195,203,207,208)*. Testicular and hypothalamic GHRH are also discordantly regulated by diabetes *(209)*. Despite their differing characteristics, testicular GHRH is equally effective as hypothalamic GH at inducing pituitary GH production *(203)* and stimulating adenylate cyclase in Sertoli cells *(210)*. However, like placental GHRH, its role in testicular GH production is unclear, especially as testicular GHRH levels are not associated with testicular IGF-I or IGF-II *(211)* and GHRH receptor mRNA was not detected in the rat testis or ovary by RT-PCR/Southern blotting *(185)*, although a different study detected GHRH receptor mRNA in Sertoli cells *(212)*. GHRH mRNA and/or peptide (but not GHRH receptor mRNA) is also present in the human and rat ovary *(185,204,208)*, but little is known about the characterization or physiology of ovarian GHRH.

Pituitary Gland

Although the primary regulator of pituitary GH release is axiomatically hypothalamic GHRH and SRIF, these peptides and their receptors are also synthesized within the pituitary gland *(185,198,213–216)*. Local interactions within the pituitary (a mini-hypophysis) may therefore modulate the hypothalamic-pituitary interactions. Local (rather than endocrine) circuits may also act within the pituitary to modulate GH synthesis, because GH stimulates pituitary IGF-I synthesis and IGF-I acts at the pituitary level to reduce GH synthesis *(32–34,217)*.

Central Nervous System

GHRH and SRIF are abundantly present in the hypothalamus, and travel down the hypophyseal tract to modulate pituitary GH synthesis. However, these peptides and their receptors are localized in hypothalamic and extrahypothalamic brain regions *(185,198)*, and may modulate hypothalamic and extrahypothalamic GH production by paracrine/autocrine mechanisms. Feedback pathways within the CNS may also mirror those of the hypothalamopituitary–liver axis, because GH induces SRIF gene expression in the cerebral hemispheres *(70)* as well as in the hypothalamus *(76,218)*. IGF-I is also synthesized in the cerebrum in response to GH *(70)* and may subsequently feedback to reduce cerebral GH synthesis.

Summary

A number of tissues, including the brain, pituitary, immune system, placenta, mammary gland, and testis, may therefore be self-contained units of GH regulation, production, and action. The production of GH and GH-releasing factors outside the hypothalamo-pituitary axis complements, rather than replaces, the traditional endocrine interactions between GH-releasing factors, GH, and its target tissues. For instance, the immune minihypophysis may serve an important role in "emergency" situations, such as stress or infection, to provide acute regulation of local GH actions. Minihypophyses in other organ systems may similarly alter GH production and action acutely and in a tissue-specific way, whereas the traditional GH axis may regulate more chronic, long-term events. Indeed, each mini-hypophysis appears to be regulated, at least in part, by tissue-specific factors such as progesterone (mammary gland GH) or cytokines (immune GH). This tissue specificity in local GH production may thus enable local reactions to local events that do not disrupt the homeostasis of other organ systems.

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