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INVITED REVIEW

Extrapituitary growth hormone

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Abstract Pituitary somatotrophs secrete growth hormone (GH) into the bloodstream, to act as a hormone at receptor sites in most, if not all, tissues. These endocrine actions of circulating GH are abolished after pituitary ablation or hypophysectomy, indicating its pituitary source. GH gene expression is, however, not confined to the pituitary gland, as it occurs in neural, immune, reproductive, alimentary, and respiratory tissues and in the integumentary, muscular, skeletal, and cardiovascular systems, in which GH may act locally rather than as an endocrine. These actions are likely to be involved in the proliferation and differentiation of cells and tissues prior to the ontogeny of the pituitary gland. They are also likely to complement the endocrine actions of GH and are likely to maintain them after pituitary senescence and the somatopause. Autocrine or paracrine actions of GH are, however, sometimes mediated through different signaling mechanisms to those mediating its endocrine actions and these may promote oncogenesis. Extrapituitary GH may thus be of physiological and pathophysiological significance.

Keywords GH · Pituitary · Extrapituitary · Embryogenesis · Cancer · Autocrine · Paracrine

Introduction

Although growth hormone (GH) secreted by the pituitary gland acts as an *endocrine* to regulate the growth, development, and metabolism of many target tissues, a large body of the literature demonstrates that GH is also present in many extrapituitary tissues, in which it may act as an *autocrine* or *paracrine* growth factor. This literature, for neural, immune, and some reproductive tissues, was briefly reviewed more than 13 years ago [1]. In this review, more recent literature for these tissues and for other sites of extrapituitary GH production is considered and the possible functional significance or pathophysiological relevance of extrapituitary GH is discussed.

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GH in neural tissues

Brain

The presence of GH mRNA in the human brain is uncertain [2], although GH gene transcription occurs in the lateral hypothalamus of the rat brain, independently of pituitary GH expression [3]. The abundance of GH mRNA (determined by the ribonuclease protection assay and 5′-rapid amplification of complimentary DNA ends-polymerase chain reaction (PCR)) in the hypothalamus is increased by GH releasing hormone (GHRH) and suppressed by stress, under conditions that induce minimal changes in pituitary GH mRNA levels [3]. It is also increased by ginseng [4]. The expression of the GH gene (determined by reverse-transcription (RT)-PCR and by transcriptional profiling) was also demonstrated in the rat hippocampus, where GH mRNA levels were higher in adults than juveniles and higher in females than males, especially during estrus, when estrogen levels are elevated [5, 6] Hippocampal GH expression was also increased in ovariectomized females after treatment with estrogen, which was able to induce GH mRNA levels in primary neuronal cultures. Hippocampal GH expression was also increased in both males and

females after acute exposure to electric shock. Hippocampal GH expression has also been demonstrated in normal mice and in Ames mice that have a pituitary GH deficiency [7, 8]. GH mRNA is also present in the brains of adult trout [9].

In addition to GH mRNA, GH immunoreactivity has been shown in the rat brain [10] and in cells of the ventricular zone of the mouse brain [11]. Although Ames mice have a pituitary GH deficiency, hippocampal GH concentrations in these mice are higher than in non-dwarf siblings [7, 8]. Neural GH has also been determined in the chicken, turkey, and dove brains, in which dense GH immunoreactive perikarya and fibers are present in the hippocampus, in periventricular, paraventricular, inferior, and infundibular hypothalamic nuclei and in medial and septal areas and in the median eminence [12]. A similar distribution of GH immunoreactivity was seen in the brains of embryonic chickens [13, 14]. In the chick, the brain develops from the neural tube at embryonic day (ED) 3 of the 21-day incubation period. At this age the divisions of the brain (the telencephalon, diencephalon, mesencephalon, metencephalon, and myelencephalon) have intense GH immunoreactivity. GH was also localized in the spinal cord [13, 15, 16], and in the otic and optic vesicles [13, 14]. It is also present within the peripheral nervous system of chick embryos, particularly in the trigeminal and vagal nerves, the extensor nerve of the limb bud, and the ethmoid nerve in the head [14, 17]. The presence of GH in these neural tissues occurs in the absence of pituitary GH, since GH secreting pituitary somatotrophs do not appear until ED 14–15 of chick embryogenesis [18, 19]. At ED 14, GH in the brain was no longer widespread and restricted to specific tissues and cells. For instance, GH-immunoreactive cells at ED 14 were present in the molecular and pyramidal layers of the cerebral cortex, in the gray matter of the cerebellum, in the choroid plexus and in the walls of the ventricles [13], and in the pineal gland [16]. At the subcellular level, GH immunoreactivity in neural tissues of the chick embryo is present in cytosolic compartments and in nuclear or perinuclear fractions [13, 16], as previously observed in peripheral tissues [15, 20]. In the turkey brain and ring dove brain, GH is present in granules within the cytoplasm of the cell bodies, whereas these granules are arranged in a continuous bead-like fashion in fibers or neurites [12]. The presence of GH in the avian brain reflects the expression of the pituitary GH gene in hypothalamic and extra-hypothalamic locations, in which 690-bp cDNA fragments generated by RT-PCR were identical to pituitary cDNA. This homology extended over a region spanning nucleotides 65 to 659 of pituitary GH cDNA that coded for amino acids 4-201 (reviewed in 1). GH has also been detected in human cerebrospinal fluid (CSF) [21], and may reflect sequestration through the blood–brain barrier [22], although as the concentration is lowered in patients with neural degeneration [23, 24], it is likely to reflect neural GH production.

Within the nervous system, roles for GH in neural development are now well established and have been reviewed in recent years [25–28]. Accumulating evidence suggests the involvement of GH in the regulation of brain growth and development and in neuronal differentiation and function. Some of these actions may reflect the entry of systemic GH into the brain and some may be mediated by the local production of GH or its local induction of IGF-1. Only a few studies have, however, assessed the possibility of GH acting as an autocrine/paracrine in the nervous system.

Scheepens et al. [10, 29, 30] found increased GH immunoreactivity in cortical pyramidal neurons after focal hypoxic–ischemic injury to the brain. The immunoreactivity was seen in myelinated axons and glial cells within and surrounding the infarcted tissues and within the ependymal cells of the choroid plexus in the injured hemisphere. This increase in neural GH content was thought to be neuroprotective, since exogenous GH markedly reduced the death of neurons after hypoxic–ischemic injury. The increased hippocampal GH content in Ames mice [7, 8] has also been correlated with their higher rates of hippocampal neurogenesis. DNA microassay analysis of hippocampal mRNA extracted following hippocampal-dependent learning also showed that GH mRNA was the primary gene to be upregulated [6], suggesting the involvement of hippocampal GH in learning and memory. Neural GH may, however, inhibit neuronal differentiation from neuroprogenitor cells, since somatostatin (SRIF which inhibits GH release from cultured brain cells [31]) and GH antiserum promoted neuronal development in vitro [11]. The widespread presence of GH-, GH-receptor (GHR), and GH-response gene (GHRG)-1 mRNA in the brain of early chick embryos [32–34] also suggests autocrine/paracrine roles for GH in neural function, as GHRG-1 is a specific marker of GH action in chickens.

Neural retina

In addition to the brain, the neural retina has been found to be a neural site of GH expression, particularly within the retinal ganglion cells (RGCs) of embryonic chicks [35]. Retinal GH mRNA in the chick embryo is identical to pituitary GH mRNA in nucleotide sequence, but the translated 24-kDa protein is rapidly converted into a 15-kDa moiety by proteolysis in retinal tissue [36]. Moreover, after secretion from the retina, this GH moiety is bound to a 45-kDa proteoglycan, opticin, in vitreous fluid [37]. GH immunoreactivity within the eye is also found in the choroid layer and in the retinal pigmented epithelium [38, 39].

A second, severely truncated GH mRNA (small chicken GH, scGH), lacking residues of the full-length transcript derived from exons 1, 2, and 3 and having an N-terminal 20 residues derived from intron C of the full-length mRNA, is also present in the neural retina of chicks [40]. This protein lacks critical residues required for binding to the GHR [41]. The 16-kDa protein coded by scGH, detected by a specific antibody, is present in extracts derived from the neural retina, pigmented epithelium, lens, cornea, and choroid of eyes from early chick embryos, although scGH immunoreactivity is mainly to a 31-kDa protein that is likely to be a dimerized form [42]. scGH is, however, not thought to be secreted and is rarely present in vitreous fluid, consistent with its lack of a signal sequence and its retention inside transfected HEK (human embryonic kidney) cells that overexpressed the protein. Specific scGH immunoreactivity is also detected by immunocytochemistry in ocular tissues, although it is not in axons in the optic fiber layer, nor in the optic nerve head, which are immunoreactive for the 15-kDa protein derived from the full-length protein [36].

The GH immunoreactivity in the axons emanating from the RGCs of the neural retina was traced from the fascicles in the optic fiber layer, through the optic nerve head at the back of the eye, into the optic nerve, through the optic chiasm, into the optic tract, and into the stratum opticum and the retinorecipient layer of the optic tectum of the brain, where the RGC axons synapse [34]. The GH immunoreactivity in the tectum is not due to the anterograde transport of retinal GH, as it is present prior to synaptogenesis within RGC axons and reflects the presence of GH mRNA in the optic tectum. The distribution of GH-immunoreactivity in the visual system of the early chick embryo (at embryonic day (ED) 7 of the 21-day incubation period) also parallels the distribution of the GHR [42, 43]. The presence of GHRG-1 in these tissues also suggests that the visual system is not just a site of GH production, but also a site of GH action.

The possibility that retinal GH may be involved in the development of the visual system during early embryogenesis [44] is supported by the finding that it is only present in the RGC axons of ED 4–ED 12 chicks, but not at ED 14–ED 18 [43, 45]. This temporal window corresponds to the period of RGC axon growth and the completion of synaptogenesis in the optic tectum. Moreover, the importance of endogenous RGC GH in axon development is shown by its siRNA-knockdown in cultured, immunopanned RGCs, which reduces axon length by at least 40%. Axon length is, conversely, increased in response to exogenous GH treatment in vitro [43].

Within the chick neural retina, retinal GH is neuroprotective for RGCs, at a time during embryogenesis when they undergo a developmental wave of apoptosis (between ED 6–ED 8 [46]). It was found that exogenous GH significantly reduces cell death in cultures of retinal explants or in immunopanned RGCs [46], whereas the immunoneutralization of endogenous GH augments cell death [46–49]. This neuroprotective action of GH is mediated by signaling mechanisms that are common to other established neurotrophins (e.g., brain-derived growth factor, insulin-like growth factor-1 (IGF-1), transforming growth factor β-1) [45]. These mechanisms include a suppression of caspase-3 expression and the expression of AIF (apoptosis inducing factor), which acts via caspase-independent death pathways [50]. The induction of apoptosis by GH antiserum is accompanied by an increase in caspase-3 and caspase-9 activation and PARP-1 (poly ADP-ribose polymerase 1) cleavage [47, 48]. Calpain activation is also a caspase-independent pathway of exogenous GH involved in PARP-1 cleavage, and a specific calpain inhibitor abrogates the apoptotic activity of the GH antiserum on RGC death [47]. Akt signaling pathways also participate in GH-induced RGC neuroprotection, since GH treatment of immunopanned RGCs reduces Akt levels while concomitantly raising the level of phosphorylated Akt (Akt-phos) [47]. GH-induced RGC neuroprotection also involves an activation of cytosolic tyrosine kinases (Trks) and extracellular-signal-related kinases (ERKs) and the activation of Akt and Trk pathways [48]. These pathways converge in the activation of CREB (cAMP response element binding protein), which initiates the transcription of pro- or anti-apoptotic genes [48]. These neuroprotective actions of GH are likely mediated in large part through the actions of IGF-1, since the simultaneous immunoneutralization of GH and IGF-1 does not increase the level of apoptosis in RGC cultures above that achieved by immunoneutralization of GH alone [49].

In addition to the chick embryo, GH and GH mRNA are similarly found in the ganglion cell layer of the neural retina in fetal rats [51] and neonatal mice [36]. A neuroprotective role of retinal GH has also been shown in a cell line derived from the neural retina of embryonic quail, in which siRNA-mediated GH gene knockdown induces cell death [52].

Growth hormone is also present in the neural retina of adult rodents [51, 53, 54] and is present in the vitreous fluid of rat eyes, at concentrations in neonates and adults that are $<$10% of those in serum [53, 54]. The rodent neural retina is likely to be an autocrine/paracrine site of GH action since the distribution of GHR immunoreactivity in this tissue mirrors that of GH [55]. Actions of GH within the retina are indicated by the increased thickness of its neuroblastic, inner plexiform and optic fiber layers in GHR gene disrupted mice (GHR−/−), in comparison with wild-type (GHR+/+) littermates [55]. In the absence of GH signaling, 4 proteins in the retinal proteome of the GHR−/− mice (identified by 2-D gels and MS) differed in

abundance with those in the wild-type mice. Brain abundant membrane attached signal protein-1 (BASP-1) was down-regulated, whereas protein kinase C inhibitor-1, cyclophilin A, KH domain-containing, RNA binding signal transduction associated protein 3 were upregulated in GHR−/− mice. These proteins are involved in retinal vascularization, neural proliferation, and neurite outgrowth, suggesting roles for GH in these processes during retinal development. The possibility that retinal GH may be neuroprotective in the rat retina is also suggested by the finding that the intravitreal administration of SRIF (which blocks GH release) ameliorated retinal cell death induced by AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid hydrobromide) [56]. Other neurophysiological roles of endogenous GH in vision have also been suggested in transgenic mice overexpressing the bovine GH gene, in which the ERG response to flashes of light are delayed and reduced in magnitude [57]. Autocrine or paracrine actions of GH within the eye are also indicated by the fact that an antisense oligonucleotide targeting the GHR inhibits neovascularization in a mouse model of diabetic retinopathy [58].

Growth hormone immunoreactivity, identical in size to pituitary GH, has also been detected in human retinal extracts and vitreous fluid [59]. This immunoreactivity is mainly found in the ganglion cell layer of the neural retina and colocalized with synuclein, an RGC marker [60]. The presence of GH in the RGCs of elderly patients correlates with cell survival, as it is not present in apoptotic (TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling-positive) RGCs, but present in most (67% of) healthy (TUNEL-negative) RGCs [60]. The loss of RGCs in diabetics is thus likely to be responsible for the low GH concentrations in the vitreous of diabetic patients with ocular dysfunction [61]. Although vitreous GH concentrations in patients with various ocular dysfunctions (epiretinal membrane, macular hole, retinal detachment, vitreous debris, vitreous hemorrhage, subretinal hemorrhage, dislocated crystalline lens, and central retinal vein occlusion) are not different from those in cadaver controls with no history of ocular disease, pituitary GH has been implicated in the etiology of diabetic retinopathy and in optic nerve dysfunctions [44]. The possibility that retinal or vitreal GH might be similarly involved in these disease states has yet to be determined.

GH in immune tissues

As reviewed previously [1], numerous studies have shown the presence of GH and GHR and their transcripts in immune tissues (including the thymus, spleen, tonsils, lymph nodes, and lymphocytes). Autocrine/paracrine roles of GH in these tissues have been established. For instance, it was shown that antisense oligonucleotides for GH mRNA inhibited lymphocyte proliferation [62], as did the immunoneutralization of endogenous GH [63]. The immunoneutralization of lymphocyte GH by GH antibodies also reduces IGF-1 production and the number of IGF-1 positive lymphocytes [64].

In more recent studies, Recher et al. [65] showed that GH mRNA, similar in nucleotide sequence to that in the pituitary, was detectable in the thymus and thymocytes of the 18-day rat fetus. It was also present in the fetal liver, but only in circulating lymphocytes and in hematopoietic cells surrounding the GH mRNA-negative hepatocytes. GH mRNA was also detected in lymphocytes in the thymus, spleen, and ileum Peyer's patches of the adult rat and in the lymph nodes of dogs [66]. GH mRNA was similarly found in fetal bovine lymphoid cells (thymocytes and splenocytes) [67] and in human thymocytes and thymic epithelial cells [68]. Despite having similar or identical GH mRNA, the GH moieties in human peripheral blood granulocytes were found to have a higher molecular weight of 37 kDa and this moiety was retained rather than secreted [69], suggesting it acts intracellularly. Malarkey et al. [70] found that the expression of GH mRNA in human lymphocytes [71, 72] was stimulated by Candida (an antibody inducing antigen) and by interleukin (IL)-12 and suppressed by cortisol and norepinephrine, at concentrations achievable in humans during stress. An autocrine or paracrine mechanism of GH action in these lymphocytes was demonstrated using a pharmaceutical GHR antagonist, B2036, which blocked endogenous GH-induced IL-12 synthesis and interferon (IFN) production [70]. The autocrine or paracrine actions of GH in these immune cells are thought to be mediated by the PI-3 kinase/Akt pathway (that promotes cell proliferation) and by the transcription factor NF-kappaB (that promotes anti-apoptosis) and by cell cycle mediators, and by c-Myc and cyclin proteins [73]. GHR antagonists (B2036 and G120k) similarly demonstrated that endogenous GH produced in murine immune cells (Pro-B Ba/F_3 cells) promoted cell proliferation [73]. These autocrine or paracrine actins are IGF-1-independent, since Ba/F_3 cells do not produce IGF-1 and the actions of GH are not blocked by IGF-1 antibodies [74].

Growth hormone immunoreactivity is also present in lymphoid tissues of chickens (spleen, bursa of Fabricius and thymus), but at concentrations <10% of those in the pituitary gland [75]. However, because of the much larger mass of these tissues, the total GH content in these tissues in 9-week-old birds is 236%, 5.2%, and 32% of that in the pituitary gland. Moreover, while most of the GH immunoreactivity in the pituitary is associated with the 26-kDa monomer (40%), the glycosylated variant (16%), the 52-kDa dimer (14%), and the 15-kDa submonomeric isoform (16%), GH immunoreactivity in chick lymphoid tissues is

primarily associated with a 17-kDa moiety, although bands of 14, 26, 29, 32, 37, 40, and 52 kDa are also present in these tissues.

The heterogeneous pattern and relative abundance of bursal GH has been determined during development between ED 13 and 9 weeks of age. The relative proportion of the 17-kDa moiety is higher (by 45–58%) in post-hatched birds than in ED 15 and ED 18 embryos (21 and 19%, respectively). The 26-kDa isoform is minimally present in embryos (<14% of total GH immunoreactivity), but in post-hatched chicks it increases to 12–20%. Conversely, while the 37-, 40-, and 45-kDa GH moieties are abundantly present in the embryonic bursa (approximately 30% at ED 13, 52% at ED 15, and 55% at ED 18), in neonatal and juvenile chicks they account for <5% of total GH immunoreactivity. These ontogenic changes are comparable to those previously reported for similar GH moieties in the chicken testis during development [76]. These results demonstrate age-related and tissue-related changes in the content and composition of GH in the immune tissues of the chicken, in which GH may be an autocrine or paracrine regulator.

The presence of GH in the bursa of Fabricius reflects the presence of GH mRNA [77] that is identical in sequence to that in the pituitary gland [1]. This transcript is mainly expressed in the cortex of the bursal follicles, comprising lymphocyte progenitor cells, but is lacking in the medulla, where lymphocytes mature. In contrast, more GH immunoreactivity is present in the medulla than in the cortex of the follicles. In non-stromal tissues, GH and GH mRNA are primarily in lymphocytes, and also in macrophage-like cells and in secretory dendritic cells. In stromal tissues, GH mRNA, GH, and GHR are expressed in cells near the connective tissue between follicles and bellow the outer serosa. In contrast, GH (but not GH mRNA or GHR) is present in cells of the interfollicular epithelium, the follicle-associated epithelium, and the interstitial corticoepithelium. This mismatch in distribution may reflect dynamic temporal changes in GH translation. Co-expression of GHR- and GH-immunoreactivity and GH mRNA and IgG occurs in immature lymphoid cells near the cortex and in IgG immunoreactive connective tissue cells, suggesting an autocrine/paracrine role for bursal GH in B-cell development and differentiation. Indeed, while GH is not thought to be involved in immune system development in mammals [73], the parallel ontogeny of GH and IgG expressing cells in the chicken bursa [78] strongly suggests GH involvement in the development of this lymphoid tissue.

GH in reproductive tissues

Growth hormone has well-established roles in male and female reproduction [79–81]. While many of these roles reflect the actions of pituitary or circulating GH, GH is produced in many reproductive tissues, in which it may have autocrine/paracrine actions [82]. Indeed, GH antibodies inhibit the in vitro differentiation of Wolffian ducts in embryonic rodents [83] and gonadal GH may be essential for normal reproductive development.

Ovarian tissue

Growth hormone immunoreactivity is not present in the stromal tissue of bovine ovaries, nor in primordial, primary, or secondary follicles, but it is present in antral follicles >2 mm diameter and its abundance increases with increased follicular size [84]. GH is similarly present in follicular fluid, in which the concentration is directly related to oocyte quality (being highest in oocytes that give rise to embryos with the best morphology and fastest cleavage rates) [85]. Within the follicles, GH immunoreactivity is present in most granulosa cells and in some, but not all, thecal cells. GH immunoreactivity is particularly present in the cumulus cells surrounding the oocyte and within the oocyte itself [84, 86]. As the oocyte and granulosa cells are avascular, separated from systemic GH by the basal lamina, GH immunoreactivity in antral follicles is likely to reflect local GH production. This possibility is supported by the finding of mRNA for pituitary (hGH-N) GH in the ovaries of pre- and post-menopausal women [87]. GH mRNA is similarly expressed in the oocyte and in the mural granulosa cells surrounding the antral cavity in bovine follicles, although it is not present in the cumulus cells of the cumulus oocyte complex (COC) [84].

In birds, GH-immunoreactivity is present in the stromal tissue of hens before and after the onset of lay and in small and large follicles, in which it is more intense in granulosa cells than in thecal cells [88]. This immunoreactivity reflects the expression of GH mRNA in the follicular epithelium and within granulosa and thecal cells.

The finding of increased GH concentrations in the ovary during folliculogenesis suggests GH involvement in oocyte maturation. This possibility is supported by the finding of GHR protein and GHR mRNA in mural granulosa cells, cumulus cells, and oocytes [89]. Indeed, it is well established that GH accelerates nuclear and cytoplasmic maturation in COCs of cattle [90–93], dogs [94], sheep [95], and mice [96]. This action is IGF-1-dependent in the rat [97], and rabbit [98] but is IGF-1-independent in the bovine ovary [89, 91, 99]. This action is thought to be mediated through the cumulus cells, since it does not occur in cumulus-denuded oocytes [97]. GH acts on the cumulus cells to cause their expansion, as a result of increased proliferation and reduced apoptosis [99–101]. In bovine COCs [99, 102], but not in equine COCs [103], GH modulates connexin-43 expression and the gap junctions

between cumulus cells, through which COC factors regulate oocyte maturation. It is also possible that GH acts directly on the oocyte to induce its maturation, since GHR mRNA is readily detectable in the oocytes of humans [104, 105], cattle [89, 106], horses and pigs [103], and in laying hens [88] and tilapia [107]. At the cellular level, the GHR has been localized in the monkey within the oocyte plasma membrane and in the ooplasm [108].

Uterine tissue

Expression of the GH gene has been demonstrated in human endometrial tissue [109], in which GH expression is upregulated in endometriosis and endometrial carcinoma. Endometrial carcinoma cell lines similarly express the GH gene [110].

GHR and GHR mRNA are also present in the uterus, including glandular and stromal cells [111–113], the decidua [114], and myometrium [111]. It is therefore possible that GH may act in an autocrine or paracrine way to regulate uterine growth or function. The uterus is a GH target site since GH promotes uterine growth [115], and the abundance of uterine GHR is strongly correlated with estrogen-induced uterine growth [116] and with pregnancy [117]. GH may thus facilitate implantation, especially as GHR-KO mice have fewer uterine implantation sites [118]. Mitogenic actions of GH in the uterus have also been implicated in the etiology of uterine and cervical cancers [109]. It is therefore of interest that the autocrine production of GH in endometrial carcinoma cells stimulates their in vitro oncogenicity by increasing cell cycle progression, decreasing apoptotic cell death, and by increasing cell migration and invasiveness [110].

Mammary tissue

Growth hormone expression has been observed in the mammary epithelial cells of dogs and cats [119–121] and in both the stromal and epithelial compartments of the human mammary gland [122]. GH and GH mRNA are similarly present in the cytoplasm of mouse mammary epithelial cells, specifically those of the terminal ducts and terminal end buds (TEBs) [123]. In the mammary glands of 3- and 6-week-old virgin mice, the GH protein is also localized to the nucleus of epithelial cells. A much weaker GH signal is also present in some cells of the stromal compartment, particularly in scattered cells of connective stroma. In the mouse mammary gland, GH expression is detectable at 2 weeks of age, is significantly increased at puberty and is less in adults during pregnancy, lactation, and involution. The GH protein is not, however, detectable in the mammary glands of pregnant, lactating, and weaned females. The mammary expression of GH in the mouse is thus thought to be of physiological significance in the morphogenic changes in the mammary gland at puberty [123].

Within mammary epithelial cells, GH has been found within secretory granules in the dog [119]. GH is secreted by the mammary epithelial cells and is at concentrations in milk and colostrum 100- to 1000-fold higher than those in plasma [124]. Mammary-derived GH is also secreted into systemic circulation, which is increased in response to progesterone and may induce an acromegalic-like state [121]. Mammary-derived GH, acting in an endocrine way, is also thought to induce endometrial hypertrophy and cancer in dogs, although this is disputed by Bhatti et al. [125].

The expression of the GH gene in the human mammary gland has been shown to be Pit-1 dependent [126], although it is Pit-1-independent in the dog [121]. The expression of GH in the mammary gland is thought to be largely dependent upon progesterone [127, 128], and mammary GH production is suppressed by ovariectomy [129] and by progesterone receptor antagonists [125, 130]. It is thus of note that the progesterone receptor is colocalized with GH in the mammary gland [130].

Growth hormone receptors have been found in epithelial and stromal compartments of mammary tissue [131–133]. In the dog, maximum GHR expression occurs during the proliferation phase of mammary development, coincident with maximum mammary GH expression [134]. In the mammary gland, GH increases the proliferation and survival of epithelial cells [123]. The importance of GH in mammary growth is shown in virgin mice, in which a GHR antagonist (pegvisomant) reduces ductal outgrowth, ductal branching, the number of TEBs, and the complexity of the gland [135]. In addition to mammogenesis, GH also has well-established roles in galactopoiesis and lactation [136, 137]. Autocrine GH is, however, thought to prevent the lactogenic differentiation of mouse mammary epithelial cells and to reduce the expression of β-casein and the expression and epithelial localization of E-cadherin [138].

Placental tissue

In humans, the pituitary GH gene (hGH-N) is not expressed in the placenta, in which a placental GH gene (hGH-V) is transcribed into at least three transcripts that are translated into several placental GH proteins [139] that have autocrine or paracrine roles in placental function [140–142]. Similar proteins are also produced in the placenta of other primates [143–145], and related proteins are also expressed in rodents [146, 147]. However, as these proteins differ from pituitary GH, placental GH and its actions are not considered in this review.

In sheep, a transcript identical to pituitary GH mRNA is expressed in the placenta after day 27 of the first trimester of pregnancy [148, 149]. The expression of this gene peaks between days 40 and 45 and declines after day 55. This transcript codes for a 22-kDa protein, as in the pituitary, and GH immunoreactivity and GH mRNA are localized in the syncytium and in the trophectoderm [148, 149]. Roles for GH in the sheep placenta are unknown, although the presence of GHR mRNA in the trophectoderm suggests the possibility of autocrine or paracrine actions. It is, however, possible that the GH gene is polymorphic in sheep and goats [150], with one haplotype expressed in the pituitary and another expressed in the placenta [142, 151].

Testicular tissue

Growth hormone receptors are widespread in the testicular tissue of fish [152, 153], rodents [154], pigs [155], and humans [156], and GH has numerous effects on spermatogenesis and steroidogenesis [81, 82]. Circulating GH, however, cannot readily access testicular cells within the blood–testis barrier. It is therefore likely that GH actions on spermatids and spermatozoa (such as an induction of spermatozoa motility [157]) reflect the local production of GH within the testis [158]. This possibility is supported by the discovery of hGH-N immunoreactivity in the human testis, although hGH-V is the predominant GH mRNA normally expressed [159–161]. The testis is also an extrapituitary site of GH expression in prejerrey fish [162] and fathead minnows [163], in which GH mRNA abundance increases during sexual development. GH is also present in the chick testis, in which GH immunoreactivity in adults is intense and widespread in the seminiferous tubules [76]. It is not, however, present in the basal compartment of rooster Sertoli cells, nor in spermatogonia or primary spermatocytes, but it is abundant in secondary spermatocytes and spermatids and in the interstitial cells and overlying myocytes. The GH immunoreactivity detected in the chicken testis is primarily (30–50%) associated with a 17-kDa moiety and to proteins of 32 and 45 kDa. The relative abundance of these proteins changes during ontogeny, in that the abundance of 14- and 40-kDa moieties is decreased while the abundance of 17- and 45-kDa GH moieties is increased with advancing age. GH mRNA (99.6% identical to pituitary GH mRNA) is also expressed in the chicken testis, but it is of low abundance and not detectable by Northern blotting [164]. In contrast with GH immunoreactivity, GH mRNA is found in spermatogonia and primary spermatocytes and is not present in secondary spermatocytes, spermatids, or spermatozoa [164]. This suggests that the expression of the GH transcript is stage-specific and does not occur in haploid cells.

Prostate tissue

Expression of the GH gene has been demonstrated in normal prostate biopsies [165], suggesting it may have local actions in prostate function.

Gastrointestinal tissues

Growth hormone-like immunoreactivity has been detected in extracts of normal human colon, small intestine, and stomach [166, 167], although only in trace amounts, which might have little biological significance. Expression of the GH gene has also been demonstrated in the liver and pyloric caeca of adult rainbow trout [9].

Hepatic tissues

In humans, low levels of GH immunoreactivity are present in extracts of normal fetal and adult liver [166, 167]. Intense GH immunoreactivity has also been observed in the liver of early chick embryos prior to the onset of pituitary GH secretion [20], although this is not present following the ontogeny of pituitary somatotrophs. Yang et al. [9] similarly detected GH mRNA in hepatic extracts of fish embryos. It is, however, possible that this merely reflects the presence of GH in lymphoid and hematopoietic cells of the liver, as Recher et al. [65] found that the GH gene was not expressed in the non-lymphoid hepatocytes of fetal rats.

Pancreatic tissue

Growth hormone-like immunoreactivity has been demonstrated in normal pancreatic islet cells of fish, cats, pigs, dogs, and humans [166–168]. GH mRNA has also been detected in normal canine pancreatic tissue by RT-PCR, which was of increased abundance in tumorous tissue [170]. GH receptor mRNA is also widespread in the pancreas [171], suggesting autocrine or paracrine actions of pancreatic GH. This possibility is supported by observations that exogenous GH can stimulate the growth of islet cells and the secretion of insulin in vitro and in vivo [172–174].

Salivary tissue

Growth hormone immunoreactivity has been detected in human parotids [167] and stimulation of rat parotid tissue with crude hypothalamic extracts can stimulate GH synthesis [175, 176]. GH is also present in the submaxillary gland of normal adult rats [177], and the GH content is increased almost 20-fold after implantation of a GHRH pellet into the gland. After GHRH treatment, GH mRNA is

also readily detectable by southern blotting and in situ hybridization. GH and GH mRNA are also present in the salivary glands of GHRH-treated and untreated normal and Ames dwarf mice, independently of the Pit-1 transcription factor required for pituitary GH expression [178]. Roles for GH in salivary function are largely unknown although the absence of granular duct cells in glands of transgenic mice expressing a GH-antagonist and in GHR knockout mice [179] suggests GH involvement in the differentiation of this gland and its production of epidermal growth factor.

Other alimentary tissues

Low levels of GH immunoreactivity have been detected in the tongue, esophagus, stomach, intestine, duodenum, colon, and liver of fetal and adult humans [166, 167], and GH mRNA is expressed in the intestines of the salmon [180] and the pyloric ceca of rainbow trout [9], but the functional significance of these observations is uncertain.

Skeletal tissue

It is well known that GH is important in the regulation of longitudinal bone growth and bone remodeling, and GH receptors have been identified in osteocytes [181–183]. The actions of GH in bone formation and bone resorption may be direct and/or mediated through the local production of IGF-1 or other growth factors.

The GH IGF-1 axis regulates longitudinal bone growth at the growth plate [184] and targeted ablation of the GHR, IGF-1, or IGF-1R thus impairs bone growth [185, 186]. This regulation involves endocrine and autocrine/paracrine mechanisms [187, 188]. Locally, injection of GH into the tibial growth plate accelerates longitudinal growth in comparison with the vehicle-injected contralateral growth plate [189]. This action is largely mediated by the local production of IGF-1 [190, 191], although GH may also have an effect that is independent of both endocrine and paracrine IGF-1 [186−188]. Indeed, while some of the actions of GH on bone cells can be blocked by IGF-1 antibodies, other actions are IGF-1-independent [192]. Similarly, the reduced in vivo femur growth in transgenic mice with GHR deficiency is not fully restored by transgenic IGF-1 overexpression [193].

The possibility that GH may have autocrine actions in the growth plate is supported by the presence of GH immunoreactivity in the cartilage [167] and synovial fluid [194, 195] of arthritic patients, at concentrations higher than those in plasma. The presence of comparable levels of GH immunoreactivity in the synovial fluid of non-arthritic patients [195] suggests synovial GH is derived from articular cartilage rather than from immune cells within inflammed joints. However, as GH is produced in immune cells, GH may act within articular joints to regulate cartilage growth and/or inflammation [196, 197]. This may explain why intra-articular SRIF treatment is effective in reducing joint pain and synovial thickness [198–200]. Indeed, the overexpression of bovine GH in transgenic mice results in lesions of the articular cartilage that are consistent with that described in osteoarthritis [201].

Dental tissue

Growth hormone immunoreactivity has been detected in odontogenic cells in embryonic rats undergoing histodifferentiation, morphodifferentiation, and dentinogenesis [202]. It is present in cells of the dental epithelium and mesenchyme at the primordial bud stage (embryonic day (E) 17 of the 21-day gestation period), prior to the expression of pituitary GH. At the cap stage of odontogenesis (E18–19) numerous cells in the dental epithelium and mesenchyme are intensely immunoreactive for GH. In the early bell stage (E20–21, when most histo-differentiation and morpho-differentiation occurs) most of the mesenchymal cells in the dental pulp are mildly positive for GH, while the dental epithelium and adjacent mesenchymal are more GH immunoreactive. In the late bell stage (postnatal day 0), GH is localized to the dental epithelium, differentiating mesenchymal cells, preodontoblasts, and mature odontoblasts. GH immunoreactivity during tooth development is also present in the extracellular matrix. It is also located with immunoreactivity for the GHR during odontogenesis, suggesting autocrine and paracrine roles for GH during tooth development. This possibility is supported by the finding that exogenous GH induces cell proliferation of both the inner dental epithelium and the dental papilla [203–205]. Molar dentin size and shape are also dependent upon GH status in transgenic mice overexpressing or underexpressing the GH gene and in transgenics lacking the GH receptor [206]. Cementum production in molar teeth of the same mice is similarly GH-dependent [207]. These actions of GH during tooth morphogenesis may be induced by IGF-1 or by bone morphometric protein (BMP)-4 [206], which is upregulated by GH stimulation [208, 209].

Integumentary tissue

Skin

Growth hormone mRNA is expressed in normal human skin [210] and in dermal fibroblasts [211]. As GHR protein and GHR mRNA are also present in human skin [212–214], in which GH actions have been described [213], skin may be an autocrine or paracrine site for GH action.

Muscular tissue

It is well established that GH stimulates muscle growth, directly or via the local production of IGF-1 [215]. It is also possible that GH may act as an autocrine/paracrine in muscle tissue to induce cellular proliferation and differentiation. This possibility is supported by studies using C2 C12 myoblast cells, which are able to differentiate into myotubules when grown in low serum-containing medium. These cells express GHRs but are unresponsive to exogenous GH [216]. However, in transfected C2 C12 cells that overexpress the GHR, sera-induced proliferation is inhibited by anti-GH and anti-IGF-1 antibodies. This suggests local GH production in muscle tissue, as confirmed by RT-PCR and radioimmunoassay and autocrine or paracrine GH actions. This is also suggested by GH overexpression in these cells which is associated with an inhibition of myotubule differentiation. Taken together, these data suggest that GH acts as an autocrine factor in myoblasts to enhance proliferation and to inhibit differentiation. These data also suggest that autocrine GH has greater affinity for the GHR than exogenous GH or that the GHR is intracellular and not accessible to exogenous GH.

Growth hormone mRNA has also been found by in situ hybridization in endothelial cells and the surrounding smooth muscle cells of veins and arteries in the liver, spleen, and thymus of rats [65], embryonic chick lungs [217], and human immune tissues [72], in which the autocrine production of GH may be involved in tissue angiogenesis. GH mRNA has similarly been found in skeletal muscles of chick embryos [14], with a distribution similar to that of the GHR [20]. GH immunoreactivity is similarly present in the skeletal muscle of human fetuses and adults [166, 167].

Cardiovascular tissue

Cardiac tissue

Growth hormone has well-established endocrine roles in cardiac and cardiovascular function [218, 219], but it may also be produced and act within the cardiovascular system. In addition to its presence in endothelial cells, GH immunoreactivity is present in the hearts of early chick embryos [20]. The possibility that the heart is an autocrine/paracrine site of GH action is supported by the widespread expression of the GHR and GH-response gene (GHRG)-1 in the heart of embryonic chicks [33]. High levels of GH mRNA have also been found in the heart of embryonic rainbow trout [9]. The heart is similarly a site of GH expression in tilapia [220] and in the human fetus [167].

Respiratory tissue

Lung tissue

The presence of GH, GHR, and GHRG-1 in lungs of chick embryos [20] suggests it might be an autocrine/paracrine site of GH action. This possibility is supported by the discovery of GH mRNA, identical in nucleotide sequence to pituitary mRNA, in the lungs of embryonic chicks [217]. In situ hybridization localized this transcript to mesenchymal and epithelial cells of developing lungs, in which specific GH immunoreactivity is similarly located. Lung GH immunoreactivity, as in other extrapituitary embryonic chick tissues, is primarily associated with a 15-kDa moiety. This immunoreactivity persists after the onset of pituitary GH secretion (approximately ED 15–ED 17) although GH mRNA is barely detectable in the lung at this time. The widespread presence of GHR in the lung during alveolarization suggests the involvement of autocrine or paracrine GH in lung development in chick embryos.

The onset of lung development and differentiation in the rat lung also occurs prior to the ontogenic differentiation of pituitary somatotrophs and it too may be induced by local actions of extrapituitary GH. GH mRNA is detected in the lungs of fetal rats in mesenchymal cells, in the mucosal epithelium, and in smooth muscle cells [221]. This transcript is expressed in the lungs of neonates until at least 14 days postnatally and is localized to type I and type II epithelial cells and to pulmonary tissue macrophages and alveolar macrophages. GH immunoreactivity is specific and parallels the cellular localization of GH mRNA throughout this period of alveolarization. Allen et al. [222] similarly found GH mRNA and immunoreactivity in rat lung macrophages, and GH immunoreactivity has been detected in extracts of fetal and adult human lungs [166, 167].

Autocrine or paracrine actions of GH in the rodent lung have been shown by GH mRNA knockout, using an aerosolized antisense oligonucleotide (ODN) directed against the GH gene [221]. Administration of the GH ODN decreased lung concentrations of IGF-1 and increased the concentrations of albumin, calcylin binding protein, superoxide dismutase, RNA binding protein motif 3 and the alpha- and beta-subunits of ATP synthase, and electron transfer flavoprotein. The GH ODN also significantly altered the abundance of 32 other, unidentified proteins in the lung. Other proteomic changes in the lungs of GHR(−/−) mice [223] may similarly reflect a loss of autocrine or paracrine GH signaling in the lung. Autocrine or paracrine actions of GH within the lung are also indicated by proteomic responses to the specific overexpression of GH within the lung [224]. GH expression increased the lung concentrations of specific enzymes (nuclear diphosphage

kinase B, Cu/Zn superoxide dismutase, glutatinione-S-transferase, and aldehyde reductase-1) and proteins (beta subunit G-protein calponin 2, beta 5 tubulin, retinoblastoma binding protein 4, and fetuin A) while the lung concentrations of haptoglobin and major acute-phase proteins were reduced.

Gills

In addition to the lung, high levels of GH mRNA have been found in the gills of rainbow trout [9]. The gill may also be a site of GH gene expression in tilapia [220]. Gills may also be an autocrine or paracrine site of GH actions since GHRs are expressed in the gills of salmon [225], flounders [226], the black porgy [227], and rainbow trout [228], and actions of GH in osmoregualtion are well established [226].

GH in embryos

Prior to organogenesis and the ontogeny of the pituitary gland, GH gene expression is widespread in many extrapituitary tissues. For instance, in rodent preimplantation embryos, GH mRNA and GH immunoreactivity are, respectively, present at the morula and blastocyst stages of development [229] after, or coincident with the expression of the GHR (from day 2). These observations suggest the involvement of autocrine/paracrine GH in early embryonic development. The GHR is similarly expressed in bovine embryos from day 2 and the abundance of the GH transcript increases sixfold by day 6 [230]. It is mainly expressed in the inner cell mass of the blastocyst, where GHR immunoreactivity is detected from day 3. GH mRNA is present in bovine embryos from day 8. A functional role for GH in the blastocyst is shown by the ability of GH antibodies to inhibit proliferation of the mouse blastocyst [231]. This autocrine/paracrine action is likely mediated through the IGF-1 pathway, as the proliferation of the blastocyst inner cell mass was blocked by an antibody against the IGF-1 receptor. This antibody did not, however, block the stimulation of trophectoderm cells induced by exogenous GH. Markham and Kaye [231] concluded that (exogenous) GH may selectively regulate the number of trophoectoderm cells and act in concert with IGF-1 to stimulate the inner cell mass, and to optimize blastocyst development. It is, however, possible that the actions of endogenous GH are mediated through different pathways to those activated by exogenous GH or that endogenous GH acts inside the cell, as an intracrine.

As GH is not secreted from chick somatotrophs until ED 15 of the 21-day incubation period, and is not present in plasma until ED 17 [20], early development of the chick embryo occurs in the complete absence of pituitary GH but in the presence of abundant extrapituitary GH [20]. Autocrine or paracrine roles for GH in chick embryonic development are therefore likely, since mRNA and GHR mRNA and GH- and GHR immunoreactive proteins are present in most cells from ED 2 or ED 3 [20]. As organogenesis proceeds during development, the extrapituitary distribution of GH becomes more restrictive, presumably reflecting the extinction of GH expression in specific cells. GH is, for instance, ubiquitous in the liver in early embryogenesis but is not present after ED 7 or ED 8 [20].

The involvement of extrapituitary GH in fish development is also indicated by the presence of GH transcripts at very high levels in embryos and larval stages of the alligator gar *Atractosteus spatula* [232]. The GH gene is similarly expressed in extrapituitary tissues prior to (in zygotes and embryos) and after organogenesis in developing rainbow trout (*Oncorhyncus mykiss* [9, 233–235]), gilthead seabream (*Sparus aurata* [236]), silver seabream (*Sparus sarba* [237]), Japanese eel (*Anguilla japonica* [238]), and orange-spotted grouper (*Epinephelus coioides* [239]).

GH in cancers

Growth hormone and/or GHR expression is correlated with tumor development in some, but not all, tissues [240], in which autocrine GH has been implicated in neoplastic transformation [241].

Human endometrial adenocarcinoma, for instance, is characterized by an upregulation of GH expression [109], which is thought to promote cellular proliferation and to reduce cell-to-cell adhesion, allowing individual cells to break away from their parent architecture. In endometrial cancer, autocrine GH may reflect its local production by endometrial GHRH, as endometrial cancer is regressed by GHRH antagonists [242], although this may also occur through GH-independent actions of the antagonist [243]. Autocrine GH is also thought to enhance the in vitro and in vivo oncogenic potential of endometrial carcinoma cells. Forced expression of hGH in endometrial carcinoma cell lines increased their cell number through enhanced cell cycle progression and decreased apoptotic cell death. In addition, autocrine hGH expression promoted anchorage-independent growth and increased cell migration and invasion in vitro. Autocrine hGH also similarly enhanced tumor size and progression in a xenograft model of human endometrial carcinoma [110].

Growth hormone mRNA expression is similarly upregulated in human primary islet cell adenomas compared with normal pancreatic tissue, and GH mRNA levels are highest in metastases [170]. Colorectal cancers have also been attributed to autocrine/paracrine actions of GH that may act as a potent mitogen or anti-apoptotic factor in the

rapidly renewing epithelial cells of the colon [244]. The expression of the GH gene in epithelial cells of the thymus is similarly thought to be causally involved in the induction of thymoma [245]. GH mRNA and immunoreactivity have also been detected in canine osteoid-producing tumors [246]. The finding of GH and GH mRNA in prostate cell lines [134, 247] has similarly suggested the involvement of autocrine/paracrine GH in prostate tumorigenesis. Indeed, a disruption of GH signaling has been shown to retard prostate carcinogenesis in rats [248]. As in the endometrium, the production of GH in these cells may be regulated by GHRH through GHRH receptors, since they express GHRH mRNA and GHRH receptor mRNA [249] and GHRH antagonist suppresses prostatic cancer growth [250]. GH may act locally in prostatic cells since they also express the GHR gene [247].

Since GH and its receptor are present in immune cells, immune GH has similarly been implicated in the development of leukemia and lymphoma [251]. Indeed, GH may act in an autocrine fashion in B-cell tumors, as the hGH gene is expressed in a Burkitt's lymphoma serum-free Ramos cell line, in which the proliferation of these cells is blocked by hGH antiserum [252]. Autocrine or paracrine actions of GH in lymphoma cells may also reflect the ability of endogenous GH to induce TGF-β1, which is similarly blocked by GH antisense oligonucleotides [253]. The induction of TGF-β1 expression by endogenous GH is not, however, suppressed by GH antibodies. The GH antibody is thought to immunoneutralize secreted GH and to block its action on surface GH receptors on these cells, but it is unlikely to pass the cell membrane and immunoneutralize GH within the cell. As most of the GH produced by lymphocytes remains intracellularly, Farmer and Weigent [253] considered the ability of endogenous GH to induce TGF-β1 was due to an autocrine or intracrine action mediated within the cell. Endogenous GH in the same lymphocyte cells was also found to enhance the production of nitric oxide (NO), most likely by a mechanism that involved an increase in the synthesis of nitric oxide synthase and an increase in the transport of arginine, leading to enhanced cell survival [254]. The overexpression of GH in these lymphoma cells also results in a decrease in the production of superoxide (O_2^-) which also protects them from apoptosis [254]. The antiapoptotic action of GH overexpression is also due to a decrease in the expression of bax, BAD, and caspases 3, 8, and 9 and by an increase in BcI_2 production. These actions are likely mediated through autocrine or paracrine mechanisms, as DNA fragmentation is increased when GH expression is prevented by GH antisense oligonucleotides [255]. The anti-apoptotic action of GH overexpression is mediated through increased IGF-1 production and IGF-1 receptors, as it is blocked by antibodies to IGF-1 or its receptor [256].

It is well established that the mammary gland is an extrapituitary site of GH expression and that mammary GH is an autocrine growth factor that promotes cancer development [119, 240]. In dogs, progesterone induces the synthesis of GH in normal and tumorous mammary glands, in which the GHR is also expressed [134]. Autocrine or paracrine actions of GH in the canine mammary gland are thought to be direct or mediated through IGF-1 [120, 121].

Mammary GH expression in the human is lowest in normal tissue, higher in hyperplastic tissues and highest in metastatic tumors [122]. GH gene expression in normal glands is restricted to luminal epithelial and myoepithelial cells of ducts and scattered stromal fibroblasts, whereas GH expression extends to cells of the reactive stromal (fibroblasts, myofibroblastic cells, and myoepithelial cells) in fibroadenoma, pre-invasive, and metastatic breast tumors.

Autocrine or paracrine mechanisms of GH action in breast cancer cells (MCF-7 cells) have largely been determined by Lobie and coworkers [241]. The induced expression of hGH in these (MCF-hGH) cells activates intracellular GH signaling pathways (involving STAT1, STAT3 and STAT5), which are partially blocked by a GH receptor antagonist (hGH-G12OR) [257, 258]. Expression of the GH gene in MCF cells also increases their ability to spread in culture upon a collagen matrix, by increasing the formation of filipodia and stress fibers in a JAK2-dependent manner [259]. Enhanced JAK2 tyrosine phosphorylation in MCF-hGH cells is blocked by B2036, another hGH antagonist, which also blocks the autocrine GH stimulated increase in total cell number and DNA synthesis.

Expression of GH in these cells increases cell number by a mechanism that is also abrogated by a non-receptor-dimerizing hGH antagonist (hGH-G120R) [259, 260]. This action is direct, since MCF-7 cells do not produce appreciable amounts of IGF-1. Autocrine GH expression also results in a change in cell morphology, in concert with increased motility and the acquisition of invasive ability [123, 138]. This metastatic transformation reflects the disruption of cell contacts, resulting from plakoglobin downregulation and E-cadherin re-localization from the periphery to the cytoplasm [261]. The repression of plakoglobin gene transcription by autocrine GH results from increased expression of DNA methyltransferase (DNMT1), DNMT3A, and DNMT3B, mediated by JAK2 and Src kinase activity, and direct hypermethylation of the plakoglobin promoter [262].

Increased mitogenesis as a consequence of autocrine GH production in these cells is prevented by inhibition of either the p38 MAPK or p42/44 MAPK pathways [259]. Increased activation of the P42/44 kinase pathway is one of the mechanism by which HOXA1 mediates oncogenic transformation of human mammary epithelial cells and its

downstream activation of Elk-1 mediated transcription [263]. Other signal transduction pathways also mediate HOXA1-stimulated oncogenesis, including STAT3, STAT5A, and STAT5B [264]. Autocrine GH-induced HOXA1 gene transcription [261, 265] also induces oncogenic transformation in the MCF-7 cell line by upregulating c-Myc, cylin D1 and Bcl-2 gene transcription [266, 267] and by increasing the activity of PAX (paired box)-5 DNA binding activity, a nuclear transcription factor [268].

Autocrine GH production in these cells stimulates transcriptional activation through STAT5, CHOP (p38 MAP kinase specific) or Elk-1 (p44/42 MAP kinase specific) and this action is similarly blocked by B2036 [260]. This hGHR antagonist also abrogates the potent antiapoptotic action of autocrine GH in protecting MCF-hGH cells from serum withdrawal [260]. The autocrine actions of hGH are therefore receptor-mediated. These authors, Mertani et al. [269] also found that autocrine GH in MCF-hGH cells upregulates 24 genes and downregulates another 28 genes. CHOP (gadd 153) was one of the upregulated genes, which results in an increase in the CHOP protein (a mediator of the antiapoptotic action of autocrine GH), in a p38 MAPK-dependent manner. The transcriptional up-regulation of CHOP is therefore one mechanism by which autocrine hGH increases mammary carcinoma cell number. Another mechanism involves the transcriptional repression of the p53-regulated placental transforming growth factor (PTGH)-β gene, inhibiting its ability to induce cell cycle arrest and apoptosis [270]. Another mechanism through which autocrine GH may induce breast carcinoma is by increasing tumor blood and lymphatic micro-vessel density [271], by actions blocked by GHR antagonism using B2036. VEGF (vascular endothelial growth factor) is a critical regulator of angiogenesis and VEGF-A expression is greatly increased by autocrine GH in MCF-7 cells [271].

Autocrine production of GH in immortalized human epithelial cells therefore enhances proliferation and protects against apoptosis and promotes abnormal mammary acinar morphogenesis, oncogenic transformation and tumor formation in vivo. The oncogenic and metastatic potential of forced autocrine GH production is in marked contrast to exogenous GH, which supports neither tumor formation nor invasion by human mammary epithelial cells; although it does promote the proliferation and spreading of mammary epithelial cells [258, 260]. Exogenous GH cannot, however, mimic the protective effect of autocrine GH against apoptosis resulting from serum withdrawal [260]. This selective effect of endogenous GH may reflect the greater augmentation of STAT5-mediated gene transcription induced by autocrine GH compared with exogenous GH [259]. Autocrine GH (but not exogenous GH) also inhibits PTGF-β gene expression [270]. As the GHR is primarily on epithelial cells, the reduced PTGF must be affecting stromal cell activity in a paracrine fashion. Higher concentrations of B2036 are also required to inhibit the action of autocrine GH, suggesting a difference between endogenous and exogenous GH exists in GH signaling mechanisms. This possibility is supported by the fact that microarray analysis of 19,000 human genes indentified a subset of 305 genes that were differentially responsive to exogenous and endogenous GH, as well as 167 genes that were regulated in common [272]. Some of the differentially regulated genes were for trefoil factors (TFFs), that promote cell survival, anchorage-independent growth, motility and oncogenic transformation [273, 274].

As autocrine GH is more oncogenic than exogenous (pituitary) GH, selective targeting of autocrine GH may therefore provide a therapeutic approach to prevent metastatic extension of human breast carcinoma [273, 274]. Consequently, as autocrine GH production was found to increase the antioxidant capacity of mammary carcinoma cells and to protect against oxidative stress-induced apoptosis (by increasing both the mRNA and protein levels of catalase, superoxide dismutase 1, glutathione peroxidase, and glutamyl synthetase, through a p44/42 MAP kinase-dependent pathway) antagonism of autocrine GH action has been proposed as a therapeutic regime for mammary carcinoma [266, 267]. Increasing cellular oxidative stress is a mechanism through which other chemo-therapeutic agents are effective. The efficacy of SRIF [275] and GHRH antagonists [276] as antitumor agents may therefore particularly reflect the blockade of endogenous GH production in cancerous tissues.

The differential actions of endogenous and exogenous GH may reflect differences in concentration and secretion, since endocrine GH is secreted episodically as a bolus, whereas endogenous GH is thought to be released continuously at low concentrations [268]. Endogenous GH may, however, be released in closer proximity to GHRs and at higher microenvironment concentrations than exogenous GH. Endogenous GH may also act at intracellular receptors directly after synthesis, in compartments not readily accessible to exogenous GH. Indeed, van den Eijnden and Strous [277] demonstrated that autocrine GH binds the GH receptor immediately after synthesis in the endoplasmic reticulum and that this facilitates the maturation of the GHR. The hormone receptor complex is then inserted into the plasma membrane, where exogenous GH is unable to bind these receptors, but signal transduction by endogenous GH only occurs after exiting the endoplasmic reticulum. This mechanism also explains why GHR antagonists are sometimes ineffective in blocking the actions of autocrine GH [241, 278]. The differential actions of endogenous and exogenous GH could also reflect differences in composition, since GH variants in extrapituitary tissues differ from those in the pituitary gland, and are largely sub-monomeric isoforms [36, 40, 75, 76].

Autocrine GH is also thought to act through nuclear receptors. Indeed, the progression of uterine cervical carcinoma in women has also been correlated with the appearance of the GHR in the nucleus of cancerous cells [279], and nuclear GHR expression is similarly a marker of tumorigenesis in other cancerous cells [241, 280]. Nuclear targeting of the GH receptor is thought to induce cell proliferation, a dysregulated proliferative arrest and an induction of cell cycle progression, through increased expression of the proliferation-related proteins Survivin and Mybbp [280]. Nuclear targeting of the GH receptor by autocrine GH and dysregulation of cell cycle progression is also associated with the expression of Dysadherin, which destabilizes cadherin-based cell contacts, leading to oncogenic transformation [280, 281].

Conclusion

Growth hormone-immunoreactivity, detected by ELISA, radioimmunoassay, immunocytochemistry, or western blotting, is present in many extrapituitary tissues. While this immunoreactivity is often at trace concentrations [166, 167], in many studies it is at concentrations greater than those in blood plasma [75, 76, 282]. It is also present in tissues that are avascular (e.g., in granulosa cells of the ovary [84]) or physically separated from blood by barrier systems (e.g., in brain tissues [16] and testicular tissues [76, 164]) and therefore unlikely to be derived from the circulation. Extrapituitary GH is also present in early development, prior to the presence of GH in the pituitary gland or in general circulation [15, 18]. It is also present in adults after pituitary GH senescence, when circulation GH levels are low or undetectable [283–285]. The presence of GH in extrapituitary tissues is therefore likely to reflect its local production.

The possibility that extrapituitary GH is produced locally is supported by the demonstration that *de novo* GH synthesis has been demonstrated in some extrapituitary tissues, e.g., in lymphocyte cells [286], in testicular cells [287], and in the salivary gland [177]. Rat lymphocytes, for instance, produce a GH cDNA that is identical to pituitary GH cDNA in its nucleotide sequence and codes for the same protein [288, 289], which is released from lymphocytes in vitro [286]. This possibility is also supported by the demonstration that GH mRNA, identical to that in the pituitary gland, is, for instance, present in hypothalamic and extra-hypothalamic regions of the chicken brain [290], in the chick neural retina [35], in chicken immune tissues [77, 78, 291], in the chicken testis [164], and in the chicken lung [217]. In summary, it is now well established that authentic GH moieties are present in many extrapituitary tissues in which they are produced.

Although extrapituitary GH is unlikely to be of biological importance when present in trace amounts, the local production of GH in some extrapituitary tissues (e.g., in the immune and nervous systems) is significant and at contents and concentrations comparable to those in the pituitary gland [282]. Extrapituitary GH, in most cases, is not, however, thought to contribute to the pool of GH in systemic circulation, since it is well established that GH in systemic circulation is largely derived from pituitary somatotrophs, as serum GH concentrations are undetectable or barely detectable following hypophysectomy. Mammary GH expression may, however, contribute to circulating GH concentrations and have endocrine actions that may be of physiological and pathological relevance. Indeed, GH overexpression in the mammary gland is responsible for elevated plasma GH concentrations in cycling dogs, since their circulating GH concentrations are suppressed by mammectomy rather than by hypophysectomy [292]. This overexpression of mammary GH is also responsible for the induction of an acromegalic-like state in bitches [120, 121] and may induce endometrial hypertrophy [125].

Most extrapituitary GH is not, however, thought to contribute to the systemic GH pool, and it is thus unlikely to be involved in endocrine function and hence with whole-body growth during development [18, 19]. A deficiency of extrapituitary GH is thus unlikely to result in a dwarf phenotype (the hallmark of deficient pituitary GH production or deficient pituitary GH signaling). Deficiencies in the production or action of extrapituitary GH can, however, result in physiological dysfunctions, demonstrating the functional importance of extrapituitary GH as an autocrine or paracrine regulator.

Table 1 Functional autocrine/paracrine actions of endogenous extrapituitary GH

Blocker of endogenous GH synthesis/action	Functional response	Species	References
GH siRNA	↑ cell death	Chicken	[52]
GH siRNA	↓ neurite length	Chicken	[43]
GH antisense	↓ neovascularization	Mouse	[58]
GH antisense	↓ cell proliferation	Rat	[62]
GH antisense	altered proteome	Rat	[221]
GH antisera	↑ cell death	Chicken	[46–49]
GH antisera	↓ cell proliferation	Mouse	[216, 231]
GH antisera	↓ cell proliferation	Human	[63]
GH antisera	↑ neuronal differentiation	Mouse	[11]
GH antisera	↓ Wolffian duct differentiation	Mouse	[83]
GH antisera	↓ IGF-1 expression	Rat	[64]
SRIF	↑ neuronal differentiation	Mouse	[11]
GHR antagonists	↑ cell death	Mouse	[73]
GHR antagonist	↓ cytokine production	Human	[70]

Table 2 Functional autocrine/paracrine actions of endogenous extrapituitary GH

Induced GH expression in specific extra-pituitary sites	Functional response	Species	References
bGH in CNS	hyperphagia-induced obesity	Mice	[293]
	↑ hypothalamic expression of NPY and agouti-related protein		
hGH in cerebral cortex	↑ dwarfism	Mice	[296]
	↑ hypothalamic SRIF mRNA		
	↓ hypothalamic GRF mRNA		
hGH in GRF neurons	↑ dwarfism	Rat	[297]
	↑ hypothalamic SRIF mRNA		[298]
	↓ hypothalamic GRF mRNA		[299]
hGH in vasopressin neurons	↑ dwarfism	Rat	[300]

Functional roles for extrapituitary GH have been clearly demonstrated by the abrogated responses that occur when extrapituitary GH synthesis or secretion is blocked by siRNA-knockdown, by GH antisense oligonucleotides, or by SRIF antagonism or when local GH action is blocked by GHR antagonism (Table 1). Functional roles for GH in local sites of production and action are also supported by studies on the transgenic expression of heterologous GH genes in specific regions of the rodent CNS, especially as the phenotypes induced after local GH expression differ from those following the overexpression of GH systemically (Table 2). For instance, the specific overexpression of bovine (b) GH in the CNS of mice, using the promoter to glial acidic fibrillary protein (GFAP), results in hyperphagia-induced obesity [293], whereas mice that systemically overexpress the bGH gene have unchanged food intake [293, 294] and a reduced percentage of body fat mass [295]. The increased hyperphagia in mice that transgenically express GH in the CNS reflects the autocrine or paracrine induction of two orexigenic hypothalamic neuropeptides, agouti-related protein, and neuropeptide Y [293]. Similarly while the systemic overexpression of bGH, results in increased body size in transgenic mice [295], the specific overexpression of human (h) GH in the cerebral cortex [296], or in hypothalamic GRF neurons [297–299] or in hypothalamic vasopressin neurons [300] results in dwarfism. This induction of dwarfism results from local GH actions that increase SRIF tone and decreases GRF, thereby inhibiting pituitary GH secretion.

Functional autocrine or paracrine actions of extrapituitary GH have also been comprehensively demonstrated by the blockade of GH production and/or GH action in non-pituitary cells in vitro (Table 3) and by the forced expression of heterologous GH genes in carcinoma cell lines (Table 4). These studies have also shown that some of the autocrine or paracrine actions of extrapituitary GH are dissimilar to the endocrine actions of pituitary (exogenous) GH. This difference is probably because of differences in GH concentration or patterns of GH secretion, and differences in GHR proximity and location. The signaling mechanisms utilized by GH in carcinoma cells may also differ from those in non-carcinoma cells and promote oncogenesis [241]. In summary, functional roles for extrapituitary GH have been clearly established both in vivo and in vitro. GH should therefore be considered, like IGF-1 [301, 302] and prolactin [303], as a local growth factor, as well as an endocrine hormone.

Table 3 Functional autocrine/paracrine actions of endogenous GH in oncogenesis

Blocker of endogenous GH synthesis/action	Functional response	References
GH antisense	↓ cytokine production	[253]
GH antisense	↑ DNA fragmentation	[255]
GH antisera	↓ cell proliferation	[253]
GHR antagonist (B2036)	↓ cell proliferation	[110, 260, 271]
	↓ cell spreading	
	↓ intracellular signaling/ transcriptional activity	
	↓ anchorage-independent growth	
	↓ cell survival	
	↓ cell migration	
	↓ cell invasion	
	↓ VEGF-A1 expression	
GHR antagonist (hGH-120R)	↓ cell proliferation	[259]

Perspective

As all cells in an individual have the same genome, all cells have the potential to express the same genes. The extrapituitary expression of the GH gene is therefore not an oddity and is consistent with the widespread expression of other pituitary hormones (e.g., the extrapituitary expression of prolactin in the placenta, uterus, ovary, testis, mammary

Table 4 Functional autocrine/paracrine actions of endogenous GH in oncogenesis

Cancerous cell line	Functional response to forced hGH expression	References
MCF-7 (human mammary carcinoma cells)	↑ cell proliferation	[258–260]
	↓ cell death	
	↑ cell spreading	
	↑ filipodia stress fibers	
	↑ JAK2 activity	
	↑ STAT5 activity	
	↑ P38 MAP kinase activity	
	↑ p44/42 MAP kinase activity	
	↑ cytoplasmic phosphotyrosine	
MCF-7	↑ anchorage-independent growth	[261, 265]
	↑ oncogenic transformation	
	↑ tumor formation in vivo	
	↑ HOXA1 expression	
	↑ cMyc expression	
	↑ cyclin D expression	
	↑ $Bc1_2$ expression	
MCF-7	↑ antioxidant activity	[267]
	↑ catalase activity	
	↑ superoxide dismutase activity	
	↑ glutathione peroxidase activity	
	↑ glutamyl synthetase activity	
MCF-7	increased DNA methyltransferase (DNMT-I, DNMT-3A, DNMT-3B) expression	[262]
MCF-7	↑ PAX 5 DNA binding activity	[268]
MCF-7	↓ placental transforming growth factor β gene expression	[270]
MCF-7	↑ trefoil factor (TFF3) expression	[272]
MCF-7	↓ plakoglobin expression	[138]
	↓ relocalization of E-cadherin from periphery to cytoplasm	
	↓ metastatic transformation of cells	
	↑ cell motility	
	↑ matrix metalloproteinase activity	
HCII mouse (mouse mammary epithelial cells)	↑ proliferation	[123]
	↑ cell survival	
	↓ β casein expression	
	↓ E-cadherin expression and loss of epithelial localization	
RL95-2/AN2 (human endometrial carcinoma cells)	↑ cell migration	[110]
	↑ invasiveness	
	↑ tumor progression in vivo	

gland, prostate, brain, adipose tissue, immune tissue, and skin [304] and in cancerous tissues [305]). It is also consistent with the occurrence of ectopic hormone syndromes [306–308], leaky gene phenomena [309], and the finding of proteins in 'aberrant' locations [310]. Moreover, although the pituitary expression of GH was thought to be due to the pituitary-specific expression of its pit-1 transcription factor, pit-1 is now known to be similarly expressed in many extrapituitary tissues [311]. It is therefore not surprising that GH expression is widespread and in many tissues, although GH expression is not pit-1-dependent in all tissues [311]. The expression of GH in pituitary and extrapituitary tissues may therefore be differentially regulated, as indicated by the expression of GH in the hippocampus and salivary glands of pituitary GH-deficient dwarf mice [7, 8, 178], in which GH deficiency results from a mutation in prop-1, an upstream transcription factor for Pit-1. GH expression in immune tissues may similarly be differentially regulated from that in the pituitary gland [312].

The widespread extrapituitary expression of the GH gene is now an established fact but the mere presence of GH in extrapituitary tissues does not, by itself, provide

evidence of extrapituitary GH action. Although most tissues and most cells have GHRs [313–315], tissue GH concentrations are largely unknown, as is the GH concentration required to activate local GHRs. Moreover, while GH immunoreactivity may be detected in a tissue, this may not correlate with GH bioactivity [316, 317] and the presence of GH mRNA may not correlate with the presence of GH protein or with identical GH isoforms [164]. The putative actions of GH in extrapituitary tissues are therefore largely speculative and based on the established actions of exogenous (pituitary) GH in the same tissues. In the absence of model systems to differentiate between pituitary and extrapituitary GH actions, functional roles for extrapituitary GH are indicated by the abrogated in vivo and in vitro biological responses observed after the blockade of local GH production or action and by the induction of physiological and phenotypic responses following locally induced GH expression (Tables 1, 2, 3, 4).

The importance of extrapituitary GH as a local growth factor is, however, difficult to assess, in view of the plethora of other autocrines/paracrines involved in growth and metabolism [19] and the existence of compensatory pathways that may maintain homeostasis in the absence of any one factor. Indeed, even the roles for pituitary GH in growth and development are sometimes difficult to assess, as some whole-body growth still occurs in the complete absence of circulating GH and in conditions of GH resistance [318]. Further research on the physiological significance of extrapituitary GH is therefore warranted.

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