REVIEW

Growth hormone: roles in female reproduction

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Abstract

GH, as its name suggests, is obligatory for growth and development. It is, however, also involved in the processes of sexual differentiation and pubertal maturation and it participates in gonadal steroidogenesis, gametogenesis and ovulation. It also has additional roles in pregnancy and lactation. These actions may reflect direct endocrine actions of pituitary GH or be mediated by its induction of

hepatic or local IGF-I production. However, as GH is also produced in gonadal, placental and mammary tissues, it may act in paracrine or autocrine ways to regulate local processes that are strategically regulated by pituitary GH. The concept that GH is an important modulator of female reproduction is the focus of this review.

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Introduction

Although the somatogenic and gonadotrophic axes have long been known to be closely linked during growth and sexual maturation (Simpson *et al.* 1944), until recently the role of growth hormone (GH) in reproduction had been described as 'more akin to fine tuning than that of a major player . . .' (Ogilvy-Stuart & Shalet 1992). Experimental studies suggest, however, that this statement underestimates the importance of GH in reproductive function, since GH modulates steroidogenesis, gametogenesis and gonadal differentiation as well as gonadotrophin secretion and responsiveness (Zachmann 1992). Mammary and placental roles for GH have also been proposed (Mol *et al.* 1996, Alsat *et al.* 1997). Moreover, while these actions may reflect endocrine roles of pituitary GH, they may also reflect local autocrine or paracrine actions of GH produced in reproductive tissues (Fig. 1).

Puberty

GH is usually, but not always, required for the timing of sexual maturation, since delayed or absent puberty is often associated with GH-deficient or GH-resistant states and GH administration accelerates puberty. For instance, in a cohort of 60 GH-deficient women, puberty occurred normally in only 16 and was delayed in 10 others (de Boer *et al.* 1997). Puberty is similarly delayed in a large proportion of GH receptor (GHR)-knockout mice (Bartke *et al.* 1999), GH-resistant women (Laron 1984) and GH-releasing hormone (GHRH)-immunized cattle

(Simpson *et al.* 1991). The importance of GH in sexual maturation is further demonstrated by the ability of exogenous GH to accelerate sexual maturation in GH-replete monkeys (Wilson *et al.* 1989) and GH-deficient children (Darendeliler *et al.* 1990, Stanhope *et al.* 1992). GH may accelerate puberty by activating the luteinizing hormone (LH)-releasing hormone pulse generator (Bartke *et al.* 1999) and/or by potentiating androgen action (Ilondo *et al.* 1982).

GH administration has not, however, been shown to accelerate pubertal development in pigs (Bryan *et al.* 1989, 1990, Andres *et al.* 1991). This may, however, reflect the reproductive state at the time of GH treatment, since GH appears to increase the rate of human sexual maturation only when a pubertal pattern of pituitary gonadotrophin secretion is established (Sharara & Giudice 1997). Moreover, since the implantation of bovine GH (bGH) in the median eminence of young female rats delays puberty (Advis *et al.* 1981), it is possible that GH exerts inhibitory effects on the hypothalamo–pituitary–gonadal axis at central sites, contrary to its stimulatory actions on pituitary gonadal function.

Ovarian Actions

Experimental studies performed *in vivo* suggest that GH acts on the ovary to affect gametogenesis and steroidogenesis. The interpretation of these *in vivo* studies is, however, complicated by the increase in circulating insulin-like growth factor-I (IGF-I) resulting from *in vivo*

Figure 1 Effects of GH in the female reproductive system. Pituitary GH stimulates the production of hepatic IGF-I, and both pituitary GH and hepatic IGF-I act to stimulate mammary, ovarian, uterine and/or oviduct function. However, GH is also produced in the mammary gland, placenta, ovary and perhaps oviduct, and may act directly or via local IGF-I to affect reproductive function. Pituitary GH and hepatic IGF-I may be involved in strategic maintenance of ovarian function (*italic text, solid lines*), whereas ovarian GH may be involved in emergency modulation of ovarian function (*normal text, dotted lines*).

GH administration and the proven ability of IGF-I to stimulate ovarian activity (Adashi *et al.* 1985). Indeed, the administration of exogenous GH results in an artificial situation in which both GH and IGF-I are elevated, whereas physiological increases in IGF-I normally result in a decrease in pituitary GH production. *In vivo* responses are thus likely to partially reflect the actions of GH-induced hepatic IGF-I. Numerous *in vitro* studies and the finding of GHR mRNA and protein in ovarian cells suggest, however, that direct ovarian actions of GH provide an important modulation of gonadotrophin-dependent and -independent functions.

Folliculogenesis and gametogenesis

The production of viable gametes and adequate steroid production requires a series of developmental events to occur in the follicle (Fig. 2) and within the oocyte. GH affects the maturation of the follicle and gamete and thereby plays a facilitatory role in fertility.

Early folliculogenesis GH may play a particularly important role in early, follicle-stimulating hormone (FSH)-independent follicular development (Fig. 2), since GH-binding activity peaks during early folliculogenesis in porcine follicles (Quesnel 1999) and fish ovarian

Figure 2 Role of GH in gametogenesis. Primary follicles (stage 1) develop into preantral follicles (stage 2) and possibly small antral follicles (stage 3) independently of FSH. A certain number of these small follicles (stages 2 and 3) undergo further FSH-dependent development each menstrual cycle into mature antral (Graafian) follicles (stage 4) prior to ovulation (stage 5) or apoptosis. These stages of folliculogenesis are characterized by increasing numbers of granulosa cells (grey) and thecal cells (black), both of which are required for the production of oestrogen. After the oocyte is expelled from the follicle, granulosa cells and, to a lesser extent, thecal cells, become luteinized (6), and acquire the ability to synthesize progesterone. GH of pituitary and/or ovarian origin binds GHRs on thecal, granulosa and luteal cells and promotes gametogenesis (+). Some of the ovarian actions of GH are modulated by ovarian and/or hepatic IGF-I (not shown; Table 1).

homogenates (Gomez *et al.* 1998). Indeed, *in vivo* and *in vitro* studies suggest that GH stimulates growth and prevents atresia in small follicles, which develop and undergo atresia throughout the menstrual cycle. For instance, GH administration *in vivo* increases the number of small follicles in cattle (Gong *et al.* 1991, 1993) and horses (Cochran *et al.* 1999). *In vitro* studies in mice, accordingly, show a stimulatory effect of GH on preantral follicle development and follicular cell proliferation in immature mice that is synergistic with (and therefore independent of) IGF-I (Kumar *et al.* 1997, Liu *et al.* 1998, Kobayashi *et al.* 2000). Other studies in perfused rabbit ovaries, however, implicate IGF-I in early folliculogenesis, since follicular growth and intraovarian IGF-I increase in a coordinate fashion following GH administration (Yoshimura *et al.* 1993, 1994). Other ovarian growth factors, such as activin, may also mediate the actions of GH, since follistatin (which binds and inactivates activin) blocks the stimulatory effect of GH on murine preantral follicle growth (Liu *et al.* 1998). GH may thus be particularly important in the recruitment of follicles and initiation of oocyte growth, perhaps by matching nutritional status with the number of growing oocytes.

Late folliculogenesis and luteinization GH acts in conjunction with gonadotrophins to stimulate later stages of folliculogenesis and luteinization (Fig. 2), since both GH and gonadotrophins are required to prevent atresia of larger follicles (>2 mm) following hypophysectomy in sheep (Eckery *et al.* 1997). GH may play a role in follicle selection, since GH-binding sites in sow granulosa cells are lost in atretic follicles (Quesnel 1999) and the development of the dominant follicle is impaired in GHR-deficient cattle (Chase *et al.* 1998). GH administration *in vivo* similarly increases the number of large follicles in pigs (DeLaSota *et al.* 1993, Lucy *et al.* 1995) and GH-deficient dwarf rats (Ozawa *et al.* 1996) and the number of corpora lutea in cattle (Lucy *et al.* 1992) and GH transgenic rats (Danilovich *et al.* 2000). The stimulatory effect of GH on follicle number and size reflects increased cell proliferation, at least in luteinized human granulosa cells (Ovesen *et al.* 1994), but also is indicative of the suppressive effect of GH on apoptosis (Eisenhauer *et al.* 1995, Sirotkin & Makarevich 1999, Danilovich *et al.* 2000). GH may enhance follicular survival and cell proliferation by potentiating LH action, since GH deficiency is associated with decreased LH receptor gene expression and LH

responsiveness in rats and GH administration corrects both defects (Advis *et al.* 1981). The folliculogenic effect of GH, at least in human luteinized granulosa cells, is dependent upon FSH and independent of IGF-I (Ovesen *et al.* 1994, Ovesen 1998).

Oocyte maturation An important role for GH in the development of the oocyte is indicated by the relationship between follicular GH concentrations and human oocyte maturity (Mendoza *et al.* 1999). Oocytes harvested from follicles with high antral fluid GH concentrations are more fertile than those from follicles with low GH concentrations, and amongst fertilized oocytes, intrafollicular GH concentration is inversely related to subsequent cleavage failures and morphological dysfunctions of the cleaved embryos (Mendoza *et al.* 1999). In contrast, prolactin, LH, interleukin-1 and tumour necrosis factor- α are unrelated to the development of competent oocytes (Mendoza *et al.* 1999). Mendoza *et al.* (1999) have therefore concluded that an early rise in the GH concentration in small antral follicles is beneficial for oocyte quality, by enhancing or acting in synergy with gonadotrophin-controlled developmental processes. Accordingly, the fertilization rate in bovine oocytes *in vitro* is increased by incubation with GH (Izadyar *et al.* 1998).

GH may enhance oocyte quality by accelerating and coordinating cytoplasmic and nuclear maturation, at least in bovine oocytes. This possibility is indicated by the greater proportion of bovine oocytes manifesting the markers of cytoplasmic maturation (for instance, the ability to decondense sperm chromatin and form sperm asters (Hyttel *et al.* 1989)) in GH-treated cell populations (Izadyar *et al.* 1997, 1998). Nuclear maturation is similarly enhanced by GH, since GH-treated bovine oocytes complete meiosis I faster and undergo zygote cleavage and blastocyst formation more frequently than untreated oocytes (Van der Westerlaken *et al.* 1994, Izadyar *et al.* 1996, 1998). This effect of GH is dependent upon cAMP and the presence of cumulus cells but is IGF-I-independent (Bevers *et al.* 1989, Zuelke & Brackett 1993, Izadyar *et al.* 1997, 1998, Kolle *et al.* 1998). GHR mRNA and protein are, moreover, not detected in oocytes from secondary or tertiary follicles of the bovine ovary (Kolle *et al.* 1998); thus, direct actions at the oocyte itself appear unlikely. GH also stimulates nuclear maturation of fox, rat, rabbit and pig oocytes; however, at least in rats, cumulus cell IGF-I appears to be the mediator and cAMP is not involved (Hagen & Graboski 1990, Yoshimura *et al.* 1993, 1994, Apa *et al.* 1994b, Kalous *et al.* 1998).

Ovulation H plays a non-essential but facilitatory role in ovulation. For instance, although GH alone fails to cause ovulation in sheep (Davis *et al.* 1990), pigs (Gilbertson *et al.* 1991) or rabbits (Yoshimura *et al.* 1993), gonadotrophin-induced ovulation in perfused rabbit ovaries is significantly improved by GH co-administration (Yoshimura *et al.*

1994). Moreover, fertility is reduced but not abolished in GHR-knockout mice (Bartke 1999) and egg production and fertility are not impaired in GH-resistant sex-linked dwarf chickens (Decuyper *et al.* 1991). In such cases, other GH-like hormones, particularly prolactin, may compensate for the lack of GH action (Bartke 1999). Indeed, unlike GHR-knockout mice, Snell and Ames mice are totally sterile, lacking GH, prolactin and thyrotrophin (Bartke 1999).

GH may facilitate ovulation by increasing sensitivity to gonadotrophins and by reducing the incidence of apoptosis in preovulatory ovarian follicles. The increased number of corpora lutea and reduced numbers of atretic follicles in the ovaries of mice transgenically expressing GH supports this view (Danilovich *et al.* 2000). The overexpression of GH in these mice has thus been correlated with an increase in the number of ova shed during each ovulation (Cecim *et al.* 1995, Danilovich *et al.* 2000). Since treatment with IGF-I also suppresses apoptotic DNA fragmentation in preovulatory follicles, this action of GH is thought to be IGF-I mediated (Danilovich *et al.* 2000). GH may also facilitate ovulation by increasing tissue plasminogen activator synthesis, which activates the serine protease required for rupture of the ovarian capsule (Politis *et al.* 1990).

The timing of ovulation may also be GH-dependent, since it is delayed in normal female mice paired with GHR-knockout mice (Bartke *et al.* 1999). A reduced secretion of the male pheromones responsible for synchronizing the ovulatory cycle in the female has been implicated (Bartke *et al.* 1999). In female GHR-knockout mice, the oestrous cycle is prolonged and irregular and the ovulation rate is reduced, resulting in smaller litters (Bartke *et al.* 1999, Danilovich *et al.* 1999).

Fertility: clinical studies Normal fertility does not always require a normal GH axis. Indeed, it is well established that a proportion of GH-deficient (de Boer *et al.* 1997) and GH-resistant (Menashe *et al.* 1991, Dor *et al.* 1992) women have normal menstrual cycles and conceive normally. However, many GH-deficient women require assisted reproductive technologies to conceive, principally for the induction of ovulation, and it has been hypothesized that other women with reproductive dysfunctions may be partially GH-deficient (de Boer *et al.* 1997). The possible use of GH as an adjunct to human menopausal gonadotrophin (hMG) to induce ovulation has thus been the focus of extensive research (Jacobs 1992, Shoham *et al.* 1992a, Homburg & Farhi 1995) and reviews (Katz *et al.* 1993, Homburg & Farhi 1995, Franks 1998). Clinical studies have shown that GH may be therapeutically useful in some, but not all, infertile women. In particular, GH administration to hypogonadotrophic anovulatory women significantly reduces the dosage and duration of hMG treatment required for ovulation induction (Blumenfeld & Lunenfeld 1989, Homburg *et al.* 1990, Volpe *et al.* 1990, Burger *et al.* 1991, Fowler & Templeton

1991, Jacobs 1992). Furthermore, a significant proportion of women who respond to GH fail to respond to hMG alone. GH administration also restores FSH responsiveness in women with Down's syndrome, as determined by serum oestradiol concentrations (Cento *et al.* 1997).

GH therapy may similarly improve the success of *in vitro* fertilization techniques by enhancing the hyperovulatory response to hMG. Numerous clinical studies have demonstrated that the addition of GH to the hMG treatment regimen improves oocyte recovery and/or the rate of successful fertilizations and pregnancies (Volpe *et al.* 1989, Ibrahim *et al.* 1991, Jacobs 1992, Stone & Marrs 1992). Responsiveness to hMG in normogonadotrophic women with polycystic ovary syndrome is similarly improved by the administration of GH (Owen *et al.* 1991*a,b*). In initial studies that employed pharmacological doses of GH, the improvement in fertility was thought to be partially due to the lipolytic action of GH and a reduction in obesity (Morales 1997). However, later studies suggested that much lower doses of GH are equally effective (Shoham *et al.* 1992*b*). Indeed, several investigators have suggested that a single GH injection enhances hMG responsiveness for several subsequent cycles (Homburg *et al.* 1990, Burger *et al.* 1991, Fowler & Templeton 1991, Blumenfeld *et al.* 1992).

GH therapy does not, however, enhance gonadotrophic responsiveness in all women with infertility (Shaker *et al.* 1992, Tapanainen *et al.* 1992, Younis *et al.* 1992). Most of the women that do respond to GH–hMG co-treatment have an impairment in their secretion of GH (Blumenfeld *et al.* 1991). The infertility in these women may thus result in part from relative GH deficiency, whereas other dysfunctions are likely to be causal in the infertility of women that fail to respond to GH–hMG co-treatment (Blumenfeld *et al.* 1991). GH responsiveness is also greatest in young, hypo-oestrogenic women who have been subjected to previous pituitary suppression (Shaker *et al.* 1992, Tapanainen *et al.* 1992, Younis *et al.* 1992, Blumenfeld & Amit 1993). Conversely, GH therapy is largely ineffective in hypergonadotrophic women (Homburg & Farhi 1995) or women experiencing incipient or current ovarian failure (Homburg *et al.* 1991). Thyroid and adrenal function, and lifestyle characteristics, such as smoking, may also be important determinants in GH treatment efficacy (Hillensjo & Bergh 1993). *In vitro* fertilization protocols using gonadotrophin-releasing hormone agonists in the treatment regimen usually report that GH improves fertilization rate but not oocyte retrieval (Bergh *et al.* 1994, Hughes *et al.* 1994). The lack of GH response in some patients may also reflect concomitant changes in follicular IGF-binding proteins (IGFBPs), which would negate the beneficial effect of GH on follicular IGF-I (Rabinovici *et al.* 1997).

Summary

A significant amount of literature supports a role for GH in the production of viable gametes, since GH modulates

gonadotrophin-independent early folliculogenesis and gonadotrophin-dependent late folliculogenesis by increasing cell proliferation and inhibiting atresia. GH also increases oocyte fertility by enhancing nuclear and cytoplasmic maturation and facilitating ovulation. Ovarian and hepatic IGF-I appear to be involved in some, but not all, of these actions in some species. As a result of these gametogenic and folliculogenic actions, GH has been shown to influence fertility.

Steroidogenesis

The production of steroid hormones by ovarian cells is essential for follicular recruitment, oocyte maturation, ovulation, corpus luteal function, the maintenance and implantation of the blastocyst and the regulation of the hypothalamo–pituitary–gonadal axis. Steroidogenesis is therefore a prerequisite for successful reproduction. Although LH and FSH are the primary regulators of ovarian steroidogenesis, GH also modulates the production of ovarian steroids (Fig. 3).

***In vivo* studies** The ovarian actions of GH are partly mediated by changes in ovarian steroidogenesis. This is indicated by the partial progesterone deficiency in GHR-deficient cattle (Chase *et al.* 1998). Plasma oestradiol-17 β levels in female killifish are, moreover, increased by exogenous GH, which also prevents the hypophysectomy-induced decline in gonadal weight (Singh *et al.* 1988). However, consistent changes in blood steroid concentrations in response to GH administration have been difficult to demonstrate. For instance, whereas Bryan *et al.* (1992) noted a stimulatory effect of GH administration on plasma oestradiol levels in pigs, Samaras *et al.* (1994) observed GH alone was ineffective and actually inhibited the gonadotrophin-induced rise in plasma oestradiol. Conversely, in GH-treated cattle, changes in progesterone but not oestradiol levels (Schemm *et al.* 1990, Gallo & Block 1991), or in oestradiol but not progesterone (Andrade *et al.* 1996), or in neither hormone (Yuan & Lucy 1996*a*) have been reported. GH administration also reduces plasma androgen concentrations in humans (Tapanainen *et al.* 1992, Volpe *et al.* 1992), but not in cattle (Andrade *et al.* 1996) or sheep (Scaramuzzi *et al.* 1999). This reduction may represent increased conversion of androgens into oestrogens, since GH enhances aromatase and 3 β -hydroxysteroid dehydrogenase activity in women (Tapanainen *et al.* 1992). GH-induced changes in follicular steroid synthesis may be independent of IGF-I, since follicular fluid IGF-I levels can be increased without parallel increases in oestrogen or progesterone in pigs (Bryan *et al.* 1992, Samaras *et al.* 1994) or cows (Andrade *et al.* 1996).

***In vitro* studies** Most, but not all, *in vitro* studies indicate a direct effect of GH on ovarian steroidogenesis. GH

Figure 3 Role of GH in steroidogenesis. Thecal and granulosa cells interact during the follicular phase to synthesize oestrogens, which are secreted. Following ovulation, granulosa cells become luteinized and acquire the ability to synthesize and secrete both oestrogens and progesterone. Experimental studies described in the text have demonstrated that GH increases (+) the activity of certain steroidogenic enzymes during the follicular and/or luteal phase, thereby increasing oestrogen or progesterone secretion. StAR is responsible for translocating cholesterol to the mitochondria for processing. The large, solid arrows indicate the release of newly synthesized steroids into interstitial fluid, from which they can access other ovarian cells or the bloodstream.

enhances oestradiol secretion from human granulosa cells (Mason *et al.* 1990, Ovesen *et al.* 1994, Doldi *et al.* 1996), perfused rabbit ovaries (Yoshimura *et al.* 1993), goldfish follicles (Van der Kraak *et al.* 1990) and bovine follicles (Sirotkin & Nitray 1994, Sirotkin 1996, Sirotkin & Makarevich 1999). Progesterone production from human (Lanzzone *et al.* 1992, Doldi *et al.* 1996), rat (Jia *et al.* 1986, Hong & Herington 1991, Apa *et al.* 1994a), bovine (Langhout *et al.* 1991, Spicer *et al.* 1993, Liebermann & Schams 1994) and sheep (Wathes *et al.* 1995) luteal cells is similarly enhanced by GH. The steroidogenic effect of GH, at least in fish, is equivalent to that of chorionic gonadotrophin (Singh & Thomas 1993). Inhibitory or insignificant effects of GH on progesterone (Ovesen *et al.* 1994) in human; Yoshimura *et al.* (1993) and Ando *et al.* (1994) in rabbit; Sirotkin & Nitray (1994) and Lucy *et al.* (1999) in cow) or oestradiol (Jia *et al.* (1986) in rat; Rajkumar *et al.* (1993) and Spicer & Stewart (1996) in pig)

levels have, however, been documented in other studies. GH responsiveness may be dependent on follicle size, since the stimulatory effect of GH on oestradiol synthesis in porcine granulosa cells was only observed in cells from small follicles (Spicer & Echternkamp 1995).

GH may induce steroidogenesis by potentiating gonadotrophin action, since GH only stimulates oestradiol production from goldfish follicles (Van der Kraak *et al.* 1990) and progesterone production from rat follicles (Singh & Thomas 1993) if gonadotrophins are present. In addition, GH stimulates androgen synthesis in LH-responsive, but not LH-resistant, bovine thecal cells (Spicer & Stewart 1996). Other studies indicate that GH and gonadotrophins act synergistically to increase oestradiol synthesis in human granulosa cells (Carlsson *et al.* 1992, Lanzzone *et al.* 1992) and progesterone synthesis in rat granulosa cells (Hsu & Hammond 1987). This synergy may reflect upregulation of gonadotrophin receptors by

Table 1 The involvement of IGF-I in the reproductive actions of GH

	Reference
Dependent on local IGF-I	
FSH-induced progesterone secretion in rat granulosa cells	Hutchinson <i>et al.</i> (1988)
Oestradiol secretion in human granulosa cells	Barreca <i>et al.</i> (1993)
Nuclear maturation in rat oocytes	Apa <i>et al.</i> (1994b)
Follicle growth in rabbit ovaries	Yoshimura <i>et al.</i> (1994)
Independent of IGF-I	
Progesterone synthesis in porcine granulosa cells	Mondschein <i>et al.</i> (1989)
Nuclear maturation in bovine oocytes	Izadyar <i>et al.</i> (1997)
Cell growth in human follicles	Ovesen (1998)
Cell growth in mice preantral follicles	Liu <i>et al.</i> (1998)

GH or the upregulation of GHRs by gonadotrophin-induced cAMP (Adashi *et al.* 1994). Indeed, at least in sheep, adequate ovarian GHR gene expression requires pituitary gonadotrophins (Juengel *et al.* 1997).

The stimulatory effects of GH on folliculogenesis and ovulation have obvious implications for steroidogenesis (Jia *et al.* 1986, Apa *et al.* 1994b). However, the steroidogenic effects of GH in some studies are too rapid to reflect cell differentiation and may instead reflect increased synthesis of steroidogenic enzymes (Fig. 3). For instance, GH stimulates steroidogenic acute regulatory protein (StAR) gene expression in the ovine corpus luteum (Juengel *et al.* 1995), facilitating the translocation of the cholesterol substrate to the mitochondrion for steroidogenic processing. GH also increases P450 side-chain cleavage (P450 scc) gene expression in porcine granulosa cells (Xu *et al.* 1997a), increasing the conversion of cholesterol to pregnenolone. GH similarly increases P450c17 mRNA in luteinized human granulosa cells, thereby increasing dehydroepiandrosterone production (Doldi *et al.* 1996). Basal and FSH-induced aromatase activity is also augmented by GH in human granulosa cells (Mason *et al.* 1990). GH also enhances aromatase activity and other unidentified steroidogenic enzymes involved in earlier stages of oestradiol synthesis in sea trout ovaries (Singh & Thomas 1993).

GH may stimulate steroid synthesis in humans by IGF-I-dependent and -independent mechanisms. The paucity of IGF-I in human follicles (Mason *et al.* 1990, Ovesen *et al.* 1994), even those treated with GH, would suggest that IGF-I does not mediate steroidogenic effects of GH in humans. Indeed, IGF-I independence is also indicated by the synergistic effect of GH and IGF-I/IGF-II on oestradiol production in human (Ovesen 1998) granulosa cells. However, IGF-I antibodies significantly inhibit GH effects on oestradiol production in human granulosa cells (Barreca *et al.* 1993). It has been hypothesized that GH may affect ovarian steroidogenesis by increasing the sensitivity to IGF-II acting through the IGF-I receptor, since IGF-II and IGFBPs are abundantly

present in human granulosa cells but IGF-I is scarce (Barreca *et al.* 1993). It is, moreover, possible that GH-induced ovarian IGF-I may act in an autocrine or even intracrine way, which would not require IGF-I secretion into the medium in detectable quantities.

Studies in animals also postulate that GH stimulates steroidogenesis by both IGF-I-dependent and -independent mechanisms (Table 1). IGF-I antibodies cannot completely block GH-induced progesterone synthesis in porcine granulosa cells (Mondschein *et al.* 1989) or androgen synthesis by rat thecal-interstitial cells (Apa *et al.* 1996). Indeed, IGF-I is not even detected in follicles from GH-treated heifers (Spicer *et al.* 1993) and ewes (Wathes *et al.* 1995), despite increases in progesterone release. IGF-I-independence is also indicated by the synergistic effect of GH and IGF-I/IGF-II on oestradiol production in porcine (Xu *et al.* 1997b) granulosa cells. The existence of distinct signalling mechanisms for GH and IGF-I is further supported by the opposite effects of cortisol and transferrin on GH- and IGF-I-induced progesterone synthesis (Hong & Herington 1991, Xu *et al.* 1995). This occurs by two distinct mechanisms, since cyanoketone treatment blocks bGH-induced oestradiol production but not bGH-induced conversion between testosterone and oestradiol (Singh & Thomas 1993). Aromatase activity, is, conversely, blocked by protein synthesis inhibitors and may thus be increased by IGF-I-dependent mechanisms (Singh & Thomas 1993).

Although GH signal transduction is normally mediated by the JAK2 cascade, cAMP may also be involved in GH-induced steroidogenesis. This possibility is suggested by the coincident increases in cAMP, IGF-I, and oestradiol in GH-treated bovine granulosa cells and the ability of protein kinase A blockers to inhibit these GH-induced changes (Sirotkin & Makarevich 1996, Sirotkin & Makarevich 1999). GH similarly induces cAMP production and subsequently steroid production in porcine (Sirotkin *et al.* 1998) and piscine (Van der Kraak *et al.* 1990) follicles and sea trout ovaries (Singh & Thomas

Table 2 GHRH and SRIF gene expression and immunoreactivity (IR) in female reproductive tissues. (R=receptor)

	Ovary	Placenta	Mammary gland
GHRH mRNA	Bagnato <i>et al.</i> (1992)	Mizobuchi <i>et al.</i> (1995)	Benlot <i>et al.</i> (1997)
GHRH-IR	Bagnatao <i>et al.</i> (1992)	Berry <i>et al.</i> (1992)	Benlot <i>et al.</i> (1997)
GHRHR mRNA/GHRHR-IR	Moretti <i>et al.</i> (1990a)	—	—
SRIF mRNA/SRIF-IR	Mori <i>et al.</i> (1984)	Lee <i>et al.</i> (1982)	Benlot <i>et al.</i> (1997)
SRIFR mRNA	Baumeister <i>et al.</i> (1998)	Caron <i>et al.</i> (1997)	—
SRIFR-IR	—	Caron <i>et al.</i> (1997)	—

1993). In pigs, this effect is dependent upon protein synthesis and acts both proximally and distally to the generation of cAMP (Xu *et al.* 1997*b*). Conversely, GH stimulates progesterone synthesis in gonadotrophin-primed rat granulosa cells independently of cAMP accumulation and *de novo* protein synthesis (Apa *et al.* 1994*a*).

Summary

GH has been shown to affect progesterone and oestrogen synthesis both *in vivo* and *in vitro*. The steroidogenic action of GH is associated with increased activity of several enzymes and may be partially responsible for the facilitatory effect of GH on folliculogenesis and gametogenesis.

The ovarian mini-hypophysis

GH synthesis Ovarian steroidogenesis and gametogenesis may be regulated by locally produced GH as well as pituitary GH (Fig. 1), since low levels of GH gene transcripts and proteins are present in the human ovary (Schwarzler *et al.* 1997). Granulosa cells and oocytes in particular may be regulated by local GH, since granulosa cells are avascular and separated from systemic circulation by the basal lamina (Lobie *et al.* 1992).

The synthesis of GH within the ovary may be regulated by locally produced GH secretagogues, since GHRH and GHRH receptors are abundantly present in ovarian tissues (Moretti *et al.* 1990*b*) (Table 2). Somatostatin (SRIF) immunoreactivity and SRIF receptors are similarly present (Mori *et al.* 1984, Baumeister *et al.* 1998) (Table 2). The importance of ovarian GHRH and/or SRIF in ovarian GH synthesis is uncertain, since GH synthesis in non-pituitary sites is often independent of traditional GH secretagogues (Harvey & Hull 1997). Moreover, these factors have been shown to have other local roles, unrelated to GH regulation (Scanes & Campbell 1995).

GHRs The possibility that ovarian GH may act at local sites is supported by the detection of high-affinity ($K_d=2.8\text{--}6.1 \times 10^{-9}$ M) low-capacity binding sites in ovarian membranes (e.g. in rabbits (Ando *et al.* 1994), swine (Quesnel 1999) and fish (Yao *et al.* 1991)) and in pig follicles (Quesnel 1999) (Table 3). In fish, this GH-

binding activity is preferentially found in intracellular membranes, and, to a lesser extent, in plasma membranes (Yao 1993). GHR mRNA and immunoreactivity are also present in the ovary and other female reproductive tissues of numerous species (Table 1).

GHR gene expression is differentially regulated in ovarian and non-ovarian tissues, suggesting that ovarian GHRs serve an important role in regulating reproductive function. For instance, ovarian and hepatic GHR and GH-binding protein (GHBP) transcripts peak 14 or 20 days post-fertilization respectively (Sakaguchi *et al.* 1998). A transitory peak in both transcripts is also observed postnatally (day 8), corresponding to the lactation period (Sakaguchi *et al.* 1998). Intestinal and renal GHR and GHBP transcripts do not follow this pattern (Sakaguchi *et al.* 1998). GHR transcripts similarly increase in abundance during gestation in cows in the liver and corpora lutea, but not in adipose tissue (Hauser *et al.* 1990, Yuan & Lucy 1996*b*).

Differential regulation of ovarian and non-ovarian GHR transcripts may reflect the use of alternate promoters. For instance an alternate splice variant (1B) has been detected in the bovine ovary and corpora lutea that contains a different promoter from the cloned hepatic GHR mRNA (1A) (Spicer & Echternkamp 1995, Heap *et al.* 1996). The 1A variant is specific to adult bovine liver but the 1B mRNA variant is found in both hepatic and non-hepatic tissues (Lucy *et al.* 1998). In rats, the 1A and 1B variants are differentially regulated by GH and reproductive steroids (Baumbach & Bingham 1995); thus, GHR synthesis, hence GH responsiveness, may thus be differentially regulated in hepatic and reproductive tissues (Lucy *et al.* 1998, Gomez *et al.* 1999).

IGFs Many of the actions of GH may be induced by the local production of IGFs (Fig. 1, Table 1 and above text), since IGF-I (Geisthoevel *et al.* 1989) and IGF-I receptors (Poretsky *et al.* 1985) are usually detectable in ovarian tissues. Moreover, GH increases IGF-I in follicular fluid from humans (Volpe *et al.* 1992), cows (Sirotkin & Makarevich 1999), pigs (Sirotkin *et al.* 1998), and sheep (Juengel *et al.* 1997) and in perfused rabbit ovaries (Yoshimura *et al.* 1994). However, circulating GH and ovarian IGF-I are not always related, since GHRH immunization of heifers decreases plasma GH and IGF-I but

Table 3 GHR/GHBP transcripts and immunoreactivity (IR) and GH-binding sites[†] in the female reproductive tract

	Species	GHR/GHBP-IR or GH-binding sites ^{†,‡}	GHR/GHBP mRNA ¹
Tissue			
Ovary	Rabbit	Ando <i>et al.</i> (1994)	—
	Cattle	—	Lucy <i>et al.</i> (1998)
Granulosa cells	Human	Carlsson <i>et al.</i> (1993), Tamura <i>et al.</i> (1994)	Carlsson <i>et al.</i> (1992, 1993), Sharara <i>et al.</i> (1994)
	Rat	Lobie <i>et al.</i> (1990)	—
	Pigs	[†] Quesnel (1999)	*Yuan & Lucy (1996b)
	Cattle	Kolle <i>et al.</i> (1998)	*Yuan & Lucy (1996b), Izadyar <i>et al.</i> (1997)
	Sheep	—	Eckery <i>et al.</i> (1997)
Luteinized granulosa cells	Human	Katz <i>et al.</i> (1993)	—
	Cattle	Kolle <i>et al.</i> (1998)	Kolle <i>et al.</i> (1998)
Luteal cells	Human	Carlsson <i>et al.</i> (1993)	Carlsson <i>et al.</i> (1993), Sharara <i>et al.</i> (1994)
	Rat	Lobie <i>et al.</i> (1990)	—
	Pig	Yuan <i>et al.</i> (1996)	Yuan <i>et al.</i> (1996)
	Cattle	Yuan <i>et al.</i> (1996)	Scott <i>et al.</i> (1992), Lucy <i>et al.</i> (1993a), Yuan & Lucy (1996b)
	Sheep	—	Juengel <i>et al.</i> (1997)
Thecal cells	Human	—	*Katz <i>et al.</i> (1993), *Sharara & Nieman (1994)
	Pig	[†] Quesnel (1999)	—
	Cattle	—	*Kolle <i>et al.</i> (1998)
	Rat	Lobie <i>et al.</i> (1990)	—
Corpus albicans	Human	—	Sharara <i>et al.</i> (1994)
Oocyte	Human	—	*Sharara <i>et al.</i> (1994)
	Rat	Lobie <i>et al.</i> (1990)	—
	Pig	[†] Quesnel (1999)	—
	Cattle	Kolle <i>et al.</i> (1998)	Izadyar <i>et al.</i> (1997), Kolle <i>et al.</i> (1998)
	Sheep	—	Eckery <i>et al.</i> (1997)
Cumulus cells	Cattle	Kolle <i>et al.</i> (1998)	Izadyar <i>et al.</i> (1997), Kolle <i>et al.</i> (1998)
Follicular fluid	Human	Amit <i>et al.</i> (1993)	—
Uterus	Human	—	Sharara & Nieman (1995)
	Mouse	—	Sharara <i>et al.</i> (1994)
	Rat	Lobie <i>et al.</i> (1990)	—
	Cattle	—	Heap <i>et al.</i> (1996), Kirby <i>et al.</i> (1996), Kolle <i>et al.</i> (1997)
Placenta	Human	Frankenne <i>et al.</i> (1992), Hill <i>et al.</i> (1992), Urbanek <i>et al.</i> (1992)	—
	Rat	Barnard <i>et al.</i> (1994)	Barnard <i>et al.</i> (1994)
	Sheep	Lacroix <i>et al.</i> (1999)	—
	Cattle	Kolle <i>et al.</i> (1997)	Kolle <i>et al.</i> (1997)
Endometrium	Rat	Lobie <i>et al.</i> (1990)	—
	Sheep	Lacroix <i>et al.</i> (1999)	—
	Cattle	—	Scott <i>et al.</i> (1992), Kirby <i>et al.</i> (1996)
Myometrium	Rat	Lobie <i>et al.</i> (1990)	—
	Cattle	—	Kirby <i>et al.</i> (1996)
Amnion	Cattle	—	Scott <i>et al.</i> (1992)
Fetal EEM [‡]	Cattle	—	Scott <i>et al.</i> (1992)
Cotyledon	Cattle	—	Scott <i>et al.</i> (1992)
Intercotyledonary membrane	Cattle	—	Scott <i>et al.</i> (1992)
Oviduct	Rat	Lobie <i>et al.</i> (1990)	—
Mullerian duct	Chickens	[†] Wang (1989)	—
Mammary gland	Human	Mertani <i>et al.</i> (1998)	Mertani <i>et al.</i> (1998)
	Human tumour	Mertani <i>et al.</i> (1998)	Mertani <i>et al.</i> (1998)
	Rat	Lincoln <i>et al.</i> (1995)	Tiong & Herington (1991)
	Rabbit	Lincoln <i>et al.</i> (1995)	Jammes <i>et al.</i> (1991)
	Mouse	—	Ilkbahar <i>et al.</i> (1995)
	Fetal Cattle	Knabel <i>et al.</i> (1998)	Knabel <i>et al.</i> (1998)
	Cattle	—	Scott <i>et al.</i> (1992), Lucy <i>et al.</i> (1998)
	Pig	—	Jammes <i>et al.</i> (1991)
	Sheep	—	Jammes <i>et al.</i> (1991)

*Not detected. [‡]Extra-embryonic membrane.¹It should be noted that the presence of GHR mRNA is indicative but not proof of function. Similarly, the presence of GHR/GHBP-IR is indicative but not proof of local synthesis and/or function.

not ovarian IGF-I (Cohick *et al.* 1996). Indeed, some investigators have failed to detect IGF-I and/or IGF-I mRNA in human granulosa cells (Ovesen *et al.* 1994) or bovine follicles (El-Roeiy *et al.* 1993). Ovarian IGF-I in the fish ovary is, moreover, significantly different in sequence from hepatic IGF-I (Kermouni *et al.* 1998). Basal IGF-I production is similarly at the lower limit of detection in isolated rabbit ovaries (Yoshimura *et al.* 1994). *In vivo* GH administration similarly does not stimulate the synthesis of IGFs or their receptors in pre-menopausal human ovaries (Penarrubia *et al.* 2000). In addition to its roles in reproduction, the local production of IGF-I in the ovary might provide negative feedback to regulate ovarian GH production, comparable to the regulation of pituitary GH secretion by peripheral IGF-I (Harvey 1995).

Summary

Components of the hypothalamo–pituitary–hepatic axis for GH are present in the ovary, including GH, GH secretagogues, GHRs, IGF-I and IGF-I receptors. The ovary may thus contain a GH ‘mini-hypophysis’, as has been previously described in immune tissues (Hull *et al.* 1997). This ‘mini-hypophysis’ may be concerned with short-term (‘emergency’) modulation of ovarian function in an autocrine or paracrine manner, whereas the traditional (‘strategic’) hypothalamo–pituitary–target organ axis may regulate more long-term functions, in an endocrine way.

Placental Actions

Roles of placental GH

In humans, it is well established that GH modulates maternal metabolism during human pregnancy to induce nutrient repartitioning for fetal development. Pituitary GH deficiency does not, however, abolish the normal pregnancy-induced increase in IGF-I (Eriksson 1989) and does not reduce fetal weight (Curran *et al.* 1998). Maternal IGF-I abundance is, in contrast, closely correlated with GH of placental origin (Beckers *et al.* 1990, Caufriez *et al.* 1993, Mirlesse *et al.* 1993) and intrauterine growth retardation results from a deficiency in placental GH-producing cells (Mirlesse *et al.* 1993, Chowen *et al.* 1996). Conversely, in animals without a placental GH variant, pituitary GH is closely linked with fetal weight. For instance, GH-deficient rats are characterized by low IGF-I, maternal weight gain, and litter size (Gargosky *et al.* 1993), and GH replacement results in heavier fetuses and faster postnatal growth of pups (Spencer *et al.* 1994). Litter size and fetal size are also reduced in female GHR-knockout mice, in comparison with normal females (Bartke *et al.* 1999). Enhanced GH secretion as a result of SRIF immunoneutralization similarly increases the mean birth weight of rat pups (Spencer *et al.* 1994). Fetal

weight in pigs is similarly increased by maternal GH administration (Sterle *et al.* 1995).

GH may enhance fetal growth by increasing placental size rather than by acting directly on the fetus, since placental GH is not detected in fetal circulation (de Zegher *et al.* 1990) and maternal GH does not cross the placental barrier (Fohlenhag *et al.* 1994). Indeed, exogenous GH stimulates placental growth in rats (Botero-Ruiz *et al.* 1997) and pigs (Sterle *et al.* 1995) and increases the weight of the myometrium and gravid uterus in ewes (Jenkinson *et al.* 1999). The stimulatory effect of GH on placental growth may be mediated at the placenta itself rather than by changes in maternal metabolism, since both pituitary and placental GH have mitogenic activity (Nickel *et al.* 1990, MacLeod *et al.* 1991). Moreover, placental GH also stimulates placental IGF-I production (Challier *et al.* 1991), and enhances endometrial cell growth (Strowitzki *et al.* 1991).

However, other investigators suggest that GH affects fetal growth independently of placental growth. For instance, Takeda & Hashimoto (1994) have shown in rats that maternal GH affects placental growth but not fetal growth, and fetal GH affects fetal but not placental growth. Placental GH may also alter the endocrine activity of the placenta, since human GH (hGH) stimulates production of placental lactogens, oestradiol and progesterone *in vitro* (Barnea *et al.* 1989, Di Simone *et al.* 1995). It also increases DNA synthesis and the growth of fetal tissues in the rat and sheep fetus during the latter part of pregnancy (Botero-Ruiz *et al.* 1997, Jenkinson *et al.* 1999).

The placental mini-hypophysis

The presence of GH or GH-like proteins in the placenta of primates (Alsat *et al.* 1998), ruminants (Anthony *et al.* 1995), rodents (Talamantes *et al.* 1988) and other mammals (Forsyth 1986) is well established. In primates, placental GH-like proteins largely result from expression of the hGH-V gene, which is at least 92% homologous to the hGH-N gene. GH-V gene expression is largely restricted to the syncytiotrophoblast layer of the placenta by proteins that are almost ubiquitous in other tissues and function to repress the hGH-V promoter (Scippo *et al.* 1993, Alsat *et al.* 1998). The hGH-V gene may, however, be weakly expressed in normal and tumorous pituitary glands (Scippo *et al.* 1991, Nickel & Cattini 1992) and the pituitary GH gene appears to be minimally expressed in human placental tissues (Lacroix *et al.* 1996).

Placental hGH is the same length (191 amino acids) as pituitary GH but contains 13 different amino acids and is more basic (Frankenne *et al.* 1988, 1990). Unlike pituitary GH, placental GH contains an N-linked glycosylation site; thus, placental GH isoforms corresponding to non-glycosylated (22 kDa) and glycosylated (25 kDa) proteins are produced (Frankenne *et al.* 1988, 1990). These small differences are thought to be responsible for the reduced

lactogenic activity of placental GH compared with pituitary GH (MacLeod *et al.* 1991). A poorly characterized GH-like protein is also produced from a splice variant of the hGH-V gene (hGH-V2) and may be membrane-bound (Cooke *et al.* 1988). This variant shows complete sequence divergence from hGH in the carboxy terminus. Two other transcripts of the hGH-V gene have also been described; one that predicts a truncated hGH-V isoform and one that predicts a novel 219 amino acid protein (hGH-V3) in which the first 124 amino acids are identical to placental GH (Boguszewski *et al.* 1998).

The GH-V gene is not present in the genomes of non-primates. GH variants are, however, present in the ovine (Lacroix *et al.* 1996) and rodent (Ogilvie *et al.* 1990) placentae, and GH mRNA has been detected in the ovine placenta, particularly in trophoectoderm and syncytium (Lacroix *et al.* 1999).

Placental GHs may act in an endocrine way to regulate extraplacental GH action, since hepatic GHR and GHBP mRNA are more abundant in mice with larger litters (Cramer *et al.* 1992), presumably because of the higher levels of placental lactogen. Placental GH and/or placental lactogens may also act in a paracrine or autocrine fashion to modulate placental function, since binding activity for placental and pituitary GH is abundantly present in the human placenta (Ray *et al.* 1990). The GH-binding activity in the placenta may reside in proteins identical to the cloned hepatic GHR, since GHR/GHBP mRNA and immunoreactivity are abundantly present in trophoblastic cells of the human (Frankenne *et al.* 1990, Hill *et al.* 1992, Urbanek *et al.* 1993), bovine (Kolle *et al.* 1997), ovine (Lacroix *et al.* 1999) and rat (Barnard *et al.* 1994) placenta (Table 3).

In primates, GH-V binds the cloned hepatic GHR with high affinity, and is not completely displaced from placental membranes by hGH-N (Frankenne *et al.* 1992). A separate, placental hGH-V receptor may thus exist but has yet to be identified. A hGHR gene isoform (hGHRd3), lacking sequences encoded by exon 3, is also present in the chorion, amnion and decidua of the placenta and is the exclusive isoform in placental villi (Urbanek *et al.* 1992). The binding characteristics of this isoform are, however, identical to the full-length receptor (Urbanek *et al.* 1993).

Summary

In addition to its well-documented effect on maternal metabolism, GH stimulates fetal growth by binding to placental GHRs and increasing placental size. Autocrine and/or paracrine actions of GH may be particularly important in the primate placenta, since the placenta is the primary source of GH during pregnancy.

Uterine Actions

Uterine roles of GH

The uterus of pregnant and non-pregnant females is also a site of GH action. For instance, exogenous GH promotes

uterine proliferation and cellular growth in rats with (Kennedy & Doktorcik 1988, Gunin 1997) or without (Miura & Koida 1970) the addition of oestrogen. Its induction of decidualization in the rat is partly mediated by an upregulation of oestradiol receptors (Chilton & Daniel 1987, Bezecny *et al.* 1992) and by an increased production of uterine IGFbPs and prostaglandins (Kennedy & Doktorcik 1988, Yallampalli *et al.* 1993). The number of implantation sites is also increased in the uteri of rats transgenically overexpressing the GH gene (Danilovich *et al.* 2000). In sheep, GH increases the weight of the myometrium and the gravid uterus (Jenkinson *et al.* 1999), probably by stimulating uterine milk protein mRNA levels and stratum spongiosum gland density (Spencer *et al.* 1999). However, unlike in rats, the uterine effects of GH do not involve the upregulation of oestradiol receptors and may be mediated by interferon tau (Spencer *et al.* 1999).

The growth promoting actions of GH in uterine tissues have also been indicated by the very high incidence (81%) of leiomyomas in women with acromegaly (Cohen *et al.* 1998) and the prevalence of GHR mRNA in the nuclei and cytoplasm of leiomyomas and myometrial tissue (Sharara & Nieman 1995). A role for GH in the formation of uterine tumours is also indicated by their suppression in mice in which GH secretion is blocked by neonatal monosodium glutamate treatment (Nagasawa *et al.* 1985) and their increased incidence in mice with enhanced GH secretion (Singtripop *et al.* 1993). The induction of cystic endometrial hyperplasia in dogs may also be mediated by GH, since GH mRNA and immunoreactive GH are present in the cytoplasm of glandular epithelial cells (Schoenmakers *et al.* 1997). The uterus is thus also an extrapituitary site of GH synthesis and action, in which GH may have paracrine or autocrine actions to regulate reproductive function.

Uterine GHRs

GH-induced changes in uterine growth may be independent of hepatic IGF-I, since GHR mRNA is present throughout the uterine layers of numerous mammalian species (Table 3). For instance, the GHR gene is expressed in the myometrium of non-pregnant humans and mice and in the endometrium, glands and stroma of non-pregnant mice (Sharara *et al.* 1994, Sharara & Nieman 1995). A splice variant of the GHR gene has been shown to be preferentially expressed in the bovine endometrium and myometrium (Heap *et al.* 1996, Lucy *et al.* 1998). This variant, which is also present in the ovary and corpus luteum, contains an alternative promoter and may permit specific regulation of GHRs involved in reproduction (Heap *et al.* 1996, Lucy *et al.* 1998). For instance, hepatic, but not uterine, GHRs are dramatically upregulated at mid-pregnancy in rats (Sakaguchi *et al.* 1998). Bovine uterine GHR transcripts appear to be more responsive to

the endocrine changes of pregnancy, since GHR mRNA is not detected in endometrium from non-pregnant cows but is readily detectable in uterine epithelium, glands and blood vessels of pregnant cows, particularly 6 months post-fertilization (Kolle *et al.* 1997). Conversely, GHR mRNA is detected from day 8 to day 120 in pregnant sheep and day 4 to day 16 in cycling sheep (Lacroix *et al.* 1999). Species-specific differences in GHR mRNA regulation by gonadal steroids may be responsible for this extensive variation between species, since uterine GHR gene expression is downregulated by GH in cows (Kirby *et al.* 1996) but unaffected by gonadal steroids in mice (Sharara *et al.* 1994).

Placental and uterine GHRs may affect reproductive fitness by IGF-I-dependent mechanisms, since IGF-I has been shown to modulate endometrial function (Wang & Chard 1999). Indeed, IGF-I is present in bovine endometrium and myometrium (Kirby *et al.* 1996) and IGFBPs are present in the rat and bovine uterus (Yallampalli *et al.* 1992, Kirby *et al.* 1996). Uterine IGF-I and IGFBPs are not, however, regulated by GH in rat (Yallampalli *et al.* 1992) or cows (Kirby *et al.* 1996); thus, their relevance to uterine GH function remains uncertain.

Summary

GH stimulates mitogenesis and, at high levels, tumorigenesis in the uterus. The presence of GH and GHR mRNA in this organ suggests that GH may be acting in a paracrine or autocrine manner.

Oviduct Actions

The presence of GHR mRNA in the bovine oviduct (Kirby *et al.* 1996) indicates that it may also be a site of GH action. This is supported by the increased content of cAMP, prostaglandin F- α and IGF-I in cultured bovine epithelial cells incubated with GH (Makarevich & Sirotkin 1997). The increased shell thickness of eggs laid by GH-treated hens (Donoghue *et al.* 1990) suggests that the avian oviduct, particularly the shell gland, is a site of GH action. This possibility is supported by the presence of GHRs and GHR mRNA in these tissues (Hull *et al.* 1999). Furthermore, the presence of GH proteins in the chicken oviduct (Harvey *et al.* 1998) suggests that this may reflect an autocrine or paracrine action of GH produced locally.

Mammary Actions

Mammogenesis

GH is obligatory for normal pubertal mammary development. Although pubertal mammary development occurs in response to an increase in oestradiol, it cannot take place

in the absence of the pituitary gland or GH in rats (Kleinberg *et al.* 1990, Feldman *et al.* 1993, Walden *et al.* 1998). Specifically, GH acts on mammary stromal and epithelial tissues in rats to induce the differentiation of ductal epithelia into terminal end buds (TEBs) and alveolar structures and promotes the morphogenesis of the TEBs in the mammary fat pad (Walden *et al.* 1998). GH administration to peri-pubertal heifers (Sejrsen *et al.* 1986, Sandles *et al.* 1987, Purup *et al.* 1993) and lambs (McFadden *et al.* 1990) similarly increases the amount of parenchymal tissue, although overall mammary size may not be increased, and immunization of heifers against GHRH similarly impairs pubertal mammary development (Sejrsen *et al.* 1999). Increased milk yield resulting from peripubertal GH administration has not, however, been observed in numerous studies in heifers (reviewed by Sejrsen *et al.* 1999).

The increased mammary growth induced by GH treatment in pregnant heifers (Stelwagen *et al.* 1991), ewes (Stelwagen *et al.* 1993) and goats (Knight *et al.* 1994) is, conversely, accompanied by increased milk yield. The increased mammary growth appears to reflect hyperplasia during pregnancy, hypertrophy postnatally, and a postponement of mammary differentiation (Sejrsen *et al.* 1999). However, neither mammary growth nor milk yield is increased by GH treatment in pregnant sows (Farmer *et al.* 1997).

Expression of the hGH transgene in mice similarly stimulates normal and neoplastic growth of the mammary glands (Bchini *et al.* 1991, Nasagawa *et al.* 1993) and GH administration to ageing monkeys increases glandular size and epithelial proliferation of the mammary glands (Ng *et al.* 1997). GH also has growth-promoting effects on human mammary cancer cells *in vitro* (Benlot *et al.* 1997). The administration of GH does, nevertheless, prevent the age-related involution of the mammary gland that normally occurs in response to increased plasmin activity (Politis *et al.* 1990).

Galactopoiesis

GH is the major galactopoietic hormone in cows and is commonly used to increase milk yield in commercial dairy herds (Tauer & Knoblauch 1997, Etherton & Bauman 1998). Indeed, treatment of dairy cows with bGH increases milk yield by 10–40%, by affecting both mammary morphogenesis and lactogenesis (Breier *et al.* 1991). The importance of GH in ruminant lactation is further shown by the correlation between GH gene polymorphisms (Lucy *et al.* 1993b, Lee *et al.* 1996, Yao *et al.* 1996), GHR gene polymorphisms (Falaki *et al.* 1996), plasma GH levels (Powell & Keisler 1995) and heritable patterns of GH secretion (Vasilatos & Wangsness 1981, Klindt 1988, Beerepoot *et al.* 1991) with milk production. GH treatment also increases milk yield in humans (Milsom *et al.* 1992) and milk yield and glucose concentration in goats

(Driancourt & Disenhaus 1997, Faulkner 1999). Indeed, hGH may provide a useful therapy for lactational insufficiency in mothers of preterm infants (Gunn *et al.* 1996). GH resistance and GH deficiency are similarly correlated with impaired lactational performance and consequently offspring survival rate (Barber *et al.* 1992, Bartke 1999, Bartke *et al.* 1999).

A variety of metabolic changes have been postulated to account for GH-induced lactation. For instance, GH alters nutrient partitioning to favour mammary gland anabolism and extramammary catabolism (McDowell *et al.* 1987*a,b*). Reduced glucose uptake and increased lactate production by skeletal muscles may permit the increased milk yield, milk fat content, milk protein, and lactose observed in GH-treated cows (McDowell *et al.* 1987*a,b*). Similarly, GH or GHRH inhibits lipogenic enzyme synthesis in adipose tissue but stimulates fatty acid synthase gene transcription (but not translation) in mammary gland tissue (Beswick & Kennelly 1998). Administration of GH antibodies reduces the metabolism of cholesterol and increases microsomal cholesterol and cholesterol ester stores in the rat mammary gland, suggesting roles for GH in mammary fat metabolism and milk production (Shand & West 1991). In addition, GH may selectively increase nutrient availability in the mammary gland, since GH increases cardiac output and mammary blood flow in cows (Davis *et al.* 1988, Breier *et al.* 1991) and goats (Mephram *et al.* 1984). Galactopoietic effects of GH may also reflect the stimulation of mammaryogenesis, since ovine GH treatment of ewes increases milk yield for 8 weeks following the treatment period (Kann *et al.* 1999).

Early studies hypothesized that systemic IGF-I mediates the effects of GH on the mammary gland in ruminants, since binding sites for IGF-I, but not GH, are easily detectable in mammary tissue and IGF-I, but not GH, exerts mammary effects *in vitro* (Akers 1985, Shamay *et al.* 1988, Cohick 1998). In addition, the mitogenic effect of serum relates more closely to the IGF-I concentration than the GH concentration (Sejrsen *et al.* 1999). An indirect mechanism of GH action is further supported by the lack of a lactational response to GH administered s.c. over the bovine mammary gland (Flint & Knight 1997).

GH may also directly affect mammary function, since GHR mRNA and protein have been detected in the mammary gland of ruminants and other species (Table 3). Experimental studies also suggest a direct effect, since GH administered through the teat canal in goats results in a small, but significant, increase in milk yield (Collier *et al.* 1993), although another study observed no change (Sejrsen & Knight 1994). Moreover, GH implants in the mammary gland of GH-deficient rats stimulates milk production in the treated, but not the contralateral gland (Flint & Gardner 1994). IGF-I of mammary, rather than hepatic, origin has also been implicated, since milk IGF-I immunoreactivity increases more rapidly than serum

IGF-I immunoreactivity following GH administration in goats (Faulkner 1999). GH thus stimulates mammary IGF-I production more rapidly than hepatic IGF-I production. Accordingly, GH rapidly stimulates IGF-I synthesis in mammary fibroblasts (Mol *et al.* 1996, Van Garderen *et al.* 1997) and, synergistically with oestradiol, in the mammary fat pad (Ruan *et al.* 1995, Walden *et al.* 1998). GH-induced IGF-I may subsequently affect local function, since IGF-I receptors are present in mammary tissue (Purup *et al.* 1995, Bassett *et al.* 1998). Indeed, the galactopoietic response to GH in goats is correlated with a sustained increase in IGF-I in milk and mammary tissue (Prosser *et al.* 1991). GH may also facilitate actions of IGF-I on the mammary gland, since the synthesis of plasma IGFBP-3 is increased in GH-treated cows (Davis *et al.* 1988, Breier *et al.* 1991).

The mammary mini-hypophysis

The mammary gland is a site of GH production as well as action (Mol *et al.* 1996). GH is found in canine mammary secretions (particularly pre-partum and colostrum) at concentrations 100–1000 times those in plasma; however, milk GH concentrations are not correlated with fetal plasma GH and GH is not absorbed intact through the canine gastrointestinal tract (Selman *et al.* 1994, Schoenmakers *et al.* 1997). The role of 'milk GH' thus remains uncertain, although mammary GH production results in the recruitment and hyperplasia of stem cells, which differentiate into ductal epithelium by clonal expansion (Mol *et al.* 1996). Mammary GH also induces maturation of the duct system into TEBs and alveolar structures (Feldman *et al.* 1993).

Immunoreactive GH in milk and mammary glands reflects local synthesis more than the sequestering of pituitary GH, since GH mRNA is readily detectable in normal and neoplastic mammary glands of humans (Mol *et al.* 1995*a*) and of dogs and cats (Mol *et al.* 1995*b*). Mammary GH may also contribute to systemic GH concentrations, since GH immunoreactivity is more abundant in mammary veins than in mammary arteries (Selman *et al.* 1994). Systemic GH is generally considered to be entirely of pituitary origin, since GH is largely not detected in hypophysectomized animals. However, under particular conditions, mammary GH production noticeably alters systemic GH and could thus exert systemic effects. For instance, progesterin-induced mammary GH can induce coat growth and increase serum IGF-I in pituitary GH-deficient German shepherd dogs (Kooistra *et al.* 1998).

The sequence of mammary GH is identical to its pituitary counterpart, but its secretory and regulatory patterns are significantly different (Mol *et al.* 1996). For instance, mammary GH secretion is non-pulsatile (Mol *et al.* 1996) and is not altered by SRIF or GHRH, despite the presence of both peptides in the mammary gland

(Table 2). This secretory pattern may be characteristic of non-pituitary GH production, since GH secretion from other extrapituitary sites (e.g. placenta) is similarly non-pulsatile and independent of traditional GH secretagogues, although GHRH and SRIF are usually present (Harvey 1995). The chronic, rather than pulsatile, pattern of mammary GH release can heighten tissue responses to GH, since progestin-induced GH production in hypophysectomized and pituitary-deficient dogs can result in acromegalic features despite non-pathophysiological levels of circulating GH (Selman *et al.* 1994, Kooistra *et al.* 1998).

GH regulation in non-pituitary sites usually reflects site-specific influences. For instance, the primary regulator of mammary GH synthesis is likely to be progestins (Loweridge & Farquharson 1993). This possibility is suggested by the symptoms of mammary GH excess that accompany progestin administration in cats and dogs, which include mammary hyperplasia and cellular proliferation (Selman *et al.* 1994, Mol *et al.* 1995b, 1996). Indeed, the non-pathological increase in progestins during the luteal phase is sufficient to stimulate mammary GH production and breast development (Rijnberk & Mol 1997). The mechanism by which progestins stimulate GH production is still uncertain. Progesterone receptors have been detected on all normal GH-secreting mammary cells, although not on all GH-secreting tumorous mammary cells (Mol *et al.* 1995a, Van Garderen *et al.* 1997). Although the sequence of mammary GH cDNAs is identical to pituitary GH cDNA in both coding and non-coding regions, mammary GH gene expression may be pit-1-independent (Lantinga-van Leeuwen *et al.* 1999). This possibility is suggested by the low or absent pit-1 gene expression in the mammary glands of dogs with progestin-induced mammary GH excess (Lantinga-van Leeuwen *et al.* 1999).

GH-binding sites are detectable in bovine mammary glands (Newbold *et al.* 1997) but are apparently absent from rabbit mammary gland membranes (Zebrowska *et al.* 1997). It is, nevertheless, well accepted that the mammary gland expresses GHRs and is thus a GH-target site, because GHR mRNA and/or immunoreactivity are readily observable in the mammary glands of numerous species (Table 3). The receptor is present in both mammary epithelium and stromal tissue, although it is much more abundant in the stroma (Ilkbahar *et al.* 1999). The importance of these receptors in mammary function in rabbits is suggested by the upregulation of GHR gene expression and immunoreactivity during epithelial proliferation and lactation (Jammes *et al.* 1991, Lincoln *et al.* 1995). In contrast, expression of both GHR and GHBP mRNA gradually decreases throughout pregnancy in rats and mice and is further reduced during lactation, reaching an overall 7-fold reduction by day 6 of lactation in comparison with mammary tissue of virgin animals (Ilkbahar *et al.* 1995, Sakaguchi *et al.* 1998, Ilkbahar *et al.* 1999).

GHR immunoreactivity and mRNA are also found in the epithelial and stromal cells of the human mammary gland (Mertani *et al.* 1998). However, unlike rabbits, the level of expression is equivalent in inactive, proliferating, and tumorous mammary glands (Mertani *et al.* 1998). The sub-cellular distribution of GHR immunoreactivity suggests that both GHRs and GHBPs are synthesized, since the plasma membrane, cytoplasm and nucleus are all immunoreactive (Lincoln *et al.* 1995). Indeed, GHBPs with similar binding characteristics to serum GHBPs have been detected in milk from numerous mammalian species (Postel-Vinay *et al.* 1991, Amit *et al.* 1997). An additional GHBP has been identified in human milk which binds hGH and hPRL with equal affinity, but it is immunologically unrelated to the GHR (Mercado & Baumann 1994, Amit *et al.* 1997). The promoter of the bovine mammary GHR transcript differs from that of the well-characterized hepatic transcript (Lucy *et al.* 1998); thus, mammary and hepatic GH-responsiveness may be differentially regulated.

Summary

The stimulatory effect of GH on mammatogenesis and lactogenesis has been well established by numerous *in vitro* and *in vivo* studies. The involvement of hepatic and local IGF-I in these actions appears to be species-dependent. The mammary gland is also a site of GH synthesis. Mammary GH probably acts locally by autocrine/paracrine mechanisms but also, at least in dogs, contributes to circulating GH.

Hepatic Actions

Vitellogenesis

Many non-mammalian vertebrates (birds, reptiles, amphibians and fish) produce eggs with substantial quantities of yolk. Yolk is deposited into the ovum in the ovary, although the yolk precursors are largely synthesized in the liver. The synthesis of these precursors, vitellogenesis, is primarily controlled by oestradiol, but GH plays an important role. Indeed, in the absence of GH, oestradiol-induced vitellogenesis is severely impaired in hypophysectomized birds (pigeons (Harvey *et al.* 1978)), reptiles (lizards (Callard *et al.* 1990), turtles (Ho *et al.* 1982)) and fish (silver eels (Peyon *et al.* 1996)) and restored by exogenous GH administration. The action of oestrogen is dependent upon GH, since GH induces and/or maintains hepatic oestrogen receptor abundance (Scanes & Harvey 1995). The interaction of GH with oestradiol in the induction of vitellogenesis is, however, synergistic rather than permissive (Paolucci 1989). In the absence of oestradiol, GH itself can promote vitellogenesis in liver explants or hepatocytes *in vitro* (Carnevali & Mosconi 1992, Peyon

et al. 1996). This may be a physiological role, since pituitary somatotrophs have greater secretory activity during vitellogenesis stages of reproductive activity (Young & Ball 1983).

Conclusion

GH has numerous gonadotrophic roles in female reproduction and is additionally progestational, mammogenic and galactopoietic. The actions of GH are generally progonadal at physiological concentrations and antigonadal at pharmacological concentrations and in pathophysiological excess. These actions are thought to reflect endocrine roles of pituitary GH and complementary autocrine or paracrine roles of GH produced within reproductive tissues. The local production of GH within these tissues may thus reflect an 'emergency' mechanism to rapidly regulate or 'fine-tune' cellular functions that are normally regulated in a 'strategic' way by pituitary GH. GH is thus an important regulator of reproduction. However, as the GH axis is not always required for fertility and as GH-resistant patients often have normal pubertal development, it is a modulator of reproduction rather than a bona fide gonadotrophin or primary regulator.

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