Growth hormone: a reproductive endocrine–paracrine regulator?

Kerry L. Hull¹ and Steve Harvey²*

¹Department of Biology, Bishop’s University, Lennoxville, Quebec, J1M 1Z7, Canada; and ²Department of Physiology, University of Alberta, Edmonton, Alberta T6G 2H7, Canada

Growth hormone (GH) is not classically considered as a reproductive hormone, although a vast literature indicates that it has roles in reproductive function. It is required for sexual differentiation and pubertal maturation and it participates in gonadal steroidogenesis, gametogenesis and ovulation. GH is also required for fetal nutrition and growth during pregnancy and for mammary development and lactation. Although some of these roles reflect the action of GH on the secretion and action of LH and FSH (Chandrashekar and Bartke, 1998), they also reflect direct actions of GH and indirect actions mediated through the local production of insulin-like growth factor I. Moreover, as GH is produced in gonadal and mammary tissues, these actions may reflect local autocrine or paracrine actions of extrapituitary GH, as well as the endocrine actions of pituitary GH. The roles of GH in reproductive function are considered in this review.

Although the somatogenic and gonadotrophic axes have long been known to be closely linked during growth and sexual maturation, the role of growth hormone (GH) in reproduction has generally been described as “...more akin to fine tuning than that of a major player...” (Ogilvy-Stuart and Shalet, 1992). However, experimental studies reveal that GH directly affects steroidogenesis, gametogenesis and gonadal differentiation as well as gonadotrophin secretion and responsiveness (Zachmann, 1992; Franks, 1998) (Table 1). Moreover, while these actions may reflect endocrine roles of pituitary GH, they may also reflect local autocrine or paracrine actions, since GH is produced in reproductive tissues. Therefore, established and putative roles for pituitary and extrapituitary GH in male and female reproduction will be considered in this review. The actions of GH in placental and mammary function lie outside the scope of this review.

Male reproductive system: a GH-target site

Testicular actions

GH is thought to play an important role in testicular growth and development, since human GH deficiency is associated with abnormally small testes (Spiteri-Grech and Nieschlag, 1992). Similarly, testicular function, including steroidogenesis and gametogenesis, may be affected by testicular and pituitary GH (Fig. 1).

Gametogenesis. GH resistance is associated with reduced fertility in men (Laron and Klinger, 1998), indicating roles for GH in testicular gametogenesis. Indeed, GH is sometimes used as an adjunct with FSH for the clinical treatment of male infertility (for review, see Shoham et al., 1992) and some forms of male infertility result, in part, from a GH deficiency. For instance, Shimonovitz et al. (1993) reported that 91% of azoospermic men were GH-deficient, whereas only 18% of oligozoospermic men had a GH deficiency. Indeed, sperm motility in men is generally reduced by GH deficiency and restored by GH administration (Gravance et al., 1997; Breier et al., 1998). Other clinical studies have also concluded that GH is required for normal sperm morphology and concentration (Gravance et al., 1997), although this finding is controversial (Breier et al., 1998). The co-ordinate increases in sperm motility and seminal insulin-like growth factor I (IGF-I) concentrations in men after GH administration may indicate that local IGF-I production mediated the gametogenic actions of GH (Ovesen et al., 1998). However, as sperm motility develops in the epididymis rather than in the seminal vesicles, and as epididymal IGF-I is not increased by GH (Breier et al., 1998), the gametogenic action of GH is likely to be direct. This possibility is supported by the demonstration that IGF-I actually impairs human sperm motility (Miao et al., 1998).

Steroidogenesis. GH may alter gametogenesis by affecting testosterone synthesis, since testosterone is necessary for sperm production and mRNA encoding growth hormone receptor (GHR) is present in rat Leydig cells (Kanzaki and Morris, 1999). Indeed, GH increases basal or hCG-stimulated testosterone production in GH-deficient men (Shoham et al., 1992) and isolated rat progenitor Leydig cells (PLCs) (Kanzaki and Morris, 1999). However, as the synthesis of steroidogenic enzymes is associated with the differentiation of PLCs into mature Leydig cells, GH-induced steroidogenesis may merely reflect its induction of cellular differentiation. However, GH is also able to induce directly the expression of several genes that code for steroidogenic enzymes in differentiated, as well as immature, Leydig cells (Kanzaki and Morris, 1999) (Fig. 1). For instance, GH stimulates the conversion of pregnenalone to progesterone by increasing the activity of 3β-hydroxysteroid dehydrogenase. GH-induced synthesis of this enzyme is dependent upon de novo protein synthesis (perhaps of IGF-I) and tyrosine
kinases (Kanzaki and Morris, 1999). Another enzyme, steroidogenic acute regulatory protein (STAR), mediates the translocation of cholesterol to the mitochondria, where it is converted into pregnenalone. Conversely, GH stimulates the production of STAR independently of de novo protein synthesis (and, therefore, of IGF-I synthesis) and tyrosine kinases (Kanzaki and Morris, 1999). Therefore, GH is likely to modulate testicular steroidogenesis by IGF-I-independent and possibly by IGF-I-dependent mechanisms, at least in rats (Fig. 1).

**Testicular GH receptors.** The possibility that GH may act locally to directly or indirectly affect reproductive function is supported by the distribution of GHRs in the male reproductive tract. For instance, GHR immunoreactivity or mRNA encoding GHR are abundantly present in the Wolffian–Müllerian duct, ureter, epididymis, vas deferens, seminal vesicles, prostate and testis (Leydig cells, Sertoli cells, spermatogonia, spermatocytes) of fetal and adult rats (Breier et al., 1998). This immunoreactivity probably corresponds to bioactive receptors, since high affinity somatogenic GHRs are present in the trout testis, particularly in Sertoli cells (Gomez et al., 1998) and GH activates STAT5b (a signalling molecule) in rat Leydig cells (Kanzaki and Morris, 1998). These receptors may affect reproductive function via local IGF-I production, since IGF-I immunoreactivity (Breier et al., 1998), mRNA encoding IGF-I (Lin et al., 1990), and IGF-I receptors (Lin et al., 1986) are also found in rat testicular cells. Indeed, GH treatment in dw/dw rats increases IGF-I concentrations in plasma, Sertoli cells, seminal vesicle fluid and epididymal fluid (Breier et al., 1998). However, testicular IGF-I in rats is also regulated by pituitary gonadotrophins (Closset et al., 1989) and is thus more loosely linked to GH than is hepatic IGF-I.

**Extratesticular actions**

Autocrine, paracrine and, possibly, endocrine actions of GH have also been implicated in the development and subsequent function of Wolffian duct-derived structures, such as the prostate and seminal vesicles. Nguyen et al. (1996) demonstrated that GH antisera blocks differentiation of the Wolffian duct in male mouse fetuses, whereas GH administration restores normal differentiation. The paucity of prenatal pituitary GH production and the detection of GH and GHR immunoreactivity in the reproductive tract of the mouse fetus indicates that it is local, rather than pituitary, GH that induces this effect (Nguyen et al., 1996). GH-induced differentiation of the mouse reproductive tract is also associated with increased androgen-binding protein concentrations and can be mimicked by IGF-I (Nguyen et al., 1996). Thus, locally produced GH may stimulate local IGF-I, and IGF-I may enable adequate androgen binding protein concentrations to permit testosterone-induced differentiation of the Wolffian duct.

Post-natal function of Wolffian-derived structures may similarly be controlled by local or systemic GH. For instance, GH administration stimulates hydrolytic enzyme activity and androgen-binding protein concentrations in the rat prostate and seminal vesicle (Reiter et al., 1999), and the expression of the bovine GH transgene increases prostate mass in mice (Ghosh and Bartke, 1993). GH may affect prostate function via local IGF-I, since GH stimulates androgen receptor, IGF-I and IGF-I receptor concentrations in the rat prostate, and GH-stimulated prostate growth is significantly reduced in IGF-I receptor gene knockout mice (Bondy et al., 1996). Moreover, prostate growth is significantly reduced in IGF-I gene knockout mice (Bondy et al., 1996). However, IGF-I can mimic the effect of GH on some, but not all, prostatic enzymes (Reiter et al., 1999) and so there may be both IGF-I-dependent and -independent GH action.

GH may also be necessary for normal development of the penis, since congenital GH deficiency or resistance is clinically associated with micropenis (Laron and Klinger, 1998). Local or hepatic IGF-I may be necessary for normal development of the penis, since congenital GH deficiency or resistance is clinically associated with micropenis (Laron and Klinger, 1998). Development of normal pubertal characteristics may also be GH-dependent, since puberty is delayed in human GH-deficiency and is restored by GH administration (Rivarola et al., 1972).

**Female reproductive system: a GH-target site**

**Female infertility**

GH-deficient women commonly require assisted reproductive technologies to conceive, indicating a physiological role for GH in promoting fertility. Indeed, reproductive dysfunctions in some women have been associated with partial GH deficiencies.

<table>
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<td>Reproductive duct differentiation</td>
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<td>Penis development</td>
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<td>Prostate, seminal vesicle enzyme synthesis</td>
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The possible use of GH as an adjunct to human menopausal gonadotrophin (hMG) for ovulation induction has been the focus of extensive research (Homburg and Farhi, 1995). 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 and increases the percentage of successfully treated patients (Homburg and Farhi, 1995). GH therapy may also 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 the rate of successful fertilization and pregnancies, particularly in women with polycystic ovary syndrome (Shoham et al., 1992). However, owing to the heterogeneous causes of female infertility, GH therapy does not always enhance gonadotrophin responsiveness (Shaker et al., 1992). Blumenfeld et al. (1991) reported that GH secretion was impaired in most women who responded to GH–hMG co-treatment. Thus, the infertility in responders may result, in part, from relative GH deficiency, whereas other dysfunctions are causal in the infertility of non-responders. However, normal fertility does not always require a normal GH axis. Indeed, GH-deficient (de Boer et al., 1997) and GH-resistant (Dor et al., 1992) women usually have normal pubertal development and menstrual cycles and conceive normally.

Steroidogenesis

The actions of GH in ovarian function are partly mediated by changes in ovarian steroidogenesis (Fig. 2), as indicated by

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Steroidogenesis

The actions of GH in ovarian function are partly mediated by changes in ovarian steroidogenesis (Fig. 2), as indicated by
the partial progesterone deficiency in GHR-deficient cattle (Chase et al., 1998). Numerous mammalian studies have demonstrated an increase in ovarian steroid production after GH administration in vivo (for example, in pigs: Bryan et al., 1992) or in vitro (for example, in cattle: Wathes et al., 1995). However, in other studies, GH is ineffective or inhibitory (for example, in pigs: Samaras et al., 1994; and, in women: Ovesen et al., 1994).

GH may induce steroidogenesis directly or by potentiating gonadotrophin action (Fig. 2). One hypothesis is that GH up-regulates LH receptors, thus enhancing LH-induced luteinization and the acquisition of progesterone synthetic ability (Jia et al., 1986). This possibility is supported by the inability of GH to induce progesterone production in the absence of gonadotrophins in rats (Jia et al., 1986). However, GH is effective in women and other species in the absence of gonadotrophins (Lanza et al., 1992) and so GH must also act independently.

Early studies assumed that IGF-I was the sole mediator of GH action in the ovary, since IGF-I or GH enhance steroid production to the same extent in rats (Hong and Herington, 1991), and GH usually (Andrade et al., 1996) increases follicular–luteal IGF-I in cows. Moreover, Hutchinson et al. (1988) observed that IGF-I antibodies significantly inhibit GH effects on FSH-induced progesterone secretion in rat ovaries. However, Wathes et al. (1995) did not detect IGF-I in the follicular fluid of GH-treated bovine follicles, despite increased progesterone release. In addition, IGF-I antibodies cannot completely block GH-induced progesterone synthesis in pig granulosa cells (Mondschein et al., 1989) or androgen synthesis by rat thecal–interstitial cells (Apa et al., 1996). Therefore, GH may stimulate ovarian steroidogenic enzymes by direct and IGF-I-mediated mechanisms (Xu et al., 1997). GH may activate some enzymes by cAMP-dependent mechanisms that involve de novo protein synthesis (perhaps IGF-I) (Singh and Thomas, 1993), but other enzymes independently of both cAMP and protein synthesis (Apa et al., 1994a). However, the steroidogenic action of GH may also reflect its induction of cellular proliferation or the differentiation of follicular cells, since the conversion of rat follicular cells into granulosa luteal cells is associated with increased progesterone synthesis and aromatase activity (Hutchinson et al., 1988).

**Table 2. Role of insulin-like growth factor I (IGF-I) in reproductive actions of GH**

<table>
<thead>
<tr>
<th>Role of IGF-I in reproductive actions of GH</th>
<th>Site of action and species</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Dependent on local IGF-I</td>
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<tr>
<td>FSH-induced progesterone secretion</td>
<td>Rat granulosa cells</td>
<td>Hutchinson et al., 1988</td>
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<tr>
<td>Testosterone synthesis, in vivo</td>
<td>Human testes</td>
<td>Laron and Klinger, 1998</td>
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<tr>
<td>Wolffian duct differentiation</td>
<td>Male mouse</td>
<td>Nguyen et al., 1996</td>
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<tr>
<td>Androgen binding protein–hydrolytic</td>
<td>Rat prostate</td>
<td>Reiter et al., 1999</td>
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<tr>
<td>enzyme synthesis</td>
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<tr>
<td>Penile growth</td>
<td>Human males</td>
<td>Laron and Klinger, 1998</td>
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<tr>
<td>Nuclear maturation</td>
<td>Rat oocyte</td>
<td>Apa et al., 1994</td>
</tr>
<tr>
<td>Aromatase activity</td>
<td>Fish testis</td>
<td>Singh and Thomas, 1993</td>
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<tr>
<td>Follicle growth</td>
<td>Rabbit ovary</td>
<td>Yoshimura et al., 1994</td>
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<tr>
<td>Independent of IGF-I</td>
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<tr>
<td>Progesterone synthesis</td>
<td>Pig granulosa cells</td>
<td>Mondschein et al., 1989</td>
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<tr>
<td>Androgen synthesis</td>
<td>Rat Leydig cells</td>
<td>Kanzaki and Morris, 1999</td>
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<tr>
<td>Androgen synthesis</td>
<td>Rat thecal–interstitial cells</td>
<td>Apa et al., 1996</td>
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<tr>
<td>Steroidogenic enzyme activity</td>
<td>Fish testis</td>
<td>Singh and Thomas, 1993</td>
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<tr>
<td>Nuclear maturation</td>
<td>Bovine oocytes</td>
<td>Izadyar et al., 1997</td>
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<tr>
<td>Cell growth</td>
<td>Human follicle</td>
<td>Ovesen, 1998</td>
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<tr>
<td>Cell growth</td>
<td>Mice preantral follicle</td>
<td>Liu et al., 1998</td>
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<tr>
<td>Hydrolytic enzyme synthesis</td>
<td>Rat prostate</td>
<td>Reiter et al., 1999</td>
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**Folliculogenesis**

The relative number of small, medium and large follicles varies over the course of the ovarian cycle. As the cycle proceeds, the growth of the dominant follicle is associated with a reduction in the number of small and medium-sized follicles. The growth and development of follicles larger than 2 mm is dependent upon pituitary hormones, since hypophysectomy in sheep results in follicular atresia and cessation of small follicle growth (Eckery et al., 1997). The resumption of normal follicular development requires the administration of gonadotrophins and GH; thus, GH may be permissive for gonadotrophin-induced follicular development (Eckery et al., 1997) (Fig. 2). Experimental studies also indicate that GH increases the number of follicles in cattle (Gong et al., 1993), although negative results have also been reported (Andrade et al., 1996). GH may stimulate particular follicle populations selectively, since it inhibits the development of preovulatory follicles and stimulates the growth of the second largest follicles in heifers (Lucy et al., 1994). However, the increase in the number of follicles is correlated more closely
with peripheral IGF-I than with GH (Gong et al., 1997), indicating an indirect mechanism of GH action.

Studies in vitro also indicate a role for GH in folliculogenesis, although the involvement of gonadotrophins and IGF-I remains unclear (Table 2). For instance, GH stimulates follicular growth in perfused rabbit ovaries independently of FSH (Yoshimura et al., 1993). This effect may be dependent on IGF-I, because follicular growth and IGF-I increase in a coordinated fashion (Yoshimura et al., 1993). Conversely, GH stimulates the proliferation of human luteinized granulosa cells via an FSH- and IGF-I-independent mechanism (Ovesen, 1998). GH-induced development of preantral follicles in immature mice is similarly independent of IGF-I but is dependent on FSH, at least in mice (Liu et al., 1998), and this effect of GH is blocked by folliculo-statin, which binds and inactivates activin. Activin can also stimulate follicle growth; therefore, GH may augment early follicular development by increasing ovarian activin production (Liu et al., 1998). Thus, the mechanism by which GH stimulates follicular development appears to be species-specific and to vary over the ovarian cycle.

Fig. 2. Role of growth hormone (GH) in ovarian function. During each ovarian cycle, primary follicles (1) develop into preantral follicles (2) and, subsequently, into antral (Graafian) follicles (3) before ovulation (4). These stages are characterized by increasing numbers of granulosa cells and thecal cells, 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, and acquire the ability to synthesize progesterone. GH of pituitary and ovarian origin binds GH receptors on thecal, granulosa and luteal cells and promotes steroidogenesis and gametogenesis (+). Thus, pituitary GH may be involved in ‘strategic’ maintenance of ovarian function, whereas ovarian GH may be involved in ‘emergency’ modulation of ovarian function. Some of the ovarian actions of GH are modulated by ovarian IGF-I (not shown; see Table 2).

Oocyte maturation

As the follicle matures, nuclear and cytoplasmic events within the oocyte are required before it can be fertilized successfully. Nuclear events include the completion of meiosis and the extrusion of the first polar body, and an accelerated rate of nuclear maturation is associated with enhanced zygote formation. Indeed, the beneficial effect of GH on female fertility noted in some studies in vivo may reflect the stimulatory effect of GH on the kinetics of nuclear maturation (Fig. 2). Experimental studies have shown that GH-treated bovine oocytes complete meiosis I faster and undergo zygote cleavage and blastocyst formation more frequently than untreated oocytes (Izadyar et al., 1998). GH stimulates nuclear maturation by IGF-I-independent actions mediated through cumulus cells, probably via changes in intracellular cAMP (Izadyar et al., 1998). GH also stimulates nuclear maturation of rat oocytes; however, cumulus cell IGF-I appears to be the mediator and cAMP is not involved (Apa et al., 1994b).

GH improves the fertilization of bovine oocytes, although this effect appears to be independent of cumulus cells and
related to enhanced cytoplasmic maturation (Izadyar et al., 1998). Indeed, rat oocytes with higher endogenous GH are fertilized more frequently than those with low GH concentrations, which, if fertilized, show a higher percentage of cleavage failure and abnormal morphology (Mendoza et al., 1999).

Cytoplasmic maturation is not necessarily associated with nuclear maturation and involves the rearrangement of cytoplasmic organelles in fully grown oocytes. In particular, cortical granules migrate to the plasma membrane and release enzymes that prevent polyspermy. The oocyte also obtains the ability to decondense sperm chromatin, resulting in the formation of sperm asters. GH incubation increases the proportion of bovine oocytes manifesting the characteristics of both cytoplasmic maturation and nuclear maturation (Izadyar et al., 1998). Thus, GH may enhance the co-ordination between nuclear and cytoplasmic maturation (Izadyar et al., 1998).

Ovarian GH receptors

The possibility that ovarian GH may act at local sites is supported by the detection of GH-binding activity, GHR immunoreactivity and mRNA encoding GHR in ovarian tissue in, for example, humans (Carlsson et al., 1992) and cows (Kolle et al., 1998). Indeed, GHR immunoreactivity has also been detected in granulosa cells, thecal cells and luteal cells (Kolle et al., 1998). An alternate splice variant that contains a different promoter from the cloned hepatic mRNA encoding GHR has been detected in the bovine ovary and uterus (Heap et al., 1996). Thus, GHR synthesis, and hence GH responsiveness, may be differentially regulated in hepatic and reproductive tissues, although ovarian and hepatic transcripts are regulated co-ordinately during pregnancy in rats (Sakaguchi et al., 1998) and during the ovarian cycle in fish (Gomez et al., 1998). However, mRNA encoding GHR abundance in the bovine ovary varies in a cell-specific way during the ovarian cycle (Kolle et al., 1998). IGF-I (Geisthoevel et al., 1989) and IGF-I receptors (Poretsky et al., 1985) are also detectable in ovarian tissue. Moreover, ovarian IGF-I in the fish ovary is significantly different in sequence from hepatic IGF-I (Kermouni et al., 1998). Nevertheless, GH increases follicular fluid IGF-I (Volpe et al., 1992). Therefore, ovarian IGF-I may mediate some, but not all, ovarian effects of GH, especially as GH increases follicular fluid IGF-I concentrations in women (Volpe et al., 1992). IGF-I may even provide negative feedback to regulate ovarian GH production.

Gonadal minihypophysis

Since the gonads are highly vascularized, many of the gonadal actions of exogenous GH are likely to reflect the endocrine actions of pituitary GH. However, as some gonadal cells (germ cells, granulosa cells and the adluminal compartments of Sertoli cells) in the ovary and testis are avascular or physically separated from systemic circulation by a barrier, some of the steroidogenic and gametogenic actions of GH may reflect the actions of GH produced locally. Indeed, the entire GH gene family (comprising GH, placental GH (hGH-V) and placental lactogens) is transcribed in the human testes and ovary (Schwarzler et al., 1997), with hGH-V being the most active gene transcriptionally (Untergasser et al., 1997).

‘Hypothalamic’ GH-regulating hormones may regulate gonadal GH synthesis in a similar manner to pituitary GH synthesis, since a mini hypothalamic-hypophyseal axis is also present in male and female reproductive tracts. GH-releasing hormone (GHRH) (Bagnato et al., 1992) and somatostatin (SRIF) (Pekary et al., 1984) are synthesized in the male and female gonad and bind to gonadal receptors (Monts et al., 1996). However, the importance of ovarian GHRH and SRIF in ovarian and testicular GH synthesis is unclear, since GH synthesis in non-pituitary sites is often independent of traditional GH secretagogues (Harvey and Hull, 1997). Moreover, these factors have been shown to have other local roles unrelated to GH regulation (Campbell and Scanes, 1995). Instead, gonadal GH synthesis may be modulated by locally relevant factors, although this possibility has yet to be assessed.

Conclusion

GH, directly or indirectly via IGF-I (Table 2), regulates reproductive function at all levels of the hypophyseal–pituitary–gonadal axis. Indeed, GH affects more target tissues (for example, the prostate gland) than gonadotrophins themselves. The actions of GH are generally progonadal at physiological concentrations and antigonadal at pharmacological concentrations and pathophysiological excess. These actions probably 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 regulate rapidly or ‘fine-tune’ cellular functions that are normally regulated ‘strategically’ by pituitary GH.

This work was supported, in part, by a grant from the Natural Sciences and Engineering Council of Canada to S. Harvey.

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