REVIEW

GH as a co-gonadotropin: the relevance of correlative changes in GH secretion and reproductive state

K L Hull and S Harvey¹

Bishop's University, Lennoxville, Quebec J1M 1Z7, Canada

¹Department of Physiology, University of Alberta, Edmonton, Alberta T6G 2H7, Canada

(Requests for offprints should be addressed to S Harvey; Email: steve.harvey@ualberta.ca)

Abstract

It is now well established that exogenous GH promotes sexual maturation and reproductive function. The possibility that this may reflect physiological actions of endogenous GH has, however, rarely been considered. Correlative changes in GH secretion and reproductive state (puberty, pregnancy, lactation, menopause and ovarian cycles) are thus the primary focus of this review. GH secretion is, for instance, elevated during major transitions in reproductive status such as puberty and pregnancy. In some cases, augmented circulating GH levels are paired with hepatic GH resistance. This interaction may permit selective activation of gonadal responses to GH without activating IGF-I-mediated systemic responses. This

selective activation may also be mediated by autocrine, paracrine or intracrine GH actions, since GH is also synthesized in reproductive tissues. Correlative changes in GH secretion and reproductive state may be mediated by events at the hypothalamic, pituitary and gonadal level. In addition to direct effects on gonadal function, GH may influence reproductive activity by increasing gonadotropin secretion at the hypothalamic and pituitary level and by enhancing gonadotropin responsiveness at the gonadal level. The close association between reproductive status and the somatotrophic axis supports the physiological importance of GH in reproductive function.

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Introduction

It is now well established that growth hormone (GH) affects gonadal function at hypothalamic, pituitary and gonadal sites, as previously reviewed (Hull & Harvey 2000, 2001a,b). Some investigators have, however, questioned the importance of GH in reproduction, since GH-deficient populations are characterized by delayed puberty and impaired fertility rather than complete reproductive dysfunction (Hull & Harvey 2001a,b). An association between reproductive status and changes in GH secretion would, however, suggest that GH action is physiologically relevant to reproduction. The literature examining GH secretion in the context of reproductive function has not been comprehensively reviewed. Changes in GH secretion during the reproductive stages of puberty, pregnancy, parturition, lactation and during the ovarian cycle are thus the focus of this paper.

GH secretion in reproduction

The reproductive life of an individual can be divided into the prepubertal period (infancy and childhood), puberty,

sexual maturity and, in the case of women, menopause. In addition, during the sexually mature years of women, dramatic perturbations in endocrine status occur over the course of each ovarian cycle and during pregnancy and lactation. Cyclical changes also occur in males and females of species that undergo seasonal breeding. The strong correlation between reproductive status and GH secretion during each of these stages suggests that GH may play a modulatory role in sexual maturation, the ovarian cycle, pregnancy and lactation.

The prepubertal period: infancy and childhood

The relationship between GH and gonadal steroid levels in children has been difficult to establish because steroid levels are very low prior to puberty. However, therapeutic administration of estrogen in doses similar to endogenous levels in prepubertal girls effectively stimulates GH secretion in hypogonadal women (Veldhuis *et al.* 1991b, Kerrigan & Rogol 1992); thus, the low levels of gonadal steroids in prepubertal boys and girls may maintain the relatively high GH levels. This possibility is also suggested

by the ability of an estrogen receptor antagonist (tamoxifen) to inhibit GH production in prepubertal boys (Metzger & Kerrigan 1994), since androgens induce GH secretion in males via aromatization to estrogens (Eakman *et al.* 1996). The higher circulating GH levels in prepubertal girls suggests that testosterone aromatization in prepubertal boys does not result in estrogen levels equivalent to those in females.

Clinicians have used females with Turner's syndrome (females who lack functioning ovaries) to investigate the effects of gonadal steroid deficiency in childhood on GH secretory dynamics. Ross *et al.* (1985) observed normal GH secretory dynamics in girls with Turner's syndrome prior to 9 years of age, but significantly decreased mean 24-h GH levels, peak amplitudes and peak frequencies in girls between 9 and 20 years of age, compared with those in age-matched normal girls. Indeed, although an age-related increase in GH pulse amplitude is observed in normal prepubertal girls, GH pulse amplitude in girls with Turner's syndrome remains the same or even declines (Massarano *et al.* 1989, Zadik *et al.* 1992). These results may, however, reflect age-related increases in obesity in girls with Turner's syndrome (Cianfarani *et al.* 1994) rather than direct effects of estrogen, since GH-releasing hormone (GHRH)-induced GH secretion and obesity are inversely related in girls with Turner's syndrome (Lu *et al.* 1991, Reiter *et al.* 1991). Conversely, the increased obesity in Turner's syndrome may represent the absence of GH-induced lipolysis. Other studies observed normal 12-h and 24-h secretion rates in prepubertal girls with Turner's syndrome (Veldhuis *et al.* 1991b, Wit *et al.* 1992).

The hypogonadal status of prepubertal girls with Turner's syndrome does, however, render them more sensitive to the stimulatory effects of gonadal steroids on the somatotrophic axis. Estradiol administration to prepubertal girls with Turner's syndrome increases GH pulse amplitude (Wit *et al.* 1992), but does not alter pulse frequency (Mauras *et al.* 1989b) or overall secretion rates (Mauras *et al.* 1990). Conversely, neither androgen nor estrogen treatment of normal prepubertal girls increases GH secretion, despite stimulating growth (Massarano *et al.* 1989).

Puberty: humans

Puberty encompasses a series of events which include the completion of growth and the maturation of the reproductive system. GH is a common link between these two processes (for reviews see Ogilvy-Stuart & Shalet 1992, Clark & Rogol 1996). GH has roles in the induction and progression of sexual maturation (Hull & Harvey 2001a,b) and is, in turn, regulated by gonadal factors at hypothalamic and pituitary sites (Fig. 1).

The transition of human juveniles into adolescence is associated with elevations of blood GH concentrations during both wakefulness and sleep periods and with a

consistent increase in the 24-h GH secretion rate (Rose *et al.* 1991). The striking increase in GH secretion in pubertal children reflects a two- to threefold increase in GH pulse amplitude without a concomitant change in pulse duration, pulse frequency or GH half-life (Rose *et al.* 1991). Data from hyposomatotrophic children have revealed that this increased pulse amplitude is necessary for the pubertal growth spurt in males and females (Stanhope *et al.* 1992, MacGillivray *et al.* 1998). Indeed, pulse amplitude, rather than pulse frequency, may be the most important determinant of the growth response to GH (Hindmarsh *et al.* 1987).

Gonadal steroids are also required for the pubertal growth spurt, since normal pubertal growth in hypopituitary children requires normalization of both gonadal steroid and GH levels (Aynsley-Green *et al.* 1976, Metzger *et al.* 1994). The close relationship between GH and gonadal steroid levels during the pubertal period suggests that gonadal steroids may stimulate linear growth, in part, by stimulating pituitary GH secretion (Wennink *et al.* 1991). Indeed, both gonadal steroid synthesis and the GH secretory pulse amplitude begin to increase earlier in girls with precocious puberty, and suppression of gonadal steroid secretion by gonadotropin-releasing hormone (GnRH) agonists in these girls also suppresses GH and insulin-like growth factor-I (IGF-I) secretion (Mansfield *et al.* 1988). The somatotrophic axis must be activated by very small increases in circulating estrogens, since GH and IGF-I concentrations rise before the initiation of sexual development (Rose *et al.* 1991) and very low doses of estrogens effectively increase GH secretion in hypogonadal states (Mauras *et al.* 1990).

The pubertal growth spurt and increase in GH pulse amplitude in boys is similarly correlated with a rise in serum testosterone and IGF-I (Martha *et al.* 1989). GH, IGF-I and testosterone levels are higher in boys with precocious puberty than in age-matched controls, and treatment with GnRH analogs to inhibit excess testosterone secretion corrects the high GH and IGF-I levels (Harris *et al.* 1985). Moreover, the induction of puberty by exogenous androgen or GnRH induces high-amplitude GH secretion (Blizzard *et al.* 1989, Foster *et al.* 1989). Very small doses of testosterone, similar to those observed in early puberty, are sufficient to increase GH pulse amplitude (Guistina *et al.* 1997), GHRH-induced GH release (Mauras *et al.* 1989a) and circulating IGF-I levels (Parker *et al.* 1984). The increase in IGF-I is due to GH rather than direct effects of testosterone, since IGF-I is increased by co-administration of GH and testosterone but not by testosterone alone in GH-deficient boys (Parker *et al.* 1984). The influence of testosterone on GH secretion is also illustrated by the ability of exogenous testosterone to correct deficient basal and GHRH-stimulated GH secretion in boys with gonadal dysfunction (Link *et al.* 1986, Mauras *et al.* 1989a). Androgens induce GH secretion via aromatization to estrogens, since non-aromatizable forms

Figure 1 Pubertal changes in GH secretion. Gonadal maturation (1), stimulated by gonadotropins and putatively GH, results in augmented levels of gonadal steroids (2). Estrogen, from the ovary or aromatized from testicular testosterone, acts at the hypothalamic level (3) and perhaps the pituitary level (not shown) to increase GH pulse amplitude (4). The resulting increase in GH secretion stimulates growth and further gonadal function (5).

of testosterone, such as dihydrotestosterone (DHT), inhibit (Keenan *et al.* 1993) or have no effect (Metzger & Kerrigan 1994, Eakman *et al.* 1996) on GH secretion in pubertal boys. Moreover, XY individuals with androgen insensitivity syndrome undergo a normal growth spurt despite androgen resistance, because of elevated circulating

estrogen concentrations (Cicognani *et al.* 1989). The importance of androgen aromatization is also suggested by the ability of androgen receptor blockers to concomitantly increase GH pulse amplitude and estrogen secretion (Metzger & Kerrigan 1993). Indeed, estrogens induce GH secretion in pubertal boys to a greater extent than

testosterone (Brook 1999). Estrogens may, however, act biphasically, since the infusion of estradiol for 20 h reduces GH and IGF-I levels in pubertal boys (Cemeroglu *et al.* 1997).

Estrogen, synthesized by the ovaries or aromatized from testosterone in peripheral tissues, therefore appears to enhance overall GH secretory rates by increasing pulse amplitude without affecting pulse frequency. This pattern suggests that GHRH synthesis and/or GHRH responsiveness may be particularly sensitive to estrogenic status, since GHRH pulses regulate pulse amplitude whereas somatostatin (SRIF) withdrawal regulates pulse frequency (Harvey & Daughaday 1995). Indeed, the stimulatory effect of testosterone on GH pulse amplitude in pubertally delayed boys is not associated with decreased SRIF release or increased pituitary responsiveness to GHRH, but is associated with increased GHRH secretion (Eakman *et al.* 1996). It is also possible that estrogen may directly stimulate pituitary GH synthesis, although this hypothesis has not been proven experimentally.

Puberty: rats

Pubertal changes in GH secretion also occur in non-primates, and have been extensively studied in rats. GH secretion in rats increases dramatically during puberty and acquires gender-specific secretory patterns (Gabriel *et al.* 1992). Prior to 33 days of age, pulsatile GH secretion is similar in males and females and low nadir GH concentrations are interspaced with infrequent, low-amplitude pulses (Gabriel *et al.* 1992, Fishman *et al.* 1993). GH pulse amplitude subsequently increases tenfold during early puberty (33–40 days) and twofold further during late puberty (41–50 days) in both sexes (Gabriel *et al.* 1992). The duration of GH pulses during the pubertal period is significantly greater in males than in females, a pattern that continues into adulthood (Gabriel *et al.* 1992). Nadir GH concentrations are also increased at this time in both sexes, with females having a higher baseline compared with males (Clark *et al.* 1987). However, only in rats over 54 days of age is the typical pattern of low basal GH secretion and high-amplitude, periodic, low-frequency GH pulses observed in males (Gabriel *et al.* 1992); this is thought to reflect regular secretory pulses of SRIF (Painson *et al.* 2000). In contrast, GH secretion in females is characterized by higher baseline levels and lower amplitude, irregular secretory pulses which increase in amplitude and frequency at night (Clark *et al.* 1987).

Pubertal changes in GH secretion reflect alterations at the hypothalamic and pituitary level. For instance, the rise in GH pulse amplitude in both sexes during early puberty is coincident with a rapid decline in the neuronal SRIF mRNA content (Argente *et al.* 1991) and a transient increase in GH gene transcription (Gonzalez-Parra *et al.* 1996). The development of sexually dimorphic patterns of GH secretion in pubertal rats, conversely, may reflect the

acquisition of differential responsiveness of GHRH neurons of the pituitary gland to adrenergic stimulation (Maszak *et al.* 1995) and also reflects differences in GH gene transcription, since GH mRNA is usually present in higher amounts in males than in females during the post-pubertal period (Gonzalez-Parra *et al.* 1996, Childs *et al.* 2000). GH mRNA levels are, however, higher in proestrous females than in males, reflecting the cyclical nature of GH gene expression in female post-pubertal rats (Childs *et al.* 2000). Sexual dimorphism is also observed in the effect of chronic administration of GnRH analogs on GH secretion, since GH secretory pulse amplitude is reduced in male rats but baseline GH levels are reduced in female rats (Gevers *et al.* 1998).

Sexually dimorphic GH secretion in pubertal and post-pubertal rats reflects gender-specific differences at the hypothalamic and pituitary level. For instance, GHRH and SRIF mRNA levels are higher in pubertal and post-pubertal males than in females of the same age (Maiter *et al.* 1991), and GHRH mRNA synthesis is less sensitive to GH-induced negative feedback in females than in males (Maiter *et al.* 1991). Gender-specific alterations in SRIF and GHRH neurons are also observed during development in the rat (Argente *et al.* 1991). Puberty-dependent changes in pituitary responsiveness have also been demonstrated in some, but not all, *in vitro* studies (Copeland *et al.* 1990). For instance, the higher GH secretion in males could be explained by the higher abundance of GHRH receptor mRNA in adult male than in adult female rats (Ono *et al.* 1995). The pubertal increase in both sexes could reflect the stimulatory effect of both estrogen and testosterone on GHRH-induced GH secretion from rat pituitary cells (Copeland *et al.* 1990), although other studies described by Copeland *et al.* (1990) showed that *in vitro* GH release was inhibited or unaffected by gonadal steroids. Estrogens are effective GH secretagogues at lower concentrations than testosterone; thus, testosterone may stimulate GH secretion via aromatization into estrogen (Simard *et al.* 1986, Copeland *et al.* 1990).

Pubertal changes in GH secretion in rats may result from neonatal imprinting by gonadal steroids, since neonatal castration, but not prepubertal castration, reduces the area under the curve for GHRH-induced GH secretion (Fishman *et al.* 1993). This effect is specific to the somatotrophic axis and acts at the level of gene transcription, since GH, but not prolactin, immunoreactivity and pituitary transcription factor-1 (pit-1) mRNA (a GH transcription factor) are reduced in neonatally castrated rats and restored by testosterone treatment (Gonzalez-Parra *et al.* 1998). Sexually dimorphic differences in the GH axis are observed even in the fetus. For instance, female rat pups are more susceptible than male pups to the blocking action of maternal alcohol consumption on the inhibitory effect of SRIF on GH release (Conway & Garbouzova 1996).

Sexually dimorphic patterns of GH secretion are, however, modified by the pubertal and post-pubertal environment, since acute or chronic androgen administration to ovariectomized or sham-ovariectomized adult female rats induces a male-like pattern of regular, intermittent peaks of GHRH-induced GH secretion (Hasegawa *et al.* 1992, Painson *et al.* 2000). Moreover, castration of adult males reduces GHRH mRNA expression in neurons of the arcuate nucleus (Zeitler *et al.* 1990) and SRIF expression in the periventricular nucleus (Argente *et al.* 1990), although a separate study did not observe any alteration in GHRH mRNA following adult gonadectomy or sex steroid administration (Maiter *et al.* 1991). The effect of testosterone on GHRH and SRIF transcription is not mediated by aromatization to estrogen, since DHT increases gene transcription whereas estradiol does not (Argente *et al.* 1990, Zeitler *et al.* 1990). Non-androgenic testicular factors may also be involved in the male pattern of hypothalamic SRIF and GHRH gene expression (Lago *et al.* 1996).

Sexual maturity: humans

The link between gonadal steroids in GH secretion is less distinct after puberty, particularly in men. For instance, GH secretion over a 24-h period is similar in post-pubertal and prepubertal males, despite elevated androgens in post-pubertal males (Martha *et al.* 1989). Indeed, chronic sex steroid exposure may desensitize the GH axis to testosterone (or estrogen) stimulation (Metzger *et al.* 1994). The somatotrophic axis in females, however, appears to maintain its estrogen sensitivity, perhaps because of the cyclical changes in gonadal activity in females but not in males. This possibility is suggested by the sexual dimorphism in GH levels in young, post-pubertal males and females. Circulating GH levels are 80-fold lower in males than in females in the morning (Engstrom *et al.* 1998, 1999). The high GH levels in women may, however, invoke a certain degree of GH resistance, since IGF-I synthesis and/or lipolysis are increased to a greater extent by acute GH injection in young men than young women (Lieberman *et al.* 1994, Vahl *et al.* 1997b). It has also been suggested, however, that body composition, rather than gonadal steroids, may be the determining factor in the higher GH concentration and relative GH resistance in post-pubertal women (Vahl *et al.* 1997a).

Ovulatory cycles

GH has been shown to stimulate folliculogenesis, steroidogenesis and ovulation in many, but not all, studies (for review see Hull & Harvey 2001a). GH is thus often considered to be a 'co-gonadotropin.' The stimulatory effects of GH administration on gonadal function may reflect a physiological role of GH, since circulating GH concentrations rise prior to normal (Ovesen *et al.* 1998) or

gonadotropin-induced (Blumenfeld *et al.* 1992) ovulation. Indeed, deconvolution analysis of serial blood samples has shown that the frequency of episodic GH release is increased during the periovulatory phase of the menstrual cycle (Ovesen *et al.* 1998). The pulsatile GH production rate and mean serum GH concentration are therefore significantly increased prior to ovulation and positively correlated with changes in serum estradiol and luteinizing hormone (LH) levels. Faria *et al.* (1992) also found that the amplitude of GH release in the periovulatory phase was greater than that during the early follicular phase. Conversely, the mean GH concentration is comparable during the early follicular and luteal phases (Stone & Marrs 1991). Plasma GH concentrations and pituitary GH mRNA abundance are similarly increased in rats during oestrus and proestrus (Childs *et al.* 2000), and GH mRNA and serum GH peak near the time of ovulation in ewes (Landerfeld & Suttie 1989). This increase may reflect a preovulatory surge of estradiol, since estradiol induces a surge in plasma GH similar to that of LH and follicle-stimulating hormone (FSH), although pituitary GH mRNA abundance is unchanged (Landerfeld & Suttie 1989). GH secretion is similarly increased in cyclic mares during their breeding season (Aurich *et al.* 1999) and during the periovulatory period in chickens (Harvey *et al.* 1979), although serum GH concentrations are unaffected by ovarian cyclicity in pigs (Estienne *et al.* 1998).

Although circulating GH levels are correlated with LH, FSH and estrogen during the ovarian cycle in humans, the administration of GH to cycling women does not markedly influence plasma concentrations of LH, FSH, testosterone, or α -sex steroid-binding globulin during the menstrual cycle (Tapanainen *et al.* 1992). Exogenous GH also has no effect on follicular fluid levels of estrogen, progesterone, or IGF-I, although it increases circulating concentrations of estrogen and progesterone and follicular concentrations of testosterone and 3β -hydroxysteroid dehydrogenase and aromatase mRNA (Tapanainen *et al.* 1992).

Estrogen may stimulate GH secretion in adult women by stimulating GHRH release and/or inhibiting SRIF release (Fig. 2), as has been shown in other mammals (Shirasu *et al.* 1990, Hassanab *et al.* 2001). Estrogens may also stimulate GH secretion in adults by inhibiting hepatic IGF-I production and thereby reducing negative feedback (Weissberger *et al.* 1991) (Fig. 2). This possibility is suggested by the inhibitory effect of oral contraceptives/hormone replacement therapy on GH-induced and/or basal IGF-I secretion in normally cycling women (Eden Engstrom *et al.* 2000, Cook *et al.* 2000), and the greater IGF-I response in men than in women (Eden Engstrom *et al.* 2000). This dissociation of pituitary GH and hepatic IGF-I by estrogen may provide a mechanism by which direct actions of GH mediated by GH receptors (GHR) are preserved but the metabolic and anabolic effects mediated by IGF-I are avoided. Estrogen may also

Figure 2 Possible sites of action for estrogen in the somatotrophic axis of the adult woman. GH secretion is regulated by stimulatory (solid lines) and inhibitory (dotted lines) pathways. Estrogen may stimulate GH secretion by reducing (−) inhibitory IGF-I tone, stimulating (+) GHRH tone and/or inhibiting SRIF tone at the hypothalamus, or enhancing pituitary sensitivity to thyrotropin-releasing hormone (TRH).

stimulate GH secretion by sensitizing the pituitary gland to TRH, since GH secretion is paradoxically increased by TRH in women taking low-dose estrogen oral contraceptives (De Leo *et al.* 1991) (Fig. 2). In addition, the higher GH secretory response to galanin in young females than in young males and in young females than old females suggests that estradiol may also sensitize the pituitary to galanin (Giustina *et al.* 1993).

Ovarian dysfunction in women is often associated with altered GH secretion. For instance, many anovulatory women are hyposomatotrophic (Ovesen *et al.* 1992). In particular, women who are amenorrheic due to weight loss are characterized by normal overall GH secretion levels during the follicular phase but lower pulse amplitude and higher pulse frequency than in control women during the luteal phase (Genazzani *et al.* 1993a). The important determinant of somatotrophic activity may be the balance of estradiol and progesterone concentrations rather than the concentration of estradiol alone, since estradiol increases GH pulse frequency and amplitude when

administered alone but not when co-administered with progesterone (Genazzani *et al.* 1993a).

Women with polycystic ovary syndrome (PCOS) also manifest a blunted GH secretory response to GHRH and dopamine (Slowinska-Srzednicka *et al.* 1992, Lanzone *et al.* 1995, Piaditis *et al.* 1995). However, hyposomatotrophism in PCOS may reflect the influence of body composition on the GH secretory axis, since many patients are obese (Slowinska-Srzednicka *et al.* 1992) and obesity inhibits GH secretion (Veldhuis *et al.* 1991a). Indeed, Morales *et al.* (1996) showed that GH pulse amplitude is actually elevated in lean PCOS but reduced in obese PCOS, although a different study observed a few cases of PCOS and hyposomatotrophism in lean women (Lanzone *et al.* 1995).

Pregnancy in primates

It is well established that circulating concentrations of GH-like immunoreactivity dramatically increase during pregnancy in primates (Handwerger & Freemark 2000). This increase is not, however, associated with increased transcription of the pituitary (hGH-N) gene. Instead, it largely reflects the production of placental GH-like proteins, which are the products of the placental GH variant gene (hGH-V) and three human chorionic somatomammotropin genes (hCS-A, hCS-B and hCS-L) (Eberhardt *et al.* 1996). Indeed, radioreceptor assays of circulating GH at term reveal that only 3% of the proteins interacting with the GHR are products of the hGH-N gene, whereas 85% result from hGH-V gene transcription and 12% from hCS gene transcription (Daughaday *et al.* 1990). The placental GH variants are thought to bind and activate the GHR, although the existence of a separate hCS receptor has been postulated (Hill *et al.* 1988). The hGH-N gene and the four placental genes are located adjacent to one another on chromosome 17 and are thought to have arisen from a single ancestral GH gene (Eberhardt *et al.* 1996). The characteristics and secretory patterns during pregnancy of the five members of the GH gene family are, nevertheless, distinct and will be discussed independently.

Pituitary GH During early pregnancy, pituitary GH is the only measurable GH in maternal serum and it is secreted in a highly pulsatile pattern (Eriksson 1989). The characteristics of GH secretion and circulating levels are similar in pregnant women during the first trimester and in non-pregnant women (Eriksson 1989). However, pituitary GH release is paradoxically stimulated by TRH during the first trimester, possibly reflecting gestational hypothyroidism (De Leo *et al.* 1998). A significant shift in the somatotrophic axis occurs between 15 and 20 weeks post-amenorrhea, since pituitary GH transcription (Stefaneanu *et al.* 1992) and secretion (Alsat *et al.* 1998) gradually decrease until hGH-N is virtually undetectable

at 24–25 weeks of gestation (Mirlesse *et al.* 1993). Somatotrophs become resistant to normal physiological stimuli such as hypothalamic GHRH (de Zegher *et al.* 1990), arginine and insulin (Yen *et al.* 1970, Artenisio *et al.* 1980) and to other provocative tests of GH release (Spellacy *et al.* 1970). These diminished responses are correlated with rising levels of placental GH, which increases serum IGF-I independently of pituitary GH (Beckers *et al.* 1990, Alsat *et al.* 1997). High levels of IGF-I subsequently inhibit pituitary GH gene transcription (Mirlesse *et al.* 1993). This diminution of pituitary GH secretion does not occur, however, in acromegalic women, because adenomatous somatotrophs are resistant to IGF-I feedback (Beckers *et al.* 1990).

The GH-N gene may also be expressed in the placenta, since immunoreactive hGH-N is detectable in human placental syncytiotrophoblasts (Al Timimi & Fox 1986) and in media conditioned with term placental cells (Evain-Brion *et al.* 1990). This immunoreactivity reflects very low and possibly inconsistent levels of hGH-N gene expression, since other investigators did not detect hGH-N transcripts in samples of human placenta (Baumann 1991). GH-N mRNA is, however, present at readily detectable levels in placenta from women with a deletion of the hGH-V and hCS genes (Alsat *et al.* 1997). Placental expression of the hGH-N gene may thus be particularly important in individuals with defective placental GH/hCS genes.

Placental GH Placental GH is the product of the hGH-V gene rather than the hGH-N gene. The proteins resulting from these two genes are of identical size (22 kDa) and length (191 amino acids) but differ in 13 residues scattered throughout the protein (Alsat *et al.* 1998). The non-homologous residues are thought to be responsible for the distinct biological activities of hGH-N and hGH-V, since hGH-V is less lactogenic (Alsat *et al.* 1998). The expression of the hGH-V gene is largely restricted to the placenta by placenta-specific enhancers and pituitary-specific repressors (Eberhardt *et al.* 1996), although limited expression in other tissues, including lymphoid tissues (Melen *et al.* 1997), normal and tumorous pituitary glands (Scippo *et al.* 1991, Nickel & Cattini 1992) and the testis (Untergasser *et al.* 1998), has been detected. The transcriptional regulation of the hGH-V gene has been the subject of several recent reviews (Eberhardt *et al.* 1996, Su *et al.* 2000) and will not be discussed here in detail.

Four different splicing patterns of the hGH-V gene result in four putative hGH-V variants with distinct characteristics. First, usage of an alternate splice acceptor site within exon 3 results in the deletion of exon 3 and the production of a 20 kDa GH isoform (Boguszewski *et al.* 1998), although some investigators have failed to find this isoform (Estes *et al.* 1994). The deletion of exon 3 is also commonly observed in the hGH-N gene and does not

alter the binding characteristics of hGH-N (Baumann 1991). The other splicing patterns of the hGH-V gene are not, however, observed in the hGH-N gene, and would substantially alter the binding activity of the resulting protein. The hGH-V2 mRNA retains intron 4, resulting in a putative membrane-bound protein, whereas the use of an alternate splice donor site in exon 4 deletes 4 bp and produces the hGH-V3 variant, resulting in a soluble protein (Boguszewski *et al.* 1998). The proteins resulting from the hGH-V2 and V3 transcripts would have a divergent binding site-1 from hGH-N- and other hGH-V-encoded proteins; thus, the ability of hGH-V2 and -V3 proteins to bind GHRs is unknown (Boguszewski *et al.* 1998). These transcriptional variants are nevertheless differentially regulated and localized (Eberhardt *et al.* 1996, Boguszewski *et al.* 1998). For instance, the proportion of hGH-V2 mRNA increases during fetal development, rising from 5–7% of the total hGH-V mRNA in the first trimester to 15–20% at term (MacLeod *et al.* 1992). This change is likely to reflect developmental control over splice site selection or increased stability of hGH-V2 mRNA (MacLeod *et al.* 1992). In either case, the finding that levels of hGH-V2 mRNA are controlled independently from hGH-V mRNA suggests different functional roles for hGH-V and hGH-V2 during gestation.

The secretion of placental GH is not episodic (unlike pituitary GH) and maternal serum GH concentrations during late pregnancy remain relatively constant during a 24-h period (Alsat *et al.* 1998). Moreover, unlike pituitary GH, placental GH is unresponsive to GHRH (de Zegher 1996) and cAMP (Eberhardt *et al.* 1996). GHRH is nevertheless produced in the human placenta (Berry *et al.* 1992), suggesting that GH-V secretion is constitutively at its maximal level (de Zegher *et al.* 1990) and/or that placental GHRH exerts roles unrelated to GH secretion, such as the regulation of fetal pituitary GH secretion (Nogues *et al.* 1997). SRIF is similarly ineffective at modulating placental GH secretion (Caron *et al.* 1997), although SRIF (Petraglia 1991) and SRIF receptors (Caron *et al.* 1997) are present in the human placenta.

Glucose, rather than releasing hormones, appears to be the primary modulator of placental GH secretion, since glucose inhibits hGH-V secretion from placental explants and trophoblast cultures (Patel *et al.* 1995) and hyperglycemia in diabetic pregnant women is associated with reduced circulating hGH-V concentrations (McIntyre *et al.* 2000). The syncytiotrophoblast may respond directly to changes in plasma glucose, since the glucose transporter, GLUT1, is present in these cells (Hauguel-de Mouzon *et al.* 1994). Placental GH may thus protect the fetus from nutrient deficiency, since hypoglycemia induces hGH-V synthesis and hGH-V increases maternal blood glucose levels (Alsat *et al.* 1998, Bjorklund *et al.* 1998). Hypoglycemia, rather than hyperglycemia, may be the important secretory control, since glycemia and hGH-V are positively correlated in normal pregnancies

(McIntyre *et al.* 2000). Thus, placental GH drives increased glycemia in the normal physiological situation, whereas hGH-V secretion is inhibited by pathophysiological levels of hyperglycemia observed in diabetes or in *in vitro* studies. Placental size and the differentiation of cytotrophoblasts into syncytiotrophoblasts are also critical determinants of hGH-V synthesis, since hGH-V production is roughly parallel to placental development and is reduced in cases of intrauterine growth retardation in which placental development is impaired (Chowen *et al.* 1996).

The importance of placental size in determining hGH-V levels is illustrated in the developmental changes in hGH-V gene expression. Transcript levels increase five- to tenfold between weeks 8 and 39, during the important period of placental growth, after which they remain relatively constant until term (Urbanek *et al.* 1992). In serum, hGH-V immunoreactivity is first detectable at 10–12 weeks of gestation, and circulating levels peak at 20 weeks (Handwerger & Freemark 2000). Placental GH levels subsequently fall with the onset of labor, probably as a result of decreased uteroplacental blood flow or increased metabolism stimulating placental protease activity. These developmental changes in maternal GH concentrations are not, however, paralleled in the fetus, because placental GH does not cross the fetal–placental barrier (Fholenhag *et al.* 1994).

Chorionic somatomammotropin The circulating form of hCS is encoded by two members of the GH gene family, hCS-A and hCS-B (Eberhardt *et al.* 1996). These two genes encode identical 22 kDa mature proteins which differ from hGH-N in 24 residues, although the hCS-A and hCS-B pre-proteins differ in a single amino acid in the signal domain (Eberhardt *et al.* 1996). The two transcripts are 98% homologous, and the divergent sequences may have implications for transcriptional stability but do not affect the structure of the mature protein (MacLeod *et al.* 1992). Transcription of the hCS genes is largely restricted to the placenta, although hCS mRNA and protein has been detected in the testis (Untergasser *et al.* 2000) and ovaries (Schwarzler *et al.* 1997). Indeed, hCS mRNA is more abundant than GH-N mRNA in the ovary, suggesting that it may have critical autocrine/paracrine roles in ovarian function (Schwarzler *et al.* 1997). Alternative splicing of the hCS-A/B pre-mRNAs, resulting in the retention of intron 4, results in an hGH-V2-like protein (hCS-A2) of 26 kDa which is membrane bound, at least in the testis (Untergasser *et al.* 2000). This membrane-bound protein may interact with GH/prolactin receptors on the cell surface, resulting in receptor dimerization/activation and/or in receptor inhibition (Untergasser *et al.* 2000). The transcriptional regulation of the hCS genes has been well reviewed recently (Eberhardt *et al.* 1996, Su *et al.* 2000) and will not be discussed here in detail.

The third hCS gene, hCS-L, was originally considered to be a pseudogene resulting from a transition in the 5' consensus splice site of the second intron (Hirt *et al.* 1987). Other dysfunctions in the gene were also postulated, since reversion of the transition does not restore transcriptional activity (Resendez-Perez *et al.* 1990). However, five major and several minor splice variants of the hCS-L gene have been detected in the placenta, a small number of which may encode low-abundance functional GH-like proteins participating in placental function (Misra-Press *et al.* 1994). The hCS-L proteins may fulfill similar functions to those of hCS in cases of hCS deficiency, since normal pregnancy and delivery occurred in an individual with an hCS-A/hCS-B gene deletion and a normal hCS-L gene (Misra-Press *et al.* 1994). Transcription of the hCS-L gene may be upregulated in this situation, since hCS-L immunoreactivity has been detected in the placenta of an individual with an hCS-A/B gene deletion (Alsat *et al.* 1997). The physiological relevance of hCS-L is also suggested by its upregulation during gestation (Hu *et al.* 1999). Unlike hCS-A/B, hCS-L may act solely as a placental autocrine/paracrine factor, since hCS-L immunoreactivity is undetectable in the plasma of pregnant women (Hu *et al.* 1999).

Circulating concentrations of hCS in humans are primarily dependent upon syncytial cell mass, since hCS mRNA concentrations in individual syncytiotrophoblasts do not change throughout pregnancy (Walker *et al.* 1991). Conversely, hCS synthesis per syncytiotrophoblast increases in late pregnancy in the baboon, concomitant with additional syncytiotrophoblast differentiation (Musicki *et al.* 1997). Factors that stimulate the differentiation of cytotrophoblasts in syncytiotrophoblasts would thus be expected to stimulate hCS production. Indeed, differentiation factors such as epidermal growth factor increase hCS release *in vitro* (Morrish *et al.* 1987) whereas transforming growth factor B1, which inhibits differentiation, reduces hCS secretion (Morrish *et al.* 1991). As reviewed by Handwerger & Freemark (2000), other autocrine and paracrine factors such as interleukins and thyroid hormones may also stimulate hCS secretion. Pit-1 may play a role in placental GH/CS gene transcription as in the pituitary, since pit-1 mRNA and protein are expressed in the human placenta and rat pit-1 protein binds and activates the human hCS and GH-V promoters *in vitro* (Nickel *et al.* 1991, Bamberger *et al.* 1995). However, since most hCS is secreted by the constitutive (rather than regulated) secretory pathway, the importance of these factors in determining circulating hCS levels is likely to be negligible (Hochberg *et al.* 1988). Curiously, despite its marked effect on hGH-V secretion, glycemia does not alter hCS secretion (Patel *et al.* 1995).

Transcription of the hCS-A/B genes is initiated early in gestation and results in equal amounts of hCS-A mRNA and hCS-B mRNA until 8 weeks (MacLeod *et al.* 1992). However, between 8 and 39 weeks, hCS-A mRNA

increases 30-fold whereas hCS-B and hCS-L mRNAs increase five- to tenfold (MacLeod *et al.* 1992). The greater abundance of hCS-A transcripts is thought to reflect increased transcript stability rather than increased transcriptional activity (MacLeod *et al.* 1992). Relative levels of hCS-A and hCS-B transcripts are, however, highly variable between individual placentae, with some placentae showing a 1:1 ratio of hCS-A and hCS-B mRNA (Walker *et al.* 1991). Immunoreactive hCS proteins are detectable at 12–17 days and 3 weeks post-conception in the placenta and serum respectively (Walker *et al.* 1991). These proteins are localized in the syncytiotrophoblast before 6 weeks and in the cytotrophoblasts for the remainder of gestation (Maruo *et al.* 1992). hCS abundance in serum undergoes a rapid increase during the first trimester and continues to increase, albeit at a lower rate, until term (Braunstein *et al.* 1980).

Pregnancy in non-primates

Circulating GH levels are unaffected by pregnancy in ewes (Al Gubory *et al.* 1999), sows (Diamini *et al.* 1995) and goats (Kornalijslijper *et al.* 1997) but significantly increase in pregnant horses (Aurich *et al.* 1999) and rodents (Soares & Talamantes 1984, Kishi *et al.* 1991). This pregnancy-induced increase in GH levels has been best studied in rats, in which maternal serum GH concentrations progressively increase in the second half of pregnancy (Kishi *et al.* 1991) and decline on the day prior to parturition (Harvey & Daughaday 1995). Basal GH levels are increased, whereas the amplitude and frequency of episodic GH release is comparable with that in non-pregnant rats, except after day 20 when pulse amplitude is increased (Carlsson *et al.* 1990a). The pregnancy-induced elevation in circulating GH concentrations reflects increased activity of the pituitary GH gene within the pituitary gland, since immunoreactive GH is undetectable in the plasma of pregnant hypophysectomized rats (Carlsson *et al.* 1990b). Moreover, the pituitary GH gene is the only member of the GH gene cluster in non-primates (Su *et al.* 2000). Although placental lactogen genes have been detected in rodents and cattle, these genes are more closely related to prolactin than to GH and evolved after the phylogenetic separation of primates (Eberhardt *et al.* 1996, Ishibashi & Imai 1999). Placental lactogens in primates and non-primates thus evolved independently and may represent an example of convergent evolution (Eberhardt *et al.* 1996).

GH concentrations increase in pregnant rats despite augmented pituitary and hypothalamic IGF-I content (Escalada *et al.* 1997). Moreover, circulating IGF-I levels paradoxically drop despite increased circulating GH (Escalada *et al.* 1997). Pregnancy therefore appears to be associated with hepatic GH resistance and reduced responsiveness of the hypothalamo-pituitary axis to negative feedback by IGF-I. Pituitary GH production in pregnant

rats is also less sensitive to stress-induced inhibition (Jahn *et al.* 1993). The pregnancy-associated rise in GH may be triggered by rising levels of estrogens (Jahn *et al.* 1993) and placental lactogens (Kishi *et al.* 1991), since both stimulate GH secretion. GH levels do not, conversely, increase in food-restricted pregnant dams (Monaco & Donovan 1996).

Although placental GH-like moieties have not been detected in non-primates, the pituitary GH gene may be active in the placenta. This possibility has been demonstrated in sheep, since GH mRNA and GH immunoreactivity are detectable in sheep syncytium and trophoctoderm from days 35 to 50 of gestation (Lacroix *et al.* 1996a,b). Placental GH would appear to act as a paracrine/autocrine factor, since serum GH levels do not rise during pregnancy in sheep (Al Gubory *et al.* 1999).

Parturition

Superimposed upon the changes in GH secretion during late pregnancy are changes due to parturition. In the rat, for instance, circulating GH levels rise two to fourfold during delivery and remain elevated for several days afterwards (Carlsson *et al.* 1990b). Since GH secretion in rats is suppressed by stress, this rise in GH secretion appears to be unrelated to the trauma involved in parturition. Circulating GH levels are similarly elevated at the time of parturition in dogs (Hoffmann *et al.* 1994), goats (Kornalijslijper *et al.* 1997) and horses (Aurich *et al.* 1999) but not in swine (Diamini *et al.* 1995). Parturition-induced changes in GH secretion in humans, however, have not been comprehensively examined. A more rapid increase in the circulating GH level also occurs in heifers, in which the GH concentration increases markedly over a few hours (Reynaert *et al.* 1976, Oda *et al.* 1989). In these animals, the rise in GH concentration peaks when the forelegs of the calf are visible in the uterus (Reynaert *et al.* 1976). After the expulsion of the calf, the GH levels may remain elevated for 1–2 days (Ronge & Blum 1988). Reynaert *et al.* (1976), in contrast, suggest that GH levels are restored to preparturient levels immediately after parturition in heifers.

Although increased GH secretion clearly occurs at the time of parturition, the physiological significance of this observation is unknown; it may occur secondary to other endocrine changes or reflect a non-specific response to the stress involved.

Lactation

Studies in numerous mammalian species have established that circulating GH levels are increased during lactation and suckling (Etherton & Bauman 1998). For instance, plasma GH concentrations in rats and mice progressively increase during pregnancy and remain high in lactating females (Escalada *et al.* 1997). The elevated GH levels at

this time reflect an increase in the proportion of large molecular weight moieties (Escalada *et al.* 1997). This lactational increase in GH secretion in rats reflects increased pituitary GH and GH mRNA content per somatotroph due to decreased inhibitory hypothalamic control and reduced IGF-I feedback (Porter *et al.* 1990, 1991). Somatotroph number, conversely, declines during lactation (Porter *et al.* 1990, 1991).

During lactation in rats, circulating GH levels are maintained at elevated pregnancy levels (Escalada *et al.* 1997). The maternal plasma GH concentration is dramatically increased by the presence of pups and upon the initiation of suckling, as a result of increased GHRH stimulation, for 30–60 min (Wehrenberg & Gaillard 1989). This increase likely reflects increased secretion but not increased synthesis, since GH stores are depleted in suckling rats (Escalada *et al.* 1997). Circulating GH levels are similarly higher in lactating gilts than hysterectomized gilts (Diamini *et al.* 1995) and suckling increases the frequency of pulsatile GH release by an opioid mechanism triggered by the tactile stimulation of the udder (Rushen *et al.* 1993, Schams *et al.* 1994). Stimulation of the teat is also responsible for the increased GH secretion in goats during suckling and can be blocked by local anesthesia (Flint & Knight 1997). Increased GH secretion in cows during lactation is, in contrast, due to an increased magnitude of pulses of GH release rather than in the frequency of secretory episodes or in baseline GH levels (Vasilatos & Wangsness 1981). The increased secretion of GH during lactation would promote mammary development and milk production (Hull & Harvey 2001a). Indeed, GH levels and milk production are positively correlated in heifers (Hoshino *et al.* 1991). This postnatal rise in circulating GH may also stimulate the induction of maternal behavior (Sara & Lazarus 1974).

Menopause

GH and IGF-I plasma levels fall after menopause, consistent with a stimulatory effect of estrogens on GH synthesis (Weissberger *et al.* 1991, Ho *et al.* 1996). Postmenopausal women therefore provide a model in which to examine the effects of gonadal steroids on GH secretion without confounding influences of endogenous steroids. Indeed, estrogen replacement in postmenopausal women increases the mean 24-h GH concentration (Weissberger *et al.* 1991, Ho *et al.* 1996) and GH pulse amplitude (Mercuri *et al.* 1993). Estradiol may increase GH secretion by inhibiting hepatic IGF-I; thereby relieving the constitutive negative feedback effect of IGF-I on GH production. This possibility is suggested by the correlation between reduced IGF-I and increased GH secretion in postmenopausal women receiving different estrogen treatment regimens (Ho *et al.* 1996). Only oral estrogens, which reduce mean IGF-I levels, increase 24-h GH levels. Transdermal estrogens decrease IGF-I levels slightly and

do not affect GH levels (Ho *et al.* 1996). However, gonadal steroids must also increase GH secretion independently of inducing GH resistance, since Hartmann *et al.* (1995) observed an increase in both GH and IGF-I levels in postmenopausal women after 10 months of oral hormone replacement therapy (both estradiol and progesterone). The GH resistance observed in some studies may indicate initial increases in body weight in response to hormone replacement therapy, since GHRH-induced GH release was inhibited and body weight increased after 1 month of hormone replacement therapy (Hartmann *et al.* 1995).

Seasonal breeding

Seasonal changes in GH secretion occur in many species (for reviews see Buys *et al.* 1990, Harvey & Daughaday 1995, Gower *et al.* 1996). Since GH regulates intermediary metabolism, many of these cycles appear to be related to changes in food intake, rather than changes in photoperiod, temperature or other environmental parameters. However, as seasonal patterns of metabolism and food intake are often closely linked to the onset and termination of seasonal breeding, seasonal changes in GH secretion may occur coincident with reproductive cycles, as occurs in adult red deer and Père David's deer (Loudon *et al.* 1989, Webster *et al.* 1996) and white-tailed deer (Bubenik *et al.* 1975). Male reindeer also have high plasma GH levels during the rutting season, when food intake is low (Suttie *et al.* 1992). In captive reindeer, which would not experience a nutritional deficiency, GH levels are highest during January and February and reach a nadir in the summer (Bubenik *et al.* 1998). This seasonal increase may be dependent upon gonadal steroids, since circulating GH levels are increased in sham-ovariectomized (but not ovariectomized) mares during the mating season (Aurich *et al.* 1999).

Nutritional insufficiency may also be responsible for the increased GH secretion in some species of fish during the breeding season (e.g. goldfish, Marchant & Peter 1986; rainbow trout, Sumpter *et al.* 1991; tilapia, Weber & Grau 1999). However, pituitary GH content is increased before serum GH in response to fasting whereas the opposite pattern is observed in brooding fish; thus, factors other than nutritional insufficiency must be involved (Weber & Grau 1999). The biphasic pattern of GH secretion in female frogs during their annual reproductive cycle does, however, appear to correlate solely with gonadal activity (Mosconi *et al.* 1994).

Seasonal patterns of GH secretion have also been observed in many feral bird species during their breeding cycles (for reviews see Scanes *et al.* 1983, 1992). In many cases, these changes also appear to be related to the energetic demands associated with gonadal growth, mating and the rearing of young. These relationships are also seen in domesticated species. For instance, the onset of lay

Figure 3 Inter-relationships in the somatotrophic and gonadotrophic axes. GH and gonadotropin (LH and FSH) secretion is regulated by stimulatory (solid lines) and inhibitory (dotted lines) pathways. Numerous interactions link these two axes. Gonadotrophs and somatotrophs interact reciprocally at the pituitary, both GH and gonadotropins affect gonadal function, and gonadal steroids (particularly estrogen) modulate the production of hypothalamic GH-releasing factors.

in chickens and turkeys is preceded by a rise in the circulating GH concentration which is sustained during the laying cycle (Scanes *et al.* 1979, Williams *et al.* 1986), declines during incubation (Harvey *et al.* 1979, Sharp *et al.* 1979) and increases with the brooding of young (Wentworth *et al.* 1983). These changes reflect differences in the numbers of pituitary somatotrophs (Ramesh *et al.* 1995, 1996) and the abundance of pituitary GH mRNA (Karatzas *et al.* 1997).

Somatotrophic–gonadotrophic interactions

Some of the actions of GH on reproductive function are likely to be indirect and mediated through its regulation of gonadotropin synthesis and release (Fig. 3). The possibility that GH may regulate gonadotroph function is indicated by the abundant GHRs/binding proteins in their cytoplasmic and nuclear compartments (Harvey *et al.* 1993). Indeed, gonadotrophs may be dependent on somatotrophs, since gonadotrophs are poorly developed (if at all) in rats following the fetal immunoneutralization of endogenous GH (Gardner & Flint 1990, Flint *et al.* 1992). The size of the gonadotroph population in teleost pituitary glands has also been shown to be regulated, in a paracrine way, by neighboring somatotrophs (Melamed *et al.* 1999). The transgenic expression of the human GH gene similarly

increases gonadotroph populations in the mouse pituitary gland (Stefaneanu & Kovacs 1995).

Consequently, circulating gonadotropin levels are also GH dependent. For instance, basal and stimulated plasma LH and FSH levels are attenuated in GH-immunoneutralized animals and in congenitally GH-deficient and GH-resistant rodents (Chandrashekar & Bartke 1996, 1998, Chandrashekar *et al.* 1999, Bartke 1999, Bartke *et al.* 1999) and cattle (Chandrashekar & Bartke 1998). Indeed, the induction of GH resistance by GHR gene knockout is correlated with a significant reduction in fertility (Chandrashekar & Bartke 1998, Bartke 1999). Exogenous GH, conversely, increases circulating LH levels in dairy cattle (Schemm *et al.* 1990) and the *in vitro* release of LH and FSH from rodent pituitary glands (Steger *et al.* 1991, Tang *et al.* 1993). The administration of bovine GH to GH-deficient Ames mice also increases plasma LH concentrations (Chandrashekar & Bartke 1993).

GH exerts negligible or inhibitory effects on LH and/or FSH secretion in some studies, indicating a narrow threshold for GH action. For instance, exogenous GH is without effect on circulating gonadotroph concentrations in girls with Turner's syndrome (Bourgignon *et al.* 1993), in monkeys during development (Wilson *et al.* 1989), in normal women (Ovesen *et al.* 1993) or in beef heifers (Hall *et al.* 1994). Conversely, exogenous GH reduces the amplitude of pulsatile LH release in amenorrheic women and the integrated LH concentration, despite increasing the frequency of pulsatile LH release, in women (Genazzani *et al.* 1993b) and lactating dairy cows (Schemm *et al.* 1990). GH may, in some cases, differentially regulate LH and FSH secretion, since chronic GH administration via osmotic minipumps is associated with a reduction in LH despite unchanging FSH levels (Chandrashekar & Bartke 1998).

The inhibitory effects of GH on circulating gonadotropin levels are particularly marked in animals transgenically expressing the GH gene (Ghosh & Bartke 1993). The quantity of β -FSH mRNA and protein (Tang *et al.* 1993, Bartke *et al.* 1994) and the number of LH-immunoreactive cells (Sasaki *et al.* 1997) are similarly reduced in GH-transgenic mice, as is the feedback control of LH release by gonadal steroids in pigs (Guthrie *et al.* 1991) and rodents (Bartke *et al.* 1996). This inhibition of gonadotropin production by pharmacological levels of GH is also associated with reproductive dysfunction, since male transgenic mice expressing the GH-V gene mount less often, ejaculate more slowly and have more frequent intromissions, impregnate fewer females and sire fewer offspring (Meliska & Bartke 1997). Rodents and pigs transgenically expressing the GH gene also exhibit reduced fertility (Guthrie *et al.* 1991, Bartke *et al.* 1996).

GH effects on gonadotropin cell number and activity may reflect interconversions between pituitary cells as well as increased gonadotroph proliferation and activity. As

Table 1 GH secretion and reproductive status

Reproductive stage	Change in GH secretion*	Purpose	Notes
Puberty in humans	↑ pulse amplitude; unchanged frequency	Pubertal growth spurt; sexual maturation	
Puberty in rats	↑ pulse amplitude; development of sexual dimorphism	Pubertal growth spurt; sexual maturation; sexually dimorphic gene expression	
Peri-ovulatory period	↑ plasma levels	Folliculogenesis; ovulation	
Pregnancy in primates	↑ plasma levels of GH-N, GH-V and hCS	Fetal/maternal metabolism	Reflects ↑ placental size (GH-V, hCS); ↑ steroid concentrations (GH-N)
Pregnancy in non-primates	↑ plasma levels of GH-N	Fetal/maternal metabolism	Reflects ↑ steroid concentrations
Parturition	↑ plasma levels of GH	Unknown	
Lactation	↑ production of mammary and pituitary GH	Mammatogenesis; galactopoiesis	
Seasonal breeding	↑ plasma GH levels during breeding	Fetal nutrient requirements	Partially, but not entirely due to fasting

reviewed by Childs (2000), pituitary cell populations have been identified containing both GH and gonadotropin immunoreactivity, both GHRH-binding sites and gonadotropin immunoreactivity, or both GnRH-binding sites and GH immunoreactivity. Indeed, 50–57% of gonadotrophs from male rats and female rats, particularly periovulatory female rats, also express GH (Childs *et al.* 2000). Differentiation of these multifunctional cells (somatogonadotrophs) in rats occurs throughout the estrous cycle and is regulated by estrogens, activin and GH (Childs 2000). Somatogonadotrophs may be cells undergoing interconversion between somatotrophs and gonadotrophs. Alternatively, they could represent a more stable cell population that would integrate gonadotropin and GH effects on reproductive function.

Summary

Changes in GH secretion and reproductive status appear to be co-ordinately regulated throughout reproductive life. This co-ordination underlies the importance of GH as a co-gonadotropin. Indeed, important landmarks such as puberty and pregnancy are consistently associated with increased GH secretion (Table 1). In some cases, augmented circulating GH levels are paired with hepatic GH resistance. This interaction may permit selective activation of gonadal responses to GH without activating IGF-I-mediated systemic responses. This selective activation may also be mediated by autocrine, paracrine or intracrine GH actions, since GH is also synthesized in reproductive tissues. The link between the reproductive and somatotrophic axes is dependent upon interactions at the hypothalamic, pituitary and gonadal level (Fig. 3). In addition to direct effects on gonadal function, GH may influence reproductive activity by increasing gonadotropin secretion at the hypothalamic and pituitary level and by enhancing gonadotropin responsiveness at the gonadal level.

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