REVIEW

Sexual dimorphism of the somatotrophic axis

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Introduction

The somatotrophic axis is one of the major hormonal systems regulating postnatal growth in mammals. Several aspects of this axis are sexually dimorphic, which might account for some of the sex differences in growth rate and body composition. This review will discuss male–female differences in the hormone levels, receptor concentrations and binding protein levels of this system. We will summarise sex differences in growth phenotype and then discuss differences in temporal profiles of growth hormone (GH), responses to GH including plasma and tissue levels of insulin-like growth factors, factors that may affect GH responsiveness, and conclude by discussing sex differences in regulation of GH synthesis and secretion. The established and potential effects of gonadal steroids acting prenatally and postnatally on the somatotrophic axis will also be examined. Readers are also referred to previous reviews on sexual dimorphism and gonadal steroid effects on growth hormone secretion (Jansson *et al.* 1985, Devesa *et al.* 1991, Kerrigan & Rogol 1992, Wehrenberg & Giustina 1992, Chowen *et al.* 1996, Veldhuis 1996).

The somatotrophic axis

GH (also known as somatotrophin) is synthesised and secreted by the anterior pituitary gland in a pulsatile manner under the co-ordinate control of two hypothalamic neuropeptide hormones, GH-releasing factor (GRF) and somatostatin (somatotrophin release-inhibiting factor, SRIF). GH is a polypeptide hormone that exhibits sequence and structural homology between species and with the related hormones, prolactin and placental lactogen, all of which are proteins of 22–23 kDa (Goffin *et al.* 1996). Most GH circulates as a monomer, although oligomeric, glycosylated and phosphorylated forms and variants arising from alternate splicing during transcription are also found (Lewis 1992). The half-life of the hormone differs between species, with a half-life of 6 min reported for rats (Badger *et al.* 1991) and one of around 25 min in

humans (Holl *et al.* 1993). GRF and SRIF are produced by neurones in the arcuate nucleus and anterior periventricular nucleus respectively, and are carried in the hypophyseal portal circulation to the anterior pituitary. Two forms of GRF are synthesised, with 40 or 44 amino acids, and both monomers and dimers of the 14-amino acid SRIF are found in the circulation (Devesa *et al.* 1992). Adenylate cyclase activity in somatotrophs is increased after binding of GRF to its G_s protein receptor, and decreased after binding of SRIF to its G_i receptor. GRF therefore increases intracellular concentrations of cAMP, which stimulates GH secretion and synthesis in somatotrophs, whereas SRIF has the opposite effect (Bertherat *et al.* 1995). Alternating pulses of GRF and SRIF secretion into hypophyseal portal blood were first demonstrated *in vivo* by Plotsky & Vale (1985) in male rats. A separate group of male rats that were sampled concurrently showed changes in GH secretion that were consistent with the observed GRF and SRIF concentrations. GH is secreted when the anterior pituitary is exposed to low concentrations of SRIF and high concentrations of GRF in hypophyseal portal blood (Tannenbaum & Ling 1984, Hartman *et al.* 1993).

GH acts via its receptor to alter the metabolism of target tissues, such as liver and muscle (Carter-Su *et al.* 1996). Many of the growth responses to GH are believed to be the result of its stimulation of the synthesis of insulin-like growth factor-I (IGF-I), although growth hormone also has direct effects on cell growth and differentiation (Spagnoli & Rosenfeld 1996). IGF-I is produced in most tissues and acts in an endocrine or paracrine manner to affect tissue metabolism through either the type 1 IGF-receptor or the insulin receptor (Cohick & Clemmons 1993). This receptor cross-reactivity is the result of structural homology between IGF-I and insulin. IGF-II is also produced in many tissues, although its effects on metabolism are less well characterised. IGF-II binds to both the type 1 and type 2 IGF receptors, but not to the insulin receptor, and the type 1 IGF receptor is believed to mediate most of the biological actions of IGF-II (Cohick & Clemmons 1993). The IGF-binding proteins are a family of at least seven proteins that bind to IGF-I and IGF-II,

and which are found both in extracellular fluids and in association with cell surfaces or extracellular matrix (Clemmons 1996, Oh *et al.* 1996). Binding to IGF-binding proteins increases the half-life of IGFs and, because they have greater binding affinities for IGFs than the type 1 IGF receptor, they also alter the biological activity of the IGFs (Clemmons 1996). This review discusses changes in total plasma IGFs – that is, those occurring after separation of IGFs from IGF-binding proteins. IGF-binding protein-3 is the major IGF-binding protein in adult blood.

Sexual dimorphism of growth phenotype

Postnatal body weight and composition differ between males and females in a large number of mammalian species, but the ontogeny of these changes is species specific. In humans, other primates, rats and rabbits, height gain or rate of weight gain, or both, become sexually dimorphic around the time of puberty (reviewed by Tanner 1962, Edén 1979). However, in cattle and sheep, rates of growth are greater in males than in females from early postnatal life, such that differences in live weight develop before puberty (Brody *et al.* 1926, Fourie *et al.* 1970, Gatford *et al.* 1996). Sex differences in body composition also arise at puberty in humans, rats and rabbits, when males more rapidly gain muscle and bone and lose fat, whereas females have much smaller gains in muscle and bone and large gains in fat (reviewed by Tanner 1962). This results in a greater proportion of total body weight as fat in adult females. For example, in one population the body fat contents of 25-year-old men and women were estimated as 14% and 23% of total body weight respectively (Brozek 1967).

Adult males are generally heavier and leaner than adult females, but species differ in the age at which sex differences in the rate and composition of gain occur.

Sexual dimorphism in temporal profiles of circulating GH

Measurement of GH concentration in samples of blood serum or plasma collected at frequent intervals from cannulated subjects has shown that circulating concentrations of GH vary episodically (Fig. 1) (Davis *et al.* 1977, Edén 1979). Species differ both in the temporal profiles of circulating GH concentration and in how these profiles differ between sexes. Humans are unusual in that mean plasma GH concentrations and GH pulse amplitude are greater in adult females than in adult males (Zadik *et al.* 1985, Ho *et al.* 1987, Albertsson-Wikland & Rosberg 1988, Costin *et al.* 1989, Winer *et al.* 1990, Rose *et al.* 1991). In contrast, mean GH concentrations and GH pulse amplitude in blood are greater in adult males than in adult females in rats (Tannenbaum & Martin 1976, Edén 1979, Jansson *et al.* 1984, Gabriel *et al.* 1992, Leidy *et al.* 1993),

mice (MacLeod *et al.* 1991), cattle (Plouzek & Trenkle 1991, Röpke *et al.* 1994), horses (Thompson *et al.* 1994) and chickens (Pampori & Shapiro 1994). Mean plasma GH concentrations are also greater in male than in female in late-gestation fetuses in sheep and pigs (Bassett & Gluckman 1986, Bauer & Parvizi 1996) and in prepubertal sheep (Gatford *et al.* 1996, 1997a). Several studies in pigs have also revealed greater mean plasma GH concentrations in males than in females (Dubreuil *et al.* 1987, Campbell & Taverner 1988, Louveau *et al.* 1991, Kraetzl *et al.* 1994), but this is not a universal observation (Owens *et al.* 1991, Buonomo & Klindt 1993). Interpulse plasma GH concentrations are greater in female rats than in males (Tannenbaum & Martin 1976, Edén 1979, Jansson *et al.* 1984, Gabriel *et al.* 1992, Leidy *et al.* 1993) and the same is true in mice (MacLeod *et al.* 1991) and humans (Winer *et al.* 1990). In contrast, interpulse plasma GH is greater in males than females in cattle (Plouzek & Trenkle 1991), chickens (Pampori & Shapiro 1994) and prepubertal sheep (Gatford *et al.* 1996, 1997a). Plasma GH pulse frequency does not differ between sexes in humans (Winer *et al.* 1990), chickens (Pampori & Shapiro 1994) or prepubertal sheep (Gatford *et al.* 1996, 1997a), whereas, in rodents, GH pulses are less frequent in males than in females (Tannenbaum & Martin 1976, Edén 1979, Jansson *et al.* 1984, MacLeod *et al.* 1991, Gabriel *et al.* 1992, Leidy *et al.* 1993). In cattle (Plouzek & Trenkle 1991) and in horses (Thompson *et al.* 1994) plasma GH pulses are more frequent in males than in females. In addition to differences in GH pulse frequency and amplitude, pulsatile GH secretion is less regular in female rats than in males (Edén 1979, Painson & Tannenbaum 1991, Pincus *et al.* 1996).

The timing of the onset of sex differences in circulating profiles of GH also varies between species. In humans (Zadik *et al.* 1985, Albertsson-Wikland & Rosberg 1988, Costin *et al.* 1989, Rose *et al.* 1991) and rats (Edén 1979, Jansson *et al.* 1984, Gabriel *et al.* 1992, Leidy *et al.* 1993), patterns and mean concentrations of circulating GH do not differ between the sexes before puberty but become apparent during the peripubertal period, concomitant with the appearance of sex differences in growth rate. In sheep, however, both growth rate and temporal profiles of GH in plasma are sexually dimorphic before puberty (Gatford *et al.* 1996). Sex differences in the pulsatile profile of circulating GH, and in mean GH concentrations, are likely to contribute to sex differences in growth and other responses to GH. Infusion of GH in male rats at a constant rate produces smaller increases in growth rate and circulating concentrations of IGF-I, but is more effective at increasing hepatic GH receptor numbers and circulating GH-binding protein concentrations, than infusion of the same GH dose as a series of pulses (Maiter *et al.* 1988, 1992, Bick *et al.* 1990, 1992). A recent study in rats has shown that growth responses are more sensitive to stimulation by the pulsatile component of a GH infusion, whereas hepatic GH receptor and plasma

Figure 1 Temporal profile of circulating GH concentrations.

GH-binding protein concentrations are sensitive to the continuous component (Gevers *et al.* 1996). Thus, in rats, the greater amplitude and lower frequency of GH pulses in males may be more effective in stimulating growth than the profile observed in females.

The *in vivo* effects of endogenous and exogenous gonadal steroids on profiles of circulating GH are well documented. Mean plasma GH concentration, area under the GH profile and GH pulse amplitude are all increased by androgens in humans (Illig & Prader 1970, Parker *et al.* 1984, Ulloa-Aguirre *et al.* 1990), rats (Jansson *et al.* 1984, 1985), cattle (Plouzek & Trenkle 1991, Schwarz *et al.* 1992, Röpke *et al.* 1994), sheep (Davis *et al.* 1977, Gatford *et al.* 1996), pigs (Dubreuil *et al.* 1989) and chickens (Pampori & Shapiro 1994). In humans, administration of testosterone to males increases mean plasma GH and GH secretion rate by increasing GH pulse amplitude (Illig & Prader 1970, Liu *et al.* 1987, Ulloa-Aguirre *et al.* 1990), whereas in rats androgens also reduce interpulse GH concentrations (Jansson *et al.* 1984, 1985).

Oestrogen treatment also increases mean plasma GH concentrations in humans (Carlson *et al.* 1973, Wiedemann *et al.* 1976, Ho *et al.* 1996), castrate female macaques (Bethea 1991), intact female baboons (Copeland *et al.* 1984), sheep (Davis *et al.* 1977) and cattle (Breier *et al.* 1988). In primate species, endogenous oestrogens appear to be more important than endogenous androgens for regulation of circulating GH. Most studies in humans have reported positive correlations between GH pulse amplitude and serum concentrations of free oestradiol (Ho *et al.* 1987, Faria *et al.* 1992), but not between mean plasma GH and plasma testosterone concentrations (Thompson *et al.* 1972, Butenandt *et al.* 1976, Ho *et al.* 1987). However, Iranmanesh *et al.* (1991) reported that GH secretion, pulse frequency and pulse amplitude were negatively correlated with free testosterone and not related to serum oestradiol in healthy men. In non-primates, endogenous oestrogen status has less effect on circulating GH profiles than has the endogenous androgen status.

Ovariectomy of cows does not alter the temporal pattern of circulating GH (Plouzek & Trenkle 1991). In rats, circulating patterns of GH do not change with stage of the oestrous cycle (Clark *et al.* 1987), but ovariectomy produces a small increase in GH pulse amplitude (Jansson *et al.* 1984, Clark *et al.* 1987) and oestrogen treatment increases interpulse GH concentrations in males (Jansson *et al.* 1983). This suggests that sex differences in endogenous oestrogen production might contribute to the smaller GH pulse amplitude and greater interpulse GH concentrations in females compared with males in this species. Oestrogen receptor-mediated pathways have been proposed as a mechanism for the effects of both steroids on circulating GH (Devesa *et al.* 1991, Metzger *et al.* 1994). However, oestrogens and androgens have different effects on circulating patterns of GH in humans. Whereas androgens increase mean plasma GH by increasing GH pulse amplitude, without changing interpulse GH concentrations or GH pulse frequency, oestrogens increase mean plasma GH by increasing interpulse GH concentrations, GH pulse amplitude, pulse frequency, or combinations of these (Dawson-Hughes *et al.* 1986, Mauras *et al.* 1990).

In addition to the effects of steroids on circulating GH after puberty, androgens and oestrogens act before puberty to exert permanent effects on circulating patterns of GH in later life. In the rat, in which sexual differentiation of brain centres regulating growth occurs shortly after birth, neonatal, but not prepubertal, castration of male rats decreases their GH pulse amplitude and increases their interpulse GH concentrations as adults (Jansson & Frohman 1987, Jansson *et al.* 1984). Neonatal gonadectomy of female rats decreased their interpulse GH concentrations and increased their GH pulse amplitude as adults, resulting in a temporal pattern of GH in the circulation that was more like that of males and increased their growth rates in later life (Jansson *et al.* 1984). However, in female sheep and cattle, in which sexual differentiation of growth regulation occurs before birth, prenatal androgen exposure increased postnatal growth and plasma IGF-I, but did not alter circulating patterns of GH (Klindt *et al.* 1987, Aldrich *et al.*

1996), implying that the IGF-I response to GH was increased.

In non-primate species, mean circulating GH concentrations are greater in males than in females, whereas in primate species, mean circulating GH concentrations are greater in females than in males. Sex differences in circulating GH profiles usually become apparent over the same period as sex differences in growth. Either androgen or oestrogen treatment increases mean circulating GH in most species, and androgen and oestrogen can also act before puberty to alter circulating profiles of GH permanently in later life.

Sexual dimorphism in responses to GH

Growth rate and body composition

Sexual dimorphism in growth rate and body composition have been discussed above. Sex differences in circulating GH profiles may be a mechanism by which steroid hormones produce these differences, at least in non-primates. However, studies in which exogenous GH has been administered have also produced evidence of sex differences in *responsiveness* to GH. In GH-deficient adults, GH treatment produced greater increases in plasma IGF-I and total body water in men than in women (Johannsson *et al.* 1996, Burman *et al.* 1997). Conversely, GH treatment of growing pigs produced greater increases in growth and protein deposition in females than in males (Campbell *et al.* 1990). Potential mechanisms for sex differences in growth and composition responses to GH are discussed below.

Insulin-like growth factor-I

The insulin-like growth factors are hormones that are believed to mediate many of the effects of GH on tissue growth and metabolism (Cohick & Clemmons 1993). If sexual dimorphism at the level of circulating GH is the mechanism responsible for sexually dimorphic patterns of growth, one would also expect sex differences at the level of the insulin-like growth factors and their binding proteins.

Plasma concentrations of IGF-I are greater in males than females in postpubertal rats (Gabriel *et al.* 1992, Hu *et al.* 1993), mice (Blair *et al.* 1987), pre- and postpubertal sheep (Roberts *et al.* 1990, Medrano & Bradford 1991, Gatford *et al.* 1996, 1997b), cattle (Bishop *et al.* 1989, Hannon *et al.* 1991, Schwarz *et al.* 1992, Röpke *et al.* 1994, Davis *et al.* 1995), late-gestation fetal and postnatal pigs (Owens *et al.* 1990, Lamberson *et al.* 1995, Bauer & Parvizi 1996) and in turkeys from 1 week of age (Bacon *et al.* 1993). In contrast, most, although not all (Juul *et al.* 1994) studies in primates have found that plasma IGF-I concentrations are greater in postpubertal females than in males (Copeland *et al.* 1985, Merimee *et al.* 1987, Yamamoto *et al.* 1991,

Schwartz & Kemnitz 1992). Plasma IGF-I concentrations in children are also greater in females than in males before and during puberty (Merimee *et al.* 1991, Juul *et al.* 1994). The direction of sex differences in IGF-I is generally consistent with that associated with GH, although meat-type chickens appear to be an exception in early postnatal life, with greater GH and growth rates, but lower plasma IGF-I concentrations in males than in females in the first few weeks after hatching. However, by 7 weeks of age, plasma IGF-I concentrations are similar, or greater, in males than in females (Johnson *et al.* 1989, Scanes *et al.* 1989, Ballard *et al.* 1990, Decuyper *et al.* 1993). As with GH, the developmental stage at which plasma IGF-I concentrations become sexually dimorphic varies between species. Plasma IGF-I concentrations do not differ between sexes in prepubertal rats and mice (Blair *et al.* 1987, Gabriel *et al.* 1992), but are sexually dimorphic in prepubertal humans (Merimee *et al.* 1991, Juul *et al.* 1994), lambs (Gatford *et al.* 1996) and pigs (Owens *et al.* 1991).

Androgens and oestrogens appear to affect plasma concentrations of IGFs via different mechanisms and their effects differ between species. Androgens are believed to affect circulating IGF-I indirectly, via increased circulating GH concentrations, as GH deficiency in rats and humans abolishes the increase in plasma IGF-I at puberty or after androgen treatment (Parker *et al.* 1984, Crawford *et al.* 1994). Androgen treatment does not affect the plasma IGF-I response to a GH challenge in prepubertal boys (Craft & Underwood 1984). The effects of oestrogens on circulating IGF-I and the mechanism for these effects may differ between sexes and species. In ovariectomised female rats, oestrogens increase circulating GH, but reduce circulating IGF-I concentrations by inhibiting the hepatic IGF-I synthetic response to GH (Murphy & Freisen 1988, Borski *et al.* 1996). Oestrogen treatment of male cattle increases plasma concentrations of both IGF-I and GH (Breier *et al.* 1988, Coxam *et al.* 1990). In humans, the reported effects of oestrogens on circulating IGF-I are extremely variable. Endogenous and administered oestrogen are variously reported to decrease (e.g. Wiedemann *et al.* 1976, Weissberger *et al.* 1991), have no effect (e.g. Wang *et al.* 1995) or increase (e.g. Weissberger *et al.* 1991, Juul *et al.* 1995a) plasma IGF-I in women and girls. The observed IGF-I response may depend on whether the oestrogen was endogenous or exogenous, the route of administration for exogenous oestrogen and the time course over which circulating IGF-I was monitored. In female chimpanzees, circulating IGF-I concentrations are less strongly correlated with plasma oestrogen than with plasma testosterone, whereas in males of this species plasma oestrogen and IGF-I concentrations are not correlated (Copeland *et al.* 1985).

Exposure to steroids during neonatal or prenatal life also modifies circulating concentrations of IGF-I in later

postnatal life. For example, in female lambs that were chronically exposed to increased testosterone as fetuses as a result of maternal testosterone implants, postnatal plasma IGF-I concentrations were increased by 29% compared with those in control lambs (DeHaan *et al.* 1990a). Prenatal exposure to androgen consistently increases postnatal growth rates and circulating IGF-I and decreases fat deposition, in male and female cattle and sheep (Klindt *et al.* 1987, DeHaan *et al.* 1988, 1990a,b, Jenkins *et al.* 1988, Aldrich *et al.* 1996). However, prenatal exposure to androgen did not alter circulating patterns of GH in female cattle (Aldrich *et al.* 1996) and sheep (Klindt *et al.* 1987), implying that prenatal exposure to androgen does not increase circulating IGF-I by stimulating GH in these species. Although neonatal exposure to steroids permanently affects growth and growth hormone secretion in the rat (Jansson *et al.* 1984, Jansson & Frohman 1987), the effects of neonatal steroid status or administration on adult plasma IGF-I concentrations in this species have not been reported.

In non-primate species, plasma IGF-I concentrations are greater in males than in females, whereas, in primate species, plasma IGF-I concentrations are greater in females than in males. Androgens increase plasma IGF-I concentrations indirectly, through increasing plasma GH, but the effects of oestrogens are variable. Sex differences in IGF-I support the hypothesis that sex differences in growth may be partially the result of gonadal steroids acting to produce sexually dimorphic patterns of circulating GH. However, studies in cattle and sheep also suggest that steroids may affect circulating IGF-I independent of effects on GH.

Insulin-like growth factor-II

Plasma IGF-II concentrations are reported not to differ between sexes in children, adolescent or young adult humans (Merimee *et al.* 1987, Juul *et al.* 1995b). In prepubertal lambs, plasma IGF-II concentrations were similar in females and males at 12 weeks of age and greater in females than in males at 23 weeks of age (Gatford *et al.* 1996). Plasma IGF-II in prepubertal pigs was also greater in females than in males (Owens *et al.* 1993). In young meat-type chickens, sex differences in plasma IGF-II concentrations follow an ontogenic pattern similar to that of IGF-I, with greater IGF-II in females than males at 2 weeks of age, but not at later ages (Scanens *et al.* 1989, Decuyper *et al.* 1993). The effect of androgens on IGF-II differs between species. In neonatal rats, androgens decrease hepatic IGF-II mRNA concentrations (Martinoli & Pelletier 1991). Plasma concentrations of IGF-II are not affected by castration in male lambs (Gatford *et al.* 1996), but are increased by castration in male pigs (Owens *et al.* 1993).

Studies to date indicate that plasma IGF-II concentrations are either similar or greater in females compared with males. Androgens may inhibit IGF-II synthesis in some, although not necessarily all, species.

Insulin-like growth factor-binding proteins

Plasma concentrations of IGF-binding protein-3, the main carrier of IGFs in blood in postnatal life, are positively regulated by GH (Clemmons 1996). Consistent with differences in circulating GH, plasma IGF-binding protein-3 concentrations are greater in women than in men (Juul *et al.* 1995b, Harrela *et al.* 1996) and greater in male than in female growing lambs (Gatford *et al.* 1996). Circulating IGF-binding protein-1 concentrations are greater in female than in male fasted humans and rats, but these differences are reduced or abolished by feeding (Rutanen *et al.* 1982, Yeoh & Baxter 1988, Lewitt *et al.* 1994, Juul *et al.* 1995b). Plasma IGF-binding protein-2 concentrations do not differ between sexes in humans and pigs before or after puberty (Buonomo & Klindt 1993, Juul *et al.* 1995b).

In male humans and sheep, androgens positively regulate circulating concentrations of IGF-binding protein-1 and IGF-binding protein-3 (Erfurth *et al.* 1996, Gatford *et al.* 1996, Pfeilschifter *et al.* 1996). Plasma IGF-binding protein-3 is positively regulated by androgens in pubertal, but not sexually mature, male chimpanzees (Crawford & Handelsman 1996). In male cattle, although circulating concentrations of IGF-binding protein-3 increase and those of IGF-binding protein-2 decrease at puberty, these changes are not affected by perturbations of circulating testosterone (Renaville *et al.* 1996).

Oestrogens may chronically, but not acutely, reduce plasma concentrations of IGF-binding protein-3. Oestrogen treatment reduces plasma IGF-binding protein-3 concentrations in female rats and pigs (Lee *et al.* 1993, Kalu *et al.* 1994), but plasma IGF-binding protein-3 does not fluctuate with ovarian cyclicity in women or in female cattle (Funston *et al.* 1995, Wang *et al.* 1995). Other IGF-binding proteins may be positively regulated by oestrogens. In women, plasma IGF-binding protein-1 concentrations increase in association with the preovulatory peak in circulating oestrogen (Wang *et al.* 1995) and after oestrogen treatment (Suikkari *et al.* 1991). Plasma IGF-binding protein-2 is positively regulated by oestrogens in female cattle (Vestergaard *et al.* 1995) but is not affected by oestrogen treatment in female pigs (Lee *et al.* 1993).

Sex differences in circulating concentrations of IGF-binding protein-3 are consistent with differences in GH. Limited data suggest that androgens may increase circulating concentrations of IGF-binding protein-3 and -1, whereas oestrogens increase circulating concentrations of IGF-binding proteins-1 and -2 and decrease circulating concentrations of IGF-binding protein-3.

Sexual dimorphism in factors affecting GH responsiveness

GH receptor

The GH receptor is a member of the cytokine/haematopoietin receptor superfamily. Binding of GH to

the GH receptor induces receptor dimerisation and activation of the tyrosine kinase, JAK2, which in turn activate signalling molecules, including Stat transcription factors, Src homologous collagen protein (SHC) and insulin receptor substrates 1 and 2. Downstream events include release of second messengers, including diacylglycerol, calcium and nitric oxide, and activation of enzymes, including mitogen-activated protein kinase, protein kinase C, phospholipase A₂ and phosphatidylinositol 3'-kinase, which affect the function of the target cell (Argetsinger & Carter-Su 1996). Genetic defects of the GH receptor in Laron syndrome cause GH resistance and result in dwarfism, obesity and low serum concentrations of IGF-I (Laron 1993). As a functional GH receptor is necessary for GH to produce responses in target tissues, sex differences in GH receptor numbers or affinity might produce differences in response to GH.

In the rat, hepatic GH binding capacity and receptor numbers are two-fold greater in males than in females after puberty (Kelly *et al.* 1974, Postel-Vinay 1976, Maes *et al.* 1983, Tiong & Herington 1991, Carmignac *et al.* 1993a, b). Despite this difference in GH binding activity, total hepatic GH receptor mRNA concentrations do not differ between sexes in the rat (Mathews *et al.* 1989, Carlsson *et al.* 1990a, Tiong & Herington 1991, Möldrup *et al.* 1993, Baumbach & Bingham 1995), although mRNA for a liver-specific receptor subtype, GHR₁, is expressed at greater concentrations in female rats than in males (Baumbach & Bingham 1995). In the adult rabbit, the abundance of neither hepatic GH binding nor GH receptor mRNA differs between sexes (Kelly *et al.* 1974, Tiong *et al.* 1989).

In rats, testosterone treatment does not affect hepatic GH binding (Carmignac *et al.* 1993a), but oestrogen treatment induces GHR₁ transcripts, resulting in increased hepatic GH binding (Carmignac *et al.* 1993a, Gabriellson *et al.* 1995, Bennett *et al.* 1996). The effect of oestrogen on GH receptors differs between species. Physiological doses of oestrogen decrease GH receptor expression and GH binding in rabbit liver (Domene *et al.* 1994). Decreased plasma GH binding protein concentrations in humans treated with oestrogen probably also reflect decreased GH receptor numbers (Kobayashi *et al.* 1994, Tato *et al.* 1995).

Sex differences in hepatic GH binding and expression of the GH receptor gene vary between species. A liver-specific receptor subtype in rats, GHR₁, is expressed at greater concentrations in female than in males and is upregulated by oestrogen. However, in other species, oestrogen appears to downregulate the GH receptor.

GH-binding protein

GH-binding protein is a truncated form of the GH receptor, corresponding to the extracellular ligand-binding domain (Leung *et al.* 1987). In rats and humans, high-affinity GH-binding proteins in plasma form complexes

with some of the GH in blood and are proposed to function as a GH reservoir and to modulate the action of GH at its receptor (Amit *et al.* 1992, Baumann 1994, Herington *et al.* 1994, Bingham *et al.* 1994). In normal adult rats, circulating concentrations of GH-binding protein are two- or threefold greater in females than in males (Carmignac *et al.* 1992, Leung *et al.* 1994). Studies in humans have also shown greater concentrations of GH-binding protein in blood from females than in that from males (Ho *et al.* 1993, Rajkovic *et al.* 1994), although earlier studies did not find such differences, probably because of the use of less sensitive detection methods (Merimee *et al.* 1991, Mercado *et al.* 1993). In cattle and sheep, GH-binding protein is present in lower concentrations in plasma than are observed in rats or humans, and is not believed to have an important role in GH metabolism (Amit *et al.* 1992, Davis *et al.* 1992, Bingham *et al.* 1994). Sex differences have not been investigated in these species. In chickens, serum GH-binding protein concentrations do not differ between the sexes (Tobar-Dupres *et al.* 1993). In the rat, the lower concentrations of circulating GH-binding protein, combined with greater GH pulse amplitude, may produce more free circulating GH during GH-secretory episodes in male than in female rats, resulting in sex differences in the availability of GH (Leung *et al.* 1994).

Because the GH-binding protein is derived either by alternate splicing of GH receptor mRNA as in rats (Baumbach *et al.* 1993), or by proteolytic cleavage of the cell-surface GH receptor protein as in humans (Sotiropoulos *et al.* 1993), it is not surprising that gonadal steroids have similar effects both on GH-binding protein concentrations in blood and GH receptor numbers in liver. Physiological doses of androgens do not affect concentrations of GH-binding protein in rats (Carmignac *et al.* 1993a) or men (Ip *et al.* 1995). However, pharmacological doses of testosterone decrease serum GH-binding protein concentrations in hypogonadal men, independent of GH status (Ip *et al.* 1995). Oestrogens increase hepatic concentrations of GH-binding protein mRNA and circulating concentrations of GH-binding protein in rats (Carmignac *et al.* 1993a, Gabriellson *et al.* 1995, Bennett *et al.* 1996). In humans, circulating GH-binding protein concentrations are generally negatively correlated with endogenous oestrogen concentrations and are reduced by physiological doses of oestrogen (Massa *et al.* 1993, Kobayashi *et al.* 1994, Tato *et al.* 1995), although Klein *et al.* (1996) did not find that plasma GH-binding protein concentrations differed with stage of the ovulatory cycle in women. Conversely, pharmacological doses of oestrogen increase plasma GH-binding protein concentrations (Weissberger *et al.* 1991, Kelly *et al.* 1993, Ho *et al.* 1993, Massa *et al.* 1993, Rajkovic *et al.* 1994).

Circulating concentrations of GH-binding protein are greater in females than in males in both rats and humans, and may

decrease the availability of circulating GH in females. The effects of gonadal steroids on GH-binding protein are species specific and differ between physiological and pharmacological doses.

Metabolic clearance rate of GH

Differences in responsiveness to either endogenous or exogenous GH may also be a result of differences in turnover of GH in blood. Rosenbaum & Gertner (1989) reported that the metabolic clearance rate of GH was 40% greater in adult men than in adult women, whereas differences in GH clearance were not apparent in prepubertal children. They calculated that the difference in GH clearance rate in adults might account for most of the observed difference in mean circulating GH concentrations. However, differences in metabolic clearance rate correspond to differences in GH half-life only if the distribution volume of GH does not differ between sexes, and this may not be the case, given sex differences in circulating concentrations of GH-binding protein. In humans, androgen treatment did not alter GH clearance in prepubertal boys, but endogenous steroids may affect GH clearance, as the half-life of GH in young men is negatively correlated with serum oestradiol concentrations (Holl *et al.* 1993) and positively correlated with serum testosterone (Iranmanesh *et al.* 1991). Conversely, in rats, the steady-state clearance of GH is decreased by oestrogen and increased by testosterone (Badger *et al.* 1991). In cattle, the metabolic clearance rate of GH did not differ between entire and castrate males and entire females (Plouzek & Trenkle 1991). The metabolic clearance rate of GH was increased by ovariectomy, but not altered by oestrogen treatment in castrate males (Gopinath & Kitts 1984, Plouzek & Trenkle 1991).

Sex differences in the clearance rate of GH differ between species, and require further investigation.

Sexual dimorphism in the regulation of GH secretion and synthesis

Sexual dimorphism in circulating patterns of GH could be due to differences in anterior pituitary synthesis and secretion of GH as a result of sex differences in either hypothalamic secretion of GRF and SRIF or the pituitary GH response to these hormones. Technical difficulties have prevented the simultaneous measurement of GH, GRF and SRIF in animals with normal feedback systems. The evidence for differences in hypothalamic GRF and SRIF secretion is therefore largely indirect. However, *in vivo* and *in vitro* evidence suggests there are sex differences in anterior pituitary responsiveness to GRF and SRIF.

Pituitary sensitivity to GRF and SRIF

In vivo GH responses to i.v. GRF are greater in males than females in rats (Wehrenberg *et al.* 1985, Arsenijevic *et al.*

1987), cattle (Plouzek & Trenkle 1991) and horses (Thompson *et al.* 1994). However, *in vivo* human studies have reported either greater pituitary sensitivity or greater pituitary responsiveness to GRF in females than in males (Gelato *et al.* 1984, Lang *et al.* 1987, Benito *et al.* 1991, Pietschmann *et al.* 1991). In rhesus monkeys, the increase in GH in response to increasing GRF dose rate did not differ between males and females (Styne 1991). *In vitro* studies suggest that sex differences in pituitary sensitivity to GRF are partially responsible for differences in the *in vivo* GH response to GRF. Basal and GRF-stimulated GH secretion rates in intact perfused anterior pituitaries, anterior pituitary cell preparations and individual somatotrophs are greater in those from male rats than in those from female rats (Cronin & Rogol 1984, Evans *et al.* 1985, Hoeffler & Frawley 1986, Critchlow *et al.* 1986, Ho *et al.* 1986, Kerrigan *et al.* 1989). The observation that GRF receptor expression in female rats was only 15% of that observed in male rats is consistent with these observations (Ono *et al.* 1995).

Sex differences in pituitary responsiveness to SRIF have also been reported. In the rat, GRF-stimulated GH secretion is inhibited by lower concentrations of SRIF in somatotrophs from females than from males (Critchlow *et al.* 1986, Kerrigan *et al.* 1989). This suggests that differences in pituitary responsiveness to GRF, and possibly also SRIF, are involved in producing sexually dimorphic profiles of GH.

Gonadal steroids have been shown to affect GH-secretory responses to GRF and SRIF. *In vivo* androgen treatment of rats increases the GH-secretory response to exogenous GRF measured *in vivo* (Wehrenberg *et al.* 1985) and *in vitro* (Evans *et al.* 1985, Wehrenberg *et al.* 1985, Ohlsson *et al.* 1987, Batson *et al.* 1989). In humans, androgens also increase GH secretion in response to GRF, measured *in vivo*, and this increase can be prevented by oestrogen receptor blockade (Lima *et al.* 1989). In rats, *in vivo* administration of oestrogen either decreases (Evans *et al.* 1985, Ohlsson *et al.* 1987, Shulman *et al.* 1987) or fails to affect (Wehrenberg *et al.* 1985, Painson *et al.* 1992) *in vivo* and *in vitro* GH release after GRF administration. The activity of adenylate cyclase in the anterior pituitary, which positively regulates GH synthesis and secretion, is also enhanced by *in vivo* administration of testosterone and inhibited by oestrogen in the rat (Gabriel *et al.* 1993). Whereas *in vivo* pituitary responses to steroid treatment may partially reflect changes in hypothalamic GRF and SRIF secretion, *in vitro* studies confirm that the pituitary is a site at which gonadal steroids exert effects on GH secretion, at least in the rat.

The reported *in vitro* effects of gonadal steroids on basal GH synthesis and secretion are contradictory. *In vitro* steroid treatment has been reported to have no effect on basal GH secretion by cultures of anterior pituitary cells

from rats (Fukata & Martin 1986, Webb *et al.* 1983) and cattle (Hassan *et al.* 1992). Similar treatments have been reported to increase basal GH secretion in anterior pituitary cell cultures from female rats (Simard *et al.* 1986), whereas the reverse has been reported for male rats (Hertz *et al.* 1989). In macaques, *in vitro* oestrogen treatment increased basal GH secretion in cultures of pituitary cells from juvenile males, but not in anterior pituitary cell cultures from juvenile females or adult males and females (Betha 1991). GH *synthesis* in anterior pituitary cells was decreased by *in vitro* testosterone or oestrogen treatment in male rat cells (Hertz *et al.* 1989), but increased by oestrogen treatment in female rat cells (Simard *et al.* 1986). The *in vitro* effects of gonadal steroids on pituitary GH-secretory responses to GRF and SRIF have been demonstrated more consistently, and depend on the sex of the animal from which the anterior pituitary cells were derived. In anterior pituitary cells from male rats and calves, *in vitro* preincubation with androgens enhanced the GH-secretory response to GRF and the inhibition of GH secretion by SRIF (Hertz *et al.* 1989, Hassan *et al.* 1992). *In vitro* treatment of male anterior pituitary cells with oestrogens has been reported either not to affect (Hertz *et al.* 1989, Hassan *et al.* 1992) or to enhance the GH-secretory response to GRF (Webb *et al.* 1983). In female rat anterior pituitary cells, the GH-secretory response to GRF has been reported to be enhanced by *in vitro* addition of oestrogen, but not of testosterone (Simard *et al.* 1986, Hertz *et al.* 1989), although Fukata & Martin (1986) found no change in pituitary responsiveness to GRF or SRIF after oestrogen or testosterone pretreatment. In male rat anterior pituitary cells, oestrogens prevented SRIF suppression of basal, but not GRF-stimulated, GH secretion (Hertz *et al.* 1989).

Several studies suggest that, in addition to these direct actions of steroids at the pituitary, the sensitivity of the pituitary to GRF and SRIF may also be permanently reset by the actions of gonadal steroids before puberty. GH-secretory responses to GRF and SRIF were sexually dimorphic in anterior pituitary cells from adolescent rats that were gonadectomised prepubertally (Hertz *et al.* 1989). The *in vitro* GH-secretory response to GRF in adult male rats was suppressed more effectively by neonatal than prepubertal gonadectomy, and androgen treatment in adulthood was able to reverse this effect only after prepubertal gonadectomy (Ohlsson *et al.* 1987, Fishman *et al.* 1993). Similarly, neonatal administration of androgen, but not oestrogen, to female rats that were gonadectomised later in life enhanced their *in vivo* GH-secretory responses to i.v. GRF as adults (Aguilar & Lopez 1988).

Pituitary sensitivity to GRF appears to be greater in males than in females in non-primates, but greater in female than in male primates. Androgen administration enhances, and oestrogen administration inhibits, GH-secretory responses to GRF in vivo, but the effects of these steroids on the GH-secretory

response to GRF in vitro depend on the sex of the animal from which the somatotrophs were obtained. In rats, exposure to androgens before puberty enhances GH-secretory responses to GRF in later life.

GH-releasing factor synthesis and secretion

Patterns of circulating GRF in hypothalamic–hypophyseal portal blood in males and females have not been reported for any species. However, *in vivo* studies in the rat have compared the effects of removal of GRF on circulating GH in males and females using either immunoneutralisation of endogenous GRF or suppression of GRF secretion by neonatal treatment with monosodium glutamate, which causes permanent lesions in the GRF-secreting regions of the hypothalamus. Both immunoneutralisation and GRF deficiency decrease GH pulse amplitude in blood in both sexes and decrease interpulse concentrations of circulating GH in females, but not in males. This implies that interpulse GH concentrations in the female rat are primarily regulated by GRF, not SRIF (Wehrenberg *et al.* 1982, Maiter *et al.* 1991a, Ono *et al.* 1991, Painson & Tannenbaum 1991). Lower interpulse GH concentrations in the male rat are postulated to be due to either greater SRIF secretion or lower GRF secretion between GH pulses than occurs in females. To date, the sheep is the only species in which GH and GRF have been measured concurrently and those studies show only partial concordance between GRF and GH pulses, possibly because of intermittent blockage of GH secretion by SRIF pulses (Frohman *et al.* 1990, Thomas *et al.* 1991, Fletcher *et al.* 1996).

Hypothalamic GRF content is greater in male than in female adult rats (Gabriel *et al.* 1989, 1993, Maiter *et al.* 1990, 1991a, Ono *et al.* 1995) and hypothalamic GRF mRNA concentrations are two to three times greater in males than in females (Argente *et al.* 1991, Maiter *et al.* 1991b, Mizobuchi *et al.* 1991, Hasegawa *et al.* 1992, Chowen *et al.* 1993). Similarly, in prepubertal lambs, the hypothalamic GRF content is approximately 50% greater in males than in females (Gatford *et al.* 1997a). Regulation of GRF synthesis and secretion also differs between sexes in rats. Release of GRF by slices of rat hypothalamic tissue in response to potassium administration is greater in males than in females (Ono *et al.* 1995, Ge *et al.* 1989). Hypothalamic GRF protein and mRNA are more sensitive to feedback inhibition by GH in male rats than in females (Maiter *et al.* 1990, 1991b).

Sex differences in GRF content may be the result of gonadal steroid action. Androgen treatment *in vivo* has been reported to increase hypothalamic GRF protein and mRNA content in adult rats of both sexes (Zeitler *et al.* 1990, Fernandez *et al.* 1992, Hasegawa *et al.* 1992, Chowen *et al.* 1993). However, others have reported no change in hypothalamic GRF mRNA or GRF content

after gonadectomy or testosterone treatment of adult male or female rats (De Gennaro Colonna *et al.* 1991, Gabriel *et al.* 1989, Maiter *et al.* 1991b). The observation that hypophysectomy of adult rats blocks the increase in hypothalamic GRF mRNA after dihydrotestosterone treatment (Hasegawa *et al.* 1992) suggests that any increase in GRF mRNA is a response to altered circulating patterns of GH, implying that androgens do not affect hypothalamic GRF synthesis directly. Most, but not all (Gabriel *et al.* 1989), studies in rats suggest that oestrogen either suppresses (Fernandez *et al.* 1992, Senaris *et al.* 1992, Bennett *et al.* 1996) or does not affect (Maiter *et al.* 1991b) GRF synthesis and secretion. In addition to the direct effects of gonadal steroids at the hypothalamus, exposure to steroids during neonatal or prenatal life may have permanent effects on subsequent GRF production. Treatment of male and female rats with testosterone on their day of birth increased and neonatal castration decreased the number of GRF neurones in the hypothalamus, although not the hypothalamic GRF mRNA content (Chowen *et al.* 1993).

Hypothalamic GRF and GRF mRNA contents are greater in male than in female rats and prepubertal sheep, and are either increased or unchanged by androgens, and decreased or unchanged by oestrogens. Exposure to androgens during neonatal life in rats increases numbers of GRF neurones in the hypothalamus and might therefore increase the capacity for GRF secretion in adulthood.

SRIF synthesis and secretion

The evidence for sexually dimorphic *in vivo* secretion of SRIF is also largely indirect. GH secretion by male rats shows an alternating pattern of responsive and refractory periods when GRF is repeatedly administered *i.v.* at intervals of less than 3-hourly, whilst female rats respond consistently to repeated GRF stimulus (Clark & Robinson 1985, Painson & Tannenbaum 1991). This implies that SRIF secretion from the hypothalamus in males is in concentrations sufficient to block the GH secretion response to GRF, except during troughs in SRIF secretion approximately every 3 h, and that SRIF secretion is lower in females. Administration of anti-SRIF serum *i.v.* in male rats increases plasma interpulse GH concentrations, but does not alter peak GH concentrations (Terry & Martin 1981, Eikelboom & Tannenbaum 1983, Painson & Tannenbaum 1991). In female rats, administration of anti-SRIF serum or lesioning of SRIF-producing regions in the hypothalamus increases both interpulse and peak circulating GH concentrations (Urman *et al.* 1985, Painson & Tannenbaum 1991). This implies that SRIF secretion is pulsatile in the male, but relatively constant in the female rat.

Although this indirect evidence suggests that SRIF secretion is sexually dimorphic in rats, most studies have failed to find sex differences in hypothalamic or median

eminence SRIF content or *in vitro* release in the rat (Gross 1980, Critchlow *et al.* 1986, Ge *et al.* 1989, Maiter *et al.* 1990, Leidy *et al.* 1993). However, Gabriel *et al.* (1993) reported a greater SRIF content in the median eminence of male rats compared with female rats. In sheep receiving food *ad libitum*, the median eminence content of SRIF did not differ between sexes (Gatford *et al.* 1997a). SRIF mRNA expression in the periventricular nucleus, a major site of SRIF synthesis, has been found to be greater in male than in female rats in most studies (Chowen-Breed *et al.* 1989, Argente *et al.* 1990, Martinoli *et al.* 1991, Hasegawa *et al.* 1992, Chowen *et al.* 1993), although one study did not observe sex differences (Zorilla *et al.* 1990). Sex differences have also been observed in the regulation of SRIF secretion in rats. Inhibition of the GH secretion response to GRF and the increase in hypothalamic SRIF content after exposure to increased plasma GH is greater in males than in females (Clark & Robinson 1985, Carlsson *et al.* 1990b, Maiter *et al.* 1990, Bercu *et al.* 1991, Painson & Tannenbaum 1991).

In the rat, castration of males near puberty decreases hypothalamic SRIF mRNA content and androgen treatment of castrate and intact males and intact females increases hypothalamic SRIF mRNA content (Baldino *et al.* 1988, Werner *et al.* 1988, Chowen-Breed *et al.* 1989, Argente *et al.* 1990, Zorilla *et al.* 1990, Chowen *et al.* 1993). Androgen status during the neonatal period also has permanent non-reversible effects on hypothalamic SRIF content. Neonatal castration of male rats reduces, and neonatal testosterone treatment of male or female rats increases, hypothalamic SRIF mRNA content in adulthood (Chowen *et al.* 1993). In contrast to the effect on GRF-synthesising neurones (Chowen *et al.* 1993), castration or testosterone treatment during the neonatal period does not alter the number of SRIF-synthesising neurones in the rat (Hasegawa *et al.* 1992). Although androgens stimulate SRIF mRNA *in vivo*, one study has reported that *in vitro* treatment of adult rat hypothalamic cell cultures with testosterone decreased SRIF synthesis and secretion (Fernandez *et al.* 1992), implying that the stimulatory effects of androgens on hypothalamic SRIF are not due to direct actions of testosterone at the hypothalamus. Consensus has not been reached regarding the effects of oestrogen on SRIF synthesis and secretion. In rats, *in vivo* oestrogen treatment increases hypothalamic content of SRIF protein and mRNA (Baldino *et al.* 1988, Werner *et al.* 1988, Gabriel *et al.* 1989, Zorilla *et al.* 1990, Senaris *et al.* 1992, Bennett *et al.* 1996) and addition of oestrogen to rat hypothalamic cell cultures inhibits SRIF secretion, but not synthesis (Fernandez *et al.* 1992). In women, oestrogen treatment reduces the proportion who are refractory to stimulation of GH secretion by GRF, suggesting that SRIF secretion may be decreased by oestrogen (Devesa *et al.* 1991).

Indirect evidence suggests that SRIF release from the hypothalamus is pulsatile in male rats, but relatively constant in female

Figure 2 Actions of steroid hormones on the somatotrophic axis. IGF-I, insulin-like growth factor-I; IGFBP, IGF-binding protein; ALS, acid-labile subunit; +, stimulatory; -, inhibitory.

rats, which may cause the low interpulse GH concentrations observed in male rats. Consistent with this, SRIF mRNA expression in the periventricular nucleus is usually greater in male than in female rats. Hypothalamic SRIF and SRIF mRNA content in adult rats are increased by androgen treatment or prenatal androgen exposure, but the effects of oestrogens on SRIF are less clear.

Conclusions

Although aspects of the somatotrophic axis such as temporal profiles of circulating GH differ between males and females in all species investigated to date, the patterns of differences and the developmental stage at which sex differences become apparent are not the same for all species. In most species, sex differences in circulating IGF-I and IGF-binding protein-3 correspond to sex differences in the temporal profile and mean circulating concentrations of GH. In non-primate species, mean circulating GH, IGF-I and IGF-binding protein-3 concentrations are generally greater in males than in females and probably cause faster growth rates in males than in females. In contrast, mean circulating concentrations of GH and total IGF-I in primates are greater in females than in males, implying either that the somatotrophic axis is less important for postnatal growth regulation in primates than it is in other species, or that growth is related to other

aspects of the axis, for example free hormone concentrations, rather than total concentrations. For example, in girls treated for central precocious puberty, IGF-I remains stable, but circulating IGF-binding protein-3 increases and growth rate decreases (Juul *et al.* 1995a).

Sex differences in the somatotrophic axis probably originate at the anterior pituitary, and possibly the hypothalamus. There is good *in vivo* and *in vitro* evidence that gonadal steroids affect pituitary GH responsiveness to GRF and SRIF. Although indirect evidence suggests that GRF and SRIF secretion may differ between sexes in the pituitary-intact animal, it has not yet been possible to characterise portal plasma concentrations of GRF and SRIF in animals in which GH secretion is undisturbed. Development of a model in which this is possible is necessary to separate the direct effects of gonadal steroids at the pituitary and hypothalamus. In addition to direct effects at the pituitary and hypothalamus, gonadal steroids may act during development to modify subsequent secretion of GRF or SRIF, or both, for example by affecting numbers of hormone-secreting neurones. Figure 2 summarises the actions of steroid hormones on the somatotrophic axis.

The actions of gonadal steroids may account for sex differences in the somatotrophic axis before, during or after puberty, depending on species, and may include changes in hormone receptor numbers or function in addition to changes in the secretion of hypothalamic or pituitary

hormones, or both, and altered responsiveness of target tissues to somatotrophic axis hormones. Thus the somatotrophic axis may be a major pathway through which steroids act to produce sex differences in growth and body composition.

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Received 10 November 1997

Accepted 23 January 1998