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Review

Growth Hormone

Roles in Male Reproduction

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Growth hormone (GH), as its name suggests, is obligatory for growth and development. It is, however, also required for sexual differentiation and pubertal maturation and participates in gonadal steroidogenesis and gametogenesis. These roles are likely to reflect the endocrine actions of pituitary GH, directly at gonadal sites and indirectly via hepatic insulin-like growth factor-1. However, because GH is also produced in gonadal tissues, it may act in paracrine or autocrine ways to regulate local processes that are strategically regulated by pituitary GH. The concept that GH is a major regulator of male reproduction is the focus of this review.

Key Words: Growth hormone; reproduction, male.

Introduction

Although the somatogenic and gonadotropic axes have long been known to be closely linked during growth and sexual maturation *(1)*, until recently the role of growth hormone (GH) in reproduction had been described as "more akin to fine tuning than that of a major player" *(2)*. Experimental studies reveal, however, that GH regulates steroidogenesis, gametogenesis, and gonadal differentiation as well as gonadotropin secretion and responsiveness *(3)*. While these actions may reflect endocrine roles of pituitary GH, they may also reflect local autocrine or paracrine actions of GH produced in reproductive tissues.

Roles in Puberty

GH is required for normal sexual maturation in mammals, because puberty is delayed in GH-deficient *(4,5)* or GH-resistant *(6)* humans. GH deficiency in rodents is similarly associated with delayed sexual maturation *(7,8)*, and gonadotropin hormone–releasing hormone (GHRH) immunoneutralization delays sexual maturation in rats and reduces testicular size, spermatogenesis, and follicle-stimulating hormone (FSH) responsiveness *(7)*. The ability of GH to accelerate pubertal maturation in GH-deficient children *(4,9–11)* and in GH-replete normal male rats *(12)* further illustrates the importance of GH in pubertal development. In some species, GH may accelerate puberty by potentiating androgen action, because GH reduces the amount of testosterone required to induce secondary sex characteristics (axillary hair) in young men *(13)*. Furthermore, GH therapy alone stimulates body hair growth in adult GH-deficient men, even when androgen levels are normal *(14)*.

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Testicular Actions

Differentiation and Development

GH is thought to play an important role in testicular differentiation and development, because a lack of GH secretion in adult rats results in a delay in the differentiation of germinal cells *(7)*. The male reproductive tract may be particularly dependent on GH action, because GH antisera blocks differentiation of the wolffian duct in male fetal mice, whereas GH administration restores normal differentiation *(15)*. Exogenous GH also stabilizes the wolffian duct in female fetuses in vitro (*15*). GH-deficient lit/lit mice have smaller seminiferous tubules than normal mice, and GH administration results in increased seminiferous tubule cell number *(16)*. GH-deficient rats and GH-resisistant boys also have abnormally small testes *(17–19)*, as have growth hormone receptor (GHR) knockout mice, with vestigial reproductive systems *(20)*. The importance of GH in testicular development is further demonstrated by the ability of exogenous GH to promote testicular growth and function in mice and hamsters with inherited or experimentally induced GH deficiency *(21,22)* and in mice transgenically expressing the GH or GHRH gene *(23,24)*. Salmon GH also prevents the hypophysectomy-induced decrease in gonadal weight in killifish *(25)*. However, because insulin-like growth factor-1 (IGF-1) transiently normalizes testis size

Table 1
Involvement of (IGF-1) in Reproductive Actions of GH

GH Action	Reference
Dependent on local IGF-1	
Testosterone synthesis, in vivo, human	*19*
Wolffian duct differentiation, male mouse	*15*
Androgen binding protein/hydrolytic enzyme synthesis, rat prostate	*95*
Penile growth, human males	*19*
Aromatase activity, fish testis	*114*
Independent of IGF-1	
Androgen synthesis, rat Leydig Cells	*60*
Androgen synthesis, rat thecal-interstitial cells	*115*
Steroidogenic enzyme activity, fish testis	*114*
Hydrolytic enzyme synthesis, rat prostate	*104*

in GH-resistant males *(19)*, hepatic or local IGF-1 may mediate this effect (Table 1). Indeed, Bartke *(26)* concluded from a comparison of the GHR and IGF-1 knockout mice that IGF-2 was an absolute requirement for male reproductive development and function, although maternal IGF-I, transmitted via the placenta or the milk, could be sufficient for normal development in the absence of locally produced IGF-1.

Gametogenesis

The possibility that GH may affect male reproductive function was considered as early as 1963 by Boccabella *(27)*, who suggested that GH may stimulate rat spermatogenesis. Although Spiteri-Grech and Nieschlag *(17)* concluded that GH had a minor role in spermatogenesis, more recent studies suggest a strong link between GH and male fertility *(28)*. For instance, sperm motility is impaired in GH-deficient rats and mice and restored by GH administration *(29–31)*. Sperm number and morphology are also reduced by GH deficiency and restored by GH administration in some *(16,29,31)* but not all *(18,30)* studies of GH-deficient rodents. The reduced sperm count may reflect an obligatory role for GH in spermatogenesis and/or spermiogenesis. Kuroda *(32)* observed decreased numbers of mature sperm but normal levels of spermatids in GH-deficient rodents; thus, GH may be affecting final maturation (spermiogenesis) rather than spermatogenesis. However, Matsushima et al. *(16)* noted smaller numbers of spermatogonia, spermatocytes, spermatids, and spermatozoa in GH-deficient rodents.

GH deficiency may also account for the impaired spermatogenesis in some cohorts of infertile men. GH resistance (e.g., Laron syndrome) is associated with impaired fertility *(6)*. Relative GH deficiency may also impair some aspects of spermatogenesis. For instance, in a study by Shimonovitz et al. (*33*), 91% of azoospermic men but only 18% of oligozoospermic men were GH deficient, as determined by the clonidine test. GH may thus be involved in maturation arrest, especially since other studies have also shown that men with severe idiopathic oligozoospermia and azoospermia are GH replete and do not respond to GH therapy *(34,35)*. The many causes of male infertility may account for discrepant reports about the efficacy of GH as a therapeutic adjunct in infertility therapy, because GH effectively increases sperm concentration and/or motility in males resistant to other forms of fertility treatment in some *(36–38)*, but not all *(39)*, clinical studies with infertile patients. Indeed, GH has been shown to rapidly induce spermatogenesis in some infertile males (within 12 wk) with surprisingly small testicular volumes *(40)*, probably by increasing Leydig and Sertoli cell differentiation.

Correlative studies also suggest a role for GH in piscine spermatogenesis, although the direct spermatogenic effects of GH have not been demonstrated. For instance, GH levels are substantially increased in the final stages of the reproductive cycle in male goldfish *(41)* and trout *(42)*. GH-binding activity in the testis and liver of the trout also show opposite, cyclical changes in abundance during the spermatogenic cycle *(43)*, in concert with changes in blood GH concentrations. GH gene polymorphisms in bulls have also been correlated with sperm production and sperm motility *(44)*. GH may thus play an important role in spermatogenesis and spermiogenesis.

The gametogenic actions of GH may be direct or mediated by IGFs (Fig. 1). However, because hepatic IGF-1 is unlikely to cross the blood-testis barrier, the gametogenic actions of GH may be mediated by gonadal IGF-1 (Table 1). Accordingly, a role for gonadal IGF-1 in gametogenesis is suggested by the coordinate increases in seminal IGF-1 and sperm motility in GH-treated infertile men *(45)* or dwarf rats *(30,46)*. Other studies in men, however, have observed that seminal IGF-1 concentration is correlated with sperm morphology but not with sperm motility *(47)* or concentration *(46)*. Furthermore, in contrast to GH, IGF-1 directly inhibits several indices of sperm motility (curvilinear velocity and amplitude of lateral head movement) *(48)*, and systemic IGF-1 improves sperm morphology but not

motility *(46)*. It thus appears likely that GH affects sperm motility directly, or by actions mediated through Sertoli cells independently of IGF-1.

The gametogenic actions of GH are likely to reflect a physiologic role; however, GH may impair fertility at pharmacologic or pathophysiologic concentrations. The transgenic expression of the GH gene, for example, has been correlated with a suppression of testicular development and function in boars and rams *(49,50)*. Reproductive performance is also greatly reduced in mice transgenically expressing heterologous GH genes *(51–53)*. Common dysfunctions include male sterility and early onset of infertility *(20,52,54,55)* as well as inability to inseminate or impregnate females (*56*). Exogenous GH at doses 5- to 12-fold those used to treat GH-deficient children have also been shown to cause anatomical and functional damage in dogs *(57,58)*. The treatment of GH-deficient children with exogenous GH has also been correlated with impaired testicular function *(59)*. Male fertility may therefore be improved or impaired by GH in a dose-related manner.

Steroidogenesis

GH may alter gametogenesis by affecting testosterone synthesis, because testosterone is necessary for sperm production (Fig. 1). This possibility is supported by the presence of GHR mRNA in purified progenitor, immature, and adult rat Leydig cells *(60)* as well as by the attenuated testosterone secretion in GH-resistant mice *(61)*. Indeed, gonadotropin-induced testosterone levels and sperm count are enhanced by GH in males with hypogonadotropic hypogonadism *(62)*. GH therapy in GH-deficient males also augments the testosterone response to human chorionic gonadotropin (*12,37,63*), increases plasma estradiol levels *(64)*, and increases the abundance of gonadotropic binding sites. The steroidogenic action of GH may thus reflect its induction of testicular luteinizing hormone (LH) receptors, especially as GH increases testicular LH receptors in GH-deficient dwarf mice *(65)*, rats *(66)*, and golden hamsters *(22)*.

Salmon GH similarly increases testosterone and 11-ketosterone production by isolated fish testes in vitro *(25)*. GH may act at early stages of testosterone synthesis, because GH enhances pregnenalone production in male rats *(67)* and 17-α-20-β dihydroprogesterone synthesis in cultured fish testicular cells, independently of gonadotrophins (*68*). The coordinate increase in plasma GH and 17-α-20-β dihydroprogesterone in fish during spermatogenesis also suggests a direct, causal relationship, since 17-α-20-β dihydroprogesterone production and its induction of spermiation are gonadotropin independent (*69*).

The steroidogenic action of GH, however, may be mediated through IGF-1, because subphysiologic concentrations of IGF-1 can also induce steroidogenesis in rat testis *(70)*. This possibility is also suggested by the ability of systemic IGF-1 to partially reverse the relative testosterone deficiency caused by GH resistance in humans *(19)*. Alternatively, local IGF-1 production may mediate the testicular effects of GH, although testicular IGF-1 responds poorly to systemic GH in rats *(71)*.

The putative steroidogenic action of GH could involve hepatic/local IGF-1 modulation, although in vitro studies suggest an IGF-1-independent role for GH in Leydig cell function (Table 1). For instance, Kanzaki and Morris *(60)* have shown that GH increases androgen (testosterone and 3-diol) synthesis within 3 h in rat progenitor Leydig cells (PLCs). GH is thought to exert its effect at initial rate-limiting steps in the steroidogenic synthetic pathway, because steroidogenic acute regulatory protein (StAR) (which regulates the translocation of cholesterol to the inner mitochondrial membrane) and 3β-hydroxysteroid dehydrogenase (3βHSD) (which converts pregnenalone into progesterone) mRNA were also increased in Kanzaki and Morris's study *(60)*. These steroidogenic enzymes, however, are thought to be activated by GH via two different signaling mechanisms. The effect of GH on StAR abundance is mediated by a serine/threonine kinase, not a tyrosine kinase, and is independent of *de novo* protein synthesis (and thus IGF-1 synthesis), whereas GH-induced 3βHSD production is blocked by tyrosine kinase inhibitors and protein synthesis blockers and mediated by a different (perhaps IGF-1–dependent) pathway. Adult Leydig cells are also sensitive to GH, albeit to a lesser extent *(60)*. The degree of GH responsiveness may be linked to GHR abundance, because GHR mRNA is more abundant in progenitor Leydig cells than in immature or adult Leydig cells *(60)*. However, GH only stimulates STAT5 activation in progenitor and immature Leydig cells *(72)*. Thus, GH may induce early Leydig cell differentiation and therefore steroid production by a STAT-5-dependent mechanism, and may additionally influence steroidogenic enzymes in a STAT-5-independent manner.

Testicular Minihypophysis

The testes are highly vascularized, and many of the testicular actions of exogenous GH are likely to reflect the endocrine actions of pituitary GH (Fig. 1). The blood-testis barrier, however, does suggest that some of the steroidogenic actions of GH in Sertoli cells and its roles in gametogenesis may reflect the actions of GH produced locally. Indeed, although the male reproductive system is a site of GH action, it is also a site of GH synthesis and autocrine and paracrine mechanisms may mediate some GH effects on testicular function (Fig. 1) . The presence of GH within the rat testis, for example, has been demonstrated by immunocytochemistry *(15)*. GH gene transcripts are also present in the human testis *(73,74)*, although the cellular location is still unknown. Moreover, while the pituitary (GH-N) gene is expressed *(75)*, the GH variant (GH-V) gene is preferentially transcribed, since GH-V splice variants (including membrane-bound GH-V2 and GH-V4)

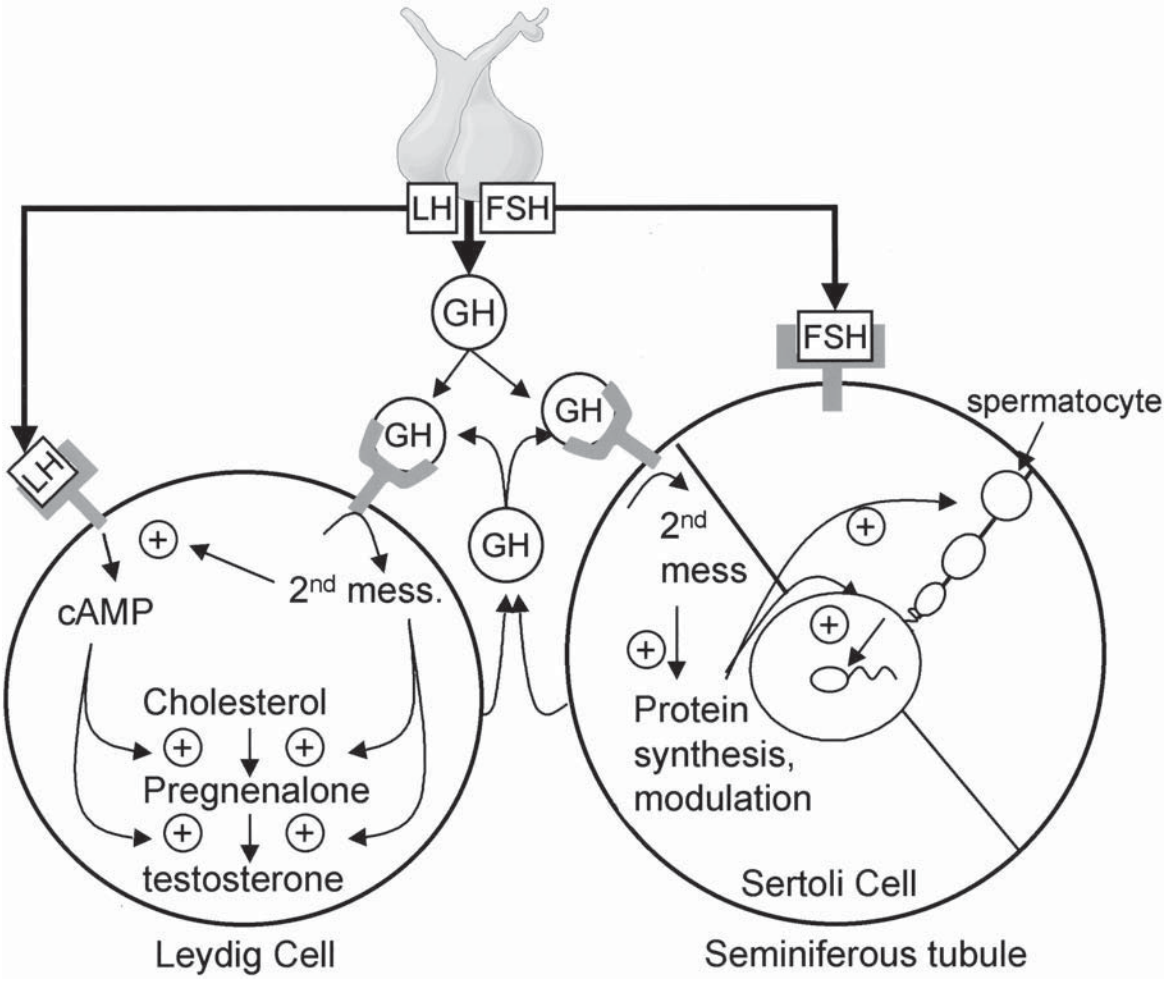

Fig. 1. Role of GH in testicular function. Steroidogenesis in Leydig cells and gametogenesis in seminiferous tubules are primarily regulated by LH and FSH, respectively. However, pituitary GH and/or testicular GH binds Leydig GHRs, activates second messenger systems, and stimulates (+) the activity of several steroidogenic enzymes directly and by increasing LH receptor abundance. Pituitary and/or gonadal GH similarly alters gametogenesis in seminiferous tubules by binding GHRs on Sertoli cells and increasing the synthesis and/or modification of proteins such as IGF-1, IGF-binding proteins, and androgen-binding protein. These products subsequently mediate the stimulatory effects of GH on the conversion of spermatogonia into spermatocytes, spermatocytes into spermatids, and spermatids into motile spermatozoa. Endocrine GH from the pituitary glands may be involved in the strategic maintenance of male reproduction, whereas testicular GH may be involved in emergency modulation of testicular function. Some of the testicular actions of GH are modulated by testicular IGF-1 (not shown; Table 1).

are more abundant than GH-N mRNA in the human testis *(73,74,76)*. The presence of GH-V transcripts in the human testis is also correlated with normal testicular function, because they are lost with the development of testicular tumors *(77)*. The presence of GH in the male reproductive tract occurs during early fetal development in the rat (*15*) and in early chick embryogenesis *(78)*, and in both species it is widespread in wolffian duct cells.

The synthesis of GH in the testis, as in the pituitary, may be regulated by "hypothalamic" GH-regulating hormones, because a minihypothalamic-hypophyseal axis is present in the male reproductive tract. Thus, GHRH mRNA and peptide are present in the human *(79–81)* and rat *(82,83)* testis, in both Sertoli and Leydig cells, and the SRIF peptide is present in rat testis *(84)*. However, the gene sequence and high-performance liquid chromatography characteristics of rat and human testicular GHRH resemble placental GHRH to a greater extent than hypothalamic GHRH *(79,85–87)*. Testicular and hypothalamic GHRH are also discordantly regulated by diabetes *(88)*. Nevertheless, testicular and hypothalamic GHRH are equally effective at inducing pituitary GH production *(79)* and stimulating adenylate cyclase in Sertoli cells *(89)* in rats. However, testicular GHRH levels are not associated with testicular IGF-1 activity in rats *(79)*; thus, the involvement of testicular GHRH and IGF-1 in the production of testicular GH is uncertain. Indeed, Matsubara et al. *(90)* failed to detect GHRH receptor mRNA in the rat testis, although GHRH receptor mRNA, GHRH-binding, and GH-induced gene expression were observed in other studies *(82,91,92)*.

Table 2
GHBP Immunoreactivity and GH-binding Sites in Male Reproductive Tract

Tissue	Species	GHR/GHBP-IR (reference)[a]
Testis	Fetal rat	(*93*)
	Fish	(*96*)*[b]
Leydig cells	Rat	(*94*)
	Rat	(*60*)
	Fish	(*43*)
Sertoli cells	Rat	(*94*)
Spermatozoa precursors	Rat	(*94*)
Spermatozoa	Rat	(*94*)[c]
Ureter	Fetal rat	(*93*)
Seminal vesicles	Rat	(*94*)
	Fetal rat	(*93*)
Vas deferens	Rat	(*94*)
	Fetal rat	(*93*)
Epididymis	Rat	(*94*)
	Fetal rat	(*93*)
Coagulating gland	Rat	(*94*)
Bulbourethral gland	Rat	(*94*)
Prostate	Rat	(*94*)

[a]GHR, growth hormone receptor; GHBP, growth hormone–binding protein; IR, immunoreactivity.
[b]GH-binding sites, rather than GHR immunoreactivity.
[c] Not detected.

The possibility that testicular GH may act locally to affect reproductive function directly or indirectly is supported by the distribution of GHR in the male reproductive tract (Table 2). For instance, GHR immunoreactivity is abundantly present in the wolffian/müllerian duct, ureter, epididymis, vas deferens, seminal vesicles, and gonads of the fetal rat *(93)*. GHR immunoreactivity and/or GHR mRNA is similarly widespread in adult rat reproductive tissues, including the vas deferens, epididymis, prostate gland and prostatic tumors, Leydig cells and Sertoli cells, and, to a lesser extent, spermatozoa precursors in the seminiferous tubules *(60,94,95)*. This immunoreactivity probably corresponds to bioactive receptors, because high-affinity somatogenic GH receptors are present in the trout testis *(96)*, in Sertoli cells rather than germ cells *(43)*, and GH activates STAT5b (a signaling molecule) in rat Leydig cells *(72)*. Testicular GH receptors appear to play an important role in gametogenesis, at least in fish, because they are differentially regulated in comparison with their hepatic counterparts. The abundance of GH-binding sites in fish testis peaks in the immature testis and decreases throughout spermatogenesis, whereas hepatic GH-binding activity peaks during the early stages of spermatogenesis and is not correlated with testicular levels *(43)*. These receptors may affect reproductive function via local IGF-1 production, because IGF-1 immunoreactivity *(97)*, mRNA *(98)*, and receptors *(99)* are also found in rat testicular cells. Indeed, GHR immunoreactivity in the rat testis is colocalized with IGF-1, and systemic GH increases IGF-1 immunoreactivity and IGF-1 levels in epididymal and seminal vesicle fluids *(46)*. Testicular IGF-1 in rodents, however, is also regulated by pituitary gonadotropins *(71,100)*.

Extratesticular Effects

Autocrine, paracrine, and possibly endocrine actions of GH have been implicated in the development and subsequent function of wolffian duct–derived structures such as the prostate and seminal vesicles. Nguyen et al. *(15)* demonstrated that GH antiserum blocks differentiation of the Wolffian duct in male fetal mice, whereas GH administration restores normal differentiation. Exogenous GH also stabilizes the Wolffian duct in female fetuses in vitro *(15)*. The paucity of prenatal pituitary GH production and the detection of GH and GHR immunoreactivity in the fetal mouse reproductive tract would suggest that local, rather than pituitary, GH is mediating this effect *(15)*. GH-induced differentiation is also associated with increased androgen-binding protein levels and can be mimicked by IGF-1. Locally produced GH may thus stimulate local IGF-1, and IGF-1 may enable adequate androgen-binding protein levels to permit testosterone-induced differentiation of the Wolffian duct.

Postnatal function of wolffian-derived structures may be similarly controlled by local and/or systemic GH. For

instance, GH administration stimulates hydrolytic enzyme activity or androgen-binding protein levels in the prostate and seminal vesicle or prostate, respectively *(95)*, and expression of the bGH transgene increases hydrolytic enzyme synthesis and prostate size *(101)*. The weights of the testes and seminal vesicles are similarly increased in male mice transgenically overexpressing the GHRH gene *(23)*.

The effect of GH on the prostate appears to be mediated by local IGF-1, because GH stimulates androgen receptor, IGF-1, and IGF-1 receptor levels in the prostate and GH-binding activity is abundantly present in rats *(94,95)*. The GH-IGF dependence of the prostate and seminal vesicles is also demonstrated by the reduction in the size of these accessory reproductive tissues in GH antagonist transgenic mice *(102)*; in GH-receptor knockout mice, in which circulating IGF-1 levels are suppressed *(61)*; and in IGF-1 gene knockout mice *(103)*. Moreover, GH does not stimulate prostatic growth in IGF-1 null animals *(102)*. However, GH also acts independently of IGF-1, because IGF-1 can mimic the effect of GH on some, but not all, prostatic enzymes in rats *(104,105)* (Table 1). GH and IGF-1 have also been implicated in the development of prostate cancer, because GHR and GH-binding protein transcripts are expressed at higher levels in human and rat prostate tumor cell lines than in normal prostate tissue *(104,105)*.

GH may also be necessary for normal penile development, because congenital GH deficiency or resistance in humans is associated with micropenis, despite normal androgen levels *(5,106,107)*. Moreover, replacement therapy with GH can normalize penis size in GH-deficient boys *(108)*. Changes in IGF-1 are likely involved, because IGF-1 treatment of Laron syndrome in boys and men shows an increase in penile size, which reverses following cessation of treatment *(19)*. Contraction of the corpus callosum is also stimulated by GH administration in dogs *(109)*, which may be responsible for acromegaly-induced erectile dysfunction *(110)*. The pathophysiologic elevation of circulating GH levels in acromegalics is also associated with a loss of libido *(110)*, which may indicate that GH normally modulates some reproductive behaviors at central sites. In addition, the transgenic expression of the GH gene reduces libido in boars *(49)*.

However, GH deficiency syndromes may also result in a loss of sexual desire or erection in human patients *(111)*, although impotence in diabetic patients is not mediated by abnormalities in serum GH level *(112)*. A reduction in copulatory behavior and an increase in the interval between matings, however, is a characteristic of male GHR-knockout mice *(26)*.

The actions of GH on male reproductive function may involve actions at hepatic sites that feminize the metabolism of gonadal steroids. For instance, GH reduces 3-hydroxysteroid dehydrogenase and 3 β-hydroxysteroid activity in rat liver, whereas it increase 5-reductase activity and reduces the 2-hydroxylation of estrogen to catecholestrogen *(113)*.

Conclusion

Although GH is traditionally associated with growth, it also has roles in sexual differentiation, puberty, gonadal steroidogenesis, gametogenesis, and sexual behavior. In addition to being a somatotropin, it is therefore a gonadotropin, integrally involved in male reproduction.

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