Chapter 6

Growth Hormone and Insulin-like Growth Factor-I: Novel Insights into the Male Reproductive Health

Mayank Choubey

Additional information is available at the end of the chapter

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Abstract

The roles of growth hormone (GH) in male reproductive health are summarized in this chapter. It has been evident in several studies that GH plays a vital physiological role in the regulation of male reproductive development and function, while the excessive release of GH can interfere with male reproductive health, sexual behavior, and fertility potentials. Several classical functions of GH include cellular proliferation, differentiation, development, and metabolism, although vast literature specifies their role in reproductive function in both humans and animals. Moreover, evidence from several studies have suggested both deficiency and overproduction of GH in adults are associated with several pathophysiological conditions, viz., metabolic derangements, central adiposity, dyslipidemia, and insulin resistance. The GH exerts its beneficial role by binding and activation to GH-receptors (GH-Rs), expressed at several target tissues, viz., in the hypothalamus and other parts of the central nervous system, and in the male gonad (testis), including Leydig and Sertoli cells. The GH may reflect either by local autocrine or paracrine actions or by the endocrine actions. The release of certain GH such as insulin-like growth factor 1 (IGF-1) plays a crucial role in the regulation of male reproductive physiology, while the excessive release of GH can interfere with male sexual behavior and fertility.

Keywords: growth hormone, IGF-1, male reproductive health, testicular metabolism, spermatogenesis, steroidogenesis

1. Introduction

Reproduction is the most essential process for any species to sustain its population. The reproductive health issues along with the infertility problems are observed very frequently nowadays. Approximately, 15% of all the couples trying to conceive are recognized as infertile,

and the male partners are found to be solely responsible for half of all the cases of global childlessness [1]. In the recent time span, circa 20 years, the empirical developments have proved that several hypothalamic and pituitary hormones, including gonadotropin-releasing hormone (GnRH), growth hormone-releasing hormone (GH-RH), gonadotropins, and growth hormone (GH) and their corresponding canonic receptors, are ubiquitously and differentially expressed having diversity of biological functions [2]. There are myriad evidences showing that these vital endocrine hormones are also expressed in extra-hypothalamic and extra-pituitary tissues and are engaged in local synthesis and action, encompassing explicit effects on reproductive growth, cellular proliferation and survival, tissue repair, immunomodulation, cellular energy homeostasis and metabolism, antioxidative functions, and neuroregeneration [3–6]. It is manifested that GH synthesis is mainly through the pituitary somatotropes and is secreted as an endocrine hormone that regulates cellular growth and differentiation during testicular development [7]. Postnatally, GH pulsatile release is required as a homeostatic factor that in many tissues is indispensable for cellular proliferation and differentiation as well as the maintenance of their metabolic actions. The GH exerts its beneficial actions either by binding and activation to GH-receptors (GH-Rs), expressed at several target tissues, viz., in the hypothalamus and other parts of the central nervous system [8], and in the male gonad (testis), including Leydig and Sertoli cells [9]. As a pituitary endocrine hormone, growth hormone has cardinal roles in accentuating reproductive growth in individuals with GH deficiency [10]. Growth hormone deficiency (GHD) happens to be the most recurrent endocrinological abnormality, followed by gonadotropin, TSH, and ACTH deficiencies [11].

2. GH actions on the hypothalamic-pituitary-testicular (HPT) axis and male reproductive physiology

Gonadotropin-releasing hormone is considered to be the primary regulator of the male reproductive system, specifically controlling the pulsatile secretion of gonadotropins, i.e., luteinizing hormone (LH) and follicle-stimulating hormone (FSH) that are essential factors for proper gonadal activity [12]. Biosynthesis and release of GnRH are under complex excitatory and inhibitory control by a number of neurotransmitters and neurotrophic factors [13]. In addition, there are a number of autocrine/paracrine factors, including GH and insulin-like growth factor-1 (IGF-1), which can also modify the GnRH synthesis and action on the pituitary gonadotrophs, thereby influencing gonadal activity [10]. Here, we have attempted to summarize the influential evidence of GH/IGF-1 on male reproductive physiology and reproductive health. Although the central role of GH in growth and development is very well established in various tissues, GH's influence on male reproductive functions is poorly understood and requires thorough investigation.

2.1. Impact of GH on testicular growth, development, and pubertal maturation

Puberty is the multifaceted process through which children mature and develop secondary sexual characteristics and acquires reproductive competence. Normally pubertal transition is

initiated through central mechanisms, with the gonadal function being driven by increased GnRH and gonadotropin secretion. Additionally, adequate energy supply and nutritional balance appear to be requisite for the central initiation of pubertal transition. At the testicular level, the GH promotes the growth and development of the gonad, in childhood and puberty, and stimulation of gametogenesis and production of steroid hormones, in puberty and reproductively mature period. The rate of GH synthesis doubles and attains a maximum peak during the pubertal maturation, and the production rate decreases with advancing age [14]. This mechanism is also supported by the IGF-1 produced in response to circulating GH levels. This is corroborated by studies that have shown the decrease in testicular volume in patients with childhood-onset growth hormone deficiency (CO-GHD) and the consequent increase in the same patients treated with replacement doses of GH [15]. GH also promotes the development and differentiation of internal testicular morphology such as seminiferous tubules (ST). In mammals, GH plays an imperative role to maintain normal sexual maturation, because puberty is deferred in GH-deficient [16, 17] or GH-resistant [15] humans. Analogously GH deficiency in rodents is associated with delayed sexual maturation [7, 18], and GnRH immunoneutralization delays sexual maturation in rats and reduces testicular mass, spermatogenesis, and follicle-stimulating hormone responsiveness [19]. The ability of GH to advance the pubertal maturation in GH-deficient children [20–23] and in GH-replete normal male rats [24] further illustrates the importance of GH in pubertal development. In some species, GH acts directly on androgen action, thereby accelerating the pubertal transition, because GH reduces the amount of testosterone required to induce secondary sexual characteristics (axillary hair) in young individuals [25].

2.2. Actions of GH on germ cell proliferation, survival, spermatogenesis, and sperm parameters

The impact of GH on testicular growth consequently influences the proliferation of germ cells. It is specifically an intricate point as it is a balance mechanism, whereby a decline in the levels of GH would lead to a simultaneous decrease in sperm count, semen volume, and sperm motility, respectively. It has been shown that surplus GH exerts the same consequences [24, 26, 27], highlighting the importance of the correct dosage of feasible therapies. Local IGF-1 may imitate GH effects on germ cells since sperm motility and morphology are recorded to be improved due to IGF-1 production. Receptors for IGF-1 are revealed in more mature haploid cells of spermatogenesis, i.e., secondary spermatocytes, spermatids, and spermatozoa as well. However, in some studies, the testicular level functions of these two entities have emphatically displayed antagonistic effects. Still, GH can act independently of IGF-1 [28]. These results illustrate the co-localization of GH and GH-RH in chicken testis and stimulatory function of GH-RH in testicular GH secretion along with a proliferation of testicular cells.

Beginning with the onset of puberty, spermatogenesis continues throughout the reproductively active periods in males. It is a highly complicated and conserved process, basically under the control of the HPG axis and intratesticular factors produced by Leydig and Sertoli cells. The hypothalamic decapeptide GnRH participates in the synthesis and release of gonadotropins, LH, and FSH into circulation by stimulating the anterior pituitary. Subsequently, these

gonadotropins bind with their specific receptors, present/positioned on Leydig and Sertoli cells, leading to prompt production of steroids and other intratesticular factors required for spermatogenesis. With the aid of cell-to-cell signaling, these intratesticular factors regulate germ cell proliferation, survival, and apoptosis-inducing production of high-quality spermatozoa. A study conducted on the chicken elucidated the co-localization of GH and GH-RH in the testis and stimulatory roles of GH-RH in testicular GH secretion and in the proliferation of testicular cells. As a primal finding, testicular GH itself promotes testicular proliferation paving a definitive reason for proliferative action of GH-RH which is likely to be mediated through the autocrine/paracrine induction of GH secretion.

Improvement of sperm morphology and motility in GH-deficient dw/dw rats [29] and prolonged overall equine spermatozoa motility in vitro also hinges upon the GH, obtained possibly by extending sperm longevity [30]. Moreover, copious indicators of sperm quantity and quality in bulls are associated with GH gene polymorphisms [31]. Gametogenesis is similarly boosted up by GH in vitro cultures of eel testicular cells [28].

The spermatogenic actions of GH may be mediated by local IGF-I production since it can also revamp sperm motility and morphology [29], and GH coordinately augments IGF-I production in seminal vesicle and sperm motility [32]. However, few reports exhibit discordant effects of both GH and IGF-I [33], suggesting that GH may act exclusively of IGF-I. Similarly, the stimulatory effect of GH on eel spermatogenesis is not dependent on IGF-I and steroid [28].

The diminished, but not abolished, fertility in GH-resistant men and GH-deficient rodents [17, 19, 34] suggest that a low degree of fertility is felicitated by enough GH-independent local testicular IGF-I production. This phenomenon in chickens rather appears to be at an acceptable level to completely restore fertility parameters, since seminal IGF-I concentrations, sperm motility, morphology, viability, and fertility do not fluctuate between GH-resistant and GH-replete chickens [35].

2.3. Actions of GH in the modulation of testicular steroidogenesis

Steroidogenesis entails multistep processes that are enzyme-mediated and responsible for converting cholesterol into a biologically active steroid hormone. Regarding the hormonal feature of testicular function, GH is a potent steroidogenic factor, particularly in vitro. GH stimulates the production of androgen and/or estradiol by Leydig cells, isolated from rodents, ruminants, humans, and fish [7, 36], but not horses [37]. The results of in vivo studies are more contentious. While chronic GH therapy improves chorionic gonadotropin-induced testosterone production, some studies of fertile GH-deficient males [24, 38] and the testosterone response to hCG delineate attenuation in GH-R knockout mice [39]. Apparently, GH treatment in hypopituitary or moderately obese men actually decreases the concentrations of total serum testosterone [36, 37], potentially due to a stimulatory effect on aromatase activity and the resulting conversion of testosterone to estradiol observed in healthy young men treated with GH [40].

The reports from in vitro study demonstrate multifarious actions of GH, viz., alteration in the activity of enzymes involved in the steroidogenic pathway; stimulation of steroidogenic

acute regulatory protein (StAR) production, which mediates cholesterol translocation across the inner mitochondrial membrane; and 3β-hydroxysteroid dehydrogenase (3β-HSD), which further converts pregnenolone into progesterone [18], in Leydig cell precursors of rodents. Similarly, GH upregulates the formation of early steroidogenic intermediates, such as 17-α 20-β dihydroprogesterone in testicular cells of fishes [41].

The gonadotrophic actions of GH may potentiate testicular steroidogenesis by promoting testicular LH sensitivity and enhancing Leydig cell proliferation and development, as GH-R knockout mice may be scarce in Leydig cells and LH receptors [39]. Similarly, GH is responsible for upregulation of LH receptors both in GH-replete (as in hamsters [42]) and GH-deficient (as in dwarf mice [43]) animals.

The bioavailability of free testosterone is curtailed because of the sex hormone-binding globulin (SHBG). Some studies corroborate that GH may potentiate testosterone activity by decreasing SHBG production. For instance, GH therapy minimizes SHBG levels in GH-deficient adults in some [37, 44], but not all [45] studies, and in hypopituitary adolescents [46]. Since the age-related decrease in SHBG concentration is not observed in GHD adolescents [47], therefore the pubertal rise in GH production may potentiate the male pubertal development.

However, ancillary studies in normal men reveal a coordinated decrease in sex hormone-binding globulin and total serum testosterone production following GH treatment [36], reduced SHBG but unaltered total serum testosterone [48], or increased LH-induced testosterone but unaltered SHBG [38]. These incongruities may reflect differences in subject age and GH administration protocol.

Some investigators have identified the importance of IGF-I in the steroidogenic actions of GH. IGF-I can imitate the effects of GH in rat testis [49] and partially reinstate testosterone synthesis in GH-resistant men [50]. Moreover, in another study conducted on rodents, GH-induced steroidogenesis required IGF-I co-administration [51]. However, de novo protein synthesis is redundant for GH-induced StAR synthesis, suggesting that at least a few testicular actions are IGF-I independent [18].

The earlier study observed a spontaneous correlation between testicular GH-R expression and StAR and p450 expression following exposure to nanoparticle-rich diesel exhaust (NR-DE) in rats [52]. However, much research work remains to be performed in order to identify a causal relationship between GH and pollutant-induced androgenesis.

2.4. Role of GH and IGF-I on the physiology of penile growth and erection

GH availability is imperative for penile growth since GH deficiency and GH resistance are frequently associated with micropenis and other penal anomalies [53]. Therefore, GH therapy improves penile growth in GH-deficient adolescents [54, 55]. IGF-I may mediate this very effect, since IGF-I administration to GH-resistant adolescents augments penile size, and this effect ceases when IGF-I therapy is withdrawn [50]. Similarly, in a study conducted on cultured postnatal foreskin fibroblasts cells, a stimulatory effect of IGF-I (but not GH) on the cellular proliferation of fibroblast was observed, independent to any changes in androgen

receptors or 5-alpha reductase activity [55], whereas a more recent study, again conducted on fibroblast, noticed significant cellular growth and proliferation as a result of stimulatory effects of GH that was at least partially mediated by local IGF-I [56].

Contrarily, the erectile dysfunction may be due to altered autocrine/paracrine actions of GH, as erection requires relaxation of penile smooth muscle and modulation of blood flow. GH may facilitate both smooth muscle relaxation and systemic vasoconstriction. During penile tumescence in healthy men or men with psychogenic erectile dysfunction, the GH concentration in systemic and cavernous blood increases, but it is not so in the case of sexually aroused patients with organogenic erectile dysfunction [57–59]. An earlier study, conversely, did not observe any variations in systemic GH concentrations during sexual arousal and orgasm [60].

By stimulating the expression of neuronal nitric oxide synthase (nNOS) in intracavernosal nerves, GH is found to improve the erection frequency and maximal intracavernous pressure in aged rats [61, 62]. Next in order, GH also improves the regeneration of nNOS-expressing nerves following cavernous nerve neurotomy, accelerating the resumption of erectile function [63, 64]. This regenerative effect may involve local IGF-I and transforming growth factor beta-2 (TGF-β2), both of which were increased as a result of GH stimulation [65]. NOS may mediate important GH effects in humans, since GH, nitric oxide (NO), and cyclic guanosine monophosphate (cGMP) share a robust nexus in systemic and cavernous blood of individuals with erectile dysfunction [60]. GH also induces both relaxation and cGMP production in human cavernous strips [66]. However, a later study indicated that GH improves cGMP signaling in human corpora cavernosa (isolated from transsexual patients receiving hormonal therapy) independently of (NO) [67].

Since the pathophysiological GH concentrations in acromegalics are associated with erectile dysfunction, erectile effects of GH may be biphasic [68]. As libido is impaired in acromegalics [68] and boar's transgenic for the GH gene [69–72] as well as in GH-deficient males [73] and GH-R-knockout mice [74], the biphasic effects of GH on erectile function may partially reflect altered libido. Also, GH at optimum concentrations present in acromegalics stimulates contraction of dog corpus callosum strips [69].

2.5. Impact of GH/Insulin/IGF-1 signaling in the regulation of testicular metabolic and energy status

The GH stimulates the production of a family of proteins, viz., IGFs in several extrahepatic tissues including testis [75]. The IGFs composed predominantly of insulin, IGF1, IGF2, and their respective canonic receptors which upon activation provide signals to regulate a variety of cellular activities including cellular survival, proliferation, differentiation, and cellular metabolism [76, 77]. Importantly, testicular IGF-1 exerts its beneficial role by binding with its respective receptor and simultaneously activating it, in an autocrine/paracrine manner, and hence contributes to the maintenance of normal male reproductive physiology. Moreover, the earlier study utilizing IGF-1 null male mice showed infertile dwarf characteristics and also exhibit a reduction in both spermatogenic activity and serum levels of testosterone by ~80% [78]. This not only suggests the primary importance of GH/insulin/IGF signaling in body growth and development but also highlights its critical role in male reproductive health (**Figure 1**).

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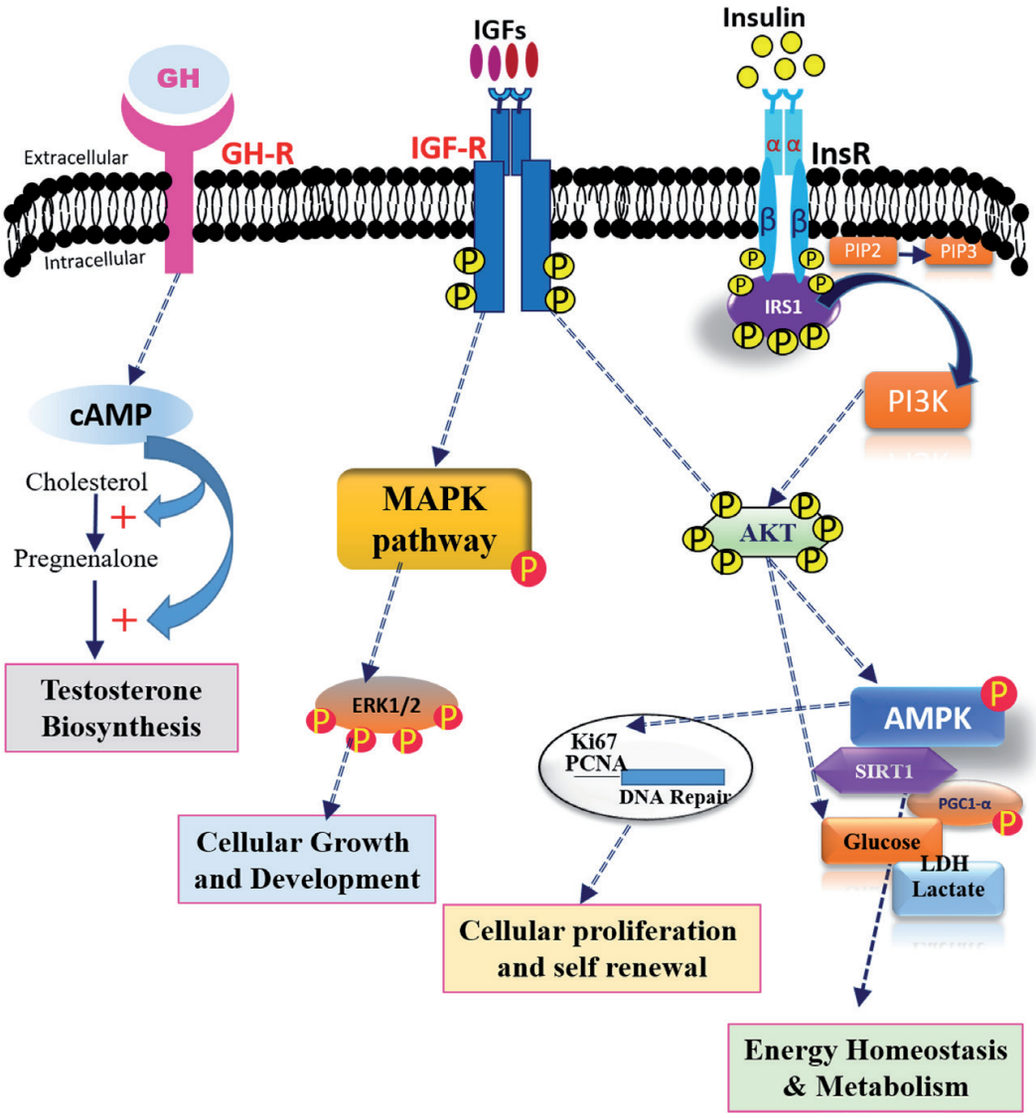

Figure 1. A schematic representation of GH/insulin/IGF signaling in the testicular axis. Both centrally (pituitary) and locally (testicular) secreted GH binds to the GH-receptors (GH-Rs) expressed in the Leydig cell and directly activates, releases secondary messenger i.e. cyclic adenosine monophosphate (cAMP), and stimulates (+) the activity of various steroidogenic enzymes (viz., StAR, p450scc, and 3β-HSD). Also it enhances the expression and abundance of luteinizing hormone receptor (LH-R) in the testis. The insulin/IGF1 signaling is mediated by a multifaceted, highly integrated network that regulates various crucial physiological processes. Two major signaling pathways are triggered by insulin/IGF1 activation, the ERK/MAPK pathway, and the ATK/PI3K/GLUT8 pathway, which are involved in numerous cellular processes such as cellular metabolism, cellular growth and proliferation, and self-renewal process of spermatogenic cells. Activation of the InsR/IGF-R signaling by insulin/IGF1/2 binding, respectively, leads to InsR (β subunits) as well as receptor tyrosine kinase phosphorylation, and this subsequently phosphorylates IRS proteins on their tyrosine residues, thereby activating the AKT/PI3K/GLUTs pathway. It is mainly responsible for the metabolic actions of insulin/IGF1 signaling (which activates the ERK/MAPK pathway and primarily regulates a variety of different downstream biological effects including mitogenesis, gene expression, and energy homeostasis by glucose and lactate transport to the developing germ cells).

Interestingly, GH-induced insulin/IGF family of growth factors activates glucose transporter 8 (GLUT8) which helps in chronological conversion of glucose into lactate by mature Sertoli cells [79, 80]. Notably, lactate is a preferred energy metabolite serving the energy requirement for proper testicular functioning and development of spermatogenic cells [81–83]. Also, the

lactate production increases, as the Sertoli cell differentiates during pubertal development. It has been reported that the concentrations of lactate are low in the testes of the cryptorchid rat and intratesticular supplementation of lactate into the rats improves the development of haploid spermatozoa [84].

3. Therapeutic potentials of GH on reproductive health and male infertility

Male subfertility/infertility is a grave problem in the field of reproductive medicine. The growth hormone contributes to the restoration of sperm concentration, morphology, and motility in GH-deficient rats [85] and in men as well. The conventional remedy encompassing gonadotropin or pulsatile LH therapy may at times fail to generate the desired response. GH therapy proves to be a non-conventional adjuvant therapy which can be used to induce spermatogenesis in such non-responsive patients suffering with hypogonadotropic hypogonadism. A detailed study conducted on nine oligozoospermic and nine asthenozoospermic men treated with GH for 12 weeks reported increased sperm motility in both the groups, and three pregnancies were determined in asthenozoospermia, but not in oligozoospermia [86].

The administration of GH has been carried out as a possible treatment for infertility, due to the just mentioned potential to increase seminal volume and sperm motility [87], but there is still insufficient evidence that it can ameliorate sperm quality in patients with asthenozoospermia and oligozoospermia.

However, animal breeders and scientists focus mainly on the role of GH in milk and meat production; it also acts as a stimulant in anabolic processes. In modern research, the functions of the GH in human and animal reproduction have become an area of immense interest. As has already been empirically established, the process of gametogenesis in both sexes involves a vital role of GH, as it stimulates gamete production and maturation and embryo development as well. Although the GH activity modus operandi is still anonymous, GH therapy causes a considerable increase in sperm cell concentration, their motility, and IGF-1 content in the blood. The IGF-1 has proved to be the main GH mediator. Furthermore, tests have acknowledged an association between the rate of morphologically normal spermatozoa as well as IGF-1 concentration in seminal plasma. The discovery of active receptors in porcine testis and in bovine spermatozoa cells has ratified the action of GH and IGF-1 on sperm cells [88]. It is essentially required for determining the onset of puberty and the induction of sexual maturation. The regulation of growth and actions of secondary sexual organs and activation of the uterus in females and the seminal vesicles and prostate in males are its other spheres of activity. Its sphere of activity in adults consists of modulation of gonadotropin secretion and its exertion of gonadotropin-dependent and gonadotropin-independent actions on the local gonadal function, including steroidogenesis and gametogenesis.

4. Conclusion

GH is intimately involved in regulating reproductive physiology and maintenance of reproductive health in both the sexes. Although GH and IGFs are conventionally associated with growth and gonadotropin secretion, it has proven a pivotal role in several crucial processes associated with male reproductive health, i.e., sexual growth and differentiation, pubertal transition, spermatogenesis, gonadal steroidogenesis, metabolism, and sexual behavior. Besides being somatotropin, it is therefore considered as gonadotropin, integrally involved in male reproductive health. Despite plenteous reports showing the physiological functions of the somatotropic axis in male reproduction, the therapeutic implications are still very much obscure. The GH administration has been a pertinent approach in small groups of infertile males, but no controlled trial exists. However, the diagnosis of adult GHD is underestimated; it cannot solely be based on the measurement of circulating IGF-1 levels but requires exhaustive tests. In the case of reduced GH secretion, the replacement therapy can be proposed, especially in patients with oligozoospermia and low semen and testicular volume, which are passive towards gonadotropin administration. The role of GH as a modulator of testicular growth, differentiation, steroid synthesis, metabolism, and oxidative status is still a very interesting area to be explored. All these actions potentiate fertility status in both sexes and partially exhibit the neuroendocrine roles of pituitary GH, but as reproductive tissues are not just sites of GH action but also sites of local GH synthesis, they may reveal autocrine/paracrine actions of GH produced within the male reproductive system.

Author details

Mayank Choubey

Address all correspondence to: choubeymayank48@gmail.com

Department of Zoology, Institute of Science, Banaras Hindu University, Varanasi, Uttar Pradesh, India

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