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Growth hormone and regulation of reproduction and immune system -A review

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ABSTRACT

The primary control of reproduction is through gonadotropins and sex-steroid hormones. The emerging evidences suggest a vital role of growth hormone (GH) and immune system in the control of pituitary and gonadal functions. There is involvement of GH in all the reproductive processes. The immune system through autocrine and/or paracrine mechanisms regualte the interaction of GH in different reproductive proceses. The role of GH, its interaction with immune system and cytokines in the control of reproductive processes has been reviewed.

Key words: Growth hormone (GH), Immune system, Lymphocytes, Reproduction

Growth hormone, a classical hormone of anterior pituitary with different isoforms can be also produced in many other tissues including immune cells (Chen *et al.* 1997, Hattori *et al.* 1999, Poppi *et al.* 2002, Dixit *et al.* 2003), and lymphocytic GH is similar to its pituitary counterpart (Weigent *et al.* 1988, Hattori *et al.* 1990).

The actions of growth hormone (GH) exert pleiotropic effects on almost all the systems in the body. GH has been reported to have effect on reproduction (Hull and Harvey 2001, Chandrashekar *et al.* 2004), immune system (Postel-Vinay *et al.* 1997, Dorshkind and Horseman 2000, Hall *et al.* 2002), nervous system (Nyberg 2000), bones (Rosen *et al.* 1997), cardiovasculoar system (Amato *et al.* 1993), and skin (Blok *et al.* 1997). GH exerts its effects through insulin like growth factor-1 (IGF-1) secreted from liver and skeletal muscles (Sadowski *et al.* 2001). Recently, it was demonstrated that growth hormone secretagogue (ghrelin) stimulates GH secretion via endothelin-1 and endothelin-3 (Than Than *et al.* 2010). This review is a survey of the 'state-of-the-art' considering the role of growth hormone in reproductive and immune system.

GH and puberty

Puberty, a complex process of neuroendocrine and genetic interactions, its onset and progression are also regulated by GH. The process is controlled by a number of complex neuroendocrine factors for its onset as well as its progression to full sexual maturity. In general, GH deficiency or GH resistance delays puberty and GH administration accelerates puberty. In GH deficient women, puberty is delayed (de- Boer *et al.* 1997). Puberty is also delayed in GH receptor (GHR) knockout mice (Bartke *et al.* 1999, Zaczek *et al.* 2002), GH-resistant women (Laron 1984) and in cattle immunized against GHRH (Simpson *et al.* 1991). Codner *et al.* (1997) suggested GH therapy during puberty. They increased GH dose during puberty to increase GH level which naturally occurs during puberty. Also to delay epiphyseal fusion they administered luteinizing hormone releasing hormone analogue along with GH. Plasma GH and LH in buffalo heifers increase before and during puberty and decrease after puberty (Haldar and Prakash 2006). They further suggested that GH and LH are positively correlated both before and after puberty indicating the interaction and/or close relationship of GH and LH in the mechanism of puberty in buffalo heifers (Haldar and Prakash 2005). Growth hormone in male mice around puberty is important in development of muscle mass and in stimulation of periosteal growth (Venken *et al.* 2007). Administration of exogenous growth hormone accelerates sexual maturation in GH-deficient monkeys (Wilson *et al.* 1989) and the reduction of GH secretion by continuous treatment of somatostatin analogue, sandostatin in monkeys leads to the deleterious effects on the completion of puberty (Wilson *et al.* 2004). In female rainbow trout there is a significant increase in plasma GH concentration during gonadal maturation, while in male there is a significant change in SRIF levels during testicular maturation (Holloway *et al.* 1999). The declining SRIF levels during gonadal activation may indicate a role for the hormone in the energy repartitioning processes that occur at this time. These effects of GH are indicative of role of GH in puberty and sexual maturity.

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GH and ovarian activity

GH administration increases the circulating insulin-like growth factor-1 (IGF-1) and IGF-1 stimulates gametogenesis and steroidogenesis in ovaries (Adashi *et al.* 1985). The expression of ovarian IGF-1 is decreased in growth hormone receptor knockout mice as compared to normal mice (Zaczek *et al.* 2002). GH administration *in vivo* increases the number of small follicles in cattle (Gong *et al.* 1993) and horses (Cochran *et al.* 1999). *In vitro* studies in mice showed a stimulatory effect of GH on preatral follicle development and follicular cell proliferation in immature mice (Kumar *et al.* 1997, Kobayashi *et al.* 2000). Growth hormone acts in conjugation with gonadotrophins to stimulate folliculogenesis and luteinization, as both GH and gonadotrophins are required to prevent atresia of larger follicles following hypophysectomy in sheep (Eckery *et al.* 1997). GH may mimic LH actions resulting in improvement of follicular survival and cell proliferation. And deficiency of GH exhibits reverse effects (Advis *et al.* 1981). The circulating levels of estradiol and progesterone during estrous cycle affect the GH secretion in cattle, suggesting the role of GH in follicular development and ovulation (Hayashi *et al.* 2008). Also GH may control ovarian activity through IGF-1 in cattle and pig (Lucy 2008). In bitches there is increased basal GH secretion during luteal phase, this indicates that the progesterone-induced GH production from the hyperplastic ductular epithelium of mammary gland may promote the proliferation and differentiation of mammary gland tissue during the luteal phase of the bitch by autocrine/paracrine effects (Kooistra and Okkens 2001, Kooistra and Okkens 2002). Also in bovines, during early luteal phase there is increase in number of cells in the pituitary that secrete both GH and prolactin (mammosomatotropes), suggesting that ovarian steroids may regulate in a feedback manner the GH secretion which in turn modulates reproductive processes (Kineman *et al.* 1991).

Development of dominant follicle is impaired in growth hormone receptor deficient cattle. These cattle have fewer small antral follicles, smaller corpus luteum smaller, lower plasma IGH-1 and progesterone concentrations than the controls (Chase *et al.* 1998). *In vitro* studies indicate that GH enhances estradiol secretion and bovine follicles (Sirotkin and Makarevich 1999). Progesterone production in luteal cells is enhanced by GH in the cow (Langhout *et al.* 1991) and ewe (Wathes *et al.* 1995). Porcine granulosa cells and theca interna cells are the sites of IGF-1 production and GH augmented 1GF-1-stimulated estrogen secretion by theca interna cells and proliferetion of granulosa cells (Kolodziejczyk *et al.* 2003). Bartolome *et al.* (2002) reported that bovine somatotropin (bST) treatment closer to day 0 (initiation of synchronization of ovulation) has a positive effect on conception rate of cows. This means that bST has a beneficial effect on the preovulatory follicle in dairy cows. The growth hormone overexpression in ovarian tissues in transgenic mice significantly decreases follicle apoptosis, and thus atresia in the mouse ovary leading to increased ovulation (Danilovich *et al.* 2000). Lebedeva *et al.* (2004) demonstrated a single class of high affinity GH-binding sites in both theca tissue and granulosa cells in hen. The binding capacities and affinities of these binding sites in the granulosa layer change during ovulatory cycle. The binding capacities and affinities of GH-binding sites in theca layer during different stages of cycle were not significantly different. These findings indicate that GH-binding sites in these tissues are regulated in a tissue specific manner.Thus as Chandrashekar *et al.* (2004) suggested in addition to GnRH and gonadotropins, GH/IGF-1 influence the pituitary and gonadal functions and regulate reproductive processes in animals and humans. These actions can be concluded as GH has effects on ovarian functions like gametogenesis, steroidogenesis and ovulation.

GH and pregnancy

The GH or GH-like proteins are present in the placenta of ruminants (Anthony *et al.* 1995). Growth hormone-deficient rats are characterized by low IGF-1, lower maternal weight gain, and smaller litter size (Gargosky *et al.* 1993) and GH replacement results in heavier fetuses and faster postnatal growth of pups (Spencer *et al.* 1994). Litter size and fetal size also are reduced in female GHR-knockout mice (Bartke *et al.* 1999). Exogenous GH promotes uterine proliferation and cellular growth in rats by changing the mechanism of estrogen in the uterus (Gunin 1997). In sheep, GH increases the weight of the myoendometerium and the gravid uterus (Jenkinson *et al.* 1999). GH-induced changes in uterine growth may be independent of hepatic IGF-1, since GH-receptor mRNA is present in uterine layers in cattle (Scott *et al.* 1992). *In vitro* culturing of cattle embryo with GH supplementation significantly improved the quality of blastocysts without affecting first zygotic cleavage (Pers-Kamczyc *et al.* 2010).

Escalada *et al.* (1997) reported that the mechanisms of the increase in plasma GH levels occurring during pregnancy include an increase in GH gene expression in the pituitary, a decrease in somatostatin secretion from the hypothalamus, an increase in the immuno-reactive IGF-1 content in the hypothalamus and in the pituitary, concomitant with a significant decrease in circulating IGF-1. The mean plasma GH concentrations are similar in pseudopregnant, hysterectomized and pregnant goats. Only during the first day after parturition, significantly elevated plasma GH levels have been recorded in goats (Kornalijnslijper *et al.* 1997). Significant elevation of plasma GH was also reported around or after parturition in the cow (Ingalls *et al.* 1973). GH treatment increases conception rate in postpartum cows (Flores *et al.* 2007). Treatment of repeat-breeding Holstein cows with recombinant bovine somatotropin at estrus improves the conception rate and this effect is associated with an increase in circulating progesterone concentrations on day 18 of the estrous cycle (Mourales-Roura *et al.* 2001).

In cyclic mares during breeding season and in pregnant mares, endogenous GH release is enhanced (Aurich *et al.* 1999). In pregnant mares, opioid antagonist naloxone-induced GH release is absent during pregnancy up to day 280 of gestation, indicating an opioidergic inhibition of GH secretion during the pregnancy (Aurich *et al.* 1999). Further, Heidler *et al.* (2003) revealed that plasma GH concentrations in mares are lower during late gestation and lactation than in non-lactating mares. Insulin like growth factor-1 (IGF-1) levels are highest in lactating mares in the week of foaling, IGF-1 concentrations decrease continuously thereafter. The authors suggested that IGF-1 concentrations in early postpartum might contribute to ovarian stimulation. Also report (Deichsel *et al.* 2006) says that IGF-1 concentrations do not differ between lactating and non-lactating mares or in stages of estrous cycle, indicating IGF-1 level is independent of lactation status and stage of estrous cycle. In cow, the fetal venous plasma concentrations of GH on day 137 and day 180 are less than on day 226 and day 250, while in uterine arterial plasma concentrations of GH do not change with stage of gestation (Reynolds *et al.* 1990) indicating that mechanisms for control of growth hormone secretion are poorly developed in bovine fetus. Also the concentrations of GH in uterine arterial plasma are 10 to 20 fold less than concentrations in fetal venous plasma (Reynolds *et al.* 1990). The treatment of underfed gilt with GH during second quarter of pregnancy increases fetal weight (Gatford *et al.* 2000), suggests that GH is able to at least partially overcome any maternal constraints to fetal growth brought about by restricted feeding of the sow during pregnancy.

Maternal blood concentrations of GH, 1GF-I and/or 1GF-II are increased during early or throughout all of pregnancy in the rat (Donovan *et al.* 1991), rabbit (Nason *et al.* 1996) and pigs (Sinha *et al.* 1990). Intrauterine growth retardation is associated with lower than normal concentrations of GH and IGF-1 in maternal plasma and GH deficiency in dams impairs fetal growth in rats (Spencer *et al.* 1994). Bauer and Parvizi (1996) demonstrated that porcine fetal GH secretion is pulsatile. The maternal GH concentrations are significantly lower than the fetal GH concentrations. The immunoreactive ovine GH is observed in highest concentration in placental extract between day 35 and day 50 of pregnancy (Lacroix *et al.* 1996). Likewise RNAs isolated from ovine placentas show that GH like mRNA signal is expressed at a high level on day 40- day 45 and then decreases after day 50 of pregnancy (Lacroix *et al.* 1996). The GH mRNA appears between day 40 and day 50 in pig fetal pituitary (Ma *et al.* 1996). Taverne *et al.* (1988) observed that the mean cow fetal plasma GH concentrations decreases gradually during the last 15 day before birth and are 4–6 times higher than mean concentrations in maternal plasma. The maternal plasma GH concentrations do not change during this period. The physiological role of fetal GH has not been clearly explained, may it be involved in prenatal growth and development. These findings are suggestive of the role of GH in maintenance of successful pregnancy and fetal development.

GH and lactation

The GH is the major galactopoietic hormone in cows and is commonly used to increase milk yield in dairy herds (Tauer and Knoblauch 1997). Breier *et al.* (1991) reported that treatment of dairy cows with bovine GH increases milk yield by 10–40% by affecting both mammogenesis and lactogenesis. GH treatment also increases milk yield in goats (Faulkner 1999), cows (VanBaale *et al.* 2005) and buffaloes (Bayram *et al.* 2006). Also bovine somatotropin (bST) treatment in lactating cows improves lactation performance in terms of milk production (Rivera *et al.* 2010). In ewes GH treatment not only increases milk yield but it also enhances milk fat, lactose and weight of mammary gland (Min *et al.* 1997). Growth hormone applied to cows resulted in improvement of lactational period (Bauman *et al.* 1999), milk yield (Van Baale *et al.* 2005) and milk fat (Kim *et al.* 1997). bGH increases milk yield and the increased milk yield and milk fat content in dairy cows treated with GH may be due to reduced glucose uptake and increased lactate production by skeletal muscles (McDowell *et al.* 1987). Also increased milk production in goats by exogenous GH may be mediated by the mechanism which increases the intracellular availability of glucose for lactose synthesis. And changes occur in the concentrations of IGF-1 in the mammary gland leading to changes in the milk composition (Faulkner 1999). GH is important in the normal development of mammary gland development. Mammary gland does not develop in absence of both the pituitary gland or GH in rats (Feldman *et al.* 1993) and GH acts on mammary stromal and epithelial tissues in rats to induce the differentiation of ductal epithelia into terminal end buds and alveolar structures and promotes the morphogenesis of terminal end buds in the mammary fat pad (Walden *et al.* 1998).

It is important to note that GH is produced in the mammary gland (Mol *et al.* 1996) in dog and cat. The sequence of mammary GH is identical to its pituitary counterpart but its secretion is non-pulsatile and is not altered by SRIF or GHRH (Mol *et al.* 1996). Mammary GH probably acts locally by autocrine/paracrine mechanisms but in dogs it contributes to circulating GH and can result in acromegalic features in hypophysectomized and pituitary deficient dogs (Selman *et al.* 1994). Keeping in view of the adverse effects of bST on milk quality in cattle its use has been banned in many developed nations like Canada, Australia, New Zealnad, Japan and all European Union countries (Anonymous 2011).

Frequencies of GH genotypes in Holstein cows were found to be 0.77. 0.21 and 0.02 for A/A, A/B and B/B genes respectively. GH A/A cows have highest milk yield with highest milk protein (Sabour *et al.* 1997, Zhou *et al.* 2005). The genetic polymorphism of the GH gene also affects the milk yield in ewes (Marques *et al.* 2006). GH receptor gene F279Y has the highest influence on milk protein and fat percentage in cattle (Viitala *et al.* 2006), thus GH genetic makeup of the animal influence the milk composition. A higher level of plasma ghrelin (an endogenous ligand of the GH secretagogue receptor) is associated with high genetic make up cows for milk production than in low genetic make up cows (Roche *et al.* 2006). Further, a T/A nucleotide variation in exon 8 of bovine GHR gene has been suggested to effect milk production in cows (Zhou and Jiang 2006) and this effect is unlikely to be mediated by the JAK2-STAT5 pathway, the currently known signaling pathway from the growth hormone receptor. These findings suggest the role of GH in milk production and secretion in animals.

GH and male reproduction

The function of the GH in animal reproduction has recently become an area of great interest. GH and lGF-1 action on sperm cells has been proven by discovering active receptors in porcine testes and in bovine spermatozoa. (Machnik and Lechniak 2000). However, because GH is also produced in testes (Harvey *et al.* 2004), it may act in paracrine or autocrine manners to regulate local processes in male reproduction (Hull and Harvey 2000). GH modulates spermatogenesis and GH insufficiency is related to spermatogenic dysfunction (Fujisawa *et al.* 2002), and GH treatment stimulates IGF-1 production from the Sertoli and/ or Leydig cells, which stimulates maturation of spermatozoa with subsequent increased sperm motility (Ovesen *et al.* 1998). Thus, GH may be an permissive factor in Leydig cell activity during puberty (Kulin *et al.* 1981). Treatment with the somatostatin analogue (octreotid) in stallion decreases semen motility and hCG-induced testosterone secretion (Aurich *et al.* (2003). Increase in circulating concentrations of IGF-1 in the GH-deficient rat can improve the motility and morphology of immature spermatozoa (Vickers *et al.* 1999), and mimic the effect of GH in GH-deficient rats.

The apparent production of GH in spermatogonia, spermatocytes and spermatids suggests a role of GH in spermatogenesis in chicken (Harvey *et al.* 2004, Luna *et al.* 2004). A combined treatment with GnRH agonist (GnRHa, it is used to downregulate the GnRH receptors to create conditions like that of GnRH deficiency or withdrawl) and GH enhances the effect of GnRH on sperm density and motility in rats (Ohyama *et al.* 1999). These results suggest that administration of GH decreases loss of germ cells at various stages of spermatogenesis under the condition of gonadotropin withdrawl. In bulls, short term administration of GH did not affect bovine spermatogenesis (Santos *et al.* 1999).

Exogenous GH administration during prepubertal period advances onset of spermatogenesis in boars by directly acting on the testicular cells (N'Diaye *et al.* 2002) and also promotes Sertoli cell size, seminiferous tubule lumen formation and spermatogenesis (Swanlund *et al.* 1995). In contrast diminished levels of GH causes decreased seminiferous tubule growth and induced degenerative changes in the spermatogenic cells (Oncu *et al.* 2004). Expression of the pituitary GH gene in primary spermatocytes in cockerels suggested autocrine or paracrine actions of GH during spermatogenesis (Harvey *et al.* 2004). Further, testicular functions in cyclophosphamide damaged rat testes can be improved by GH treatment (Satoh *et al.* 2002) and GH with gonadotropin treatment enhances testosterone levels and testicular volume (Giagulli 1999). Ghrelin, the endogenous ligand for the GH secretagogue receptor, has been suggested to have a role in mammalian testicular functions (Gaytan *et al.* 2004). Recently, Chandrashekar and Bartke (2005) reviewed the role of GH and IGF-1 in the control of neuroendocrine-testicular functions in animals. In animals with altered IGF-1 secretion, the gonadotropin and androgen secretions are affected. A GHRH-related peptide derived from proteolytic processing of pro-GHRH activates spermatogenesis (Nillni *et al.* 1999). Kuwahara *et al.* (2000) reported that during non-breeding season in mice there is decrease in testicular and epididymal weight, arrest of spermatogenesis, decrease in serum testosterone level along with decreased GH- immunoreactive cells in the pituitary. The above findings suggest the actions of GH in different male reproductive processes.

GH and immune system

The postnatal growth is regulated by GH and IGF-1 genes. The cells of the hematopoietic system are controlled by these two genes. The proinflammatory cytokines particularly tumor necrosis factor (TNF)-alfa from the immune system regulate the GH and IGF-1 axis indicating the interaction of immune system and GH (Kelley 2004). Moreover, the production of mannan-binding lectin, a plasma protein that plays an important role in innate immunity through activation of the complement cascade and inflammation can be influenced by GH (Hansen 2003). GH corrects the immuno-deficiency in hypophysectomized animals indicating role of GH in immune system (Gala 1991, Murphy *et al.* 1995). One of the routes of GH modulation of the immune system is through inhibition of Fas-induced apoptosis in activated B and T lymphocytes by increasing Bcl-2 expression and down regulation of caspase-3 expression (Mitsunaka *et al.* 2001). The apoptosis of lymphocytes induced by methyl methanesulfonate can be prevented by endogenous GH through the production of nitric oxide (Arnold and Weigent 2004). Restriction of calorie intake in rats diminishes plasma GH levels and modifies the distributions of T and B lymphocytes in the submaxillary lymph nodes as well as their proliferative capacity (Lopez-Varela *et al.* 2004).

The GH mRNAs is detected in thymus and liver in 18-day old rat fetus. GH gene is also expressed in circulating lymphocytes and in hematopoietic cells surrounding GH mRNA-negative hepatocytes in rat fetal liver (Recher *et al.* 2001). The peripheral lymphocytes show 2 isoforms of the GH receptors (GHR), one having exon 3 (GHR3+) and other without exon 3 (GHR3-). Normal subjects express predominantly GHR 3- isoform which has a negative correlation with IGF-1 levels, while acromegalic patients express both isoforms equally (Ochoa *et al.* 2003). GH gene expression in rainbow trout leucocytes is regulated by cortisol, thereby suggesting a physiological significance of GH produced in the fish immune system (Yada *et al.* 2005). Cytokines enhance GH secretion from immune cells. GH has several biological actions in immune system, viz. enhancing thymopoiesis and B and T cell development, modulating cytokine production and antibody production (Hattori 2009). GH can reduce or reverse age related change in immune functions such as lymphoproliferative actions and natural killer cell activity in aged rats (Baeza *et al.* 2008). Peripheral blood mononuclear cells (PBMCs) from normal adults secrete GH, which is similar to its pituitary counterpart (Weigent *et al.* 1988, Hattori *et al.* 1990) and can be further enhanced when PBMCs are stimulated with phytohemagglutinin (PHA). The addition of exogenous GH during the culture augments endogeneous GH secretion from PHA-stimulated PBMCs while addition of GH releasing hormone and a somatostatin analogue do not affect GH secretion from non-stimulated and PHA-stimulated PBMCs (Hattori *et al.* 1990). It suggests that PBMCs secrete immuno reactive GH in a different manner from that in the anterior pituitary because addition of GHRH and somatostatin analogue did not affect GH secretion from the PBMCs. Stephanou *et al.* (1991) reported that the lymphocyte derived immuno reactive GH releasing hormone and GH releasing hormone 1–44 are biologically active and they enhance the transcription of GH mRNA both in dispersed rat pituitary and in peripheral blood lymphocytes. The mice T-cells can be stimulated with canavalin A or anti-CD3 antibody. The bovine GH stimulates the proliferation of activated mice T-cells as indicated by increased uptake of thymidine (Postel-Vinay *et al.* 1997). In addition, the lymphoproliferation can be blocked by specific antibodies to GH (Weigent *et al.* 1988).

The GH influences the humoral immune response in a manner that the high endogenous GH levels inhibit specific antibody production and peripheral T-cell populations in mice. And low levels of endogenous GH do not inhibit specific antibody production but increases peripheral T helper-2 cells (Hall *et al.* 2002). The GH improves *in vivo* thymic functions by enhancing thymocyte proliferation and migration, this may underline the importance of GH in T-cell associated immuno deficiencies (Savino *et al.* 2003). GH deficiency significantly impaired natural killer (NK) cell activity, reduced NK cell concentration and increased total and proportional CD4+ cells (Sneppen *et al.* 2002). The treatment of GH-deficient patients with GH significantly increased IGF-1 (Sneppen *et al.* 2002). GH and pituitary-1 (growth hormone factor 1) transcripts are detected in thymocytes and splenocytes from bovine fetuses at 60, 90, 120 and 270 days of gestation (Chen *et al.* 1997). Lymphocytic GH may function as an autocrine and/or paracrine factor during the development and maturation of the bovine fetal immune system (Chen *et al.* 1997). The cells from bovine fetal spleen and thymus possess GH receptor during early and mid-gestation and treatment with GH increases transcript levels for interleukin (IL)-1 alpha, IL-1 beta and IL-6 (Chen *et al.* 1998) in these cells. These findings showed that GH is intimately involved in lymphocyte function and expression of certain cytokines during a critical period of fetal immune development. Transgenic mice over expressing bovine GH gene show decreased T-cell functions (Esquifino *et al.* 2002). These decreased T-cell functions are in terms of lower natural killer cell activity, lower percentage of T-cells in transgenic mice in comparison to normal. Also basal and mitogen induced proliferation capacity of splenocytes are reduced in transgenic mice. The care-givers of patients with Alzheimer's dementia suffer from stress of caring these patients. This stress in human results in poor immune response and poor expression of GH mRNA from peripheral blood mononuclear cells and B-cells than that in the control group (which were not care-givers or free from such stress) (Wu *et al.* 1999). Khorram *et al.* (2001) observed that GH releasing hormone is expressed in a small percentage of peripheral lymphocytes. The administration of GHRH to age-advanced patients results in potent activation of T-lymphocytes, monocytes and B-cell function with 1 month of treatment (Khorram *et al.* 1997). They further suggested that GHRH gene expression is upregulated by tumorigenic process and down regulated by aging process. It is unclear from this study whether the effects of GHRH are mediated through the GH/IGF-1 axis of immune origin (Khorram *et al.* 1997). Human lymphocytes have been shown to synthesize and secrete a biologically active GHRH peptide capable of stimulating GH release from both the pituitary gland and lymphocytes (Stephanou *et al.* 1991).

An inhibitory effects of GH on immune function have also been reported. When GH deficient children are treated with GH they show a decline in the number B–cell (Spadoni *et al.* 1991) and a decrease in circulating immunoglobulins (Lebl *et al.* 2000). The GH receptor is expressed as one active, full-sequence isoform and one truncated, inactive module that lacks the intracellular signaling domain. Human B-lymphocytes express both isoforms of GHR (Vottero *et al.* 2003).

Poppi *et al.* (2002) studied the effect of GH releasing hormone (GHRH) and GH releasing peptide-6 (GHRP-6) analogue, hexarelin on lymphocytic GH secretion from bovine and porcine lymphocytes. They observed that GHRH and GHRP-6 analogue (hexarelin) significantly increase GH production from bovine and porcine lymphocytes, without any synergistic or additive actions after treatment of cells with GHRH and hexarelin simultaneously. Neither the basal nor the GHRH-induced GH secretion is significantly changed in response to somatotrophin releasing inhibitory factor (SRIF) treatments. These findings suggested that the stimulatory mechanism of lymphocytic and the pituitary GH secretion may be similar. Whereas, the inhibitory control mechanisms of these 2 GH systems are apparently different. Contrary to these findings, addition of exogenous GH in culture of PHA-M stimulated human PBMCs increases lymphocytic GH secretion, while GHRH and somatostatin analogue, SMS 201–995, do not affect GH secretion from non-stimulated and PHA-M stimulated PMBC's (Hattori *et al.* 1990, Kao and Meyer 1992). Recently, Rose and Parvizi (2011) reported that the lymphocytic GH secretion is highest during luteal phase of estrous cycle in cow, then it decreases during pregnancy reaching nadir around mid- pregnancy and again starts rising in advanced pregnancy. The lowest level of lymphocytic GH secretion is at a time when the lymphocytic ACTH secretion is very high (Dixit and Parvizi 2001). Also decreased level of lymphocytic GH during pregnancy may contribute to increased Th2 cell populations (Hall *et al.* 2002), which might be important for survival and development of the fetus (Piccinni *et al.* 1998). Reverse is also true from the report (Takagi *et al.* 1998) that treatment of burned mice with GH increases Th1 cytokine production and decreases Th 2 cytokine production and an increase in Th1 type cytokines is associated with altered GH/IGF-1 axis (Liu *et al.* 2008). Further, proteomic analysis revealed the negative role of proinflammatory S100 proteins by GH in human white blood cells (Chung *et al.* 2009), thus suggesting the role of GH in alteration of Th1/Th2 cell populations. This alteration in Th1/Th2 cell population is important in successful implantation, survival and development of the fetus. Previously, Rose (2005) also reported that cytokines like LIF and IL-10 increases lymphocytic GH secretion during pregnancy indicating role of cytokines (LIF and IL-10) in immunomodulation during pregnancy in cattle without any significant effect in cyclic non-pregnant animals. These cytokines failed to exhibit any effect on lymphocytic nitric oxide secretion. Hence suggest that the effect of cytokines on lymphocytic GH secretion is independent of nitric oxide dependent mechanism during pregnancy in cattle.

Dixit *et al.* (2003) studied the control mechanism of GH secretion by porcine peripheral blood mononuclear cells (PBMCs). They reported that leptin and nitric oxide (NO) donor, sodium nitroprusside (SNP), result in a significant increase in GH secretion. This stimulated GH secretion can be blocked by nitric oxide synthase (NOS) inhibtor, N-nitro-L-arginine methyl ester (L-NAME), and protein kinase-C inhibitor, calphostin C, suggesting that leptin binding to its receptors in lymphocytes and resultant signaling is dependent

Table 1. Extra hypophyseal sites of GH production

Organ/tissue	Species	References
Lymphocytes	Cattle, human, pig	1 - 7
Placenta	Human, sheep, ruminants,	8 - 10
Mammary gland	Cat, dog, human	Mol *et al.* (1996)
Fetal thymus and spleen cells	Sheep	Chen *et al.*(1997)
Hippocampus	Rat	Donahue *et al.* (2006)
Testes	Chicken	Harvey *et al.* (2004)
Bursa of fabricius	Chicken	Rodriguez-Mendez *et al.* (2010)

[1]Hattori *et al.* (1999), [2]Hattori *et al.* (1990), [3]Dixit *et al.* (2003), [4]Poppi *et al.*(2002); [5]Goerner (1995), [6]Glatz-Vinke (1998), [7]Rose (2005), [8]Frankenne *et al.* (1988); [9]Anthony *et al.* (1995), [10]Lacroix *et al.* (1996).

Table 2.GH receptors/binding sites*

Organ/tissue	Species	References
Lymphocytes	Cattle, human, monkey	1 - 6
Lymphoid cells	Pig, cattle	4 - 5
Granulosa and theca cells	Cattle, hen, human, pig, rabbit	7 - 11
Luteal cells	Cattle, human, rat	11 - 15
Uterus	Cattle, human, rat	15 - 18
Placenta	Cattle, human, rat, sheep	19 -22
Liver	Goldfish	Zhang and Marchant (1996)
Mammary gland	Rabbit, rat	Lincoln *et al.* (1995)
Choroid plexus, hippocampus, hypothalamus and spinal cord	Human, rat	Nyberg (2000)
Adipocytes	Human	Thimmarayappa *et al.* (2006)

[1]Ochoa *et al.* (2003), [2]Bresson *et al.* (1999), [3]Rapaport *et al.* (!995), [4]Chen *et al.* (1998); [5]Dixit *et al.* (2003), [6]Vottero *et al.*(2003), [7]Lebedeva *et al.* (2004), [8]Kolle *et al.* (1997); [9]Ando *et al.* (1994), [10]Quesnel (1999), [11]Sharara and Nieman (1994), [12]Yuan and Lucy (1996), [13]Carlsson *et al.* (1993), [14]Yuan *et al.* (1996), [15]Lobie *et al.* (1990), [16]Scott *et al.* (1992), [17]Sharara and Nieman (1995), [18]Lacroix *et al.* (1999), [19]Frankenne *et al.* (1992); [20]Hill *et al.* (1992), [21]Kolle *et al.* (1998), [22]Barnard *et al.* (1994); ***,** Skeletal muscles and liver as the two classical GH targets are not included.

Table 3. Actions of GH*

Target organ/system	Species	Actions	References
Immune system	Mice	Altered humoral immune response	Hall *et al.* (2002)
Immune system	Mice	Lymphocyte development	Dorshkind and Horseman (2000)
Immune system	Mice	Increased proliferation of T-lymphocytes	Postel-Vinay *et al.* (1997)
Nervous system (Brain)	Human	Memory and cognitive functions	Nyberg (2000)
Bones	Human	GH deficiency causes fracture	Rosen *et al.* (1997)
Cardiovascular system (heart)	Human	Improve heart structure and functions	Amato *et al.* (1993)
Skin	Human	Improved hair growth	Blok *et al.* (1997)
Reproduction	Monkey	Accelerate sexual maturity	Wilson *et al.*(1989)
Ovary	Cattle, Horse	Increased no. of follicles	Cochran *et al.* (1999), Gong *et al.* (1993)
Ovary	Mammals	Folliculogenesis and luteinization	Eckery *et al.* (1997), Mazerbourg *et al.* (2003)
Mammary gland	Bitch, Human, Rat	Development of mammary tissue	1 - 3
Ovary/granulose cells	Cattle, Human	Increased estradiol secretion	Doldi *et al.* (1996), Sirotkin and Makarevich, (1999)
Ovary/luteal cells	Cattle, Sheep	Increased progesterone secretion	Langhout *et al.* (1991), Wathes *et al.* (1995)
Reproduction	Cow	Increased conception rate	Bartolome *et al.* (2002)
Uterus	Rats	Increased proliferation of uterine tissue	Gunin (1997)
Udder/mammary tissue	Cattle, Goat, Human	Increased milk yield	4 - 7
Thymus gland	Mice	Increased thymocytes proliferation	Savino *et al.* (2003)
Hypothalamo pituitary gonadal axis	Rat	Regulate gonadotropin secretion	Chandrashekar and Bartke (1998)
Testis	Rat	Gametogenesis and steroidogenesis	Barlett *et al.*(1990)
Penis	Human	Erection	Becker *et al.*(2002)
Vascular endothelium	Human	Incresed nitric oxide production	Thum *et al.* (2003)
Aorta	Rat	Incresed nitric oxide production	Wickman *et al.* (2002)

[1]Kooistra and Okkens (2001), [2]Walden *et al.* (1998), [3]Feldman *et al.* (1993), [4]Breier *et al.* (1991),[5]Tauer and Knoblauch (1997), [6]Faulkner (1999), [7]Milsom *et al.*(1992). *Effect on general metabolism and body growth are not included.

on protein kinase-C and nitric oxide. Leptin induces GH secretion from PMBCs via a protein kinase-C and nitric oxide-dependent mechanism. All these discussions explain the interaction among the GH, immune system and regulation of reproduction.

In conclusion, GH is involved in all the reproductive processes in male and female animals. One of the vital mechanisms of GH on reproductive system is via immune system. There is scanty literature available on the immuno-enodcrinology of reproduction of buffalo. Keeping in view the above discussion and various sites of GH secretion (Table 1), GH receptors (Table 2) and its varied functions

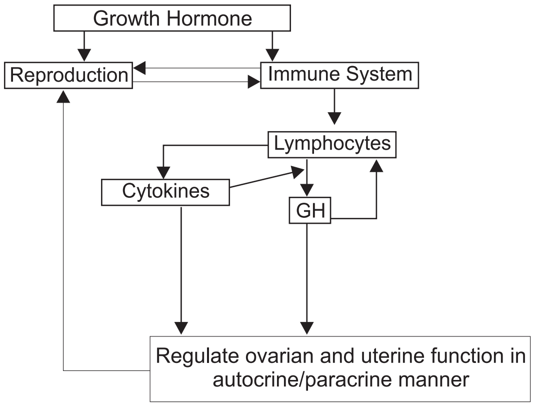

Fig. 1. GH balances the immune system for acceptance of the semiallogeneic fetus and protection of the mother from the infection.

(Table 3, Fig. 1) further investigations are required for specific involvement of GH in reproductive processes at cellular and molecular levels in coordination with immune system particularly in buffaloes.

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