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Estrogen and Growth Hormone and their Roles in Reproductive Function

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Abstract: The aim of this study was to review the effect of estrogen on growth hormone secretion and the roles of estrogen and growth hormone in reproductive function. Estrogen is the main hormone affecting growth, development, maturation and functioning of reproductive tract as well as the sexual differentiation and the behavior. Growth hormone is also important factor in sexual maturation and attainment of puberty. The impact of estrogen on growth hormone secretion has been reported in rodents and primates. However, the precise mechanism for the alterations in growth hormone secretion is not clearly known. Estrogen may possibility have a direct affect on growth hormone secretion via the binding to estrogen receptor-α due to its co-expression in growth hormone neurons in the medial preoptic area and arcuate nucleus. Estrogen may also have an indirect effect via the reducing insulin-like growth factor-1 feedback inhibition resulting with increased growth hormone secretion.

Keywords: Estrogen, growth, hormone, ovary, reproduction, testis

INTRODUCTION

Estrogen is an intra ovarian factor affecting the function of hypothalamus, pituitary, liver, skeleton and calcium homeostasis (Turner *et al*., 1994). It is also a main reproductive hormone affecting growth, development, maturation and functioning of reproductive tract as well as the sexual differentiation and the behavior (Balthazart *et al*., 2009). It was hypothesed that exogenous estrogens enhance GH secretion (Eden, 1979) and promote somatic growth. Therefore exogenous estrogens have been used to increase the secretory characteristics of GH in several species including sheep (Misztal *et al*., 2007), cattle (Colak *et al*., 2011) and human (Weissberger *et al*., 1991). The main aim of this study was to review the effect of estrogen on growth hormone secretion and the roles of estrogen and growth hormone in reproductive function.

ESTROGEN

Estrogen is named for its importance in the estrous cycle. Animal body naturally produce three main forms of estrogen, which are estradiol17β (E_2), Estrone (E_1) and Estriol (E_3). Estrone and estriol were firstly identified in the urine of pregnant women and this was followed by the identification of E_2 in the follicular fluid of sow by Edward Adelbert Doisy between 1929-1936 (Simoni *et al*., 2002). Estradiol and estrone are formed, respectively, from testosterone and androstenedione by aromatase which catalyzes an aromatic hydroxylation of the A ring of C19 androgens. Estrone and estradiol are inter-converted by 17-hydroxysteroid dehydrogenase; both can be converted to estriol by 16α-hydroxylase, mainly in the liver (Moghrabi *et al*., 1997).

In the ovary, E_2 is the most physiologically active type of estrogen produced by granulosa cells of pre-ovulatory follicles through the aromatization of thecal androgen by the granulose cells of growing follicles. In the testis, some E_2 is produced by Sertoli cells through the aromatization of the androgen synthesized from the Leydig cells. Estrogen is also synthesized in extragonadal sites including the mesenchymal cells of adipose tissue and skin, osteoblasts and chondrocytes of bone, vascular endothelium and aortic smooth muscle cells as well as several sites in the brain, including the anterior hypothalamus and the medial basal hypothalamus (Bayard *et al*., 1995; Sasano *et al*., 1999).

Estrogen receptors: Estrogens act via two types of receptors (ERα and ERβ), which are members of a large super family of proteins that function as ligand-activated transcription factors (Katzenellenbogen and Katzenellenbogen, 1996). Both receptors have direct differentiative influences on reproductive organs and have similar binding affinity to estradiol (Kuiper *et al*., 1997; Drummond *et al*., 1999). Although, there are significant amino acid differences in the regions of these receptors that would be expected to influence transcriptional activity (Hall and McDonnell, 1999). More recently, two Estrogen-Related Receptors, (ERRα/ERR1) and (ERRβ/ERR2) have also been characterized.

The presence of oestrogen receptors have been shown within the hypothalamus, pituitary, ovary, oviduct, uterus, cervix and vagina of several species including *human* (Brodowska *et al*., 2007), *sheep*

Table 1: Epression of erstogen receptors in reproductive organs of different animal species

	Hypothalamus	Pituitary	Ovary	Oviduct	Uterus	Cervix	Vagina
F. primat	+α /+β	+β	+α/+β	+α/+β	+α/+β	+α	+α/-β
Ewe	+α/+β	+α/+β	+α/+β	+α	+α/+β	+α	No data
Cow	+α/+β	+α/+β	+α/+β	+α/+β	+α/+β	+α	+α
F. goat	No data	+α/+β	+β	No data	+α	No data	No data
Porcine	+α/+β	+α/+β	+α/+β	+α	+α/+β	+α	No data
F. rat	+α/+β	+α/-β	+α/+β	+α/-β	+α/-β	+α/-β	+α/-β
F. mause	+α/+β	+α/-β	+α/+β	+α/-β	+α/+β	+α/+β	+α/+β

Plus (+) indicates the presence while mines (-) indicates its absence; References are in the text

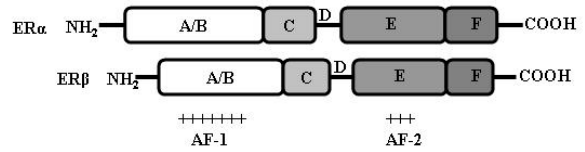

Fig. 1: Oestrogen receptor is composed of several functional regions

(Juengel *et al*., 2006), *cow* (Sağsöz, 2011), *goat* (Cui *et al*., 2009), *Porcine* (Knapczyk-Stwora *et al*., 2011), *rat* (Okada *et al*., 2003) and *mouse* (Hułas-Stasiak and Gawron, 2007) (Table 1). Estrogen signaling is selectively stimulated or inhibited depending upon a balance between ERα and ERβ activities in target organs. ERs have five distinct regions (Skafar and Zhao, 2008). These distinct regions correspond to functional and structural units called domain (Fig. 1).

The N-terminal of the A and B domains are highly conserved only between chicken and human estrogen receptors, but this distinction is much less clear in the other steroid Receptors. Therefore, region A and B are combined into A/B region in most cases. This region is a modulatory region and it is the most variable both in size and sequence. The A/B domain consists of Activation Function 1 (AF1), which contributes to the transcriptional activity of ERs and is an essential domain for interaction with co-regulators. The C domain is DNA Binding Domain (DBD) and the most conserved region of the estrogen receptors. It is essential for sequence specific binging of ERs to DNA. The D domain is not well conserved among the different receptors and serves a hinge between the DBD and the Ligand Binding Domain (LBD) allowing rotation of the DBD. Domain E is the Ligand Binding Domain (LBD), which contains COOH-terminal AF-2 motif responsible for ligand-dependent transcriptional activation. The LBDs are folded into a three-layered, anti-parallel helical sandwich. A central core layer of three helices is packed between two additional layers to create a cavity. This cavity is completely partitioned from the external environment and is closed by helix 12 of the ligand binding domain, operating as a lid after hormone has entered binding pocket (Fig. 2). The relocation of helix 12 over the hormone binding sited generates new surfaces that allow co-activator to bind ligand binding domain, thereby mediating the activity of AF-2. The F region is essential for hormone binding in the ERα.

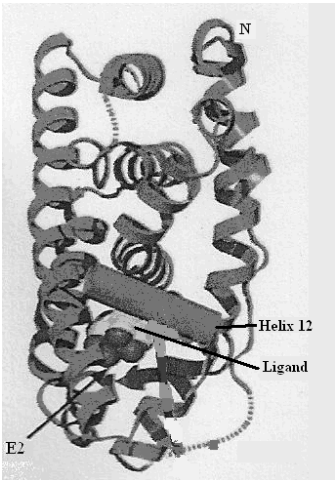

Fig. 2: Ligand Bindig Domain (LBD) of human oestrogen Receptor-α (ERα) complexed with the natural ligand 17β-oestradiol. A central core layer of three helices is packed between two additional layers to create a cavity. This cavity is completely partitioned from the external environment and is closed by helix 12 (Adopted from the Fig. 6 of Beato and Klug (2000)

Effect of estradiol on reproductive function: Chromosomal sex is determined at the time of fertilization by the entry of an X or Y chromosome from the sperm pronucleus into the pronucleus of the oocyte (Marshall Graves, 2000). In accord to the chromozomal sex, gonads are formed. It was suggested that under the influence of the Y chromosome, the undifferentiated genital ridge develops into testis and in its absence, ovaries form by default. Therefore, the existence of two candidate genes (SRY and ZFY), former being confirmed as Testis Determining Factor (TDF), on the Y chromosome was predicted following the mutation analysis (Jost *et al*., 1973; Marshall Graves, 2000).

Gonadal hormone secretion is under the control of chromosomal sex, which, in turn, controls the phenotype of non-gonadal tissue. The hormonal regulation of sexual differentiation of the mammalian reproductive system was established in the late 1940s by Jost. In his study, testes were removed from fetal male rabbits, inducing a female phenotype at birth. In contrast, transplantation of testis into female embryos induced a male phenotype. The early fetus has the potential to be either male or female and possesses not

only an undifferentiated gonadal ridge, but also 'precursors' for both Mullerian and Wolfian ducts. Once the testis are formed, they secrete Mullerian Inhibitory Substance (MIS), which induces regression of the Mullerian duct and they also produce testosterone, which stimulates development of the Wolfian duct. In the absence of testis and thus, MIS and testosterone, the Mullerian duct develops and the Wolfian duct regresses. Thus, it was established that male sexual development requires hormonal control and that the female reproductive system develops in the absence of these hormones (Jost *et al*., 1973). Other studies have confirmed that estrogen has no effect on mullerian duct formation. Because, treatment of the pregnant mice with Diethylstilboestrol (DES) did not affect Müllerian duct formation in female embryos (Newbold and McLachlan, 1982). However, the presence of estrogen receptors in both male and female mice from gestational day 10 and later (Gorski and Hou, 1995) indicate that estrogen has role in reproductive tract development and functioning. According to a study, in mutant mice lacking responsiveness to estradiol by disrupting the estrogen receptor gene by gene targeting showed abnormal reproductive tract development. It was also noted that the males were infertile (Lubahn *et al*., 1993). Experimental inhibition of the formation or action of estrogen in the female chicken and Japanese quail embryos can result in almost complete phenotypic sex-reversal, such as formation of testis-like ovaries, development of male secondary sex characteristics, lack of oviductal development and male-like growth of the cloacal gland in response to testosterone (Elbrecht and Smith, 1992).

The sex differences in the morphological and functional phenotype of the body and brain underlie gender identity, sexual orientation, sexual behavior and differences in certain non-reproductive behaviors. In most mammals, the principal hormone masculinizing the brain is testosterone. However, testosterone is the principal hormone causing brain musculinisation, but its metabolite, oestradiol, acting on estrogen receptors α and β (ERα and β) control separate aspects of differentiation. ERα is primarily involved in masculinization, while ERβ mediates defeminization of sexual behaviors, but not masculinization (Kudwa *et al*., 2006).

Estrogen also acts as an intra-gonadal factor and has negative and positive feedback influences on the hypothalamic-pituitary axis to regulate gonadotrophin secretion. It has been known for many years that estrogen has a direct influence on folliculogenesis. Oestradiol-17β (E_2) and its analogues have both proliferative and differentiative effects on somatic cells of follicles (Findlay *et al*., 2001). It stimulates the proliferation of granulosa cells in follicles and serves to facilitate the actions of Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) (Richards, 1980). Thus, it permits follicle growth because, increase in follicle size is due directly to an increase in granulosa cell number and not due to the antrum formation (Goldenberg *et al*., 1972). Estrogen is also responsible for facilitating the differentiation of granulosa cells including the induction of receptor systems for FSH, LH and prolactin and it can influence post-receptor mechanisms. There is a strong consensus that both ERα and ERβ are expressed in granulosa cells of preantral and antral follicles (Drummond *et al*., 1999). Esrogen Recptor-α Knockout (ERKO) female mice are acyclic, infertile and possess hyperemic ovaries devoid of corpora lutea (Couse and Korach, 1999). Folliculogenesis is arrested at the antral stage with large secondary follicles becoming cystic and hemorrhagic within 3 weeks of birth. In contrast, Estrogen Receptor-B Knockout (BERKO) females have small ovaries, some arrested follicular development and their fertility is compromised with reduced numbers of offspring per litter, consistent with the reduced number of corpora lutea observed (Krege *et al*., 1998).

Estrogen is also synthesized in the male reproductive system and it is found in high concentrations in rete testis and seminal fluids. Both estrogen receptors (ERα and ERβ) are found in various regions of the male reproductive tract. It was reported that estradiol (E_2) induces spermatogenesis in gonadotropin-deficient hypogonadal (*hpg*) mice (Allan *et al*., 2010). It was concluded that E_2-induced spermatogenesis in hypogonadal (*hpg*) mice involves an ERα-dependent neuroendocrine mechanism increasing blood FSH and Sertoli cell function (Allan et *al*., 2010). The main breakthrough in this field was brought forth by estrogen receptor knockout mice. Phenotypically, these mice have significant alteration in testes histology, spermiogenesis and they suffer from infertility (Eddy *et al*., 1996).

GROWTH HORMONE STRUCTURE AND SİGNALING

Growth Hormone (GH) is an anti-parallel four-helix bundle protein (Chantalat *et al*., 1995) secreted in a pulsatile manner by somatotrophs in the anterior pituitary gland (Edmondson *et al*., 2003). Its secretion is controlled by two neuropeptides namely Growth Hormone-Releasing Hormone (GHRH) and the Somatostatin (SS). Somatostatin (SS) inhibits GH release without affecting GH synthesis. Several lines of evidence suggest that GHRH initiates GH pulses and somatostatin modulates the amplitude of GH pulses. Blocking the action of GHRH, either by passive immunization in rats or with a GHRH antagonist in rats or humans, abolishes pulsatile GH release. Growth hormone also exerts a negative feedback effect on its own secretion. Daily subcutaneous administration of GH for 2-5 days decrease the endogenous GH response

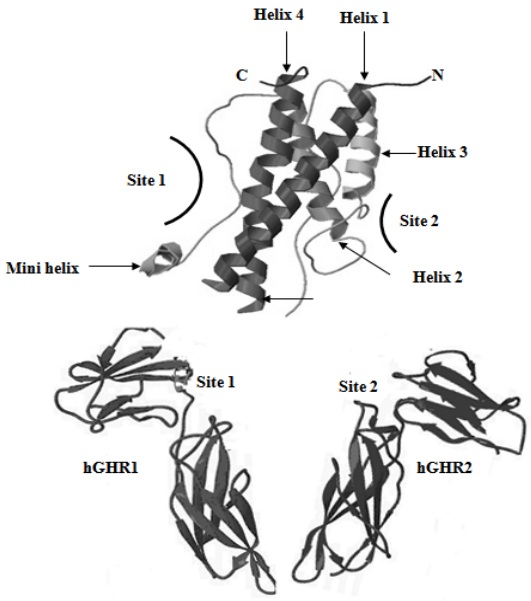

Fig. 3: The chrystal structure of the human GH and extracellular domain of its receptor. GH has two distinct binding faces to GHR on either side of the molecule, known as site 1 and 2. The extracellular domain of GHR comprises two beta sandwiches named domain GHR1 and GHR2

to GHRH (Ross *et al*., 1987). This effect may be mediated through the secretion of IGF from the liver.

The anterior pituitary gland synthesizes different GH isoforms. In human, the genetic locus encoding GH resides is located in long arm of chromosome 17 (17q24.2.) Two genes, in the cluster, encode two distinct GH variants and are named GH1 (or GH-N) and GH2 (or GH-V). GH1 is the principal and most abundant GH form in the pituitary. The GH2 gene product, GH2 (or GH-V) is similar in structure to the GH1. Its sequence differs from that of GH1 at 13 amino acid positions. Two other isoforms are Chorionic Somatomammotropin (CS), also known as Placental Lactogen (PL) named as CS1 (or CSA) and CS2 (or CSB) expressed in the placenta.

Growth hormone has two distinct binding faces to its receptor (GHR) on either side of the molecule, known as site 1 and 2, which are buried by essentially identical receptor domains upon binding (De Vos *et al*., 1992). The first binding site (site 1) has a concave shape and is formed by residues that are exposed on helix 4 of the helix bundle, together with residues on the connecting loop between helix 1 and 2 to produce an extensive binding crevice (De Vos *et al*., 1992). The second binding site (site 2) is made-up of the exposed sites of helices 1 and 3. In contrast to the concave character of site 1, site 2 is relatively flat. The hormone interacts through site-1 with the first molecule of GHR and promotes the dimerization of the receptor by interaction of the lower-affinity binding site 2 (Fig. 3).

Upon binding, GH causes dimerization of GHR, activation of the GHR-associated JAK2 tyrosine kinase and tyrosyl phosphorylation of both JAK2 and GHR. These events recruit and/or activate a variety of signaling molecules, including MAP kinases, insulin receptor substrates, phosphatidylinositol 3' phosphate kinase, diacylglycerol, protein kinase C, intracellular calcium and STAT transcription factors. These signaling molecules contribute to the GH-induced changes in enzymatic activity, transport function and gene expression that ultimately culminate in changes in growth and metabolism.

Effect of growth hormone on reproductive function: Growth Hormone (GH) is important factor in sexual maturation and attainment of puberty. External administration of GH has been shown to accelerate sexual maturation in monkeys (Wilson *et al*., 1989) and GH-deficient children (Stanhope *et al*., 1992). GH may accelerate puberty by activating the Luteinizing Hormone (LH) -releasing hormone pulse generator (Bartke *et al*., 1999) and/or by potentiating androgen action (Ilondo *et al*., 1982). However, GH administration has not been shown to accelerate pubertal development in pigs (Andres *et al*., 1991). In human, GH appears to increase the rate of human sexual maturation only when a pubertal pattern of pituitary gonadotrophin secretion is established (Sharara and Giudice, 1997). This shows that effect of external GH administration on sexual maturation depends on the reproductive state at the time of GH treatment. In young female rat, the injection of bovine GH (bGH) to the median eminence delays puberty (Advis *et al*., 1981), it is possible that GH exerts inhibitory effects on the hypothalamo-pituitary-gonadal axis at central sites, contrary to its stimulatory actions on pituitary gonadal function.

Growth hormone gene is also expressed within the gonads. By using cDNA primers for pituitary GH in Reverse Transcription-Polymerase Chain Reaction (RT-PCR), GH mRNA was shown within testis of fetal mice (Nguyen *et al*., 1996), adult cockerels (Harvey *et al*., 2004; Luna *et al*., 2004) and human (Berger *et al*., 1999). By using in situ hybridization and immunohistochemistry, GH mRNA and protein expression were shown in the ovary of hen (Ahumada-Solórzano *et al*., 2012). In the chicken testis, the GH-immunoreactivity was not present in spermatogonia, but it was mainly in the primary and secondary spermatocytes and spermatids and in the luminal compartments of Sertoli cells, but was also in surrounding myocytes and interstitial cells. The localization of GH in spermatocytes and spermatids suggests unsuspected roles in gamete development.

Within the ovary, GH play important role in early, Follicle-Stimulating Hormone (FSH) -independent follicular development, since GH-binding activity peaks

during early folliculogenesis in porcine follicles (Quesnel, 1999) and fish ovarian homogenates (Gomez *et al*., 1998). *In vivo* and *in vitro* studies suggest that GH stimulates growth and prevents atresia in small follicles. Growth hormone is important factor in follicle recruitment and initiation of oocyte growth. It acts together with gonadotrophins to stimulate later stages of folliculogenesis and luteinization, since both GH and gonadotrophins are required to prevent atresia of larger follicles (>2 mm) following hypophysectomy in sheep (Eckery *et al*., 1997). GH administration *in vivo* increases the number of large follicles in pigs (Lucy *et al*., 1995), GH-deficient dwarf rats (Ozawa *et al*., 1996) and the number of corpora lutea in cattle (Lucy *et al*., 1992). GH may play a role in follicle selection, since GH-binding sites in sow granulosa cells are lost in atretic follicles (Quesnel, 1999) and the development of the dominant follicle is impaired in GHR deficient cattle (Chase *et al*., 1998).

GH may facilitate ovulation by increasing sensitivity to gonadotrophins and by reducing the incidence of apoptosis in preovulatory ovarian follicles. The increased number of corpora lutea and reduced numbers of atretic follicles in the ovaries of mice transgenically expressing GH supports this view (Danilovich *et al*., 2000). The over expression of GH in these mice has thus been correlated with an increase in the number of ova shed during each ovulation (Danilovich *et al*., 2000).

Effect of estrogen on growth hormone secretion: Estrogen effect growth and reproduction at numerous physiological levels at target sites, including direct actions at the hypothalamic and pituitary levels to modulate Growth Hormone (GH) production and secretion. In ovary-intact mice GH mRNA in the arcuate nucleus and Medial Preoptic Area (MPOA) had elevated, while ovariectomy decreased GH mRNA in both regions (Addison and Rissman, 2012). When gonadectomized adults of both sexes were treated with estradiol, GH mRNA increased in females but had no effect in castrated males. It was also found that estrogen receptor-α is co-expressed in GH neurons in the MPOA and arcuate nucleus (Addison and Rissman, 2012). In man, estrogen produced locally from aromatization plays a major role in the regulation of GH secretion (Birzniece *et al*., 2010). It was proposed that exogenous estrogens enhance GH secretion (Eden, 1979). In women, the effect of exogenous estrogen on the regulation of GH secretion is route-dependent. Oral administration of estrogen enhances GH secretion; however, this does not happen when estrogen is replaced by a physiological non-oral route (Weissberger *et al*., 1991). There is no consensus on a mechanism (especially in ruminants) for alterations in the GH axis by estrogenic substances (Carroll *et al*., 2007). Since not all estrogens have the same effect on pulsatile GH, the dose of estradiol may influence the type of effects of estradiol on GH pulses.

Estrogens may also indirectly stimulate GH secretion by reducing IGF-I feedback inhibition through IGF-I modulation. IGF-I mediates a negative feedback control of GH secretion by acting directly on hypothalamic GHRH and Somatostatin (SS) neurons that the route of administration is a major determinant of the effect of estrogen on the GH/IGF-I axis (Leung *et al*., 2004).

CONCLUSION

Both estrogen and growth hormone have major impacts on steroidogenesis, gametogenesis, gonadal differentiation as well as the attainment of sexual maturity. Estrogen modulates growth hormone secretion via the different pathways Such as an effect on hypothalamic neurons and/or directly via effect on pituitary somatotrops also and/or indirectly via the reducing IGF-I feedback inhibition. The effect of external estrogen administration depends on dose, rote of administration, spices, gender and age. The presence of multi GH isofoms presents difficulties for an exact measurement of the hormone in body fluids and for the clear understanding of its physiology.

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