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The Bovine Testes-II: Role of Hormones During Pre and Post Natal Development

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Hormonal Regulation of Male Reproductive Function

The Hypothalamus: The hypothalamus lies at the base of the brain and constitutes a part of nervous system. Anteriorly it is bordered by the optic chiasma and posteriorly by the mammillary bodies. The thalamus lies to its dorsal and sphenoid bone to the ventral borders. Many of its nuclei lie close to the third ventricle (Reeves, 1980). As in the adult life, the hypothalamus is involved in coordinating the function of fetal endocrine organs. The exposure to certain hormone stimuli, of fetal hypothalamus can bring about permanent changes contrary to the adult hypothalamus (Liggins, 1982). The vascular connection between the hypothalamus and anterior pituitary is established through superior and inferior hypophyseal arteries which serve to transport hypothalamic releasing and inhibiting factors to anterior pituitary. Venous blood carried from pituitary to hypothalamus also carries some hormones from pituitary to hypothalamus thus regulating their pituitary production by a short loop feed back system.

Hypothalamus is the center to integrate inputs from CNS, the pituitary and the gonads. The median eminence, arcuate nucleus, suprachiasmatic nucleus and preoptic nucleus seem to contain the highest concentrations of GnRH (Palkovits *et al.*, 1974). Norepinephrine stimulates and dopamine inhibits the GnRH release (Sawyer, 1975). Testosterone and estradiol receptors are present in hypothalamus and may be a potential site of steroid modulation of GnRH secretion (Greeley *et al.*, 1975). GnRH is carried to the pituitary gonadotrophs through portal vessels where it binds to gonadotropin releasing hormone receptor (Steinberger *et al.*, 1978). GnRH causes the release of both LH and FSH which mediate both testicular androgen biosynthesis and spermatogenesis (Swerdlow and Heber, 1981).

Bovine Pituitary Gland: The bovine pituitary gland lies at the base of the brain above the sella turcica. It is divided into three lobes, the anterior, intermediate and posterior lobes (Gilmore and Petersen, 1941). The anterior lobe of the gland is functional in fetal life and its trophic hormones act to stimulate the growth of target organs. Removal of fetal pituitary prevents normal testes development. The negative feedback mechanism in the fetus operates similar to that in adult life in regulation of trophic hormones (Liggins, 1982). The bovine pituitary gland increases in weight from 0.39 grams at birth to about 1.27 grams at one year of age (Macmillan and Hafz, 1968a). The pituitary gland shows rapid weight increase between birth to 16 weeks, intermediate increase between 16 and 32 weeks and a slower increase upto 64 weeks of age. This growth curve has been explained as curvilinear convex (Abdel-Raouf, 1960). In young bulls, the pituitary gland is pear shaped with almost equal thickness and breadth. As the animal grows, it assumes oval or round shape. At eight months of age, it measures about $1.6 \times 1.3 \times 1.0$ cm (Abdel-Raouf, 1960). The acidophilic, basophilic and chromophobic cells are scattered throughout the anterior pituitary of bovines (Gilmore and Petersen, 1941). Somatotrophs and lactotrophs which are subdivisions of acidophilic cells, secrete growth hormone and prolactin, respectively. Based on positional, morphological and functional differences, the basophilic cells are divided into beta

and delta cells. Beta cells consist of two kinds of cells, thyrotrophs which produce thyrotrophic stimulating hormone (TSH) and corticotrophs that produce adrenal corticotrophic hormone (ACTH). Delta cells which are comparatively much smaller than the beta cells, synthesize gonadotrophins. Gonadotrophic cells are distributed in the pars distalis and are numerous in the basophilic zone. These cells are medium sized, oval or round in shape, containing an eccentrically located large nucleus with prominent nucleolus. The mitochondria of these cells are spherical or elongated and Golgi apparatuses are moderately developed (Dacheux and Dubois, 1976). Chromophobes have not been known to produce any known hormone and are considered resting or precursor cells (Jubb and McEntee, 1955; Heath, 1970; Dacheux and Dubois, 1976; McDonald, 1980).

Hormonal Levels in the Bull Plasma

Gonadotrophins: The release of LH and FSH depends on gonadotrophin releasing hormone (GnRH) which is released from the hypothalamus and reaches the gonadotrophs of the anterior pituitary via the portal system. Luteinizing hormone is secreted in pulses from the anterior pituitary whereas FSH does not have a pulsatile pattern (Tannen and Convey, 1977; Amann, 1983; Amann and Schanbacher, 1983; Schanbacher *et al.*, 1983). Secretion of GnRH and gonadotrophins starts shortly after sex differentiation in fetal life of bull calves. Though the vascular relationship between the pituitary and the hypothalamus is rudimentary, the regulatory mechanism of SW and LH is the same as in adult bulls (Levasseur and Thibault, 1980). The concentration of LH in bovine fetal pituitary continues to increase with advancing fetal age toward term. Fetal pituitary can synthesize LH *in vitro* (Oxender *et al.*, 1972a). The levels of LH in fetal serum however, were high in early fetal life and showed a decrease during last two months of fetal life (Oxender *et al.*, 1972b; Challis *et al.*, 1974; Levasseur and Thibault, 1980). The decrease in LH before birth may indicate the maturation of the central nervous system or negative feedback from testosterone production by the fetal testis (Shemesh *et al.*, 1978).

Follicle Stimulating Hormone: The pituitary FSH concentration and content reached to maximums at 2 and 5 months respectively in postnatal period and declined after 6 months of age (Macmillan and Hafz, 1968b). It appears that the levels of FSH vary with age and show two periods of increase, the second one coinciding with puberty in bulls (Schams *et al.*, 1981). The plasma FSH levels do not fluctuate a great deal during first year of life in bulls (Bass *et al.*, 1979; Schanbacher, 1979; Pelletier *et al.*, 1981; Amann and Walker, 1983). Though the pulses of GnRH are responsible for the production of FSH by the gonadotrophs, the FSH profile in bulls does not show a distinct episodic release as does that of LH (McCarthy *et al.*, 1979a; Amann, 1983; Amann and Walker, 1983). The non episodic release pattern of FSH may be attributed to a slow clearance rate and a separate negative feedback system from LH (Akbar *et al.*, 1974; Amann, 1983). Only Sertoli cells amongst all the elements of the seminiferous tubule have receptors for FSH (Means *et al.*, 1976) and the

number of these receptors increases with maturity in bulls (Schanbacher, 1979; Dias and Reeves, 1982). Sertoli cells in response to FSH produce regulatory hormones and other secretions responsible for the regulation of FSH and the process of spermatogenesis (Waites and Gladwell, 1982). In addition, to stimulation of protein synthesis in general, Sertoli cells secrete androgen binding protein (ABP) (Means *et al.*, 1976), plasminogen activator (Lacroix *et al.*, 1977a), inhibin and two proteins that remain in Sertoli cells including kinase inhibitor and gamma glutamyl transpeptidase (Kruger *et al.*, 1974). Though the spermatogenesis can be restored in regressed testis with testosterone, the FSH is necessary for the completion of spermiogenesis (Steinberger, 1971). During the first year of life in bulls, the plasma FSH does not alter (Pelletier *et al.*, 1981; Amann and Walker, 1983; Schanbacher, 1979). A slight increase at 115 d and 220 days in plasma FSH levels of bulls was reported (Al-Haboby, 1986). FSH in bulls does not have a clear episodic release pattern (Amann and Walker, 1983; Amann, 1983).

Luteinizing Hormone: During postnatal life, the concentration and contents of pituitary LH reach maximum at 1 month and 6 months of age in bulls (Macmillan and Hafs, 1968b). A gradual increase in LH levels until adulthood has been reported (Gombe *et al.*, 1973; Mori *et al.*, 1974; Lunstra *et al.*, 1978). Most reports agree that LH level in bulls during first year of life is triphasic. The first phase which is characterized by low LH level occurs during neonatal life. The second phase occurs between 2-5 months and is characterized by intense LH release with high episodic discharge activity and amplitude whereas the third phase is characterized by a drop in LH level (Lacroix *et al.*, 1977a; Rawlings *et al.*, 1978; Bass *et al.*, 1979; Pelletier *et al.*, 1981; Schams *et al.*, 1981; Amann and Walker, 1983). The differences in blood sampling regimen may be the reason for differences in LH pattern with age in these studies as this is an important criterion since LH is secreted in a pulsatile pattern from the pituitary and follows the episodic activity of neurons that discharge gonadotrophin releasing hormone (Desjardins, 1981). The increase between 2-5 months of age, in mean LH concentration in bulls is a result of increased number of LH peaks and heights of these peaks. The maximum number of peaks (3 per hour) have been reported at 3 months (Lacroix and Pelletier, 1979) and at 4 months (McCarthy *et al.*, 1979a). Intensive blood sampling has shown that LH elevation in bulls has a duration of 69 ± 15 min (Schams *et al.*, 1978) and a rapid clearance rate from the blood ($T_5 = 26$ min) (Smith *et al.*, 1973).

Leydig cells of the testis are the primary site of action for LH. LH stimulates testosterone production by Leydig cells both *in vivo* and *in vitro* and these cells exhibit structural changes when treated with LH or HCG (De Kretser, 1967; Russo and Sacerdote, 1971; Chemes *et al.*, 1976).

The episodic LH release is important for testicular growth as well as testosterone production by Leydig cells (Schanbacher *et al.*, 1982; Schanbacher, 1981), which otherwise may become refractory. The highest plasma LH levels were reported to be at the age of 100 days and 220 days in Holstein bulls (Al-Haboby, 1986).

Growth Hormone and Prolactin: Prolactin (prl) increases the activity of β -glucuronidase in the testis and also stimulates spermatogenesis of LH treated hypophysectomized rat (Bartke, 1971). It positively effects the LH stimulated testosterone production in rat testis (Bartke and Dalterio, 1976; Bartke, 1971) and prolactin therapy has been reported

to reduce testicular atrophy in hamster (Bartke *et al.*, 1975). The concentrations of prolactin and testosterone in the peripheral circulation of adult men has been correlated and may have an effect on steroidogenesis in man (Rubin *et al.*, 1975) and concomitant increase in prl levels with those of testosterone in bulls has been reported (Al-Haboby, 1986). It has been reported that bovine pituitaries produce prolactin *in vitro* and in intact animals their activity is increased from 90 day old fetus till 260 days of fetal age (Oxender *et al.*, 1972a). A drop in the prolactin levels of 1 day old bull calf has been attributed to the recovery from stress of parturition (Oxender *et al.*, 1972b). Immediately after birth, the prolactin levels continue to decline during the first 5 months followed by an increase at 6 and 7 months after which they gradually decrease (Schams *et al.*, 1981). A significant increase in prl levels at day 100 and day 235 was reported in Holstein bulls (Al-Haboby, 1986). Varying results have been reported regarding the association of age and prolactin levels in bulls (Schams and Reinhardt, 1974; Lacroix *et al.*, 1977a; McCarthy *et al.*, 1979b; Al-Haboby, 1986). Effect of season and photoperiod on prl levels in cattle has been reported (Wettemann and Tucker, 1974; Schams and Reinhardt, 1974; Lacroix *et al.*, 1977b).

Growth Hormone: Growth hormone plays an important role in the reproductive development of male. Growth hormone secretion is regulated by growth hormone releasing factor (GRF) shown to be present in median eminence, arcuate and ventromedial nucleus; and growth hormone inhibiting factor (somatostatin) present in the median eminence, ventromedial nucleus and preoptic and anterior periventricular hypothalamus. Growth hormone is secreted in a pulsatile fashion (Jansson *et al.*, 1985).

GH levels in bovine fetal pituitaries increase with age. GH secretion in fetal life is dependent upon the hypothalamic stimulation (Oxender *et al.*, 1972a) and fetus itself is the source of GH production rather than the mother (Oxender *et al.*, 1972b). GH in Holstein bull calves was lower in first 5 months of age and increased between 130-190 days of age (Al-Haboby, 1986). Prepubertal bulls have been reported to have higher GH levels and more number of peaks compared to pubertal bulls (McCarthy *et al.*, 1979b). Higher GH levels in male cattle of all ages have been reported (Keller *et al.*, 1979; Reynaert *et al.*, 1976).

Testicular Steroids and Regulation of Steroidogenesis: A variety of steroids synthesized from cholesterol are secreted by the testis. The primary source of steroid production is Leydig cells. These steroids include androsterone, dehydroepiandrosterone, 17-hydroxyprogesterone and dihydro-testosterone and testosterone (Amann, 1983; Amann and Ganjam, 1976; Lindner and Rowson, 1961). Testosterone is the principal secretory product of Leydig cells. Testosterone production proceeds through a biosynthetic pathway where in various steps are completed in different parts of the Leydig cells (Samuels and Eik-Nes, 1968). Conversion of cholesterol esters into cholesterol takes place in lipid droplets which, then, is carried to mitochondria for conversion into 20 α , 22R dihydroxycholesterol and the removal of side chain here, results in the production of pregnenolone (Moyle *et al.*, 1973). Rest of the steps of pregnenolone conversion into testosterone takes place in the smooth endoplasmic reticulum (Bun-ichi, 1973; Shikita and Tamaoki, 1965). Steroid production of the testis and amount of smooth endoplasmic reticulum in the Leydig cells are

correlated (Zirkin *et al.*, 1980). Boar and stallion testes also produce relatively larger amounts of estrogens (Oh and Tamaoki, 1970; Bedrak and Samuels, 1969). Cultured bovine testes exhibit testosterone secretion at 42 days of gestation (Shemesh *et al.*, 1978). Fetal testosterone concentrations decrease towards the time of birth but androstenedione is noticeably high at this time. The decrease in testosterone immediately before birth and decrease in number of Leydig cells at the same time can be correlated (Bascom, 1923). A decrease from 1:1 at 4 months to 1:10 in 9 months in androstenedione to testosterone ratio has been reported (McCarthy *et al.*, 1979a, b; Bedair and Thibier, 1979; Swanson *et al.*, 1971).

In vitro investigations have shown that testosterone is the principal steroid produced by bull testis at 5 months of age (Kiser *et al.*, 1974). Testosterone is produced either in untraceable or negligible amounts during the first months of life, steadily increasing up to 6-8 months and then gradually increasing in impulsive fashion until 1.5 years of age (Karg *et al.*, 1976; Lacroix *et al.*, 1977a; Lunstra *et al.*, 1978; Rawlings *et al.*, 1978; Bedair and Thibier, 1979; Lacroix and Pelletier, 1979; McCarthy *et al.*, 1979a; Oltner *et al.*, 1979; Amann *et al.*, 1986; Al-Haboby, 1986).

The mean testosterone levels were undetectable at 25-85 days of age and were highest at 220 days. The testosterone levels started to increase at 130 days of age in Holstein bull calves (Al-Haboby, 1986).

Receptors for LH are found in the Leydig cells and it stimulates testosterone production. In most mammals a rise in LH secretion is followed by testosterone rise. In bulls, testosterone peaks lag LH peaks by 20 minutes and have a duration of 128 minutes (McCarthy *et al.*, 1979a; Schams *et al.*, 1978). It is inferred that Leydig cell differentiation restricts testosterone production in early months as continuous presence of LH receptors is required for androstenedione production. As the differentiation progresses, the LH stimulated testosterone secretion becomes evident (Amann and Walker, 1983). A significant amount of estradiol and estrone in male bovine fetus is found at parturition (Challis *et al.*, 1974) and lower levels of estradiol have been detected in bull calf serum in early weeks of life followed by a marked decrease after 10 weeks of age (Amann *et al.*, 1986). A very high intratesticular concentrations of testosterone are reported (Amann and Ganjam, 1976), that are necessary for epididymal growth, spermatogenesis, differentiation of supporting cells and establishment of blood testis barrier (Amann and Schanbacher, 1983; Amann and Walker, 1983).

Somatomedin-C(Sm-c) or Insuline Like Growth Factor (IGF-I): Sm-c or IGF-I has both replicative and cytodifferentiative properties (Adashi *et al.*, 1985; Clemmons and van Wyk, 1981; Turo and Florini, 1982). IGF's along with other growth factors have been indicated to play a role in initiating and maintaining the growth of mesenchymal tissues (Bradshaw and Sporn, 1983; Daughaday *et al.*, 1982). Sm-c/IGF-I has been reported to have more stringent growth hormone dependence (Van Wyk, 1984); and promoted higher growth rates of mesenchymal cells *in vivo* (Schoenle *et al.*, 1982). As opposed to other somatomedins like IGF II or rIGF-II the serum levels of 5 m-a increase significantly during puberty and have been suggested to play a role in linear skeletal growth (Van Wyk, 1984). Though the site of Sm-c/IGF-I gene expression has been mainly thought of as liver but other

extrahepatic tissues have been reported to be the site of Sm-c synthesis playing at or on adjacent tissue, its autocrine or paracrine regulatory role (Clemmons and van Wyk, 1981; D'Ercole *et al.*, 1980). IGF's are bound to specific carrier proteins in the plasma (Adashi *et al.*, 1985) and the production of such protein molecules is also growth hormone dependent (Adams *et al.*, 1983; Scott *et al.*, 1985a, b). It was also reported that tissue concentrations of Sm-c/IGF-I are growth hormone dependent and these changes proceed those in the serum level and the treatment of hypophysectomized rat with OGH resulting in elevated Sm-c concentrations is itself an evidence that the Sm-c extracted from a tissue was synthesized in that tissue (D'Ercole *et al.*, 1984). Bovine growth hormone (bGH) stimulated IGF-I and binding protein (BP) production in rat hepatocytes *in vitro* and *in vivo*. Prior high GH status of animals from which cells were taken also resulted in higher IGF-I and BP production. Incubation of hepatocytes in the presence of OH, increased the production of IGF-I and BP (Scott *et al.*, 1985a). IGF-I stimulated in dosage dependent manner, the growth of hypophysectomized rats that supported the idea that action of growth hormone is mediated by IGF's decrease in case of hypopituitarism (Zapf *et al.*, 1981) and are elevated by GH therapy in human (Kemp *et al.*, 1981; Furlanetto *et al.*, 1977). IGF-I has direct stimulatory effect on growth and the increase in growth is comparable with that resulting with HGF treatment in rats (Schoenle *et al.*, 1982).

Action of Sm-c/IGF-I on Testicular Components: Rat Sertoli cells produce IGF-I (Ritzen, 1983) and whereas immature rat Sertoli cells do not respond to FSH, testosterone or cAMP analogues (Tres *et al.*, 1983; Smith *et al.*, 1984); low concentrations of hGH did cause the release of IGF-I by Sertoli cells (Tres *et al.*, 1983). Sertoli cell IGF-I has been reported to exist in the form of discrete intracellular granules and released in response to FSH and or OH stimulation (Smith *et al.*, 1984). The hypophysectomized rats showed a decrease of 27.7% in total IGF-I content of testis and this effect reversed by systemic oGH administration (D'Ercole *et al.*, 1980), which appears to be mediated by somatogenic receptors of testis. Above observations may suggest that gonadal IGF-I may be GH dependent rather than gonadotropin dependent. Rat Sertoli cells and Sertoli cell membranes have a very high number of receptors of type I that have a very high affinity for IGF-I (Borland *et al.*, 1984). Keeping in view the role of Sertoli cells in spermatogenesis, where in Sertoli cells act as intermediary between germ cells and plasma factors (including hormones). It might be possible that Sertoli cells respond to stimulation by germ cells (Means *et al.*, 1980). Although no conclusive evidence regarding the presence of Sm-c and its role in bull reproduction exists at this time, there is circumstantial evidence reported (Al-Haboby, 1986).

Epidermal Growth Factors (EGF): EGF's exert their mitogenic effect on a variety of epidermal and non-epidermal cells (Carpenter and Cohen, 1979; Gospodarowicz and Moran, 1976). The EGF's have been reported to have inhibiting effect upon LH receptors of testicular Leydig tumor cells (Ascoli, 1981); whereas, HCG stimulation of rat Leydig cell *in vitro* increases the testosterone production, the EGF exert an inhibiting effect on this stimulation. Bartke *et al.* (1975) and Byyny *et al.* (1974) reported a stimulating effect of androgens on EGF synthesis in the mouse submaxillary gland. This may pose a question of possible role of EGF in reproduction, in that the possible endocrine interrelationship of gonadal

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steroidogenesis and EGF biosynthesis may be of interest as the EGF can be found in various body fluids (Carpenter and Cohen, 1979).

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