Review Article CODEN: IJPRNK Impact Factor: 5.567 ISSN: 2277-8713
Subha Ganguly, IJPRBS, 2018; Volume 7(3): 18-25 IJPRBS

INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

ROLE OF GHRELIN AND LEPTIN IN REGULATION OF PUBERTY IN ANIMALS: A REVIEW

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Accepted Date: 23/06/2018; Published Date: 27/06/2018

Abstract: Lifetime reproductive efficiency of an animal chiefly depends on time of onset of puberty. Hormonal factors play a key role in the onset of puberty. Ghrelin and leptin, being important neuronal signalling factors, are involved in directing the onset of puberty and regulating other reproductive aspects by their action on CNS. Higher plasma concentration of leptin, while lower plasma concentration of ghrelin, have been found to be associated with the early onset of puberty. Present review encompasses detailed aspects of the role of ghrelin and leptin in different species in the regulation of age at puberty and other reproductive aspects.

Keywords: Ghrelin, Leptin, Puberty

PAPER-QR CODE

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Access Online On:

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How to Cite This Article:

Subha Ganguly, IJPRBS, 2018; Volume 7(3): 18-25

INTRODUCTION

Bull fertility is an important aspect because one bull may serve around twenty females under natural conditions or several thousand of females under an artificial insemination program. Onset of puberty and its time of occurrence is an important episode that contributes significantly to lifetime reproductive efficiency of any animal. Bulls have a greater and longer lasting genetic impact in each herd compared to females. *Bos taurus* bulls attain puberty around 8–10 months of age [1], however, *Bos indicus* bulls generally do not reach puberty until 16–18 months of age [2] and can only be used as breeding bulls at 2 years of age. [3] Individual genetics and metabolic factors such as body weight, growth and body fat influences the age at onset of puberty. [4]

Ghrelin and leptin are secreted mainly from the hypothalamus, gastrointestinal tract and adipose tissue. They have been discovered to exert different effects on several reproductive aspects. Ghrelin is now known as a novel peripheral growth hormone stimulant in most of the species including humans, rodents and domestic animals. [5] Ghrelin has been reported to stimulate GH secretion in dairy cattle at different physiological stages. Recently, it has been found that ghrelin also has different regulatory effects on plasma pancreatic hormone levels and on glucose concentration. [6] The amount of fat in the carcass has been proposed as a regulator of initiation of puberty in cattle. Wylie [7] has postulated that leptin acts as a permissive signal to the occurrence of puberty. Therefore, insufficient nutrient availability or depleted body reserves followed by depressed plasma leptin may suppress the ability of other signals to trigger. [8] Increase in circulating concentrations of leptin precedes the onset of puberty in several species, including cattle, and leptin has been shown to regulate the onset of puberty in rodents. [9, 10]

These findings suggest that leptin and ghrelin may be involved in regulation of puberty in animals. Present review highlights the functions of ghrelin and leptin, which may play important role in the regulation of puberty in different animals.

Ghrelin and Puberty Regulation

Ghrelin was initially discovered as a ligand for the growth hormone secretagogue (GHS-R1a) receptor and reported to induce GH secretion. [11] Ghrelin is secreted mainly by the stomach, although its expression has been detected in many other organs exerting both endocrine and paracrine effects. [12-14] It is involved in a series of biological functions including regulation of food intake [15], sleep [16], body weight [17], gastrointestinal motility [18], cardiovascular functions [18], cell proliferation [19], production of proinflammatory cytokines [20] and reproduction [21] in many species.

Ghrelin is a 28-amino acid peptide derived from preproghrelin. [22] The active form of bovine and ovine ghrelin has a 27 amino acid sequence (28 amino acids in most other species) with an n-octanoylation at the third serine residue. [23-27] It has two major endogenous forms: a des-acylated form (des-acyl ghrelin) and a form acylated at serine 3 (ghrelin) which is essential for the hormone biological activity. [28, 29] Ghrelin is synthesized by an endocrine cell population, the X/A-like cells, in the stomach mucosa [30] and their expression is also reported in pancreas, lymphocytes, placenta, kidney, lung, heart, pituitary, brain, ovary, and testis. [31-34] Ghrelin exerts direct regulatory effects on GnRH neurons via GHS-R, and modulates the firing of GnRH neurons in an ovarian-cycle and endocannabinoid dependent manner [35], melanocortigenic system and NPY receptors. [36] Kisspeptins signaling has an essential role in the activation of the HPG axis, the ability of ghrelin to down-regulate Kiss1 expression in medial preoptic area is a contributing factor in ghrelin -related suppression of pulsatile LH secretion. [37] Ghrelin affects the gonadotropin release by acting at the level of hypothalamus as well as directly on the pituitary gland. [38] In pituitary, ghrelin suppresses LH pulse frequency in rats, sheep [39], monkeys [40] and humans [41]. An inhibitory effect of ghrelin on progesterone secretion by luteal cells was observed. [42] Thus, ghrelin has the ability to modulate gonadotropin secretion, to influence puberty onset, and to directly regulate gonadal physiology. [43, 44]

Ghrelin and Onset of Puberty

Puberty in Rat

Fernandez-Fernandez *et al.* [44] reported that daily subcutaneous injection of ghrelin (0.5 nmol/12 h; between postnatal d 33 and 43) significantly decreased serum LH, testosterone levels and partially delayed the onset of puberty in pubertal male rats. However, twice daily injection of 1 nmol ghrelin for 10 days was sufficient to delay vaginal opening, ovarian follicular development and ovulation in pubertal female rats. Martini *et al.* [45] reported a similar result, which suggests that daily injection of ghrelin and unacylated ghrelin, throughout puberty in male rats, significantly decreased serum LH concentration.

Lebrethon *et al.* [35] reported that ghrelin exhibits inhibitory effects on pulsatile GnRH secretion after *in vivo* administration whereas stimulatory effects were observed *in vitro* in rat. Fernandez-Fernandez *et al.* [37]; Furuta *et al.* [46] reported that intra-cerebro-ventricular administration of ghrelin evoked a significant inhibition of LH secretion in cyclic female rats as well as in ovariectomized females. Similarly, gonadotropin-releasing hormone (GnRH) secretion by hypothalamic fragments from ovariectomized females was also significantly inhibited by ghrelin.

These data suggest that both male and female rats are sensitive to the elevated levels of ghrelin on delaying puberty onset.

Puberty in Human

Serum ghrelin levels are influenced by growth and by pubertal development, with serum levels increasing during the first two years of extra-uterine life, followed by a later decrease until the end of puberty. [48, 49] Matkovic *et al.* [47] observed that the leptin/ghrelin ratio in female beta-thalassemic patients was lower than the values obtained in the healthy persons and a significant negative correlation were detected between circulating levels of acylated-ghrelin and LH, FSH and sex hormones in both female and male beta-thalassemic patients. The lower values of leptin and ghrelin in patients with β-thalassemia possibly constitute another hormonal imbalance, which may contribute to the phenotype of impaired growth and sexual maturation encountered in these patients. Pomerants *et al.* [48] reported that during fasting ghrelin decreased, while leptin and insulin did not change, and testosterone increased during puberty. Therefore, they found a negative correlation between serum ghrelin and testosterone concentrations in pubertal boys, which indicate that ghrelin, may have a role in male puberty onset.

Whatmore *et al.* [9] observed that prepubertal children had higher ghrelin concentrations than those in puberty, with significant negative correlations between ghrelin and age, and pubertal stage. The decrease in ghrelin with advancing pubertal stage/age was more marked in boys than girls. In the whole group, ghrelin was negatively correlated with BMI and to weight. Lebenthal *et al.* [50] reported that after giving testosterone injection in boys, increased testosterone to pubertal levels induced a marked decrease in ghrelin.

Puberty in Goat

Farifteh *et al.* [51] reported that injection of 1 and 2 mg ghrelin/kg BW decreased the mean plasma concentration of LH in the female Sannan goat; however it had no significant effect on the mean plasma concentration of FSH.

Leptin

Leptin is a 16.4 kD peptide hormone consisting of 167 amino acids, product of the obese gene, is secreted primarily in adipocytes. [52-57] Leptin receptors exhibit widespread distribution in mammalian tissue, including liver, heart, brain, kidney, lung, small intestine, testes, ovaries, spleen, pancreas and adipose tissue. [58, 59] It is involved in regulation of feed intake, energy balance, fertility, milk production and immune functions. [57, 60] It plays a critical role in the regulation of body weight by inhibiting food intake and stimulating energy expenditure. [53] Its role in reproduction includes important actions on the hypothalamus to bring about release of

GnRH (especially, LH releasing hormone), thereby triggering gonadotropin release and leading to development of the reproductive tract and induction of puberty. [54] It is a permissive factor in the initiation of puberty. [55] Administration of leptin to obese, leptin -deficient mutant mice caused decreased food intake, body weight loss, increased ovarian weight, increase in ovarian follicles and restoration of fertility. [56-59] The effects of leptin on GnRH release and to cause an upregulation of LH pulses are mediated through inter neuronal pathways involving NPY, proopiomelanocortin (POMC) and Kisspeptin. [60] Furthermore, leptin regulates reproductive function by altering the sensitivity of the pituitary gland to GnRH.

Role of Leptin in regulation of onset of puberty

Puberty in Pig

In the pig, presence of biologically-active leptin receptor (OB-rb) in the hypothalamus and pituitary [61], and the fact that leptin increased LH secretion from pig pituitary cells and GnRH release from hypothalamic tissue [62] *in vitro* suggests that leptin acts through the hypothalamic-pituitary axis to modulate LH secretion. There is strong evidence from co-localization of leptin receptor mRNA with NPY gene expression that hypothalamic NPY is a potential target for leptin in the pig. [63] Moreover, central administration of NPY suppressed LH secretion, and stimulated feed intake by reversing the inhibitory action of leptin. [62] Leptin treatment stimulated basal LH secretion directly from pig anterior pituitary cells in culture, and GnRH release from hypothalamic-preoptic tissue explants from intact and ovariectomized prepubertal gilts on maintenance rations. [64] Qian *et al.* [65] reported that leptin concentration increases during puberty.

Puberty in Sheep

Miller *et al.* [50] reported that intra-cerebroventricular injection of leptin stimulated LH secretion in steroid-implanted castrated male sheep, however, chronic intra-cerebro-ventricular administration of leptin failed to stimulate LH secretion in well-nourished ovariectomized ewes with no steroid replacement [66] and in intact ewe lambs [67]. Morrison *et al.* [22] stamped that inhibition of LH secretion by nutrient restriction in the ewe lamb was reversed by leptin treatment, demonstrating a positive association between LH secretion and leptin.

Puberty in Cattle

Chronic intra-cerebro-ventricular administration of leptin stimulated LH secretion in the feed-restricted ovariectomized cow. [68] Serum leptin concentrations increased as did leptin gene expression in heifers during pubertal development, which coincided with increase in serum IGF-I concentrations and body weight. [69] Beginning at 16 weeks before puberty, serum leptin concentrations (3.8±0.4 ng/ml) began a linear increase ($P<0.0001$) and averaged 6.4±0.4 ng/ml

during the week of puberty in cattle. [69] Leptin gene expression and circulating leptin increase markedly during sexual maturation in pubertal heifers. [39] The *in vivo* data in cattle revealed that increased plasma leptin concentrations are associated with elevated progesterone secretion in dairy cows. [70] Leptin also plays a significant role in promoting angiogenesis, steroidogenesis in luteal ce3lls. [71] However, Maciel *et al.* [63] reported that exogenous leptin did not alter the secretion of LH, GH, insulin and IGF-1, and had no effect on puberty in heifers.

Puberty in Human

Matkovic *et al.* [47] reported that age at first menarche was inversely related to serum leptin concentrations. Serum leptin concentrations rise in young girls starting as early as at the age of 7 years and continuing to rise, as they progressed through puberty, up to at least 15 years of age [71-74], and these changes in concentrations of leptin were paralleled by increasing body fat during female puberty. Garcia-Mayor *et al.* [71] suggested that this is consistent with the hypothesis that leptin concentrations reach a putative threshold which allows puberty to progress.

Puberty in Rat

Almog *et al.* [75] reported that the administration of leptin to rats, starting at age of 21 d, advanced the age at puberty in 100% of the animals. Israel *et al.* [76] demonstrated that melanocortin signalling is an important component in the leptin -mediated regulation of GnRH neuron activity, initiation of puberty, and fertility in female mice. However, some reports indicated that blood leptin concentrations remain relatively unchanged during pubertal development in the female mouse and rat [77-79], while leptin administration failed to advance puberty onset in well nourished female mice. [80] In other words as circulating leptin concentrations increase during pubertal development, a threshold may be reached that permits activation of the reproductive axis [81] (Fig. 1). In this respect, leptin is a permissive signal for puberty, as opposed to a triggering signal for puberty.

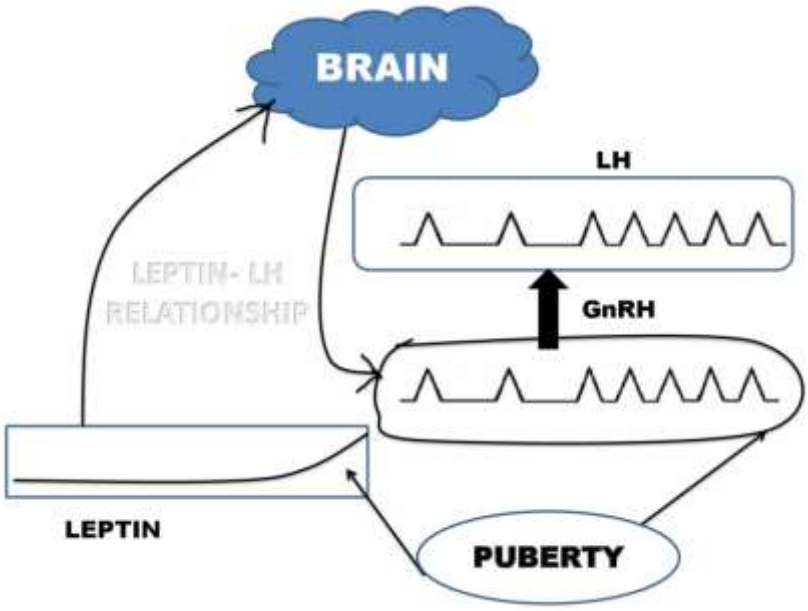

Fig.1. Relationship between Leptin, GnRH and LH secretion

CONCLUSION

Ghrelin and leptin by acting as neurohormones, are involved in the complex interplay of endocrines and neuroendocrines, which regulate the onset of puberty. Their varying levels in the neuronal circuits regulate the complex GnRH- gonadotropins - sex steroids axis, and ultimately the secretion of sex steroids. Ghrelin is known to play role in number of biological functions including regulation of food intake, sleep, body weight, gastrointestinal motility, cell proliferation and reproduction in many species. Its expression is reported in placenta, heart, pituitary, brain, ovary and testis. Ghrelin exerts direct regulatory effects on GnRH neurons via GHS-R, and modulates the firing of GnRH neurons in an ovarian-cycle. Circulating Leptin concentrations increase during pubertal development, its threshold permits activation of the reproductive axis. Therefore, Leptin acts as a permissive signal for onset of puberty. Nesfatin, ghrelin and leptin play a role in regulation of onset of puberty. They can be used as a tool for early detection and manipulation of puberty.

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