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Review

# Role of Leptin in Onset of Puberty in Cattle

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## Abstract

*Puberty in cattle is influenced by adipose tissue and body weight. Adipose tissue mass and weight of the pubertal animal are related to body condition score near puberty. Leptin hormone levels are associated with regulating body condition scores in mammals. Puberty is a complex developmental phenomenon regulated by actions of many endogenous and environmental signals. In fact, the timing of puberty is strongly related to the deregulation of energy homeostasis and metabolism. Moreover, the critical body weight in cattle is associated with the start of sexual maturation or puberty. Chemical or hormonal signals have been linked to body weight while linking adiposity to pubertal onset is still awaiting any definite relation in the documented literature so far. Also, metabolic signals influencing puberty constitute a large number of peripherally originating substances, acting centrally to modify neuronal activity. As per a comprehensive review of studies, leptin is considered to effectively stimulate the hypothalamic-gonadotropic axis in cattle, sheep, and other animals. It also is linked to stimulating tissues pre-exposed to profound negative energy balance. Thus, a relationship between adipose tissue, energy homeostasis, and their influence on the attainment of puberty by animals is a widely accepted phenomenon. The multifactorial nature of leptin in the reproductive pathway is documented. Leptin is related to gonadotropic hormones to cause reproduction events via leptin receptors in the hypothalamus, activating GnRH secretion at puberty. Recent studies show a permissive role of leptin in the onset of puberty relayed by Kiss1 neurons. Leptin, as a metabolic signal is also associated with the onset of sexual maturation. Body weight gain during early postnatal development results in increased circulating levels of leptin which ultimately contribute to promoting early puberty. As per our insight into the literature, multiple endocrine and metabolic pathways have been identified to play a part in puberty but central mechanisms of leptin-mediated reproductive events at puberty in cattle are not fully established. This paper discusses the nature of leptin, its origin, and its role in reproductive events, particularly at puberty and the early onset of puberty by leptin in cattle.*

**Keywords:** Cattle, Hormone, Leptin, Puberty

## Introduction

Adipose tissue mass and body weight determine puberty in cattle (Maciel *et al*., 2003). As reported in various studies, body condition score and adipose mass are significantly regulated by the leptin hormone in mammals (Laksmi, 2018). Leptin, a 16kDa protein, with 146 amino acids, is synthesized in adipose tissue and finally released into the circulation of mammals after modification by cleavage of the 21 amino acid signal peptides. Leptin is associated with the regulation of puberty, feed intake, neuroendocrine axis, and immunological processes in animals. The leptin gene is important for improving cattle reproduction and production potentials (Dubay *et al*., 2007). The hormone leptin has been related to puberty onset in mice, rats, and humans (Chenab *et al*., 1997 Cheung *et al*., 1997). Its role in puberty has been studied widely in lab animals and is associated well with puberty in cattle and other farm animals. Leptin elevated luteinizing hormone (LH) levels in full-fed rats and pigs through stimulation of the hypothalamic–gonadotropic axis. In cattle and sheep, the LH levels are raised predominantly in animals and tissues pre-exposed to profound negative energy balance. Leptin also prevents a reduction in LH frequency in fasting peripubertal heifers. Besides, it augments the magnitude of LH and Gonadotropic Releasing Hormone (GnRH) pulses in cattle fasted for a few hours. Leptin enhanced basal secretion of LH in vivo as well as in adenohypophyseal explants of fasted cows (Zieba *et al*., 2005). It has already been suggested that altered metabolic conditions or nutritional stress completely impair reproductive onset and suppress the GnRH drive on gonadotropin secretion (Foster *et al*., 1998). Bruinje *et al* (2021) established an interesting relationship between leptin with puberty, saying that for every 1 ng/mL increase in leptin, a reduction of 22 days in the attainment of puberty can be ascertained in cattle. Henry *et al* (1999) have studied leptin concentrations and revealed serum leptin concentrations increased linearly from 3.8±0.4 ng/ml (16 weeks before puberty) to 6.4±0.4 ng/ml during the last week of puberty. The rise in plasma leptin concentrations elevates progesterone secretion in dairy cows owing to its role in promoting angiogenesis and steroidogenesis in luteal cells (Amstalden *et al* 2002). These findings indicate leptin's clear role in reproductive events like puberty in cattle. Similar results have been well documented in the literature regarding sheep, pigs, humans, and laboratory animals. More recently in 2019, Heryani *et al* reported leptin levels strongly correlated to body condition and puberty in cattle. The study in Bali cattle revealed an average of 5.62 ng/ml plasma leptin concentrations around the first estrus or emergence of puberty.

It is also well established that leptin does not accelerate the frequency of LH pulses in prepubertal heifers and has no effect on the secretion of GnRH and LH in full-fed cattle or even in explants of hypothalamic or hypophyseal parts. Garcia *et al*., (2002) observed an increase in serum concentrations of leptin and leptin gene expression as puberty approached in heifers. The increase in serum leptin was linear regardless of the season of pubertal onset. Leptin gene expression and circulating leptin increase markedly during sexual maturation in heifers reaching puberty during late spring or early summer (Carvalho *et al*., 2013). Based on the above findings and some recent reports, the leptin gene in cattle may contribute to an array of important reproductive events, including puberty. Sexual maturation and nutritional status determine more than how leptin affects ruminants' hypothalamic-hypophyseal axis. Kisspeptin and sexually dimorphic expression of kisspeptin neurons (Bianco 2012) and their receptor co-expression with leptin in rats at puberty (Cravo *et al*., 2013) has been observed but how leptin physiologically signals Kiss1 neurons remains yet to be studied comprehensively. Leptin in this review will be discussed in relation to the energy status of animals, receptor-mediated actions of leptin-central and peripheral, leptin and reproductive hormones, and its role as a key metabolic regulator of puberty in cattle.

## Energy Balance-Leptin-Puberty and Other Reproductive Functions in Cow

Zebu heifers subjected to high energy intake showed increased leptin concentration, improved body gain, and accelerated follicular development which might ultimately result in puberty onset (Carvalho *et al*., 2013). The available literature compiling these facts in cow heifers comprehensively includes studies by Baile *et al*., (2000), Ingvartsen and Boisclair (2001), Williams *et al*., (2002), Barb and Kraeling (2004), Barb *et al*. (2005) and Zieba *et al*. (2005), Chilliard *et al*., (2005) and Barb *et al* (2006). Leptin as a mediator of adipocyte endocrine activity is documented by Ahima and Flier (2000), Harris (2000) Margetic *et al*., (2002a), Kershaw and Flier (2004), and Miner (2004). Nutritional imbalances alter the endocrine function and delay the onset of puberty and interfere with normal estrous cycles have been observed in gilts (Barb *et al*., 1997), cow heifers (Houseknecht *et al*., 1988) and ewes (Estienne *et al*., 1990). Thus, as a conclusive remark of various studies, puberty has been suggested to be metabolically gated and metabolic signals are important in the initiation of puberty. True *et al*., (2011) depicted the role of leptin as a key metabolic signal. Thus, as a metabolic signal, leptin can greatly influence puberty through stimulation of the hypothalamic-gonadotropic axis in cattle, sheep, and other animals and tissues pre-exposed to

profound negative energy balance. Full proof evidences are awaited in the literature regarding leptin rich feeds to animals initiating the early onset of puberty.

As per various literature observations, leptin has been suggested as a general stimulator of whole reproductive events and a central regulation of reproduction in cattle (Carvalho *et al*., 2013). Administration of leptin to mice restored reproduction by acting through its receptors. The leptin receptor (LR) is a member of the class 1 cytokine family of receptors distributed in the brain and pituitary of all species. Elevated serum leptin levels, hypothalamic leptin receptor mRNA, and estrogen-induced leptin gene expression in fat with age and adiposity have been well observed in pigs. The same also happens when expected puberty (Barb *et al*., 2005).

## Leptin Receptors and Site of Action

The LR family comprises of six receptor isoforms that arise from alternative splicing. LR isoforms-long form (OB-rb), short forms possessing variable lengths of the cytoplasmic tail (OB-ra, OB-rc, OB-rd and OB-rf), and soluble form (OB-re) consisting of the extracellular loop and circulates in plasma (Tartaglia, 1997). The receptors being a class 1 cytokine receptor family member act via janus-activated kinases (JAK)-signal transducers and activators of transcription (STAT) activation. The long-form LR signals via JAK-STAT activation (Houseknecht and Portocarrero, 1998) while the short isoforms signal by mitogen-activated protein kinase (MAPK) or phosphotidyl inositol-3 (PI-3) kinase pathway (Bjorbaek *et al*., 1997).

OB-rb is the most varying receptor type among species and OB-rb mRNA abundance has been localized in the ventromedial and arcuate nuclei of the hypothalamus and anterior pituitary of the pig (Lin *et al*., 2001), ewe (Dyer *et al*., 1997), rat (Zamorano *et al*., 1997), and mouse (Tartaglia *et al*., 1995). Leptin can act on the brain and pituitary to regulate gonadotropin secretion. In fact, leptin acts directly on GnRH neurons as proposed in the available literature in mammals (Sullivan and Meonter, 2004). Neuropeptide Y (NPY), proopiomelanocortin (POMC), and gama-aminobutyric acid (GABA) also mediate the action of leptin (Cunningham *et al*., 1999; Iqbal *et al*., 2001; Williams *et al*., 2002; Sullivan and Meonter, 2004). Hypothalamic NPY has been suggested as a potential target for leptin due to co-localization of leptin receptor mRNA with NPY gene expression in rats, humans (Cunningham *et al*., 1999) and ovine (Iqbal *et al*., 2001).

## Leptin and Hypothalamic Centers

Hypothalamic NPY has been implicated in the regulation of GnRH/luteinizing hormone (LH) secretion in the rodent (Kalra, 1993), primates (Kaynard *et al*., 1990), ewe (Morrison *et al*., 2003), cows (Thomas *et al*., 1999) and pig (Barb *et al*., 1999). Administration of NPY stimulated appetite in the ewe (Miner, 1992) and pig (Barb *et al*., 2001a). In cattle, a number of studies have shown that leptin may play an important role as a signal linking nutritional status to the central reproductive axis. The metabolic status has a clear impact on the timing of puberty but the mechanisms underlying this phenomenon are complex and likely involve different regulatory pathways. Moreover, according to various studies, it can be inferred that understanding the interaction between energy balance and fertility has critical implications for the GnRH neurons. Stimulation of the hypothalamic–gonadotropic axis by leptin in cattle and sheep is observed predominantly in animals and tissues pre-exposed to profound negative energy balance. Some other neuronal systems also mediate the action of leptin and fertility being partially restored by leptin treatment in the ob/ob mouse with a homozygous null mutation for NPY (Erickson *et al*., 1996). It is also ascertained that in vivo perfusion of the median eminence-arcuate nucleus complex with leptin fails to affect NPY secretion While it increases growth hormone releasing factor (GH-GRF) and GH secretion (Watanobe and Habu, 2002). It also does not stimulate any NPY release during in vitro treatment of hypothalamic tissue in mice (Jang *et al*., 2000), rats (King *et al*., 2000), and pigs (Barb *et al*., 1999). In periods of nutritional stress, hypothalamic NPY mRNA is elevated with such experiments and in farm animal species, NPY has been shown to suppress LH secretion and stimulate feeding behavior (Barb *et al*., 1999). It can be concluded that activation of the NPY system with leptin administration also appears to be related to chronic physiologic changes associated with fasting.

Leptin stimulates the release of GnRH from rat and porcine hypothalamic explants even if its receptor has not been found on GnRH neurons. Leptin acts specifically on at HPA and GnRH neurons (Lin *et al*., 2001). Higher amount of Ob-Rb expression within the hypothalamic nuclei - ME, ARC, VMH-stimulate the release of GnRH. Leptin exerts its effects trans-synoptically via NPY and POMC neuronal networks (; Sullivan and Meonter, 2004). Cocaine and amphetamine-regulated transcript (CART), Agouti-related protein (AGRP), orexin, Melanin-concentrating

hormone (MCH) and Galanin hypothalamic neurons also express OB-rb and thus are direct targets of leptin (Iqbal *et al*., 2001; Bjorbaek and Kahn, 2004). There is a co-expression of leptin and the kiss 1 gene at puberty and leptin signaling in Kiss1 neurons only occurs after the completion of sexual maturation. However, kisspeptin neurons do not directly mediate the action of leptin on pubertal development. Further leptin signaling in Kiss1 neurons only occurs after completion of sexual maturation, i.e., in adult life, hence kisspeptin neurons do not directly mediate the action of leptin on pubertal development. The physiologic role of leptin signaling in Kiss1 neurons is yet to be demonstrated. Hypothalamic levels of Kiss1 mRNA and numbers of kisspeptin immunoreactive neurons increase during pubertal development (Desroziers *et al*., 2012). Studies of the relevant role of the kisspeptin- GPR54 system in reproductive physiology and the co-expression of the Kiss1 and Lepr genes in hypothalamic neurons have postulated the permissive role of leptin in the onset of puberty, relayed by Kiss1 neurons (Terasawa *et al*., 2012; Pinilla *et al*., 2012).

## Leptin: A Metabolic Gate for The Onset of Puberty in Farm Animals

Leptin has been proposed as a physiological link between adiposity status and the start of sexual maturation (Bluher and Mantzoros, 2007). Leptin serves as a trigger and a permissive factor in the onset of puberty (Rutters 2009). Exogenous leptin treatment of normal mice advanced vaginal opening by a few days (Ahima *et al*., 1997; Chehab *et al*., 1997). However, in ad libitum-fed rats, leptin did not significantly alter the normal course of puberty, although it was able to partially reverse the delay in sexual maturation caused by reduced feeding (Cheung *et al*., 1997). It is also well documented that earlier sexual maturation in animals is associated with an increase in serum leptin or leptin receptor gene expression in the hypothalamus or gene expression in the HPG axis. Garcia *et al*., (2002) have suggested that the approach of puberty in heifers is associated with increased leptin gene expression and circulating concentrations.

The control of the reproductive function by the brain must be responsive to the metabolic state of the animal. Animals and humans if exposed to energy deprivation before puberty show delayed onset of puberty till a favorable energy balance is achieved. Hence reproduction needs to be optimized in environments of fluctuating energy availability. Body fat reserves around puberty may act as energy for the periods of pubertal changes. Excess body fat has been documented to trigger the early onset of puberty, especially in females. Prevalence of delayed puberty is more in males compared to females giving another indication that sexual dimorphism can be a sensitizing factor of the reproductive axis to metabolic cues. Understanding the interaction between energy balance and fertility has critical implications for the GnRH neurons on their own seem to sense few metabolic cues. Circulating factors serve as signals of the nutritional state of the individual- leptin, insulin, and ghrelin are perceived by neighboring neurons and glia. If these cells are not able to sense metabolic cues, for example in states of insulin or leptin resistance, the repercussions may include both imbalanced metabolic homeostasis and reproductive dysfunction. Indeed, leptin-deficient patients become hyperphagic, massively obese, and infertile.

True *et al*. (2011) emphasized that although leptin may be an important permissive signal for reproductive function as indicated by many years of research, factors other than leptin must critically contribute to negative energy balance-induced reproductive inhibition. Schneider *et al*. (2012) call attention to the "metabolic hypothesis," which predicts that sensory systems monitor the availability of oxidizable metabolic fuels and allow behavioral responses to optimize reproductive success. The Kisspeptin system is the converging target of environmental, metabolic, and hormonal signals Bianco (2012). Xu *et al*., (2012) propose that pro-opiomelanocortin (POMC) neurons in the arcuate nucleus and the steroidogenic factor-1 (SF1) neurons in the ventromedial hypothalamic nucleus play an important part in the above signals to mediate puberty and reproduction. In fact, disruption of metabolic signals due to leptin and insulin or reproductive signals related to estradiol in these neurons leads to impaired regulation of both energy homeostasis and fertility. Donato *et al*., (2011) have demonstrated the probable role of the ventral pre-mammillary nucleus as an integrator of environmental, metabolic, and reproductive cues, and its emergence as a critical site linking metabolism and reproduction. Also, Acosta-Martínez (2012) proposes a role for phosphatidylinositol-3-kinase (PI3K) signaling pathway as a potential integrator of a number of peripheral metabolic cues, including insulin and leptin, in the metabolic control of the reproductive function. in Pubertal timing, there may be a potential role of endogenous timing mechanisms including cellular circadian clocks in pubertal initiation. These clocks have been proposed to be altered by metabolic factors leading to reproductive deficits (Tolson and Chappell 2012). Metabolism might influence sexual behavior and food intake or food hoarding in hamsters (Klingerman *et al*., 2011), suggesting some role for neuropeptide Y (NPY) and gonadotropin inhibiting hormone (GnIH) expressing cells in these processes

Amstalden *et al*. (2011) emphasize observations made in ruminant species in a very welcome comparative perspective. The neurons expressing kisspeptins, the products of the Kiss1 gene that have emerged recently as essential upstream regulators of GnRH neurons, operate as key sensors of the metabolic state and funnel of the reproductive effects of leptin. The exclusion of a major leptin signaling event in the hypothalamus stemmed from the finding that mutation of the critical tyrosine 1138 phosphorylation site in the long form of the leptin receptor, largely responsible for signal transducer and activator of transcription (STAT)-3 activation, resulted in an obese but fertile mouse (Bates *et al*., 2003). Thus, the pathway elicited by tyrosine 1138 phosphorylation is not critical for reproduction. These observations suggest that the leptin-reproductive pathway bifurcates from the leptin-energy homeostasis pathway prior to the MC4-R and may involve a separate signaling pathway at other leptin receptor sites. The complexity of this pathway is demonstrated by the fact that modifier genes rescued the sterility phenotype of leptin-deficient mice, demonstrating the multifactorial nature of the leptin reproductive pathway (Ewart-Toland *et al*., 1999; Qiu *et al*., 2001).

## Central Effects of Leptin on the Hypothalamic-Pituitary Axis

Acute intracerebroventricular (ICV) injection of leptin stimulated LH secretion in the estrogen-primed OVX rat (Yu *et al*., 1997) and steroid-implanted castrate male sheep (Miller *et al*., 2002). Chronic ICV administration of leptin stimulated LH secretion in the feed-restricted cow (Amstalden *et al*., 2002) and ewe (Henry *et al*., 2001). In contrast, chronic ICV administration of leptin failed to stimulate LH secretion in well-nourished OVX ewes with no steroid replacement and in intact ewe lambs (Morrison *et al*., 2001, 2003). Leptin treatment mediates LH secretion from pituitary explants in fasted cows through stimulation of GnRH. (Amstalden *et al*., 2003). This again indicated that the metabolic state appears to be a primary determinant of the hypothalamic-pituitary response to leptin in ruminants. Also, leptin treatment mediates LH secretion directly from anterior pituitary cells and GnRH release from hypothalamic-preoptic tissue explants from intact and ovariectomized prepubertal gilts on maintenance rations (Barb *et al*., 2004). The effect of leptin on LH secretion in the pig during pubertal development is associated with the stage of sexual maturation and subsequent change in the negative feedback action of estradiol on LH secretion. Moreover, the negative feedback action of estradiol on the GnRH pulse generator during pubertal development can be due to the deprivation of neuroanatomical connections of hypothalamic tissue with extra hypothalamic tissues.

## Leptin and Puberty in Cattle and Sheep

In the prepubertal ruminant, short-term feed restriction reduced adipose leptin gene expression and leptin secretion, but increased hypothalamic OB-rb expression (Dyer *et al*.,1997; Amstalden *et al*., 2000). This was associated with decreased serum insulin, IGF-I and LH pulse frequency (Amstalden *et al*., 2000; Morrison *et al*., 2001). Furthermore, serum leptin concentrations increased as did leptin gene expression in heifers during pubertal development coincident with increases in serum IGF-I concentrations and body weight (Garcia *et al*., 2002). In contrast to the prepubertal heifer (Amstalden *et al*., 2000), short-term fasting failed to reduce pulsatile LH secretion in the mature cow (Amstalden *et al*., 2002). This suggests that there is a heightened sensitivity of the hypothalamic-pituitary axis to variations in energy availability in the heifer. Previous reports demonstrated that inhibition of LH secretion by nutrient restriction was reversed by leptin treatment demonstrating a positive association between LH secretion and leptin (Henry *et al*., 2001; Morrison *et al*., 2001; Amstalden *et al*., 2002). Thus, leptin may act as a metabolic gate for puberty. In other words, as circulating leptin concentrations increase during pubertal development, a threshold that permits activation of the reproductive axis may be reached

In heifers near the time of pubertal transition, it was observed that fasting for 2 d markedly decreased leptin mRNA in adipose tissue, as well as circulating concentrations of leptin, and reduced the number of pulses of LH compared to non-fasted animals (Amstalden *et al*., 2000). Also, the pattern of adipose mRNA expression for leptin and serum concentrations of leptin during pubertal development were correlated with body weight and adiposity, bound/free leptin proportions, and IGF-1 concentrations in serum (Garcia *et al*., 2002). Moreover, body weight accounted for the greatest variation associated with the time of onset of puberty and was highly correlated with circulating leptin and serum concentrations of leptin, IGF-1, and leptin gene expression increased as puberty approached in heifers reaching sexual maturation from early spring to mid-summer. There is no evidence for the presence of leptin-binding proteins in bovine serum (Garcia *et al*., 1999). On the contrary, in humans, marked decreases in leptin-binding activity in serum accompany pubertal increases in circulating leptin, (Quinton *et al*., 1999).

## Leptin: GnRH, Estrogen and LH

Puberty, a complex physiological process requires maturation of the reproductive neuroendocrine system and subsequent episodic release of GnRH and LH in female animals. Leptin plays a critical role in conveying nutritional information to the neuroendocrine axis and controlling pubertal progression through increased LH pulse frequency (Cardoso *et al* 2018). Leptin treatments in normally fed heifers (Maciel *et al*., 2004), normal-growth or restricted growth heifers (zieba *et al*., 2004) were not found capable of accelerating the development of a sexually mature pattern of gonadotropin secretion. These observations are supported by studies in male lambs (Jackson *et al*., 2002), demonstrating that leptin cannot drive GnRH secretion in individuals incapable of producing pulses due to developmental constraints. With approaching puberty, plasma leptin concentrations increase in dairy heifers. In intact and ovariectomized rodents, estrogen has been shown to modulate the expression of leptin and its receptor (Ob-R). To determine if estrogen regulates the bovine leptin system, prepubertal dairy heifers were ovariectomized greater estrogen secretion does not cause increased plasma leptin in prepubertal dairy heifers but estradiol can modulate Ob-R expression in some estrogen-responsive tissues. However, leptin has been seen to increase the concentration of GnRH and the size of individual pulses of GnRH in CSF collected from the third ventricle. The inability of leptin to stimulate an increase in circulating concentrations of LH in full-fed cattle and sheep (Maciel *et al*., 2004), and in primary cell cultures or explants from full-fed cattle (Amstalden *et al*., 2005), is not completely understood; however, the published literature increasingly supports a consensus that leptin stimulates the hypothalamic–adenohypophyseal axis mainly in nutritionally stressed animals. Furthermore, leptin effects are dose-dependent on the hypothalamic-pituitary axis. In fact, intravenously injected recombinant oleptin leads to a dose-related increase in basal plasma concentrations of LH in ovariectomized, estradiol-implanted cows fasted for 60 h (zieba *et al*., 2003).

## Conclusions

Puberty is hormonally mediated and occurs only when body energy stores are adequate. Leptin provides a putative mechanism of energy retention and signals the brain for pubertal changes. Exogenous leptin acts on hypothalamic receptors and restores gonadotropin secretion. Leptin may act as a metabolic signal to control the onset of sexual maturation. Leptin-mediated increases in LH secretion in the cow are affected at both hypothalamic and anterior pituitary levels. A bunch of studies reveals several endocrine and metabolic pathways identified but the central mechanisms involved in leptin-mediated reproductive events, particularly at puberty onset are still unclear. Further studies are warranted to manipulate serum leptin concentrations for attaining early puberty in cattle. No set protocols are available to use exogenous leptin in cattle calves for the early onset of puberty. Moreover, the time or stage of the animal at which leptin should be given to induce the early onset of puberty in farm animals is not defined accurately in the literature. Also, it is yet to establish how the perinatal nutritional environment can program the reproductive neuroendocrine axis and to what extent sexually inactive heifers respond to leptin for the attainment of puberty and sexual maturity.

## Contribution by Authors

All the authors contributed equally to writing the manuscript. The final manuscript was read by all others and consented to publication.

## Conflict of Interests

There is no conflict of interest.

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