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Understanding leptin's influence on calf development: A review of metabolic and reproductive mechanisms

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SUMMARY

Leptin, a hormone primarily produced by adipose tissue, regulates the energy balance, metabolism, and reproductive functions. This review explores leptin's role in calf development from embryogenesis to puberty. Leptin expression is strongly influenced by the nutritional status, with circulating levels dependent on adipose tissue mass and modulated by metabolic hormones such as insulin and glucocorticoids. It plays a regulatory role in the embryonic cell division, adipogenesis, and postnatal energy metabolism. Additionally, leptin modulates appetite, the growth hormone secretion, and the reproductive system maturation. Its presence in the colostrum and milk highlights its significance in the early calf development, influencing the neonatal metabolism and immune function. As calves approach puberty, leptin serves as a key metabolic signal for reproductive maturation. A deeper understanding of leptin's multifunctional role in calf development could contribute to improved livestock growth and reproductive management strategies.

Keywords: *leptin; hypothalamus; adenohypophysis; reproduction; cattle*

INTRODUCTION

Leptin is a hormone primarily secreted by adipose tissue, which is involved in regulating energy balance, metabolism, and reproductive function, not only in mammals but also in non-mammalian vertebrates. Although discovered as recently as 1994 in mice and soon after in humans, leptin has been the subject of extensive study, particularly regarding its role in the neuroendocrine axis that signals nutritional status to the brain (Zhang et al., 1994; Friedman et al., 1998). In ruminants, such as cattle, leptin is considered one of the key metabolic regulators, influencing feed intake, energy expenditure, and reproduction.

In calves, leptin may be considered an important hormone since it takes part in all physiological stages from embryogenesis to puberty. It promotes the formation of adipose tissue, exerts regulatory actions on growth hormone secretion, and informs the hypothalamic-pituitary axis about energy reserves, thus controlling reproductive maturation. Moreover, the presence of leptin in colostrum and milk underlines its role in neonatal development by controlling metabolic and immune function (Chilliard et al., 2005; Campfield et al., 1995).

Thus, the present review represents an overall compilation of available literature on the multifunctional aspects of leptin in calf development: the relation of metabolism, growth, reproduction, and immune status to it aims to point out the critical role played by this hormone in shaping the development features of calves and its possible applications in livestock management.

Leptin serves as a permissive signal for the onset of puberty and is essential for communicating nutritional status to the mammalian central reproductive axis. The amount of adipose tissue directly correlates with leptin expression and release, and feed intake variations acutely regulate these levels. Furthermore, in heifers, circulating leptin rises throughout pubertal development (Zieba et al., 2005).

LEPTIN'S ROLE IN ENERGY BALANCE, METABOLIC REGULATION, AND REPRODUCTION

Leptin influences a wide range of metabolic hormones to regulate lipid metabolism, energy balance, and reproductive function. Among them, insulin plays a crucial role in promoting triglyceride storage instead of lipid oxidation, and ob gene expression regulation. Ceddia et al. (2001) demonstrated that in skeletal muscle, insulin and leptin exert opposite effects: leptin increases lipid oxidation, whereas insulin increases lipid storage.

Other hormones like glucocorticoids, growth hormone, and thyroid hormones (T3 and T4) influence leptin expression as well as circulating levels. Adipose cell count, body condition score, and nutritional status are all favorably correlated with cattle plasma leptin levels (Chilliard et al., 2001). Research has further shown that plasma leptin levels increase with the deposition of fat in beef cattle (Kawakita et al., 2001), and ob mRNA expression is connected with fat cell size and overall adiposity (Houseknecht et al., 1998). As much as cattle breed variation concerning fat deposition is established, their mechanisms are still not well characterized (Higashiyama et al., 2003).

In rodents, leptin is said to suppress insulin and glucocorticoid levels by central actions or endocrine feedback but induce the secretion of growth hormone, catecholamines, and thyroid hormones. All these actions act together to enhance tissue energy expenditure, induce lipolysis, and reduce lipogenesis in

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both hepatic and adipose tissues (Chilliard et al., 2005). Directly, peripherally, it mobilizes lipid and inhibits the synthesis of fat, increases insulin sensitivity and glucose uptake in muscle, and increases the oxidation of fatty acids in a number of tissues, including muscle, liver, and adipose depots.

Much of our current understanding of leptin's metabolic effects is based on animal studies, which have demonstrated that it is a multifunctional regulator of physiological and endocrine responses. Leptin is an important metabolic signal, particularly in the context of caloric deficit or energy imbalance states. In undernutrition, falling leptin levels instruct the hypothalamus to conserve energy by reducing secretion of thyroid, gonadal, and growth hormones and increasing cortisol levels. This signaling is mediated primarily by hypothalamic leptin receptors, but leptin also directly affects pituitary cells and has effects on adrenal and thyroid function through receptor expression in these glands.

Leptin secretion is proportional to the overall mass of adipose tissue and provides the brain with information regarding the energy stores. Interestingly, subcutaneous fat releases more leptin than visceral adipose tissue, and serum levels are typically higher in female than in men (Stepien et al., 2011).

In cattle, as in other monogastrics and man, leptin plays a part in central reproductive control by integrating energy status with reproductive signaling pathways. Leptin gene expression and plasma levels increase at puberty in heifers, consistent with a permissive function in the initiation of reproductive function. Gene expression data in cattle and sheep indicate that leptin targets both the hypothalamic-pituitary axis and endocrine pancreas, particularly under some nutritional circumstances (Williams et al., 2002).

To this end, Garcia et al. (2003) reported a linear increase in beef heifers' plasma leptin levels, as similarly observed in dairy heifers by Diaz-Torga et al. (2001), though not confirmed by Block et al. (2010). Because slow growth rates delay the onset of puberty (Yelich et al., 1995) and because deficiencies in nutrients suppress plasma leptin levels (Block et al., 2003), low leptin signaling was hypothesized to play a role in delayed sexual development in slow-growing heifers.

THE PHYSIOLOGY OF LEPTIN

Adipose tissue, one of the body's main endocrine organs, plays a critical role in multiple physiological processes. There are two distinct types: brown adipose tissue (BAT) and white adipose tissue (WAT), differing in both morphology and function. BAT contains numerous small lipid droplets and abundant mitochondria. It is specialized for non-shivering thermogenesis, a process essential for neonatal survival and cold adaptation in hibernating mammals. This thermogenic ability is largely attributed to the expression of uncoupling protein 1 (UCP1) in the inner mitochondrial membrane, which converts fatty acid-derived chemical energy into heat (Cannon et al., 2004).

Although BAT was long believed to be functional only in infants, recent studies have confirmed the presence of active BAT in adult humans, with continuing UCP1 expression (Lean et al., 1986; Nedergaard et al., 2007). BAT is predominantly located in the interscapular, axillary, cervical, and perirenal regions. Thermogenic activity can be stimulated by cold exposure and noradrenergic activation (Park et al., 2014).

In contrast, WAT, traditionally viewed as an inert energy storage depot, is now recognized as a dynamic endocrine organ. It contains large unilocular lipid droplets and few mitochondria. Anatomically, WAT is distributed across subcutaneous and visceral depots, such as mesenteric, omental, and perigonadal regions (Frayn et al., 2003; Pond, 1992). Beyond its roles in insulation, cushioning, and energy storage, WAT actively secretes a variety of bioactive substances, termed adipokines or adipocytokines, which regulate processes including energy metabolism, inflammation, angiogenesis, and immune responses (Zhang et al., 1994).

Among these adipokines, leptin was the first to be discovered and has since been recognized as a key hormone linking adiposity to energy homeostasis. WAT also secretes other molecules such as adiponectin, resistin, visfatin, and pro-inflammatory cytokines like TNF-α, IL-6, TGF-β, and PAI-1. The secretory profile of adipose tissue varies by location, influencing its metabolic impact. Subcutaneous fat contributes to thermoregulation and body shape, while visceral fat plays structural roles and is more closely linked to metabolic diseases (Conde et al., 2011).

Interestingly, a third adipocyte phenotype – beige or brite adipocytes – has been identified within WAT depots, especially in subcutaneous fat. These cells exhibit characteristics of both brown and white adipocytes. Under certain stimuli, such as cold exposure, these cells undergo “browning,” acquiring a thermogenic profile characterized by UCP1 and PRDM16 expression (Petrovich et al., 2010). While UCP1 is essential for heat production, PRDM16 maintains the beige phenotype. This transformation is promoted by sympathetic nervous system activity, governed by hypothalamic centers.

Various factors influence browning, including thyroid hormones, BMPs, nicotine, FGF21, immune cells, starvation, and cold exposure. Notably, leptin also contributes to this regulation. Despite being produced by adipose tissue, leptin facilitates lipolysis and thermogenesis, acting as a central metabolic signal coordinating energy expenditure and adipose tissue function.

LEPTIN’S ROLE IN EMBRYOGENESIS

Leptin plays a significant role in bovine embryogenesis, particularly during in vitro maturation (IVM) and early embryo development. Studies have shown that leptin supplementation during IVM

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enhances oocyte maturation, improves cleavage rates, and increases blastocyst formation in calf oocytes (Jia et al., 2012; Kaya et al., 2017). Leptin and its receptor (LEPR) are expressed throughout preimplantation development in bovine embryos, with distinct distribution patterns observed at different stages (Madeja et al., 2009). The addition of leptin to IVM medium has been found to improve embryo quality by increasing total cell numbers and reducing apoptosis in blastocysts (Jia et al., 2012; Kaya et al., 2017). However, the effects of leptin on prepubertal calf oocytes may differ, as one study found no significant improvements in developmental capacity or reduction in apoptosis with leptin supplementation (Córdova et al., 2011). These findings highlight the complex role of leptin in bovine embryogenesis and its potential for optimizing in vitro embryo production.

THE RELATIONSHIP BETWEEN COLOSTRUM AND LEPTIN

Milk contains a wide array of biologically active substances with peptide properties, many of which are thought to play important physiological roles in the newborn. This review highlights the potential significance of these peptides based on their observed effects in suckling mammals following gastrointestinal administration. Thyrotropin-releasing hormone (TRH), thyroid-stimulating hormone (TSH), growth hormone-releasing factor (GHRF), luteinizing hormone-releasing hormone (LHRH), adrenocorticotropic hormone (ACTH), erythropoietin (EPO), bombesin-like peptides, calcitonin, beta-casomorphins, and delta-sleep-inducing peptides are some of the bioactive substances that have been found (Koldovský, 1989).

Hormones like glucocorticoids can alter plasma leptin levels, which are influenced by caloric consumption and fat reserves. Premature calves (born on day 277 of gestation) and full-term calves (born on day 290 of gestation) fed comparable quantities of food, colostrum, or milk-derived formula had their plasma leptin concentrations evaluated throughout the first week of life. Leptin concentrations in fully developed calves fed colostrum were constant from day 1 to day 4, but they dropped and were lower when fed diets with comparable caloric and macronutrient contents to colostrum.

Concentrations were lower in calves fed a bucket or automatic feeder than in suckling calves; they increased in suckling calves from day 1 to day 2, and they remained high but unchanged. Plasma leptin in young calves reacts to metabolic changes, nutritional effects (low calorie intake), and hormonal changes (glucocorticoids) (Blum et al., 2005). During the first month of lactation, they measured the amount of leptin in cattle colostrum, milk, and plasma. They also looked at the relationships between specific milk components and the amount of leptin in milk. Leptin levels in colostrum and milk were correlated with fat and choline phospholipids. Leptin levels in plasma and milk decreased during the first month but remained higher in milk and were highest in colostrum. Thus, leptin is present in high amounts in colostrum, in less amounts and more variable in untreated milk, and probably decreases in skim milk. The utilization of untreated milk and colostrum-based (functional) meals may be affected by these findings (Pinotti et al., 2006).

Leptin levels in neonates are crucial for long-term metabolic control, hypothalamic development, and food intake management. It has not been investigated in dairy cattle, but in sheep, the leptin surge stops when the mother overfeeds and her body condition score (BCS) rises. Twenty-one days before to the anticipated calving, the dams' BCS was established. Blood was extracted from the calves on days 0, 3, 5, and 7 as well as within 4 hours of birth. Leptin, cortisol, blood urea nitrogen, β-hydroxybutyrate (BHB), free fatty acids (FFA), triglycerides, and total protein (TP) concentrations were measured in serum. Separate statistical analyses of calves bred from Holstein (HOL) or Angus (HOL-ANG) bulls were conducted. After delivery, leptin levels in HOL calves normally dropped, but there was no proof that leptin and BCS were related. Only on day 0 did cortisol levels in HOL calves rise in tandem with an increase in mother BCS. Depending on the paternal breed and day of birth, there was a variable relationship between maternal BCS and calf BHB and TP levels. In order to ascertain the impact of mother nutrition and energy status on offspring performance throughout pregnancy as well as the effects of these factors on offspring metabolism and performance during gestation, more research is required (Brown et al., 2023).

LEPTIN'S ROLE IN CALF METABOLISM

Leptin plays a crucial role in the energy metabolism and reproductive development of dairy cattle. Nutritional status influences plasma leptin levels, with higher nutritional levels leading to increased leptin concentrations in early postnatal life (Block et al., 2003). Leptin enhances oocyte maturation and embryo development in vitro, improves blastocyst quality and cell number (Jia et al., 2012). In neonatal calves, exogenous cortisol administration affects leptin production and hypothalamic development, potentially influencing future feed intake. Two experiments were carried out on Holstein bulls and calves from commercial Angus cows in order to examine the effects of exogenous cortisol on leptin concentrations in perinatal calves and voluntary feed intake as yearlings. Calves were infused with low cortisol, high cortisol, or a control (CON) and administered a half dose 24 hours postpartum. At 5 days of age, the brain and hypothalamic tissue were collected and analyzed. In the second experiment, yearling calves entered a GROWSAFE System and daily feed intake was measured. Results showed that perinatal dairy bull calves had decreased serum and CSF leptin concentrations, decreased hypothalamic expression of BDNF, FGF1 and FGF2, and increased daily feed intake in LC compared to HC and CON heifers (Long-McCarty, 2023).Higher nutritional levels in early calving promote the development of the hypothalamic-

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pituitary-ovarian axis, resulting in changes in gonadotropin and estradiol concentrations and enhanced development of reproductive organs.The study looked at how nutrition affected the hypothalamic-pituitary-ovarian (HPO) axis' endocrinological control in beef heifer calves during a crucial period of calfhood sexual development. From 3 to 21 weeks of age, 40 heifers were placed in either the high (HI) or moderate (MOD) nutritional categories. Following blood samples collected at various stages of life, an 8-hour window bleed was conducted to detect luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol. According to the findings, MOD calves had higher levels of FSH and estrogen in their blood, whereas HI calves had higher levels of insulin, glucose, and IGF-1. The study came to the conclusion that improved feeding during the early stages of calfhood promotes the HPO axis' ontogeny development. (Kelly et al., 2020). These findings highlight the complex interaction between nutrition, leptin and reproductive development in calves, emphasising the importance of early nutrition in shaping metabolic and reproductive outcomes.

ENERGY BALANCE AND NUTRIENT PARTITIONING IN CALVES

Research on energy balance and nutrient partitioning in calves highlights the complexity of metabolic processes during early development. Gerrits et al. (1997) created a mechanistic model that combines the energy and protein metabolism of preruminant calves, offering information on how nutrients are distributed. Arieli et al. (1995) observed that young calves require about two weeks to adapt to new environmental temperatures and feeding levels, with changes in energy utilization and metabolic partitioning occurring during this period. Quigley (2019) found that total-tract digestibility and metabolizable energy from calf starter increase with age and cumulative intake of non-fiber carbohydrates, indicating gastrointestinal maturation. Cammell et al. (1993) examined energy utilization in cattle at near- and sub-maintenance levels, noting differences in metabolizable energy requirements between age groups. These studies collectively emphasize the dynamic nature of energy metabolism in young calves and the importance of considering factors such as age, diet composition, and environmental conditions when assessing nutrient requirements and utilization.

Leptin plays a crucial role in regulating energy metabolism and growth in calves. Studies have shown that plasma leptin levels are influenced by nutritional status, with higher nutrition leading to increased leptin concentrations in early postnatal life (Block et al., 2003; Lee et al., 2006). However, the relationship between leptin and puberty onset in dairy cattle is not straightforward, as puberty can occur with both constant and rising leptin levels (Block et al., 2003). Leptin has been found to stimulate growth hormone release when administered intracerebroventricularly in castrated calves (Nonaka et al., 2006). Interestingly, plasma leptin concentrations decrease during puberty in bull calves, while testosterone levels increase (Gholami et al., 2010). The growth hormone/insulin-like growth factor-1 axis also interacts with leptin, affecting feed intake and plasma leptin levels (Lee et al., 2006). These findings highlight the complex interplay between leptin, nutritional status, and growth in calves, emphasizing its importance in developmental processes.

LEPTIN AND PUBERTY

In heifers, as in other female mammals, the final developmental step toward sexual maturity occurs in the hypothalamus (Cardoso et al., 2018). Initially, GnRH (gonadotropin-releasing hormone) is released at a low frequency during prepubertal development. As puberty approaches, this shifts to a high-frequency release pattern, triggering an increase in LH (luteinizing hormone) secretion, which promotes the final maturation of ovarian follicles and leads to the first ovulation (Day et al., 1984).

However, a rise in LH pulse frequency typically occurs only around 50 days before puberty onset, making it an unreliable early predictor. Importantly, prepubertal infertility is not due to low LH stores, as GnRH secretion – even at low frequency – still maintains LHβ synthesis and normal pituitary LH reserves (Kinder et al., 1987).

While FSH (follicle-stimulating hormone) is also regulated by GnRH, it is not the limiting factor during puberty. Instead, FSH levels are more influenced by oestradiol-17β, inhibin, and activin than by GnRH itself (Bertlewski et al., 2000).

Historically, GnRH was regarded as the master regulator of reproduction. It was confirmed to originate from synchronized GnRH neuron activity (Clarke et al., 1982; Tanaka et al., 1995). This rhythmic activity, referred to as the GnRH pulse generator, remained a "black box" until the discovery of kisspeptin in the early 2000s.

Although cattle studies are limited, insights from ewes reveal the presence of KNDy neurons in the arcuate nucleus (ARC), co-expressing kisspeptin, neurokinin B (NKB), and dynorphin (Lehman et al., 2010). These neurons regulate kisspeptin secretion via NKB, stimulating GnRH neurons, and are subsequently inhibited by dynorphin. This cyclic feedback is now the leading model for the GnRH pulse generator (Herbison, 2018).

On the other hand, kisspeptin neurons in the preoptic region (POA) express estrogen receptor-alpha (ER-α) but neither dynorphin nor NKB (Franceschini et al., 2006). Estradiol inhibits Kiss1 transcription in the ARC while stimulating it in the POA (Franceschini et al., 2006). Normal pubertal progression is prevented when ESR1 (encoding ER-α) in kisspeptin neurons is knocked out, demonstrating the restrictive effect of estradiol via ER-α (Mayer et al., 2010).

The hypothalamus also integrates metabolic signals via circulating hormones such as insulin, IGF-1, leptin, and ghrelin, which modulate GnRH and LH secretion

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(Williams et al., 2014). While insulin and IGF-1 respond to nutritional intake and stimulate GnRH release, ghrelin, secreted during fasting, may delay puberty. Positive energy balance leads to rising levels of insulin, IGF-1, and leptin as puberty nears (Garcia et al., 2002).

Discovered in the mid-1990s, leptin is secreted primarily by adipocytes and is associated with rising plasma levels in developing females (Zhang et al., 2005). It contributes to pubertal onset in a permissive manner. Lifelong infertility is caused by the genetic absence of leptin or its receptor, but leptin supplementation makes leptin-deficient mice fertile again (Barash et al., 1996; Chehab et al., 1996). This supports the theory proposed by Frisch (1985) that a critical fat threshold is necessary for reproductive competence.

According to Amstalden et al. (2000), leptin causes the hypothalamus and pituitary to secrete more GnRH and LH when there is dietary stress. Nevertheless, neither ER-α nor leptin receptors are expressed by GnRH neurons (Quennell et al., 2009; Dorling et al., 2003). Rather, other hypothalamic neurons that affect GnRH activity, like neuropeptide Y (NPY) and proopiomelanocortin (POMC) neurons, mediate the effects of leptin (Gazal et al., 1998). Chelikani et al. (2009) examined how leptin helps dairy cattle's reproductive axis receive signals about their energy stores. During the prepubescent and postpubescent phases, their study assessed the effects of various calorie and protein density diets on a number of measures, such as dry matter intake (DMI), body weight (BW), body condition score (BCS), backfat thickness (BF), and plasma hormone levels.

Chelikani et al. (2009) highlighted the following important conclusions from their investigation into the impact of diets varying in energy and protein density in dairy heifers:

1. Dry matter intake (18%), body weight (17%), and backfat thickness (5%) collectively accounted for 40% of the variation in plasma leptin concentration ($r^2 = 0.396$).
2. Plasma leptin concentrations did not exhibit a distinct postprandial profile, in contrast to plasma insulin, which demonstrated an acute postprandial increase with increasing nutritional density (H: 1.42 ± 0.09, M: 1.02 ± 0.09, L: 0.68 ± 0.11 ng/mL).
3. Pubertal leptin levels did not differ substantially among dietary regimens (H: 5.63 ± 2.48, M: 4.28 ± 0.55, L: 4.12 ± 0.72 ng/mL), and there was no indication of a sudden prepubertal transition, despite the fact that plasma leptin rose with age.
4. While plasma leptin seems necessary for the start of puberty in heifers with normal or restricted growth rates, it may not be a crucial puberty trigger in heifers that grow quickly.
5. While growth hormone (GH) exhibited no response, plasma concentrations of insulin (H: 0.59 ± 0.07, M: 0.43 ± 0.09, L: 0.30 ± 0.09 ng/mL), IGF-1 (H: 151.08 ± 16.47, L: 82.51 ± 17.47 ng/mL), and glucose (H: 81.35 ± 3.39, M: 73.59 ± 2.34, L: 68.25 ± 3.39 mg/dL) were indicative of nutritional density.

LEPTIN LEVELS AND THE IMMUNE SYSTEM

There appears to be a connection between other indicators of inflammation and variables that have an immediate impact on leptin levels. These include body fat percentages, mental stress, sleep, testosterone, and calorie restriction. Even though it is commonly known that leptin regulates the inflammatory response (Lord et al., 1998), further research suggests that leptin may specifically respond to inflammatory cytokines from adipose tissue. Leptin shares similarities with IL-6 in terms of both structure and function and is a member of the cytokine superfamily (Madej et al., 1995). There is evidence to suggest that circulating leptin may affect the HPA axis, which could imply a role for leptin in the stress response. It would seem that leptin may also play a role in the stress response (Heiman et al., 1997). There is some evidence to suggest that elevated leptin concentrations in both men and women are associated with elevated white blood cell counts (Mabuchi et al., 2005). Chronically high leptin levels appear to be linked to obesity, overeating, and inflammation-related illnesses such cardiovascular disease, metabolic syndrome, and hypertension in addition to those seen in chronic inflammation. Leptin seems to be unaffected by exercise, yet it is linked to body fat mass, the size of individual fat cells, and overeating. For comparison, it should be mentioned that muscle contractions cause the release of IL-6. It seems reasonable to suggest that leptin responds specifically to fat-induced inflammation. (Hamilton et al., 1995) Leptin is thought to be a pro-angiogenic, pro-inflammatory and mitogenic factor, whose effects may be enhanced by cross-talk with IL-1 family cytokines in cancer (Perrier et al., 2009). There is also evidence to suggest that high leptin levels may be present in patients with COVID-19 pneumonia (Tonon et al., 2022). To stop overeating from causing excessive cellular stress, leptin levels rise in response to caloric intake, acting as an acute pro-inflammatory response mechanism. When the capacity of fat cells to expand in size or number is exceeded by the intake of calories, the subsequent stress response results in cellular inflammation and ectopic fat storage. This is characterized by the unhealthful buildup of body fat in the muscles, arteries, and/or internal organs. Elevated cortisol levels amplify the dose-dependent increase in leptin that results from the rise in insulin levels in response to a caloric load (Wabitsch et al., 1996). This insulin-leptin relationship is strikingly analogous to the time- and dose-dependent impact of insulin on the elevation in IL-6 gene expression and secretion by preadipocytes. In addition, despite concurrent hypocaloric diets and weight loss, it has been noted that when acipimox is used to stop lipolysis, plasma leptin concentrations gradually rise. These results imply that stress reactions that raise leptin are triggered by a large caloric load that exceeds the adipocytes' storage capacity. This then functions as an anti-inflammatory agent in adipose tissue, suggesting

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that food consumption should be stopped to avoid high levels of inflammation originating from adipose tissue. The association between persistently high leptin levels and ectopic fat storage in obese people may be explained by this reaction, which could then shield the harmful process of ectopic fat accumulation (Caro et al., 1996).

LEPTIN AND STRESS RESPONSES

Recent studies have explored the relationship between leptin and stress responses in calves. Exogenous cortisol administration in perinatal dairy bull calves was found to reduce leptin concentrations in both serum and cerebrospinal fluid (Morris et al., 2020). This suggests a link between cortisol and leptin levels in early life. Leukocyte heat shock protein expression, neutrophil-related gene expression, and oxidative stress markers were used to identify individual differences in stress responses among recently arrived calves (Eitam et al., 2010). These variations may be predictive of future respiratory health. Leptin, primarily produced by white adipose tissue, interacts with the hypothalamo-pituitary-adrenal (HPA) stress axis at multiple levels, including the hypothalamus, pituitary, and adrenal glands (Roubos et al., 2012). This interaction plays a crucial role in stress adaptation and energy homeostasis regulation, highlighting the complex relationship between leptin and stress responses in calves.

GAPS IN KNOWLEDGE AND FUTURE DIRECTIONS

Recent research has highlighted the importance of leptin in calf development and nutrition. Leptin expression in the gastrointestinal tract, particularly the abomasum and jejunum, is higher in calves compared to cows, suggesting a crucial role during the suckling period (Hayashi et al., 2020). Leptin influences various physiological processes, including puberty onset, reproduction, and immune function (Mukherjee et al., 2023). However, knowledge gaps remain in calf nutrition, especially during critical developmental stages from conception to puberty (van Niekerk et al., 2021). Studies have shown that exogenous cortisol administration in perinatal calves affects leptin production and hypothalamic development, potentially influencing future feed intake and growth (Long-McCarty, 2023). These findings underscore the need for further research on leptin's role in calf development, particularly its interactions with other hormones and its long-term effects on animal productivity and health.

CONCLUSION

Leptin is a hormone that plays a very significant role in the development of calves, starting from the embryonic stage through puberty. During the initial phases of embryonic development, leptin acts by participating in the normal process of cell proliferation and energy balance regulation. Leptin rises with fetal development, facilitating the development of adipose tissue and metabolic processes. Following parturition, leptin plays a central role in the regulation of appetite and energy utilization, an important aspect of normal growth and development in calves. Furthermore, the hormone influences the secretion of growth hormone, which plays a significant role in body mass and size development. During the pre-pubertal phase of calves, leptin relays the information on the body's energy reserves and plays a role in the maturation of the reproductive tract. Leptin is therefore a significant regulator of not only metabolism but also growth and reproduction during calf development. Apart from that, leptin may also play a role in the development of the immune system, which is extremely crucial for the healthy development of young calves.

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