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Leptin in farm animals: Productive and reproductive effects

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Abstract

The *ob* factor, Leptin, produced from white adipose tissue is classified as a "metabolism modifier" or lipostat" or "adipostat" and it have myriad effects on tissues and endocrine systems that ultimately lead to the coordination of whole-body energy metabolism. Leptin seem to be involved in pregnancy, puberty, immune modulation, inflammation, wound healing and mutation. In coordination with mammary milk leptin, plasma leptin may act as an autocrine or paracrine signaling molecule on the mammary gland epithelial cell proliferation, differentiation, growth, apoptosis and function during early lactation period; by repartitioning of plasma nutrients towards milk secretion. It seems that the basal level of plasma leptin might be important for mammary gland to function normally and it might be involved in thermoregulation, satiation, endocrine homeostasis and systemic regulation in the neonate.

Keywords: Leptin, farm animal, reproduction, mammary function

Introduction

Adipose tissue, which considered a passive site of lipid storage, is now known to carry out a number of complex metabolic and endocrine functions; secreting a range of hormones known as adipokines, or adipocytokines; such as tumour necrosis factor alpha and interleukin 6 (IL6), acylation-stimulating protein, leptin, ghrelin, adipontectin, aromatized steroid hormones (plasminogen activator inhibitor-1 and adiponectin) and resistin (**Miner, 2004**).

Observations from Parabiosis experiments showed that *ob/ob* partners of *db/db* mice experienced rapid weight loss, ate little food, became hypoglycemic, and died within 26 days of surgery, indicated that *ob/ob* mice lack a factor in their blood that suppresses eating, whereas *db/db* mice lack the ability to decrease food intake in response to this factor **(Coleman, 1973 and 1978)**.

The *ob* factor identified and characterized later as Leptin meanwhile *db* gene product known as leptin receptor. Leptin (from the Greek leptos, meaning thin) a polypeptide hormone with a 16kDa molecular weight of 167 amino acid chain; primarily produced by white adipose tissue **(Zhang *et al.*, 1994).**

The initial view of leptin hormone has been extended to a wider variety of functions including metabolism, development, neuroendocrine and immune functions.

All of which are related to energy balance, and acting both through central and peripheral mechanisms (**De la Hoya *et al.*, 2015**).

Leptin gene, hormonal structure and leptin receptor

Leptin gene consists of three exons separated by two introns, further; the coding region for *ob* protein is located in exons 2 and 3. Both introns and exons were sequenced with total of 20 polymorphisms **(Amraei *et al.*, 2014)**.

Leptin gene is transcribed into 3.5kb mRNA that encodes leptin pro-hormone with 167amino acid **(Ahima and Flier 2000)**. A sequence of 21AA removed prior releasing leptin into circulation with a molecular mass of 14kDa and 146AA as active form. The structure of the elongated leptin molecule is similar to members of the long-chain helical cytokine family with a dimensions of 2·0×2·5×4·5 nm; consists of four anti-parallel α-helices; connected by two long crossover links and one short loop arranged in a left-handed helical bundle; forms two layers packing with 20^{o} skew angle between them **(Jackson and Ahima, 2006)** as illustrated in figure (1)**.**

On the other hand, leptin receptor gene in human (*Ob-R*) consists of 20 exons (4kb) divided over a region of approximately 170kb (**Tartaglia, 1997**). The leptin receptor (LR) is a glycoprotein with a single trans-membrane spanning region. Six leptin receptor isoforms were reported (a, b, c, d, e and f) in different tissues, derived from a single gene by alternative mRNA splicing and differs in the intracellular domain's length. The leptin receptors are localized in different tissues in the body especially hypothalamus, adipose tissue, placenta and heart. The isoform Ob-Rb is so-called 'long form' thought to be the most important for transmitting leptin signal in cells **(Hafeezullah, 2006)**.

Daily and annual rhythm of leptin secretion

A daily rhythm in plasma leptin levels has been observed in fed Cosmina ewes **(Bertolucci *et al.*, 2005)** with a minimum level during the light phase and a peak during the dark phase; showing a pulsatile secretion pattern, with15 irregular periodicity pulses in cattle during the 24 h **(Kawakita *et al.*, 2001).** However, in Blackface ewes no pulsatile rhythm was observed **(Daniel *et al.*, 2002)**.

In both ovariectomised ewes **(Bocquier *et al.*, 1998)**, cows **(Accorsi *et al.*, 2005)** and rams **(Lincoln *et al.*, 2001)** serum leptin levels were observed to be decreased especially in winter (short day) than in summer (long day), independently of the feeding regime. It is like to be an adaptive behavior to decrease energy expenditure.

Kinetic studies proved that leptin had a biological half-life of 3.4 and 71min for free and bounded leptin in rats respectively **(Hill *et al.*, 1998)**; while the half-life for both bounded and free forms in humans was estimated to be 25min **(Klein *et al.*, 1996)**. However biological half-life in ruminants has yet been proven undoubtedly.

Generally; leptin synthesis is down regulated by fasting **(Chelikani *et al.*, 2004),** thyroid hormones, IL-6, growth hormone (GH), androgens and cAMP at cellular level.

However, cold exposure (**Asakuma *et al.*, 2003**) estrogens, prolactin, transforming neucrosis factor-α-glucocorticoids and insulin **(Faulconnier *et al.*, 2003)** rise the rate of leptin synthesis in white adipose tissue (**Frühbeck, 2001 and Reist *et al.*, 2003).**

Leptin signaling pathway and leptin resistance

Binding of leptin with its receptor, activate janus tyrosine kinases (JAKs), and in particular JAK2 **(Bjorbaek *et al.*, 1997)** that associates with specific C-terminal domains of the leptin receptor; results in trans-phosphorylation of JAK2 and subsequent phosphorylation of specific tyrosine residues located within the C-terminal domain. This chain of events acts as a catalyst to enable the recruitment and activation of various downstream signaling molecules including signal transducers and activators of transcription, insulin receptor substrate proteins, phosphoinositide 3-kinase and the Mitogen activated protein kinase signaling pathway (**Hegyi *et al.*, 2004**).

Although high amounts of leptin exhibited in blood circulating (**Banks *et al.*, 1999)**, but it doesn't affect appetite or energy expenditure. This is termed "leptin resistance" **(Friedman and Halaas, 1998)**, as a result of leptin expression or secretion defect (**Leury *et al.*, 2003**); i.e. response of adipose tissue to β-adrenergic signals, transporter system defect of leptin through the blood-brain barrier **(Jéquier, 2002)**, receptor expression defect of target tissue or the occurrence of any possible defect/s in blood circulation (figure 2). So, even though the body has more than enough leptin in it, it doesn't respond.

Leptin in relation to central nervous system, hypothalamus and pituitary functions

Leptin mRNA is expressed in 32–37% of *in vitro* cultured pituitary cells of male rats (**Akhter *et al.*, 2007**). Additionally, leptin treatment stimulate the reproductive endocrine deficiency in *ob*/*ob* mice **(Cioffi *et al.*, 1996),** leading to a significant increase in plasma levels of LH in *ob*/*ob* female, while *ob*/*ob* males exhibited a significant increase in FSH levels accompanied by increase in uterine or seminal vesicle weight for both sexes.

Furthermore, exposure to leptin significantly increase GnRH secretion *in vitro* from hypothalamic arcuate nucleus (ARC), median eminence (ME) explants of male rats (**Yu *et al.*, 1997)** and consequently increased LH or LH and FSH levels in the serum of fasted mice **(Ahima *et al.*, 1996)**, ewes (**Towhidi *et al.*, 2007**) and cow **(Amstalden *et al.*, 2002**). Also, leptin stimulates the release of LH, GH and prolactin from *in vitro* cultured bovine anterior pituitary cells of fully-fed steers (**Nonaka *et al.*, 2005**). Thus leptin may act as a metabolic signal for GnRH-LH/FSH axis axis

Also, leptin significantly decreases hypothalamic Melanin-concentrating hormone expression and prevents its stimulus effect on food intake. Suggesting that leptin also acts centrally at the level of the hypothalamus to influence reproductive function. On the other hand, Leptin can alter expression of hypothalamic neuropeptides implicated in the

regulation of energy homeostasis such as neuropeptide Y (NPY) that mRNA levels rapidly inhibited in the ARC of adrealectomized mice (**Jang *et al.*, 2000)** and male rat (**Wang *et al.*, 1997)**.

Meantime; leptin stimulates the levels of Corticotropin-Releasing Hormone (CRH) mRNA secretion; in the paraventricular nucleus (**Schwartz *et al.*, 1996**). Suggest that CRH is involved in mediating the effects of leptin on food intake and the hypothalamic-pituitaryadrenal axis **(Ingvartsen and Boisclair 2001)**.

Leptin in relation to body weight, body fat content and energy homeostasis

Most research has focused on the role of leptin as a "lipostat" or "adipostat" in the regulation of body weight **(Reidy and Weber, 2000)**, since the reduction in fat stores leads to a decrease in leptin concentration, food intake and basal metabolic rate, together with a decrease in energy use. The daily leptin treatment cause about 30% weight loss, fat mobilization and reduced food intake in *ob/ob* and lean but not *db/db* mice (**Halaas *et al.*, 1995**). This usually requires 2–4 days of continuous leptin treatment in ruminants to show its effects (**Morrison *et al.*, 2001**).

There is a strong positive correlation between serum leptin concentrations and body fat percent. The accumulation of triglycerides (TAG) increases the adipocytes size, which synthesize more leptin that affects Body Weight (BW) through hypothalamic centers controlling food intake and energy expenditure which is measured as increase in oxygen consumption, higher body temperature and adipose tissue mass loss **(Hafeezullah, 2006)**.

Therefore, **Leòn *et al.* (2004)** found a positive correlation between plasma concentrations of leptin and Body Condition Score (BCS) in heifers; according to nutritional status (r=0.47 to 0.83). Whereas, in goat; BCS or BCS with BW affect serum leptin concentration in a direct and proportional way (**Gamez-Vazquez *et al.*, 2008**).

Within white adipose tissue, leptin inhibit acetyl-CoA carboxylase and fatty acid synthase mRNA expressions in adipocytes *in vivo* **(Zhou *et al.*, 1999)** and *in vitro* (**Wang *et al.*, 1999**). Indicating that leptin might decrease lipogenesis, stimulate lipolysis; especially the breakdown of triglycerides and inhibiting its synthesis on adipocytes.

Moreover; the presence of leptin rise the β-oxidation and uncoupling (proton leak) process; that increase metabolic rates at rest above basal levels by the stimulation of substrate cycles **(Reidy and Weber, 2000)**. The sum of previous actions leads to the elevations in plasma glycerol and Free Fatty Acids (FFA). All previous supposed that the leptin is a sensitive indicator of nutritional status, but others hormones and metabolites are also involved in the signaling and control of body energetic store **(Sansinanea *et al.*, 2001).** So that; leptin is so called Metabolic or Metabolism modifier.

Leptin in relation to food intake and appetite

Many studies (**Sorensen *et al.*, 1996; Ahima and Flier, 2000; Elmquist, 2000 and Havel 2000)** revealed that, leptin affects the secretion of NPY, the most potent inducers of feeding behavior, and CRH. Leptin crosses the blood brain barrier aided by the short form LR, and then binds to the long form LR in the hypothalamic nuclei. The long-form is co-expressed with neurons producing NPY, Agouti-related peptide (AgRP), Cocaine and amphetamine regulated transcript (CART) and proopiomelanocortin (POMC). NPY and AgRP both stimulate feeding behavior whereas POMC and CART suppress feeding. Leptin binding to the NPY and AgRP neurons suppresses NPY and AgRP release whereas it's binding to POMC and CART neurons increases the release of POMC (precursor of a MSH) and CART. The net effect is a suppression of appetite and feeding, increased energy expenditure, thermogenesis and autonomic activity.

Leptin was found to be secreted by the lower half of the stomach glands both in the pepsinogen granules of chief cells and in the granules of a specific endocrine cell type, suggesting that leptin may serve to coordinate long and short-term regulation of feeding behavior acting in collaboration with satiety peptides such as cholecystokinin. These actions gives information to the brain on the availability of external (food) and internal (fat depots) energy resources **(Picó *et al.*, 2003).** Furthermore in the intestinal lumen leptin regulates sugar absorption by reduces glucose or galactose absorption in a rapid and reversible manner (**Ducroc, 2007).**

Leptin in relation to plasma hormones and metabolites concentrations

Treatment of GH has an inhibiting effect on leptin plasma concentrations in dairy cows depending on their endocrine and/or metabolic status; meanwhile GH stimulates leptin mRNA expression on adipose in growing ruminants (**Sauerwein *et al.*, 2004**).

Leptin indirectly affect pancreatic endocrine functions, through its stimulating effects on the sympathetic nervous system (**Poitout *et al.*, 1998**). In order to that leptin treatment inhibit insulin secretion only when rodent's pancreatic α-cells islets are maximally stimulated with high concentrations of glucose. At calving in Brahman cows; (**Strauch *et al.*, 2003)** and Zebu-Brown Swiss crossbred heifers (**León *et al.*, 2004)**, leptin significantly correlated with both IGF-I (r=0.32 and 0.36 resp.) and insulin (r= 0.18).

In Fatter cows or those with positive energy balance (EB), Insulin is a positive regulator of plasma leptin (**Block *et al.*, 2003a)** and had higher plasma leptin concentrations **(Kokkonen *et al.*, 2005)** whereas; nutritional deficiency leads to a reduction in plasma insulin which mediating a portion of the fall in plasma leptin.

In comparison between beef (Charolaise) and dairy (German Holstein) bulls, leptin positively related to glucose in both and respectively (r=0.47 and r= 0.32) with a negative correlation between leptin and HDL-cholesterol (r=-0.66) in Charolaise bulls

(Bellmann *et al.*, 2004). Similarly, **Hussein *et al.* (2011)** found a positive correlation between leptin and total cholesterol (r=0.31) in Frisian cows.

In addition, leptin treatment partly prevented the fall in serum T_4 on fasting (**Leonhard *et al.*, 1998**). Additionally, with advantage of gestation; plasma T_3 levels goes in parallel with the pattern of plasma leptin in albino rats **(Tag El-Din *et al.*, 2008)** and Frisian cows **(Hussein, 2011).**

Hence, at the level of rat white adipose tissue (**Cammisotto *et al.*, 2003**), long-chain fatty acids mimic the effects of norepinephrine on leptin secretion and may play a regulatory role as messengers between stimulation of lipolysis by norepinephrine and inhibition of leptin secretion (**Sonnenberg *et al.*, 2001**).

One week prepartum leptin negatively correlated with plasma urea in both primiparous and multiparous Holstein cows (r=-0.12 and -0.15 resp.) and with non-esterified fatty acids (NEFA, r=-0.14) in multiparous individuals. Meanwhile after two weeks postpartum leptin only correlated negatively with NEFA (r=-0.13) in primiparous animals **(Wathes *et al.*, 2007a)**

Leptin Role in puberty

Exogenous leptin of female mice; resulted in an earlier onset of vaginal opening and estrus cycling. Leptin might be a factor in determination of puberty time (**Rogol, 1998**). It was noticed that, leptin levels increase in normal children before puberty and reach their peak at the onset of puberty **(Garcio-Mayor *et al.*, 1997).** After which, plasma leptin levels begins to decline in boys but continue to increase in girls with levels depending upon the fat mass. However, in large ruminants leptin alone is not sufficient to initiate sexual maturation in prepubertal heifers **(Zieba *et al.*, 2004);** even under accelerated fat deposition conditions in growing dairy cattle (**Block *et al.*, 2003b)**. Moreover, leptin directly modulates hypothalamic GnRH secretion in mature, nutritionally stressed cattle, beside to its direct effects at the adenohypophysis and hypothalamus.

Leptin is and its long receptor isoform (Ob-Rb) found to be secreted in in the seminal plasma of adult rat by the seminal vesicle and prostate gland. This leptin might have a direct effect on epithelial cells of the accessory male genital glands and consequently on the spermatozoa via spermatozoan leptin receptors (**Sayed-Ahmed *et al.*, 2012**).

Leptin during pregnancy and parturition

Although leptin is elevated during pregnancy **(Tag El-Din *et al.*, 2008**), it was proven that pregnancy in rat is a leptin-resistant state because of the presence of LR soluble form, which primarily increased plasma leptin-binding activity rather than to receptor expression in the hypothalamus **(Seeber *et al.*, 2002)**.

However, before calving in Holstein cows, a significant negative correlations between leptin and progesterone was found (r=-0.36) with a positive correlation with

IGF-I at calving. Furthermore leptin negatively correlated (r=-0.29 and -0.27) with postpartum interval and the postpartum periods (**Strauch *et al.,* 2003**).

In human; **(Lepercq and de Mouzon, 2002)** plasma leptin elevated in early pregnancy which was significantly higher during late pregnancy, when placenta synthesis leptin as well as in other primates, (**Henson *et al.,* 1998).**

In ruminants, concentration of leptin is generally tends to be in high levels (5–9 ng/ml) in dry, late pregnant cows then decreased to nadir (3-6 ng/ml) one month pre-partum and during the first week postpartum. Then concentrations slightly increased during the first 3rd to 4th weeks of lactation and continued to increase slightly or decrease again to a second nadir at 5th to 7th weeks postpartum **(Boisclair *et al.,* 2003; Liefers *et al.,* 2003; Chilliard *et al.,* 2005 and Hussein *et al.,* 2011).**

From early to late pregnancy in primiparous goats **(Bonnet *et al.,* 2005)** and from mid to late pregnancy in sheep (**Forhead *et al.,* 2002 and 2008)**; circulating leptin levels increased by 2 folds and remained elevated until late pregnancy then declined thereafter through late pregnancy and early lactation **(Ehrhardt *et al.,* 2001 and 2002).**

Although, leptin concentrations elevated during mid to late pregnancy in ruminants, bovine placenta does not seem to synthesize leptin (**Leury *et al.,* 2003**) or only produced negligible levels of leptin (**Liefers *et al.,* 2005)**.

However, Leptin is present on the trophectoderm layer of the late gestation (day 128) ovine placenta during pregnancy. Leptin and its mRNA and has been demonstrated in placentae from a wide range of species, despite different forms of placentation. Moreover, the placenta produces both short and long forms of LR in mice (**Holness *et al.,* 1999**). The short form corresponds to the transport of the LR isoform and transportation and/or removal of leptin from maternal/fetal circulation (**Gavrilova *et al.,* 1997**). Supporting the theory that, placental-derived leptin integrates maternal nutrient storage to the nutrient requirements of the fetus through both autocrine and paracrine mechanisms (figure 4) as an important factor that regulate fetal fuel handling as a growth factor; including angiogenesis, growth and immunomodulation (**Ashworth *et al.,* 2000**).

Role of Leptin in ovarian function and assisted reproductive technology

The role for leptin in the follicular fluid is unclear but it has been reported that a lower follicular leptin concentration favored a successful outcome of assisted reproduction in women (**Mantzoros *et al.,* 2000**).

Leptin appears to inhibit ovarian function on the basis of a variety of parameters **(Caprio *et al.,* 2001)**. Since ovarian granulosa and theca cells have high affinity receptors for leptin (**Mancini and de Aloysio, 2005)**. Leptin directly antagonizes insulin's stimulatory effect on granulosa cell steroidogenesis, and in the absence of insulin, had little or no effect on granulosa. However, increasing but moderate

concentrations of leptin (i.e., 10-20 ng/ml) trigger the reproductive axis at the level of the hypothalamus and pituitary (**Spicer, 2001**) as presented in figure 4.

Early oestrus cycle in albino female rats (proestrous phase) leptin concentrations was higher than estous, metestrous, or diestrous **(Tag El-Din *et al.*, 2008)**. Thus, leptin might be important to start a new estrous cycle in rats and might be regulated by the same neuroendocrine hormones that regulate gonadotropes and somatotropes.

Wherefore; a relationship between the nadir of leptin levels and first postpartum ovulation was found **(Kadokawa *et al.*, 2000),** since, leptin levels increases before first postpartum ovulation and oestrus. Supporting the hypothesis that leptin also found to be correlate with luteinizing hormone secretion in early postpartum **(Kadokawa *et al.*, 2006),** suggesting that cows with appropriate concentrations of leptin postpartum may exhibit shorter postpartum interval.

The occurrence of some cycle abnormalities in lactating Holstein cows was associated with increased milk yield, lower rate of gain of BW, BCS and low plasma leptin concentrations as well **(Mann *et al.*, 2005).** Generally The acyclic animals were characterized by lower levels of leptin, meanwhile cows having greater concentrations of leptin after calving took longer to resume cyclicity and delayed commencement of luteal activity **(Kulcsár, 2007)**

In addition, leptin inhibits the IGF-1 augmentation of FSH-stimulated estradiol production by the ovarian granulosa cells (**Agarwal *et al.*, 1999**) and this may be one of the possible mechanism of infertility in obese women.

Several records established the potential of leptin supplementation to bovine oocytes and embryos culture media. Leptin can improve nuclear oocytes maturation in buffalo's (**Khaki *et al.*, 2014**) and goat (**Kakisina, 2013**) with a mechanism discovered in porcine oocyte (**Craig *et al.*, 2004**) by increasing phosphorylated Mitogen-Activated Protein Kinase Pathway content by 2.8-fold. This action is blocked by a specific inhibitor of that pathway, U0126. Leptin also can increase both fertilization rate and blastocyst production by reducing apoptosis of *in vitro* produced blastocysts in cow's (**Boelhauve *et al.*, 2005**), camels **(Gabr *et al.*, 2014**). In addition, leptin increase pregnancy and delivery rates of cloned pig embryos **(Wei *et al.*, 2008).** Other *in vitro* studies on rabbits showed that addition of leptin has a deleterious effect on oocyte's maturation **(Ahmed *et al.*, 2008a)**.

Plasma leptin concentration during early lactation period

There are a lot of endocrine and metabolic changes that increase metabolic efficiency and decrease energy expenditure during lactation **(Akers, 2002)**. For this reason, plasma leptin concentrations varied across the pregnancy–lactation cycle, due to an interaction between physiological stage and parity. But; it remains possible that leptin modulates mammary parenchymal development (**Block *et al.*, 2003b**).

Although some studies on Brahman and Swedish cows **(Strauch *et al.*, 2003 and Konigsson *et al.*, 2008)**, reported no differences in plasma leptin levels according to periods of pre-partum, calving, early lactation and time to first estrus, most studies established that the transition period of dairy cows from pregnancy to lactation is associated with a reduction in plasma leptin (**Leury *et al.*, 2003**) to nadir till the subsequent conception which proved by the decrease of its mRNA at the level of adipose tissue by 50% and 30% after parturition in Holstein lactating cows and heifers respectively **(Amstalden *et al.*, 2000 and Block *et al.*, 2001**). This period described by high plasma glucose concentration at the 2nd month, whereas it was low at the 8th month, when insulin was low till the 3rd month of lactation (**Eryavuz *et al.*, 2008).**

Plasma circulating leptin found to be higher in primiparous than multiparous cows before calving and in heifers compared with the cows in the first lactation but not mature cows up to 2 lactations (**Gentry Jr., 2007)** and found to be negatively correlated with both milk solid not-fat and milk protein (r=-0.26 and r=-0.28) yields **(Hussein, 2010).** Leptin through to influence the expression of milk protein gene at the mammary gland level **(Lin and Li, 2005)**.

Although plasma leptin does not correlated with milk yield till the 7th week of lactation (**Hussein, 2011**) in cows; mammary tissue explants; leptin enhance fatty acid synthesis **(Feuermann *et al.*, 2006)** and expression of α-casein and β-lactoglobulin **(Parola *et al.*, 2007)** with the condition of the presence of prolactin.

Previous data indicate that leptin plays an important role in mammary gland lactogenesis, and that the expression of leptin and/or leptin action requires the presence of prolactin. This decline of leptin concentration towards parturition is might be important for inducing the hyperphagia that is necessary for milk production acts as a signal to stimulate energy intake (**Zhang and Wang, 2008**); however the expected increase in leptin concentration in response to this hyperphagia is suppressed during lactation (**Liefers *et al.*, 2003**). On the other hand, **Hussein, (2010)** inquired if leptin affects fetus's weights during the last gestational period; when found that mothers with lower plasma leptin have heavier newborn calf.

Leptin and mammary gland function

During lactation, leptin mRNA was found to be expressed by the myoepithelial and both undifferentiated and functionally differentiated stages of bovine mammary epithelial cell (**Sayed-Ahmed *et al.*, 2004** and **Yonekura *et al.*, 2006**) which is not insulin dependent expression **(Leury *et al.*, 2003**).

In Holstein cows (**Pinotti and Rosi, 2006**), ewes (**Whitley *et al.*, 2005 and 2009**) and saws (**Estienne *et al.*, 2000**), Milk leptin significantly decreased by 28-56% within 10 days of lactation, but remained steady the 20 days afterwards. Furthermore, leptin was found in suckled lamb serum correlated with milk serum leptin, but not ewe blood serum leptin which increased from birth to d 5 and declined thereafter to nadir then

elevated by d 19. That might provide a way for thermoregulation, satiation, and homeostatic endocrine control in the neonate **(McFadin *et al.*, 2002).** However, other studies (**Rasmussen *et al.*, 2008**), could not prove any indication of absorption of the colostral and/or milk leptin in systemic regulation in the goat kid neonate.

In most of the species studied **(Smith and Sheffield, 2002)**; leptin concentration was higher (2 to 66 fold) in whole milk than in skim milk. However, the significance of these results remains controversial because leptin may be is linked to the milk fat globules and/or could result from an analysis artifact induced by further link **(Bonnet *et al.*, 2002)**.

A Significant correlation (r=0.39) was found between milk serum leptin and plasma glucose levels **(Hussein *et al.*, 2011),** supporting the idea that, during early lactating period; body tends to permit the direct use of most glucose required for milk lactose synthesis, while glucose utilization and oxidation in extra-mammary tissue is reduced (**Kokkonen *et al.*, 2005**).

No such significant correlation between milk leptin and plasma leptin concentrations (r=-0.09 to 0.35) was observed on lactating ruminants or saws in many studies (**Pinotti and Rosi, 2006; Rasmussen *et al.*, 2008 and Hussein *et al.*, 2011)** except weak but significant one (r=0.028; P=0.04) was reported in ewes (**McFadin *et al.*, 2002**). Leading to that plasma leptin does not appear to be involved in regulation of the leptin expression by the mammary gland epithelial cells.

A diagrammatic scheme (figure 6) was suggested by **Hussein *et al.*, (2011)** in the role of leptin in milk production. Confirming the theory that basal concentration of plasma leptin with coordination with milk serum leptin; might be functioning as an autocrine or paracrine regulating signal at the level of the mammary gland tissue and regulate the synthesis of milk by the mammary gland epithelial cells during early lactation period.

Other possible Role/s of leptin hormone

In malnutrition mice, administration of exogenous leptin not only contribute in the recovery of immune suppression by inhibiting monocytes and lymphocyte apoptosis and induced mutation **(Fujita *et al.*, 2002),** but also, stimulates the production of proinflammatory cytokines (Th1) from cultured monocytes (**Matarese *et al.*, 2005**), increased the thymic cellularity and CD4/CD8 ratio **(Härle and Straub, 2006);** in addition to the increase of interferon (IFNɣ) and suppressing interleukin (IL2) production stimulated from T lymphocytes in cows (**Ahmed *et al.*, 2008b**). This might be used therapeutically to treat immunodeficiency caused by severe malnutrition. Leptin also found to accelerate wound healing mediated by its receptor in *ob/ob* but not *db/db* mice **(Lu and Li, 2000).** Moreover Leptin also stimulates Tyrphosphorylation of the RNA-binding protein mediating the dissociation from RNA. This actions of leptin was done through previously discussed pathways **(Sánchez-Margalet *et al.*, 2003)**.

Prediction of leptin hormone concentration

Few studies proposed a predictive models for leptin concentration such as **Wathes *et al.* (2007b)** who found that the best fit equation of leptin concentration as a function of days in milk (DIM) for primiparous and multiparous cows respectively as follows:

Leptin, ng/dl = 2.905−0.0924DIM + 0.0035DIM −0.00004DIM

Leptin, ng/dl = 2.905−0.2995−0.0408DIM + 0.0012DIM −0.000016DIM

Also, **Hussein *et al.* (2011)** predicted plasma and milk leptin concentration as a function in body weight (BW, kg) daily milk yield (DMY, kg) and solids not fat (SNF, g/kg) using stepwise regression and their relation to each other using simple linear model regression as follows:

Plasma leptin, ng/dl = 541.48+BW×-0.40+MYD×-22.77+SNF×420.32

Milk serum leptin, ng/dl =2.82+MYD×-0.14+SNF×2.65

Plasma leptin, ng/dl = 5.98 + Milk serum leptin, ng/dl × 0.53

Milk serum leptin, ng/dl = 2.17 + Plasma leptin, ng/dl × -0.02

Future of leptin in animal production

Generally; the relation between plasma leptin and milk leptin and their relation to plasma hormones, quantitative milk production, milk constituents, neonate physiology and immunology are still inscrutable, remained unclear and need more *in vitro* and *in vivo*investigations to find out if leptin transports from or to mammary gland secretions; aside from the relation between milk leptin and milk fat globules since that milk leptin concentrations in whole milk found to be higher than milk serum.

In addition to the role of leptin in acyclic animals and its uses to treat these animal extend our knowledge about how far leptin affects the physiology of the lactating farm animals especially in ruminants?

Until then, successful enhancement of reproductive function or manipulation of nutrients could be achieved through the regulation of leptin production or sensitivity to leptin through nutritional or metabolic manipulation, and if leptin is involved in animal resistance to disease, immune modulation, inflammation, wound healing and mutation. It will be an important therapy in the treatment of animal disease and better performance.

Thus, direct leptin treatment will not be feasible in livestock production unless affordable or delivery systems are developed or discovered molecules from medical plants which has leptin-like activity. Then the leptin manipulation and action will be of interest to scientists and pharmaceutical commercial companies.

Conclusion

Leptin is classified as a “metabolism modifier” it is likely that leptin influences, through tissue-specific mechanisms, the sensitivity to insulin and hence glucose uptake by the cells, in order to direct nutrients towards organs or tissues that are metabolically

more active. Moreover; the decrease in leptin plasma concentration at calving may also be correlated with the intensive lipolysis and fat mobilization and thus with the reduction in fatty tissue that possibly responsible for reducing leptin levels associated with the drop of body condition score with the advantage of lactation during the early lactation period. In addition to that mammary gland tissue has the ability to express lepin mRNA. Moreover, leptin can influence the branches of ducts and the proliferation of the mammary epithelial cells and during lactation, it influences the expression of milk protein gene and delays the involution in rodents. These facts elucidate that leptin might be involved in the remodeling of the mammary gland epithelial cells tissue; which is important for subsequent lactation; since that leptin reached its maximum concentrations during late lactation and dry periods.

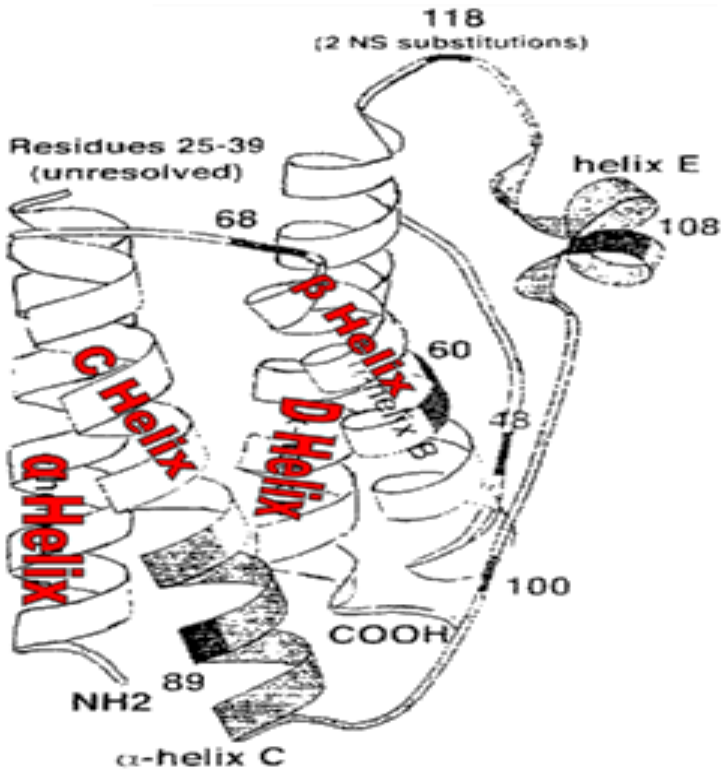

Figure 1: Diagrammatic scheme of leptin structure

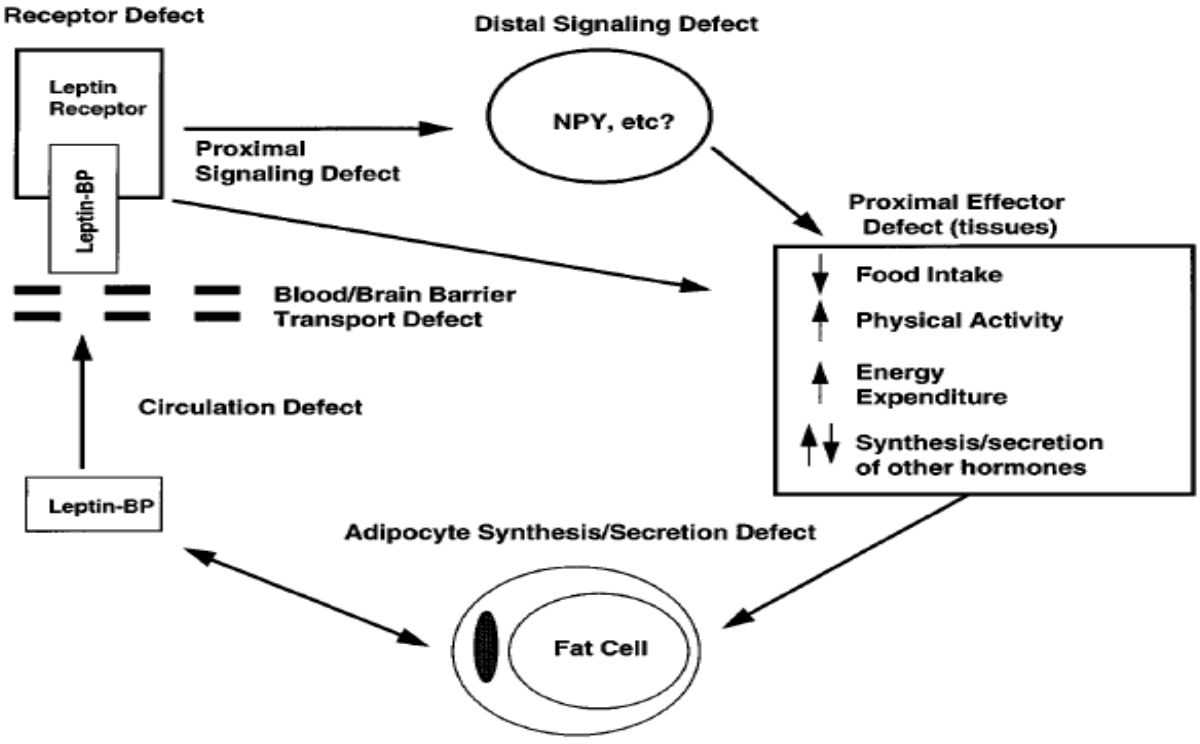

Figure 2: Possible Leptin signaling resistance

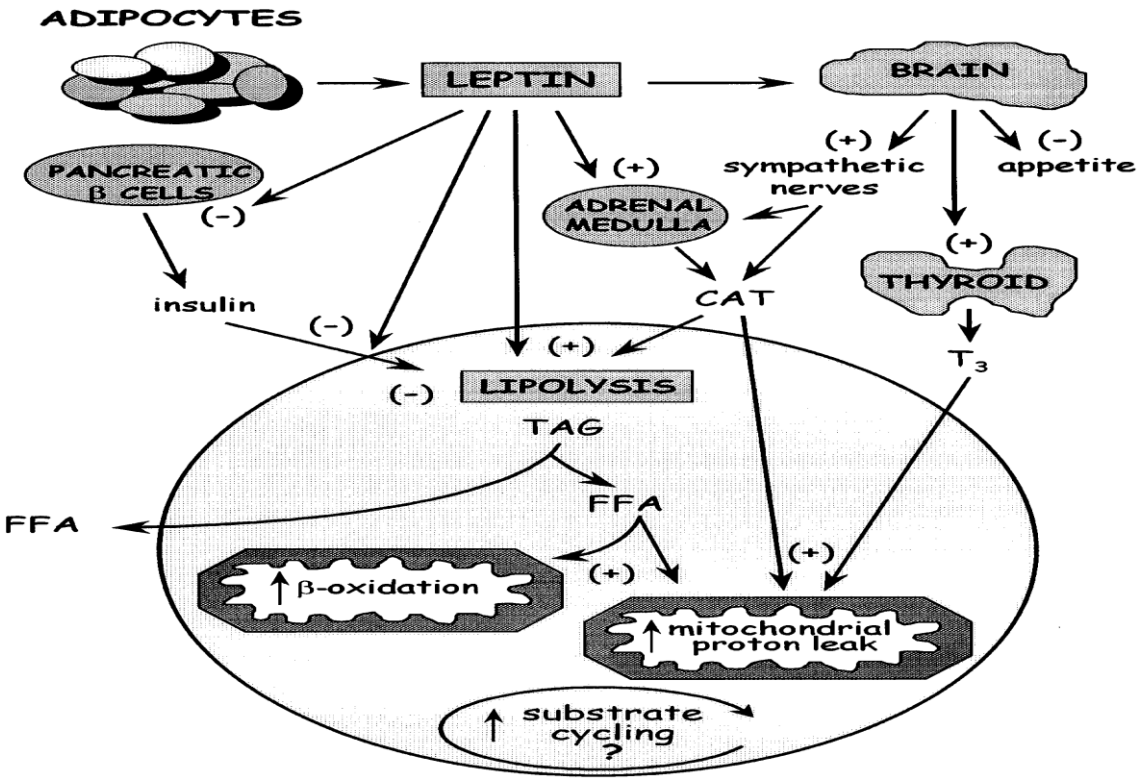

Figure 3: Leptin effects and pathways on lipid metabolism, (-) decrease and (+)

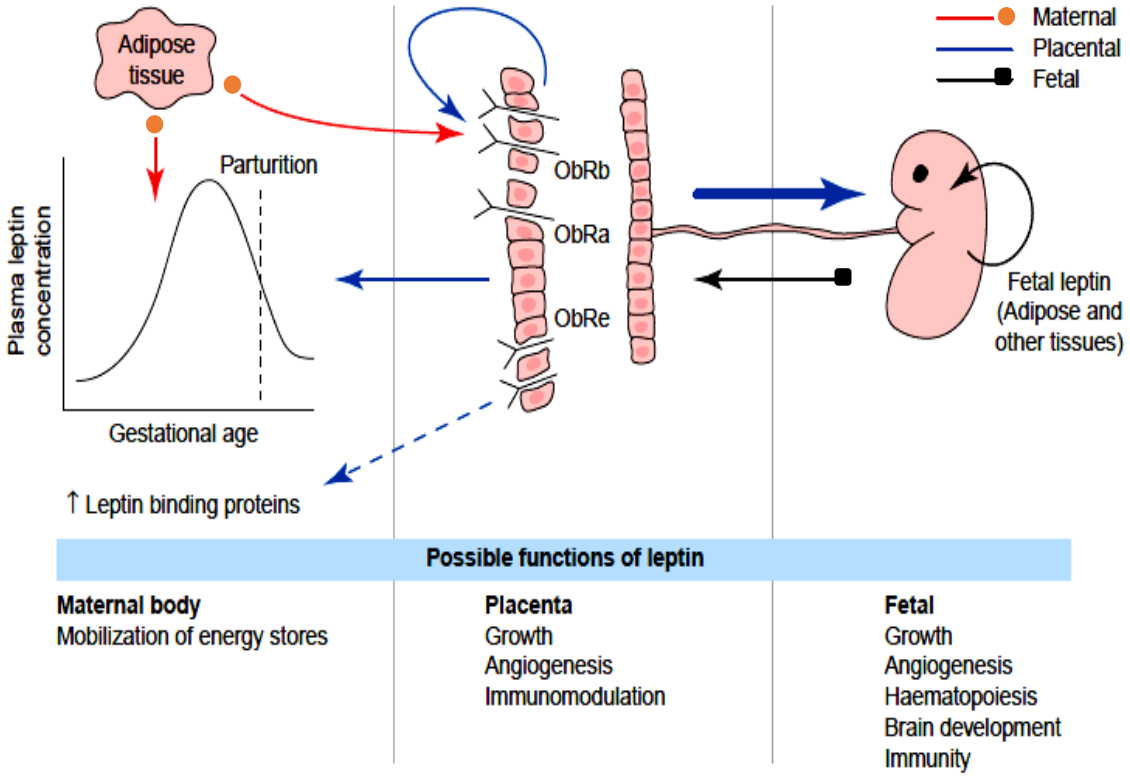

Figure 4: Possible roles of leptin at the maternal–fetal interface. ObR: leptin receptor solid line indicates a stimulatory effect; "- -" and dashed inhibitory

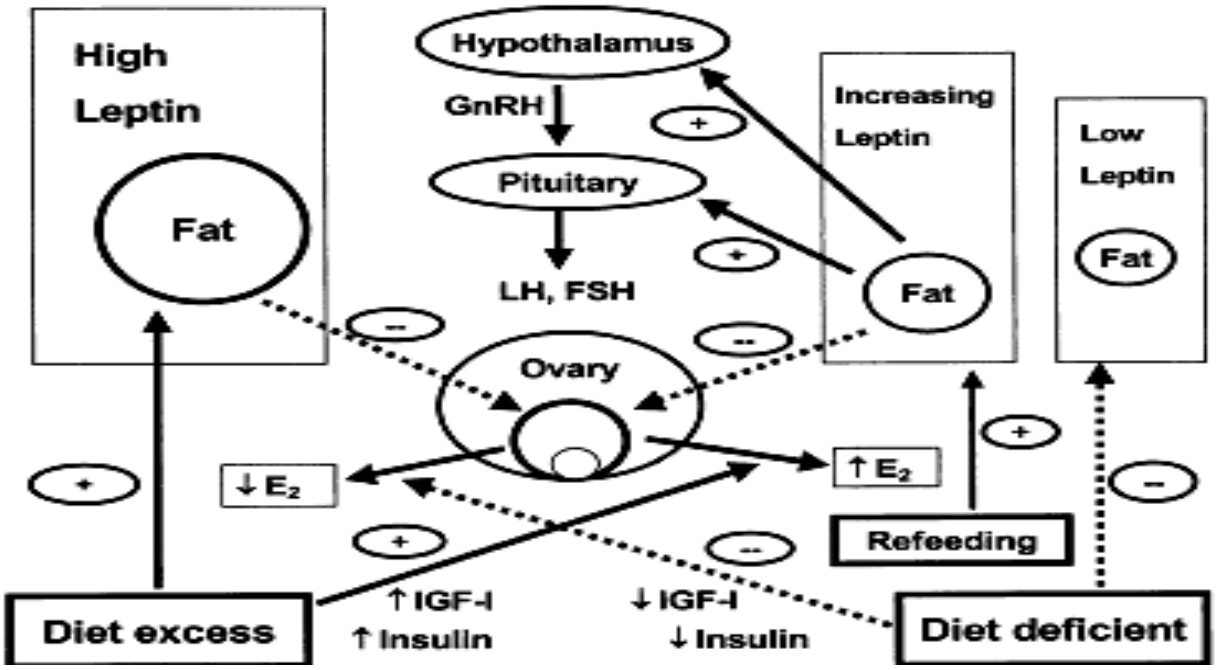

Figure 5: the role of leptin in regulating reproductive function. Encircled "+" and solid line indicates a stimulatory effect; "- -" and dashed line indicates an inhibitory effect

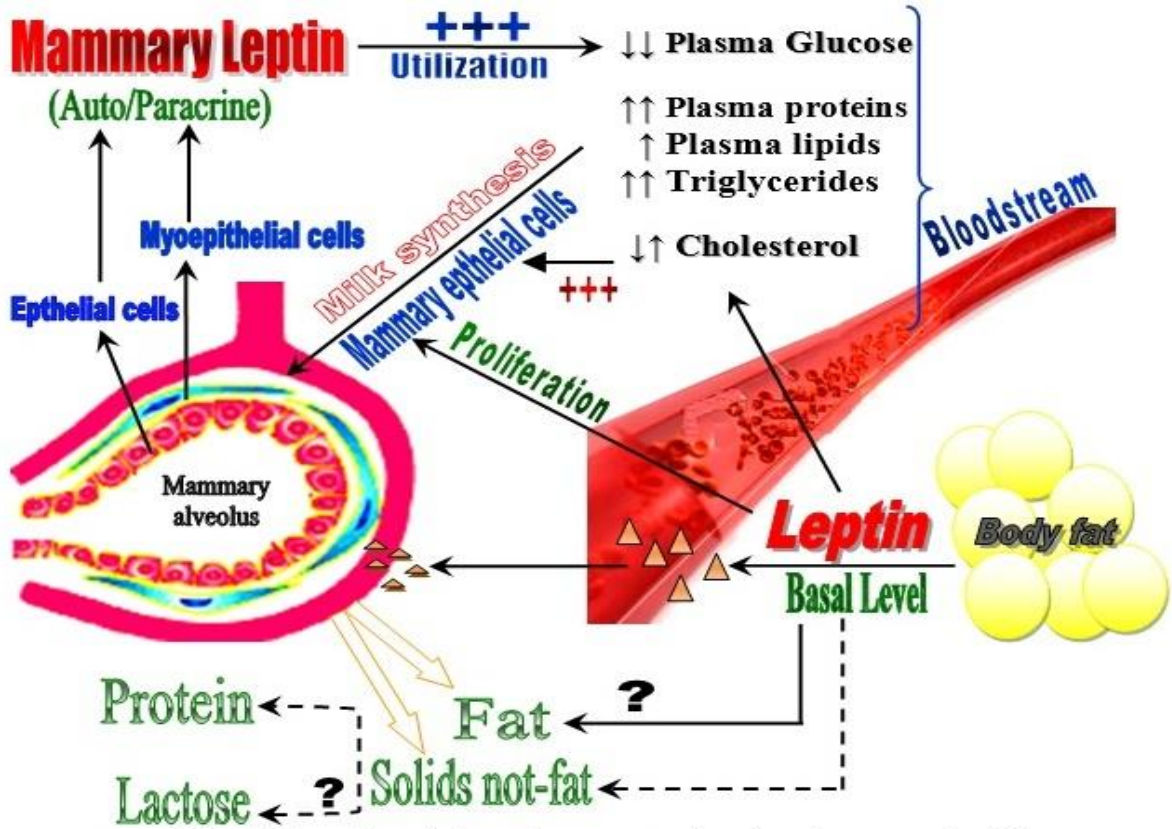

Figure 6: Possible role/s of leptin basal concentration in plasma and milk serum to coordinate and regulate the synthesis of milk by the mammary gland epithelial cells, when ↑= high level; ↓= low level, +++ =increase, and --- = decrease.

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