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Biology and significance of leptin in animal production: A perspective

A MUKHERJEE[1], I SAMANTA[1] and S N JOARDAR[1]✉

West Bengal University of Animal and Fishery Sciences, Kolkata, West Bengal 700 037 India

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ABSTRACT

Leptin, an adipocyte-derived cytokine (adipokine) has plethora of physiological roles in the body, particularly in the onset of puberty, viz. reproduction and immune function of an animal. Moreover, body fatness which is a crucial determinant of meat quality is governed by blood leptin level. Since its discovery in 1994, various research groups have explored its potential role in animal production, reproductive fitness and immune function which ultimately determine the profitability of livestock rearing. Leptin binds with leptin receptor (LEPR) and activates different intracellular signaling pathways to activate downstream gene expression process to execute its functions. Intensive research works have shed light on the central role of this molecule in intricate circuitry of nutrition, metabolism, energy homeostasis and immune response. Single nucleotide polymorphisms (SNPs) detected on promoter or exon or intron region of leptin gene has been found to be associated with various key traits of animal productivity. The present review focusses to summarise about this gene structure and function in domestic mammalian species and need of future research efforts on leptin and related pathways for augmenting production of farm animals.

Keywords: Animal, Cytokine, Leptin, Livestock

Leptin, an adipocyte-derived cytokine has given a new paradigm for understanding the endocrine function of adipose tissue since its discovery twenty-seven years ago. The effects of leptin were initially identified in the obese (ob/ob) and diabetic (db/db) mice lines, which had inheritable obese phenotypes (Hummel *et al*. 1966). In pioneering work, D L Coleman demonstrated that the db/db mice carried a blood-borne component which caused substantial weight loss and hunger in their parabiotic companion (Coleman 1973, 2010). Coleman hypothesized that the ob/ob mouse lacked the secreted factor, whereas, the db/db mouse generated it but was unable to respond to it. Although Coleman's team discovered the factor in adipose tissue they were never able to isolate it. Zhang and others (in Dr. Friedman's lab) identified the factor using positional cloning in 1994, and named it as leptin after the Greek word "leptos" which means "thin" (Zhang *et al.* 1994). Later in 1995, the leptin receptor, the product of db gene, was characterized (Tartaglia *et al*. 1995). The discovery of Coleman's "satiety factor" and associated receptors ushered in a new era of physiological understanding of energy homeostasis.

Leptin, a non-glycosylated peptide cytokine, is a product of the *obese* (*ob*) or *leptin* (*LEP*) gene. Leptin is mainly produced by white adipose tissue (WAT) (Masuzaki *et al*. 1995). Circulatory leptin concentration is directly proportional to the total body fat mass (Klein *et al*. 1996) and obesity (Obradovic *et al*. 2021). The molecular weight of leptin is within the range of 16-18 kDa (Takahashi *et al*. 2002). The molecular mass of affinity-purified recombinant human leptin protein was estimated to be approximately 16 kDa by SDS-PAGE, whereas, the molecular mass of endogenous human leptin was reported as 16,026±9 by MALDI-TOF analysis (Cohen *et al*. 1996). In laboratory, molecular mass of affinity-purified native goat (*Capra hircus*), mithun (*Bos frontalis*) and rohu fish (*Labeo rohita*) was ascertained as 15,948.72 Da, 17,214.26 Da and 16283.38 Da, respectively by MALDI-TOF mass spectrometric analysis (Alam *et al*. 2014a, Alam *et al*. 2014b, Joardar *et al*. 2017).

Metabolism of adipose tissue and fat deposition are essential in animals, since it has impact on feed intake, product quality (meat, milk, etc.) and it provides energy reserves for reproduction and lactation. Several studies have highlighted the association of leptin gene polymorphisms with animal product quality traits (Buchanan *et al*. 2002, Lagonigro *et al*. 2003, Silva *et al*. 2014). Potential role of leptin in multiple aspects of animal reproduction have been delved by different research groups, so far (Williams *et al*. 2002, Zieba *et al.* 2005, Scaramuzzi *et al.* 2011, Wylie 2011, Haldar *et al*. 2014). Role of leptin in inflammation and immunological responses of animals against infection and stress is well established (Wylie 2011). Discovery of candidate genes impacting the production and reproduction of livestock population is the major research focus in the field of animal breeding. Leveraging molecular

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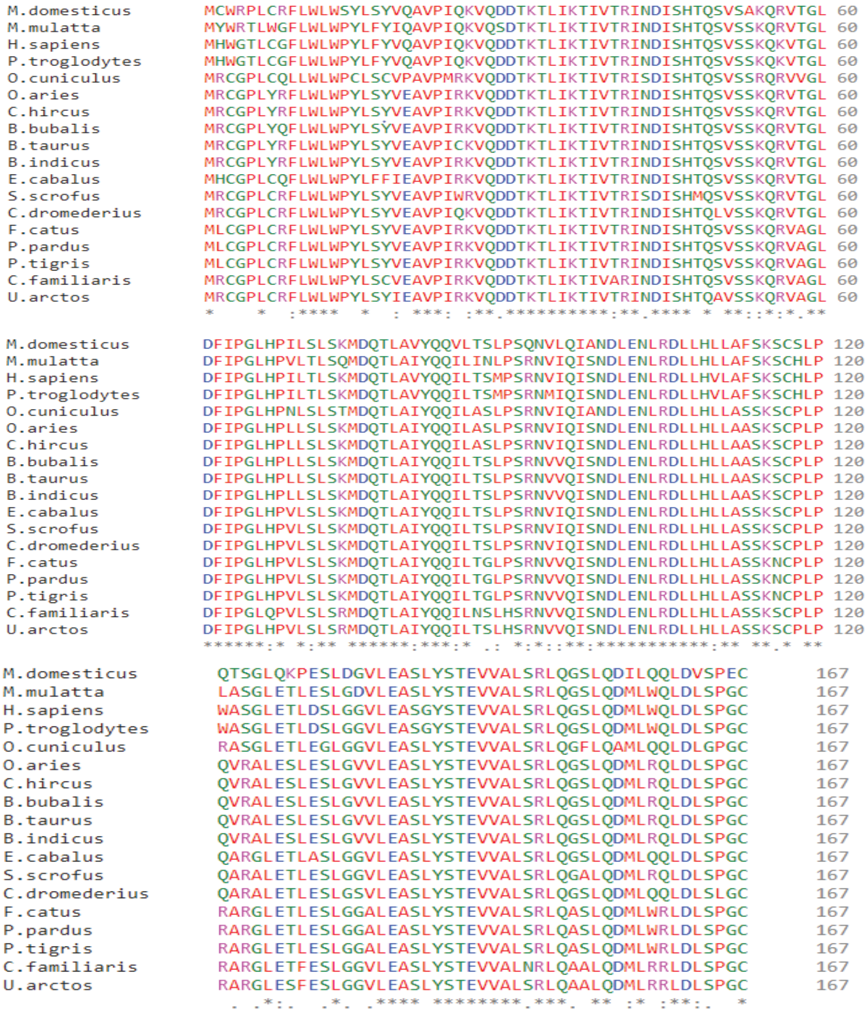
Present address: [1]West Bengal University of Animal and Fishery Sciences, Kolkata, Belgachia, West Bengal. ✉Corresponding author email: joardar69@gmail.com

Table 1. Leptin gene and protein characteristics in different mammalian species

Species	Chromosomal position	Gene size (base pair)	No. of exons	No. of introns	Protein size (amino acids)	Accession no.
Taurine cattle	4	16824	3	2	167	NC_037331.1
Indicine cattle	4	16805	3	2	167	NC_032653.1
Buffalo	8	2260	2	1	167	NC_037552.1
Goat	4	16370	3	2	167	NC_040255.1
Sheep	4	16244	2	1	167	NC_056057.1
Pig	18	17205	3	2	167	NC_010460.4
Human	7	16429	3	2	167	NC_000007.14
Chimpanzee	7	16644	3	2	167	NC_036886.1
Rhesus Monkey	3	14056	3	2	167	NC_041756.1
House Mouse	6	13656	3	2	167	NC_000072.7
Rabbit	7	12874	3	2	167	NC_013675.1
Dog	14		4	3	167	NC_051818.1
Camel	7	13588	3	2	167	NC_044517.1
Horse	4	2121	2	1	167	NC_009147.3
Cat	A2	13556	3	2	167	NC_018724.3
Amur Tiger	Unknown	13734	5	4	167	NW_006711794.1
Leopard	Unknown	14331	6	5	167	NW_017619868.1
Grizzly Bear	Unknown	14625	5	4	167	NW_020656122.1



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M.domesticus     MCWRPLCRFLWLWSYLSYVQAVPIQKVQDDTKTLIKTIVTRINDISHTQSVSAKQRVTGL 60
M.mulatta        MYWRTLWGFLWLWPYLFYIQAVPIQKVQSDTKTLIKTIVTRINDISHTQSVSSKQRVTGL 60
H.sapiens        MHWGTLCGFLWLWPYLFYVQAVPIQKVQDDTKTLIKTIVTRINDISHTQSVSSKQKVTGL 60
P.troglodytes    MHWGTLCGFLWLWPYLFYVQAVPIQKVQDDTKTLIKTIVTRINDISHTQSVSSKQKVTGL 60
O.cuniculus      MRCGPLCQLLWLWPCLSCVPAVPMRKVQDDTKTLIKTIVTRISDISHTQSVSSRQRVVGL 60
O.aries          MRCGPLYRFLWLWPYLSYVEAVPIRKVQDDTKTLIKTIVTRINDISHTQSVSSKQRVTGL 60
C.hircus         MRCGPLYRFLWLWPYLSYVEAVPIRKVQDDTKTLIKTIVTRINDISHTQSVSSKQRVTGL 60
B.bubalis        MRCGPLYQFLWLWPYLSYVEAVPIRKVQDDTKTLIKTIVTRINDISHTQSVSSKQRVTGL 60
B.taurus         MRCGPLYRFLWLWPYLSYVEAVPICKVQDDTKTLIKTIVTRINDISHTQSVSSKQRVTGL 60
B.indicus        MRCGPLYRFLWLWPYLSYVEAVPIRKVQDDTKTLIKTIVTRINDISHTQSVSSKQRVTGL 60
E.cabalus        MHCGPLCQFLWLWPYLFFIEAVPIRKVQDDTKTLIKTIVTRINDISHTQSVSSKQRVTGL 60
S.scrofus        MRCGPLCRFLWLWPYLSYVEAVPIWRVQDDTKTLIKTIVTRISDISHMQSVSSKQRVTGL 60
C.dromederius    MRCGPLCRFLWLWPYLSYVEAVPIQKVQDDTKTLIKTIVTRINDISHTQLVSSKQRVTGL 60
F.catus          MLCGPLCRFLWLWPYLSYVEAVPIRKVQDDTKTLIKTIVTRINDISHTQSVSSKQRVAGL 60
P.pardus         MLCGPLCRFLWLWPYLSYVEAVPIRKVQDDTKTLIKTIVTRINDISHTQSVSSKQRVAGL 60
P.tigris         MLCGPLCRFLWLWPYLSYVEAVPIRKVQDDTKTLIKTIVTRINDISHTQSVSSKQRVAGL 60
C.familiaris     MRCGPLCRFLWLWPYLSCVEAVPIRKVQDDTKTLIKTIVARINDISHTQSVSSKQRVAGL 60
U.arctos         MRCGPLCRFLWLWPYLSYIEAVPIRKVQDDTKTLIKTIVTRINDISHTQAVSSKQRVAGL 60
                 *    *  :****  *  : ***: :**.**********:**.**** * **::*:*.**

M.domesticus     DFIPGLHPILSLSKMDQTLAVYQQVLTSLPSQNVLQIANDLENLRDLLHLLAFSKSCSLP 120
M.mulatta        DFIPGLHPVLTLSQMDQTLAIYQQILINLPSRNVIQISNDLENLRDLLHLLAFSKSCHLP 120
H.sapiens        DFIPGLHPILTLSKMDQTLAVYQQILTSMPSRNVIQISNDLENLRDLLHVLAFSKSCHLP 120
P.troglodytes    DFIPGLHPILTLSKMDQTLAVYQQILTSMPSRNMIQISNDLENLRDLLHVLAFSKSCHLP 120
O.cuniculus      DFIPGLHPNLSLSTMDQTLAIYQQILASLPSRNVIQIANDLENLRDLLHLLASSKSCPLP 120
O.aries          DFIPGLHPLLSLSKMDQTLAIYQQILASLPSRNVIQISNDLENLRDLLHLLAASKSCPLP 120
C.hircus         DFIPGLHPLLSLSKMDQTLAIYQQILASLPSRNVIQISNDLENLRDLLHLLAASKSCPLP 120
B.bubalis        DFIPGLHPLLSLSKMDQTLAIYQQILTSLPSRNVVQISNDLENLRDLLHLLAASKSCPLP 120
B.taurus         DFIPGLHPLLSLSKMDQTLAIYQQILTSLPSRNVVQISNDLENLRDLLHLLAASKSCPLP 120
B.indicus        DFIPGLHPLLSLSKMDQTLAIYQQILTSLPSRNVVQISNDLENLRDLLHLLAASKSCPLP 120
E.cabalus        DFIPGLHPVLSLSKMDQTLAIYQQILTSLPSRNVIQISNDLENLRDLLHLLASSKSCPLP 120
S.scrofus        DFIPGLHPVLSLSKMDQTLAIYQQILTSLPSRNVIQISNDLENLRDLLHLLASSKSCPLP 120
C.dromederius    DFIPGLHPVLSLSKMDQTLAIYQQILTSLPSRNVIQISNDLENLRDLLHLLASSKSCPLP 120
F.catus          DFIPGLHPVLSLSKMDQTLAIYQQILTGLPSRNVVQISNDLENLRDLLHLLASSKNCPLP 120
P.pardus         DFIPGLHPVLSLSKMDQTLAIYQQILTGLPSRNVVQISNDLENLRDLLHLLASSKNCPLP 120
P.tigris         DFIPGLHPVLSLSKMDQTLAIYQQILTGLPSRNVVQISNDLENLRDLLHLLASSKNCPLP 120
C.familiaris     DFIPGLQPVLSLSRMDQTLAIYQQILNSLHSRNVVQISNDLENLRDLLHLLASSKSCPLP 120
U.arctos         DFIPGLHPVLSLSRMDQTLAIYQQILTSLHSRNVVQISNDLENLRDLLHLLASSKSCPLP 120
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M.domesticus      QTSGLQKPESLDGVLEASLYSTEVVALSRLQGSLQDILQQLDVSPEC       167
M.mulatta         LASGLETLESLGDVLEASLYSTEVVALSRLQGSLQDMLWQLDLSPGC       167
H.sapiens         WASGLETLDSLGGVLEASGYSTEVVALSRLQGSLQDMLWQLDLSPGC       167
P.troglodytes     WASGLETLDSLGGVLEASGYSTEVVALSRLQGSLQDMLWQLDLSPGC       167
O.cuniculus       RASGLETLEGLGGVLEASLYSTEVVALSRLQGFLQAMLQQLDLGPGC       167
O.aries           QVRALESLESLGVVLEASLYSTEVVALSRLQGSLQDMLRQLDLSPGC       167
C.hircus          QVRALESLESLGVVLEASLYSTEVVALSRLQGSLQDMLRQLDLSPGC       167
B.bubalis         QVRALESLESLGVVLEASLYSTEVVALSRLQGSLQDMLRQLDLSPGC       167
B.taurus          QVRALESLESLGVVLEASLYSTEVVALSRLQGSLQDMLRQLDLSPGC       167
B.indicus         QVRALESLESLGVVLEASLYSTEVVALSRLQGSLQDMLRQLDLSPGC       167
E.cabalus         QARGLETLASLGGVLEASLYSTEVVALSRLQGSLQDMLQQLDLSPGC       167
S.scrofus         QARALETLESLGGVLEASLYSTEVVALSRLQGALQDMLRQLDLSPGC       167
C.dromederius     QARALETLESLGSVLEASLYSTEVVALSRLQGSLQDMLQQLDLSLGC       167
F.catus           RARGLETLESLGGALEASLYSTEVVALSRLQASLQDMLWRLDLSPGC       167
P.pardus          RARGLETLESLGGALEASLYSTEVVALSRLQASLQDMLWRLDLSPGC       167
P.tigris          RARGLETLESLGGALEASLYSTEVVALSRLQASLQDMLWRLDLSPGC       167
C.familiaris      RARGLETFESLGGVLEASLYSTEVVALNRLQAALQDMLRRLDLSPGC       167
U.arctos          RARGLESFESLGGVLEASLYSTEVVALSRLQAALQDMLRRLDLSPGC       167
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Fig. 1. Multiple sequence alignment of leptin protein from different species. Leptin protein sequences of different mammalian species were retrieved from NCBI and aligned with ClustalW.

information about the leptin gene appears to have inspired researchers in the field of molecular breeding to conduct association studies with production and reproduction traits in livestock species. Present review focusses the structure of leptin gene in different domestic animal species, association of gene polymorphisms with various reproductive parameters of farm animals and recent development of our understanding about the biology of leptin with particular emphasis on animal production.

Leptin gene and tissue-specific expression in mammalian species

Major advances in genome sequencing technologies have made it possible to unravel the leptin gene features in different species. Table 1 provides details of leptin gene and proteins in different mammalian species, collected from sequence repository. Although the protein is conserved with 167 amino acids in all the mammalian species the chromosomal positions and gene sizes differ between the species. The primary amino acid sequences of domestic animal leptin proteins have been aligned and it shows high degree of conseron among different species (Fig.1). The phylogenetic relationship among the orthologous gene sequences have been determined by MEGA X using neighbour-joining algorithm (Fig. 2). As evident from the rooted phylogenetic tree exotic and indigenous cattle, buffalo, sheep and goat are evolutionarily closely related. Similarly, canids and felids were also detected in the same cluster in the phylogenetic tree. Also, the primate species and human have common ancestor as evident from leptin protein sequence-based phylogenetic tree. Although adipose tissue is the most common source of leptin, expression of leptin has also been found in the stomach (Sobhani *et al*. 2000), skeletal muscle (Wang *et al.* 1998), foetal cartilage (Hoggard *et al*. 1998), pituitary (Jin *et al*. 1999), mammary tissue (Smith-Kirwin *et al*. 1998), and placenta (Masuzaki*et al*. 1997).

Leptin and intracellular signaling

The LEPR contains a single membrane-spanning domain and is found in a variety of isoforms (Ob-Ra, Ob-Rb, OB-Rc, Ob-Rd, Ob-Re, and Ob-Rf) resulting from alternative mRNA splicing. The ligand-binding domains of all isoforms are identical, but the intracellular domain at the C-terminus differs (Bjørbæk *et al.* 1997). The Ob-Rb with its lengthy intracellular domain is the only isoform having both of the protein motifs required for activation of Janus kinase 2 and signal transducers and activators of transcription (JAK-STAT) pathway (Uotani *et al.* 2006). Although the JAK2/STAT3 pathway has been identified as the primary signaling route triggered by the LR, other signaling pathways such as mitogen-activated protein kinase (MAPK) (Niswender *et al.* 2001) and phosphatidylinositol-3 kinase (PI-3K)(Niswender *et al.* 2001) also exists.

JAK/STAT pathway: The JAK/STAT (janus kinase/ signal transducers and activators of transcription) pathway is the well-studied leptin-activated pathway (Fig. 3). The conserved Ob Rb phosphotyrosine 1138 motif acts as a binding site for the STAT 3 SH 2 domain after ligand engagement and JAK2 activation. STAT3 will then be phosphorylated on Tyrosine705 by JAKs and translocated

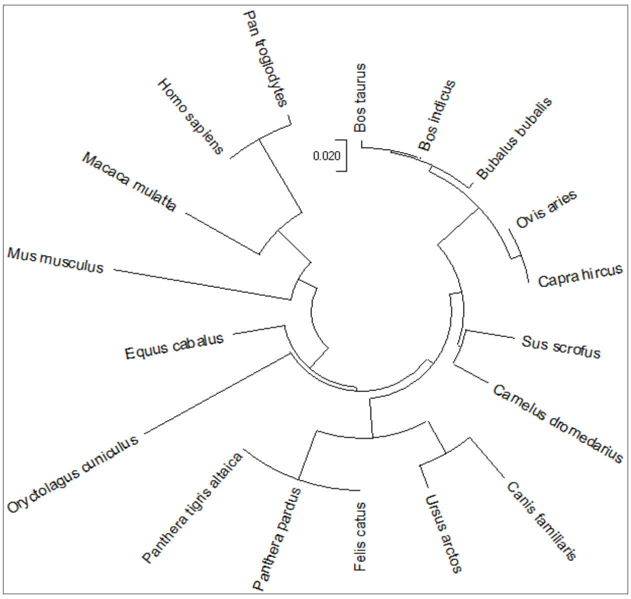

Fig. 2. Phylogenetic tree drawn by MEGA-X by neighbour joining method with 500 bootstarp value. The optimal tree is shown. The tree is drawn to scale, with branch lengths in the same units as those of the evolutionary distances used to infer the phylogenetic tree. The evolutionary distances were computed using the Poisson correction method and are in the units of the number of amino acid substitutions per site.

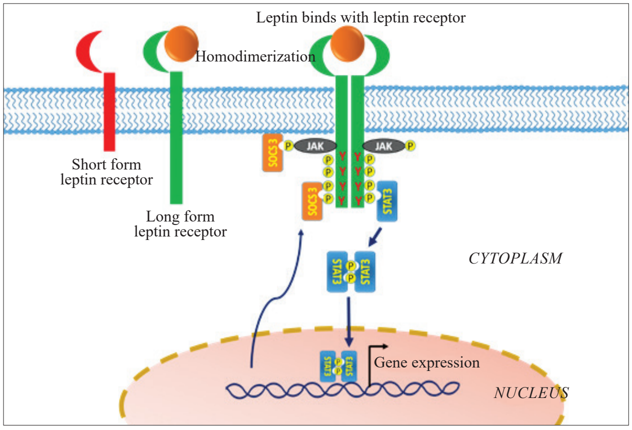

Fig. 3. JAK/STAT pathway, the major signaling pathway activated by Leptin-Leptin receptor interaction. Leptin binds with the soluble isoform (not shown), the short isoform, and the long isoform of its receptor (LEPR). When leptin binds to the long form of LEPR, it dimerizes and activates janus kinase 2 (JAK2), which phosphorylates tyrosine residues present in the cytoplasmatic domain of LEPR. Each of phosphorylated tyrosine serves as a docking site for cytoplasmic adaptors. Phosphorylated-Tyr1138 residue of LEPR interacts with signalling transducer and activator of transcription 3 (STAT3), which dimerizes and translocates to the nucleus. STAT3 activates gene transcription of target genes like suppressor of cytokine signaling 3 (SOCS3), which acts as a negative feedback signaling.

into the nucleus as dimers, modulating the expression of numerous STAT3-responsive target genes including suppressor of cytokine signaling 3 (SOCS3) (Vaisse *et al.* 1996, Waelput *et al.* 2000). Following STAT3, leptin also activates STAT1, STAT5, and STAT6 in cell culture system (Rosenblum *et al.* 1996). Activated STAT5 interacts to the ObRb's phosphorylated Tyrosine1077 (pY1077) and, to a lesser extent, the ObRb's phosphorylated Tyrosine (pY1138). STAT5 binding to pY1077 was discovered to be important in the reproductive activities of leptin in a mouse model.

Significance of leptin in fat store and meat quality in domestic animal species

The major function of leptin is to make the brain cautious about the amount of the body's fat reserves, allowing for short- and long-term evaluation of energy balance. The brain regulates the gonadotrophic axis to enable or restrict reproductive activity by influencing changes in intake, energy consumption, and thermogenesis. Leptin also has probable role in determining the immune function (Abella *et al.* 2017).

Leptin and body fat store: Preliminary study with Linco multi-species radioimuunoassay (RIA) established the role of serum leptin as an indicator of body fatness (12th rib back fat depth) in beef cattle (Minton 1998). Later a specific radioimuunoassay (RIA) based on anti-recombinant ovine leptin was developed (Delavaud *et al.* 2000) which showed significant positive correlation between body fatness or body condition score and plasma leptin levels. In another RIA-based study with antibody against bovine-ovine leptin, back-fat thickness in female and castrated male sheep were also found to be positively correlated with plasma concentrations of leptin (Blache *et al.* 2000). Correlation was also observed between 12th/13th rib fat depth ($r = 0.34$ to 0.46) and kidney, pelvic, heart (KPH) fat ($r = 0.42$ to 0.46) with leptin in crossbred steers and heifers slaughtered at 14 to 17 months (Geary *et al.* 2003).

Relationship between leptin and carcass quality has also been observed in bovine and ovine species. Yamada *et al.* (2003) found strong correlation ($r = 0.802$) between leptin level and body fat when pooled data were used in Japanese Black Holstein steers. Similar results were experienced in sheep (Wylie 2004) and cattle (Ehrhardt *et al.* 2000). Leptin and fat depot masses correlated in 35 and 45 kg lambs with greater values (0.53 to 0.64) for pooled data, while leptin and ultrasound estimations of carcass fat showed equal accuracy ($R^2 = 0.818$) (Altmann *et al.* 2005).

Not only overall body fat mass but leptin content differs in individual body fat depot of an animal. Independent investigations in cattle unraveled highly distinct correlations between blood leptin levels and fat in different fat depots, with visceral fat being more strongly linked than subcutaneous fat depth (Minton 1998, Geary *et al.* 2003, McFadin *et al.* 2003). Leptin levels were shown to have a substantial correlation with total fat ($r = 0.802$), visceral fat (0.807), subcutaneous fat (0.745), and intramuscular fat (0.793), but only a modest link with renal fat (0.694) and intramuscular fat (0.592) (Zembayashi *et al.* 1995). Serum leptin levels at slaughter in lambs were shown to be highly correlated with omental and renal fat, but poorly with mesenteric fat (Wylie 2004). Correlation between leptin level and omental fat have been reported by (Altmann *et al.* 2006) in ram lambs and in monogastric animals like pig (Shan *et al.* 2008).

Leptin and meat quality: Triglycerides make up the majority of the intramuscular and marbling fat in meat, which helps with improving cooking and eating quality. In an initial attempt Minton (1998) showed direct correlation between leptin and marbling score in beef cattle and *Longissimus dorsi* muscle area. Leptin concentration in blood one to three days before slaughter was shown to be similarly linked with marbling in 14 to 17 months crossbred steers and heifers (Geary *et al*. 2003), but only weak correlation was found with *L. dorsi* area. Leptin levels were unrelated to subcutaneous fat depth in all groups of steers with 0%, 50%, and 75%. Wagyu (Japanese beef cattle) genetics, but correlation was positive with percentage of fat in the *pars costalis* and *Musculus longissimus* in zero-Wagyu steers at 16 weeks ($r = 0.69$, 0.59) and 4 weeks ($r = 0.52$, 0.51) before slaughter (Brandt *et al*. 2007). Blood leptin level, and leptin expression in subcutaneous fat of Belgian Blue, Angus, and Limousin bulls were compared (Daix *et al*. 2008). The highly muscular Belgian Blues had the lowest leptin expression. Belgian Blues have low marbling, which is consistent with the inverse relationship between leptin and marbling found in cattle with strong Wagyu ancestry (Wegner *et al*. 2001).

Role of leptin in animal reproduction

In mammals, birds, and reptiles, sexual activity that leads to reproduction begins after puberty. Puberty is a hormonally controlled process that happens only when the body's energy reserves are sufficient. Leptin is the key molecule that signals the brain that adequate energy has been conserved. Leptin is thought to have a role in the initiation of puberty by introducing the nocturnal gonadotropin surges that are associated with puberty. Before reproduction can begin, enough energy stores must be established, especially in female individuals of mammalian species. Serum leptin levels, which are strongly correlated with body fat percentage, supply the hypothalamus with the necessary information on energy status. The process in male individual is not clear.

The exact mechanism how leptin ignites GnRH neurons to secrete gonadotropins remains obscure. GnRH neurons lack leptin receptors, hence, leptin activation of gonadotropins must occur through a secondary route. Kisspeptin neurons have been hyothesised to have a function in this respect; however, kisspeptin neurons appear to possess few leptin receptors (Louis *et al*. 2011 and hence may not stimulate GnRH release. In an alternate pathway, polymorphonuclear (PMN) cells have been reported to express a high number of leptin receptors, and

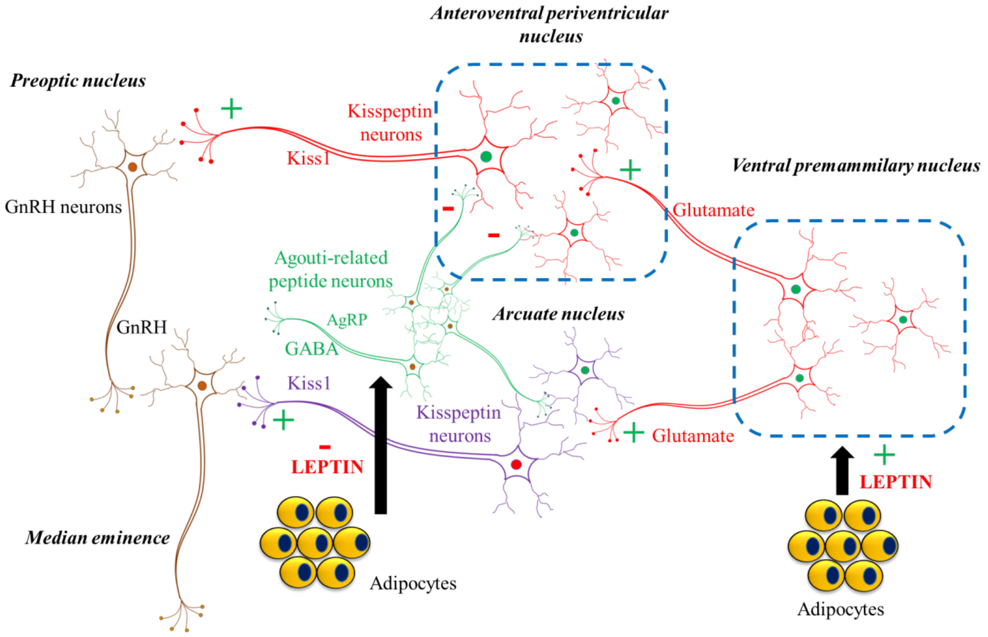

Fig. 4. Activity of leptin in hypothalamus. Stimulation by leptin is mediated by neurons in the ventral premammillary nucleus (PMV). PMV transmits connections to Kisspeptin neurons in the anteroventral periventricular and caudal arcuate nuclei, where glutamate increases Kiss1 expression. Leptin also suppresses the orexigenic AgRP-NPY-GABAergic neurons in the Arcuate in a normal state. These neurons communicate Kisspeptin neurons in the AVPV and caudal Arcuate when leptin signals are decreased, suppressing Kiss1 expression via AgRP or GABA. These activities affect gonadotropin release and the LH surge by stimulating or inhibiting GnRH neurons and modulating pulsatile activity.

PMN cells project onto kisspeptin and GnRH neurons (Leshanand Pfaff 2014). As a result, leptin may activate the PMN, which then stimulates the GnRH neurons, both directly and perhaps indirectly by the kisspeptin neurons, causing the gonadotropins to be released (Fig. 4).

Leptin and onset of puberty

Cunningham *et al.* (1999) and others have defined leptin as a "metabolic gate" for beginning reproductive activity in the hypothalamus, the centre of hunger control. In cattle (Garcia *et al.* 2002) and pigs (Barb and Kraeling 2004), changes in leptin level and leptin mRNA expression were linked to the onset of puberty. Williams *et al.* (2002) found that leptin level rose in heifers passing through puberty. However, several studies have not found any correlation between leptin level and attainment of pubertyin domestic animals. Block *et al.* (2003) examined heifers entering puberty early or late (286 days vs. 414 days) and reported that early heifers were lighter, leaner, and had lower leptin levels (2.6 ng/ml vs. 4.3 ng/ml), suggesting that leptin is not a necessary factor for puberty. Chelikani *et al.* (2009) also found no significant peripubertal leptin rise in heifers fed to gain at 0.5, 0.8, or 1.1 kg/day.

Role of leptin in gonadal function

Presence of leptin receptor mRNA in immature and mature bovine oocytes and embryos suggest that leptin has a function in implantation, embryo development (Madeja *et al.* 2009), ovary development, and steroidogenesis (Henson and Castracane 2000). In rodent, bovine, and primate models, *in vitro* studies on theca, granulosa, and luteinized granulosa cells show that leptin has a direct inhibitory effect on steroidogenesis (Karlsson *et al.* 1997, Spicer and Francisco 1997, Zachowand Magoffin 1997, Agarwal *et al.* 1999). LR mRNA has been found in adult human granulosa, theca, and interstitial cells (Cioffi *et al.* 1996, 1997, Karlsson e*t al.* 1997) as well as porcine ovary (Lin *et al.* 2000). In bovine granulosa and theca cells, leptin can suppress insulin-induced progesterone and estradiol synthesis, as well as insulin-induced progesterone and androstenedione production (Spicer and Francisco 1997). Abavisani *et al.* (2009) reported the presence of leptin transcript in testicular tissue of Holstein bull. The same study suggested that in addition to its endocrine actions at the hypothalamic-pituitary axis, leptin may act as autocrine and/or paracrine regulator of bull testicular function (Abavisani *et al.* 2009). A recent study conducted by Yadav *et al.* (2020) genotyped 125 Hardhenu cows targeting the loci g.92450765 G>A and revealed that cattle carrying AA genotype were superior in terms of service period (SP), calving interval (CI) and artificial insemination (AI) per conception compared to AG and GG genotyped cows.

Role of leptin in immune response to infection

Leptin is considered as link between the neuroendocrine and immune systems (Carlton *et al.* 2012). Pro-inflammatory actions of leptin in the immune system act as a potent enhancer of immune functions (Behnes *et al.* 2012). Leptin can act on different immune cells, specifically by promoting activation of monocytes or macrophages and natural killer (NK) cells, inducing chemotaxis of neutrophils and degranulation of basophils, among other functions (Abella *et al*. 2017). Various roles played by leptin to modulate innate and adaptive immunity have been recently reviewed by Mukherjee *et al*. (2023). In present study serodiagnostic potentiality of goat, fish and mithun leptin was explored (Alam *et al.*, 2014a, Alam *et al*. 2014b, Joardar *et al*. 2017). Recently, Yadav *et al.* (2020) screened genomic region of leptin gene (loci g. 92450765 G>A) with anobjective to find the association of genotypes with fertility and production traits. The animals harboring GG genotype were observed to be more susceptible to reproductive disorders.

Leptin and parasitic infection in animals

Recurrent gut parasite infections induce under performance in ruminants due to nutritional conflict between the immune system and growth, and anorexia is a frequent symptom of nematode infection (Kulcsár *et al*. 2005). The influence of leptin molecules on T-cells and proinflammatory cytokines IL-6 and TNF-α help well-fed animals to withstand or eradicate illness (Lord *et al.* 1998). Amarante *et al.* 2004) reported that faster-growing Suffolk lambs are more vulnerable than slower-growing breeds and that their anorexia is more severe and lasts longer. A non-significant rise in leptin was reported in restricted Merinos infected with *Trichostrongylus colubriformis* and *Teladorsagia circumcinctav* (Liu *et al.* 2007). Zaralis *et al*. (2008) infected Scottish Blackface and Suffolk × Greyface lambs with *T. circumcincta* for 12 weeks and found that Suffolk-Greyface lambs had a 13% decrease in intake. Also, the group observed that infected lambs had greater leptin levels than non-infected lambs with equal feed consumption.

Future challenges and direction

Leptin and leptin antagonists as therapeutics Recombinant leptin is already approved for the treatment of congenital leptin deficiency in human, while the synthetic leptin analogue metreleptin is approved for the treatment of lipodystrophy (Tchang *et al.* 2015). Leptin and their antagonists have major potential to be used in human medicine as therapeutics for the treatment of autoimmune diseases and cancer. Various strategies have been developed to identify novel antagonist molecules of leptin. Some of them are (i) Leptin antagonistic mutants that bind but do not activate the receptor; (ii) leptin peptide antagonists that consist of parts of the leptin sequence; (iii) leptin and LR specific (monoclonal) antibodies or nanobodies that prevent productive binding of leptin; and (iv) soluble LR variants that trap free leptin in the circulation. However, the use of leptin antagonists in animals is still not verified. More knowledge of the LR activation mechanism, signaling, and physiology in farm animal species will aid in the development of these antagonists as growth promoter, immunomodulator, anti-inflammatory drugs, etc. Use of leptin antagonists in livestock especially in poultry may replace the antibiotic growth promoters which are banned in different countries due to precise role in emergence of antimicrobial resistance.

DNA-based marker assisted selection

The leptin gene is a candidate gene for fat deposition and meat quality. Increased intramuscular fat and low subcutaneous fat are desirable for quality meat production (Hocquette *et al.* 2007, 2010). Various single nucleotide polymophisms (SNPs) in leptin gene have been associated with fat deposition parameters in livestock. Corva *et al.* (2009) observed correlations between backfat thickness, rib-eye muscle area, and carcass yield in Brangus (5/8 Angus, 3/8 Brahman) steers with two leptin gene SNPs (one in exon 2, one in the promoter). Significant association was found between three SNPs in leptin gene with perinatal mortality in Holstein-Friesian heifers (Brickell *et al.* 2010). Recently a PCR-RFLP study found that significant relationship prevails between a specific SNP (LEP-A422B) and internal crude fat weight and the fat yield in the carcasses of bull calves in Hereford and Limousin cattle (Sedykh *et al*. 2020). Implementation of prudent breeding strategies using these findings will enhance profit through livestock rearing.

Conclusion

Since the discovery of leptin, research has shown that adipose tissue plays a critical role in metabolic and immune function regulation and undoubtedly, there is still plenty to reveal, especially in the context of livestock biology. Its contributions as a hormone operating at many organs include the hypothalamus, adenohypophysis, pancreas, and gonads, have now been demonstrated which play critical roles in fat deposition, reproductive fitness and disease resistance. The intricate circuitry of leptin differs from one cell type to another which is poorly understood, so far. Translational research has not been carried out utilising the information on genomic and proteomic features of leptin. The focus of future research efforts should be delineating the leptin machinery in different cell types and its role in maintaining energy homeostasis so that they can be manipulated effectively for augmenting production from farm animals and designing leptin-based therapeutics.

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