Review Article

Role of Leptin in Growth, Reproduction and Milk Production in Farm Animals: A Review

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Abstract | Livestock species of agri-based countries, like Pakistan, need special attention for the improvement and sustainability of their productive traits because the economy and huge population is largely dependent on livestock. Therefore it is necessary to adopt some strategies to get more adaptive and productive animals. Leptin, a hormone produced mostly by white adipose tissues of body, has many roles including body energy balance, tissue growth, body composition, reproduction and immunity. Leptin helps in reducing feed intake of animal through feed-back mechanism by informing CNS about body energy and fat reserves. The gene responsible for leptin production has many forms which are associated with leptin production, its level in blood and working. The physiological role of leptin and association of different forms of leptin (LEP) gene with multiple economic traits has made it a potential candidate to be studied and improve animals through proper breeding and management strategies. This current review article discusses the role of leptin in various economic traits of farm animals.

Keywords | Leptin, Growth, Reproduction, Milk production, Farm animals

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INTRODUCTION

Hormones regulate various productive and reproductive traits in the body. The metabolism of energy in farm animals is controlled by a lot of hormonal factors like thyroid hormones and leptin. Leptin (Greek: *leptos*=thin) is a 16 KDa peptide hormone and is generally produced in white adipose tissue. Its function is to signal the nervous system about the overall fat reserves of the body. It seems that leptin has a great influence in regulating whole body energy metabolism and may be attributed as a "metabolism modifier". It is also accepted to be a biological marker that reflects the degree of fatness in the body. Leptin is encoded by LEP/ob gene, comprises of three exons and two introns and is located on 4th and 5th chromosome in cattle (Pomp et al., 1997) and sheep, respectively. Among exons, only exon two and three are translated into protein (Javanmard et al., 2008). It has been demonstrated that LEP gene affects reproduction and milk performance in cattle (Nassiri et al., 2007). It also has key role in reproduction by regulating the secretion of gonadotropins in farm animals (Barb and Kraeling, 2004). Difference of LEP gene in human is shown to be related with low levels of leptin, obesity or over weight and non-insulin-dependent diabetes mellitus (Van der Lende et al., 2005). Leptin has a role in regulating the energy balance when acts on nervous system (CNS) and affects deposition of fat in animals by controlling appetite and energy consumption (Houseknecht et al., 1998). Leptin, through its receptors in the peripheral tissues, has been involved in several roles, including lipid oxidation, glucose metabolism, endocrine system, angiogenesis, blood pressure, cell differentiation & proliferation, brain development and wound healing (Ahima et al., 1996; Frank et al., 2000; Agarwal et al., 2009). Leptin is also related with other living processes such as immune system, production of blood cells, bone producing cells and reproduction (Olusi et al., 2003; Hafez, 2013). Leptin can be in focus of interest in cattle because nutritional and metabolic

disorders are major problems in this species.

ACTION

Research studies which stated that the food consumption of animals is regulated by the body fat content leaded the discovery of leptin (Hossner, 1998). Leptin is chiefly synthesized by adipose tissues of body (Kulig et al., 2009) as the result of expression of LEP/ob gene and it has role in energy balance, fertility and immune response of individuals (Hashemi et al., 2011). Kennedy in 1953 proposed "lipostat" role of leptin which reflects its involvement in the regulation of body energy reserves. The physiology of leptin actions is all about its interactions with specific receptors in hypothalamus for energy regulation, its receptors exist in several forms; which can be divided into two broad classes, one with small cytoplasmic domains and other have a long cytoplasmic tail (Hossner et al., 1997). The receptors with long cytoplasmic tail are considered to be the potential receptors that regulate most of leptin effects, acting through the JAK-STAT signal transduction pathway (Hossner, 1998). While circulating in blood, leptin requires some binding proteins for increased half-life. In blood, it binds with three binding proteins with molecular weight 85, 176 and 240 KDa and the level of binding proteins in blood varies with genotype and feeding practices of individual (Houseknecht et al. 1998). Sinha et al. (1996) showed chromatographically the affinity of leptin with six binding proteins of molecular weight 68, 75, 80, 100, 130 and 280 KDa. Kidneys (renal medulla) are considered to be the organ of mammals where most of the plasma leptin is catabolize. Many studies showing the significant effectiveness of leptin when inserted in the lateral or third brain ventrical confirmed the primary site of leptin actions is central nervous system (Geary et al., 2003).

LEP GENE POLYMORPHISM

Polymorphisms in the LEP gene of bovines has been described by Lusk (2007), Shin and Chung (2007), Yang et al. (2007) and Guo et al. (2008). Lagonigro et al. (2003) and Nkrumah et al. (2005) studied its relationship with food intake. Association of leptin with meat quality and carcass traits has been demonstrated by Schenkel et al. (2005), Boucher et al. (2006), Chung et al. (2008), Kulig and Kmieć (2009), de Oliveira et al. (2013) and Tian et al. (2013). Buchanan et al. (2003) and Liefers et al. (2003) have done research experiments to find out the role of leptin in milk production. Polymorphism in LEP gene of ovine has also been discussed (Zhou et al., 2009) and its association with growth traits has been described by Barzehkar et al. (2009), Tahmoorespur et al. (2010), Shojaei et al. (2011), and Hajihosseinlo et al. (2012). In caprine, polymorphism in LEP gene has been reported by Singh et al. (2009) and Wang et al. (2011). Yet, association studies concerning markers in LEP gene have shown indecisive consequences. It could be said that the variations are due to alterations in environmental factors such as nutrition and genetic information of the animals, which are potential sources of genetic × environment relationship. Nutritional level, both in terms of quality and quantity of nutrients, becomes an imperative limitation in production systems that only depend on direct grazing of animals (Corva et al., 2009). Above described conclusions advocate that variation in LEP gene in domestic animals might be significant in fat deposition and feed intake, thus affecting growth and meat quality traits.

ROLE IN GROWTH

Adipose tissue of a living body has a pertinent part in controlling the secretion of growth hormone (GH). GH and IGF-1, both intervene the fatness in individuals and their level is often reduced in fatty individuals (Casabiell et al., 2001). Genetic alterations in LEP/ob gene or in their receptors (LEPR) alter the level of growth hormone in blood plasma (Clement et al., 1998). Growth hormone has a significant role in growth and development, as well as an important influence on composition of body and circulation of fats (Wauters et al., 2000).

Moreover, structure of leptin is similar to that of GH and there exists likelihood of leptin binding to growth hormone binding proteins. LEPRs were recognized in arcuate and periventricular nuclei of hypothalamus (Hashemi et al., 2011). In these hypothalamic nuclei, growth hormone and somatostatin releasing hormone neurons are also located. Though processes by which leptin mediate its actions are not entirely concluded, presence of LEPRs in nuclei of hypothalamus advocates the role of leptin at hypothalamus level.

The hypophysis cerebri is the expression site of LEPR, where leptin mediate the release of growth hormone (Shimon et al., 1998). The confirmation about involvement of leptin in the release of growth hormone was confirmed by intra-cerebro-ventricular (ICV) inoculation of leptin. The results showed that leptin antiserum administration to normal rats caused definite reduction in growth hormone levels in plasma. This study showed that different levels of leptin in body causes increase or decrease in GH secretion levels. Forty eight hours deprivation of food also decreased growth hormone production. When leptin was administered ICV, it showed the repressive effect on growth hormone and growth hormone releasing hormone secretions (Carro et al., 2000).

Leptin might be obligatory for typical development and growth of brain-endocrine (pituitary) system and has role in the expression of glial and neuronal proteins. This proposes that leptin might have a significant role in develop-

ment (Morash et al., 2000). Leptin also seemed to be an important factor for growth of many cell types as pancreatic cells (Tanabe et al., 1997), white blood cells (Lord et al., 1998), and epithelial cells of trachea and squamous cells of lungs (Tsuchiya et al., 1999).

ROLE IN REPRODUCTION

Sexual maturity in normal or obese animals is the result of maturation of the hypothalamic pituitary gonadal axis and its start is related to rise in gonadotropin releasing hormone action, which induces the release of sex steroid hormones and gonadotropins. This activation can be triggered by leptin which provokes the pituitary gland to release two hormones, follicle stimulating hormone (FSH) and luteinizing hormone (LH) (Agarwal et al., 2009).

There are some animals which are found hypogonadic because of mutation in LEP gene (Strobel et al., 1998). Numerous research studies showed that leptin controls sexual maturity at hypothalamus level (Casanueva and Dieguez, 1999; Ehrhardt et al., 2002; Agarwal et al., 2009). Moreover the occurrence and involvement of LEPRs in hypothalamus with release of gonadotropic hormone confirms its role in sexual maturity or reproduction (Magni et al., 1999).

In a research study on leptin treated macaques, mean levels and frequency of pulsatile secretion of FSH and LH in plasma varied significantly as compared to macaques on fast (Finn et al., 1998). Maternal leptin level influences LH secretion in young ones. The frequencies of LH pulsatile secretions were less in diet restricted lambs than the ones which were fed more leptin (Morrison et al., 2001). In feed-restricted cows and sheep, hypothalamic neuropeptide Y, inhibitor of secretion of luteinizing hormone in these species, was present in high amount (Keisler et al., 1999). Subcutaneous administration of leptin induced the GH and LH secretion during fasting in estradiol-treated and castrated male sheep (Nagatani et al., 2000). Intra-cerebro-ventricular administration of recombinant leptin in sheep caused a noticeable secretion of luteinizing hormone in cattle and *in-vitro* researches confirm influence at the pituitary level. Low level of fertility related with malnourishment is a foremost interest for animal breeder. Under-nourished individuals will not attain sexual maturity unless they are well-nourished. Likewise, adult with normal estrous cycle will halt their cyclic activity when raised in under-nutrition conditions. These findings favor the assumptions of role of leptin as nutritive factor for reproductive physiology of animals. Isoforms of leptin receptor, together with long signaling form exist in gonadal tissues which indicate a direct endocrine activity of leptin on the gonads. On the other hand, local influence of leptin appears repressive for synthesis of steroids. *In-vitro* researches revealed, leptin subdues ovarian production of estradiol and progesterone (Karlsson et al., 1997).

During gestation period levels of leptin in plasma are increased (Stein et al., 1998), higher level during second trimester (Tamura et al., 1998), and decrease abruptly as parturition occurs. This decrease in leptin concentration during gestation happens with the incidence of circulating form of leptin, acting as a binding protein (Lewandowski et al., 1999). Leptin production in placenta and developing fetus is also the cause of increased level of leptin in body. Involvement of synthesized leptin with growth of fetus or indication of energy status between dam and fetus is not much obvious (Wauters et al., 2000). The leptin receptor (long signaling and short transporting form) is also expressed by the placenta, signifying its role in development and growth of fetus (Hoggard et al., 1998).

A significant amount of leptin is also produced by placenta of growing fetus and act as growth factor for fetus, signaling about the state of nutrition from the dam to her unborn (Masuzaki et al., 1997). The incidence of leptin was described in pre-implantated embryos as well. Leptin and its intra-cellular second messenger protein (STAT3) has been found in bovine embryos (Boelhauve et al., 2005). This shows the significance of leptin in development of embryos and it will help researchers and scientists for improving implantation rates by conducting research studies on administration of exogenous leptin.

ROLE IN MILK PRODUCTION

Leptin is considered as a potential candidate marker and has been found associated with milk yield and quality traits i.e. fat % and protein content of cattle milk. Association of different haplotypes of leptin (A59V/Sau3AI) have been found associated with fat, protein and milk yield in Polish Friesian black and white cattle (Kulig, 2005). Leptin is secreted in the mammary glands during lactation and it has also been found in the colostrum of cattle and other livestock species (McFadin et al., 2002). There are some propositions that leptin might has role in informing the CNS about energy/ fat reserves sufficient to support the energy demand of animal to ensure the successful lactation (Casabiell et al., 2001).

CONCLUSION

Many scientists have detected LEP gene polymorphism in bovines, caprines, ovines and swines. They have also found significant associations of LEP gene variation with various productive and reproductive traits. Current genetic improvement schemes can be enhanced by using these research studies which might take part in increasing the productivity in our indigenous animals. The prospect to change the body composition by management or selection

can assist the livestock farmers to produce meat that likely fulfils the expectations of consumers. The research findings could be indicative of other important traits in animals, yet more research work is obligatory to validate the results before their implication in marker-assisted selection (MAS).

FUTURE PERSPECTIVES

Leptin has important role in regulating many productive and reproductive traits. It has been studied in various animals like cattle, buffalo, sheep, goat and pigs in Brazil, Egypt, India, Iran, Italy and Romania, to name a few. There is very less work done on leptin in Pakistan thus it would be pertinent to characterize and find single nucleotide polymorphism in LEP gene in our indigenous breeds and also its relationship with numerous productive and reproductive traits. The amount of circulating leptin would be a sign of fat contents present in live animals. This would enable the farmers to develop more suitable strategies for fattening and milking management, thus increasing the easy sale of animals to market. Still, a lot of research work is required in this regard.

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