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LETTERS

Leptin in Energy homeostasis, Male reproduction, and Immune regulation

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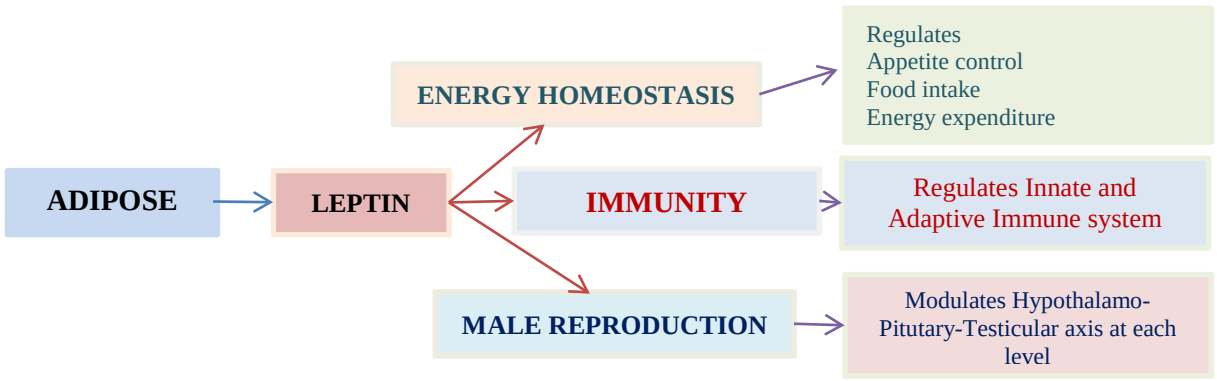
ABSTRACT



Discovery of leptin has changed the view of adipose tissue from energy storehouse to active neuroendocrine and immune organ. Adipokineleptin is a16 kDa amino acid protein, encoded by LEP gene, secreted by adipose tissue, and acts through leptin receptor which is a cytokine receptor. Leptin is a central regulator of energy homeostasis by regulating food intake, appetite, satiety and basal metabolism. Leptin acts at each level of hypothalamus pituitary gonadal axis (HPG) and has a key role in initiation, progression of pubertal events and sexual maturation. Leptin acts directly at testicular level and affects the spermatogenesis, sperm quality and capacitation thus have important role in male reproduction and fertility. Leptin receptors are present on every cell involved in innate and adaptive immunity and regulate the functions of these cells. Leptin acts as common link between energy homeostasis, reproduction, stress responses and immune system by modulating common complex neuronal circuits. Leptin is implicated in pathogenesis of multiple disorders like obesity, type 2 diabetes mellitus, Systemic Lupus Erythematosis, osteoarthritis, rheumatoid arthritis, male infertility and other chronic inflammatory disorders. Therapies based on modulating the functions of leptin can be the key area of research in future for treatment of these chronic disorders.

Keywords: AgRP, Cocaine, hypothalamo-pituitary gonadal axis, Leptin Receptor, Neuropeptide Y, POMC, Systemic Erythematosis Lupus

INTRODUCTION

Adipose tissue once considered an energy storehouse, is now considered as an active endocrine and immune organ after the discovery of various adipokines like leptin, adiponectin, resistin, visfatin, TNF-alpha, Interleukin-6 etc.[1-3] These adipokines acts in an autocrine or paracrine fashion having complex physiological effects and affects the whole-body homeostasis. Leptin is the most studied amongst various adipokines and since its discovery in 1994, its role has been extensively studied in various physiological and pathological processes which predominantly include energy hemostasis, reproduction, immunity, inflammation, glucose, lipid and bone metabolism and rheumatologic disorders. Leptin is secreted by adipose tissue and regulates food intake, metabolism, neuroendocrine axis, immune and various other physiological functions. Leptin is a 16 kDa, 167 amino acid non-glycosylated protein encoded by LEP gene and exerts its biological actions by binding to its receptor, leptin receptor. Leptin receptor (LepR) belongs to the class I cytokine receptor superfamily having several isoforms and acts mainly through Janus-Kinase (JAK) and Signal Transducer and Activator of Transcription-3 (STAT-3) pathways.[4-6] Leptin is predominantly secreted by the white adipose tissue (WAT); however, skeletal muscles, cartilage, placenta, brain, immune cells and intestines are other minor source of leptin.[7] Leptin levels correlates with amount of body fat, has pulsatile secretion, exhibits sexual dimorphism with women having higher levels and its secretion is influenced by various factors like insulin, glucocorticoids, catecholamines and cytokines.[8-11] Diverse biological actions of leptin and other adipokines makes adipose

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tissue not only a dynamic endocrine organ but also an organ having essential role in immune system.[4, 12-13]

Leptin modulates the neuronal circuits like AgRP/NPY and POMC/CART in the brain which are involved in the energy homeostasis.[4] These pathways also interact and modulates the neuronal circuits in the brain like Kiss-1 gene which regulates the GnRH pulse generator which in turn control the pituitary gonadotropins secretion. Leptin affects one of the important hormones involved in energy homeostasis, insulin, insulin resistant states alter the GnRH neurons pulse pattern and thus altered pattern of gonadotropin secretion. This altered pattern of gonadotropins is seen in chronic disorders like polycystic ovarian disease. Chronic inflammatory state induced by the leptin as seen in obesity stimulates the corticotropin adrenal axis which not only alters the immune responses but also negatively impact the HPG-axis. Thus, leptin acts as common link between energy homeostasis, reproduction and immune system.[11-12,14-15]

This review discusses the role of leptin in energy homeostasis, immune regulation and male reproduction.

LEPTIN AND ENERGY HOMEOSTASIS

Maintenance of energy homeostasis requires balance between mechanisms involving food intake, appetite control and energy expenditure. Appetite and food intake is based upon psychobiological events which includes hunger, perception craving, hedonic sensations, behavioral events like meal intake, snacks and macronutrient intake; while energy expenditure depends upon thermoregulation, basal metabolism and physical activity. Both the processes of food intake/appetite and energy expenditure depends upon interactions between neurotransmitters, hormones, metabolic milieu at peripheral and central nervous system level. Imbalance in energy homeostasis leads to pathological states like obesity, starvation, reproductive dysfunction and altered immunity.[16]

Leptin has a central role in appetite control and food intake by interacting with complex neuronal circuit. Most of actions of leptin in the brain are mediated by LepRb-expressing neurons, which are present in the hypothalamic nuclei (ARC-Arcuate Nuclei, DMH-Dorsomedial, VMH-Ventromedial, LHA- Lateral Hypothalamic Area, PMV-Ventral Premammillary) and other areas of brain like ventral tegmental area, raphe nuclei, brainstem, periaqueductal gray matter, nucleus of tractus solitarius (NTS).)[17-18]

Neuronal circuit in the arcuate nucleus of hypothalamus consisting of orexigenic neurons synthesizes agouti-related proteins (AgRP) and neuropeptide Y (NPY) which are inhibited by leptin; while anorexigenic neurons which synthesizes pro-opiomelanocortin (POMC) and cocaine-and amphetamine-regulated transcript (CART) are activated by leptin. POMC is cleaved into α-melanocyte stimulating hormone (α-MSH) which stimulates the melanocortin 4 receptors (MC4-R) located on the neurons in the hypothalamus while AgRP directly inhibits the α-MSH activation of MC4-R thus influencing the appetite and satiety. Decrease in the level of leptin in fasting states stimulates expression of AgRP/ NPY neurons and suppresses the POMC/CART neurons thus increasing the food intake and decreasing the energy expenditure.[4,13]

Satiety is one of the mechanisms whereby individual terminates feeding. Arcuate and ventromedial nucleus of the hypothalamus is called satiety centers. Activation of LepRb-POMC/CART pathway in the arcuate nucleus by leptin results in termination of feeding.[19,21] Leptin activates VMH-LepRb neurons co-expressing SF-1 (Steroidogenic Factor-1) which contributes to the satiety. NTS is a brainstem nucleus which contain LepRb neurons and receives inputs from gastrointestinal tract. Neurons of NTS are synergistically regulated by gut hormones glucagon like peptide-1 (GLP-1), Cholecystokinin (CCK) and leptin leading to satiety.[22] LepRb expressing neurons are present on the lateral hypothalamic area which innervates the ventral tegmental area and other parts of mesolimbic dopamine system. Leptin directly modulates the activity of these neurons in the LHA and mesolimbic dopamine system thus influencing the hedonic drive to feed.[23-24]

Non shivering thermogenesis is one of the key mechanisms of energy expenditure. It occurs in the brown adipose tissue (BAT) and is mediated by uncoupling protein-1(UCP-1),which uncouples the fatty acid oxidation from adenosine triphosphate production in mitochondria leading to thermogenesis. Leptin increases the thermogenesis by increasing the expression of UCP-1 by increasing the sympathetic activity in BAT.[25-26]

Melanin concentrating hormone (MCH) is a hypothalamic neuropeptide, predominantly secreted form the lateral hypothalamic area and is involved in the energy expenditure, appetite regulation, reproduction apart from its role in skin pigmentation.[27]Levels of MCH are positively correlated with fat mass and body mass index and levels are higher in women than men. Increase in the food intake and decrease in the energy expenditure by the MCH is inhibited by leptin thus decreasing the obesity induced by MCH. In low leptin states like fasting, genetic leptin deficiency and leptin resistant states; expression of MCH is induced. Leptin exerts its action on MCH neuron mainly through AgRP/NPY neurons.[28]MCH stimulates the leptin mRNA expression and its secretion.[29]

Transcription factor FOXO1 is expressed predominantly in the steroidogenic factor-1 (SF-1) neurons of the dorsomedial and ventromedial nucleus of the hypothalamus; and regulates the energy homeostasis by modulating the leptin and insulin action in the brain.[30] FOXO1 exerts its effects by directly modulating the POMC and AgRP genes. FOXO1 leads to leptin resistance by inhibiting the STAT-3 phosphorylation mediated regulation of POMC by biding to specificity protein 1 (SP1)-pro-opiomelanocortin (POMC) promoter complex.[31-32]

Leptin is implicated in glucose homeostasis with wide ranging functions by directly affecting the organs involved in glucose homeostasis or through leptin activated neural pathways at the hypothalamic or extra-hypothalamic sites.[33]Leptin inhibits the insulin secretion from pancreatic beta cells, inhibits glucagon secretion from alpha cells, suppresses insulin signaling and action in the adipocytes, increases the hepatic glucose insensitivity and have variable effects on skeletal insulin sensitivity thus effecting the various sites involved in glucose

homeostasis.[34] Central effects of leptin on glucose homeostasis are mediated by alterations in the sympathetic and parasympathetic nervous system.[35] High glucose levels leads to activation of anorexigenic POMC neurons while at lower concentrations orexigenic AgRP neurons are activated, and these effects are mediated by leptin.[36]

Leptin has neurotrophic effects i.e., neurogenesis, axonal growth and synaptogenesis of the neuron involved in the energy homeostasis.[37] Leptin also affects prenatal as well as postnatal development of the brain. Imaging studies of the brain has shown that structural and functional abnormalities are reversible with leptin therapy in patients of congenital leptin deficiency.[38]

Endocrine disorders result from hormone deficiency which can be either partial /complete or there can be resistance to the actions of hormones. Leptin resistance in one of the key abnormalities in obesity similar to insulin resistance seen in patients with type 2 diabetes mellitus. Leptin resistance is associated with high endogenous levels of leptin and diminished effects of exogenous leptin administration on food intake and decrease in body weight.[39]Mechanisms of leptin resistance are heterogeneous and includes induction of PTP1b and/or SOCS3 in the cells expressing the leptin receptor, defects in melanocortin signaling, diminish transport of leptin across blood brain barrier, impaired trafficking of LepRb across the neuronal membranes in the hypothalamus, endoplasmic stress and pro-inflammatory cytokines.[40-41]Patients with complete or partial leptin deficiency as seen in lipodystrophies, leptin treatment reverses all of the metabolic abnormalities and improves food intake. Treatment with leptin reduces weight in obese people with low leptin levels and also decreases food intake and adipose fat mass in lean healthy individuals with normal leptin levels.[42]

LEPTIN AND MALE REPRODUCTION

Normal human reproduction requires intact and normal functioning of hypothalamo-pituitary-gonadal axis (HPG-axis). Sexual maturation is well coordinated process in the humans which starts as mini puberty in initial years of life with increase in testicular volume in males. Further initiation and progression of puberty occurs with appearance of pubic and axillary hairs, increase in testicular volume and increase in penile length leading to sexual maturation. Alterations in the nutritional status and energy stores can leads to the changes in the complex interplay of gonadotropins and gonadal hormones which are essential for reproduction. Male infertility/subfertility is multifactorial and is most often labeled as idiopathic. Rising incidence of obesity has positively correlated with male infertility or subfertility. Obese people have higher estrogen levels as compared to lean subjects and thus occurs due to increased adipose tissue mass leading to increased cytochrome aromatase activity; an enzyme which converts the testosterone to estradiol. Testosterone: estrogen ratio is essential factor for normal functioning of GnRH pulse generator and thus gonadotrophs and testicular functions. Alteration of this ratio leads to functional hypogonadism in obese people thus affects fertility.[1,43-44]

There is ample evidence to suggest that leptin is the link between adipose fat mass and hypothalamic centers which control reproduction.[45]The first evidence that leptin is involved in the reproduction came from studies from genetically obese mouse with mutation in ob gene having leptin deficiency. They were infertile and the leptin administration restores the reproductive functions. Chronic leptin excess in animal models like transgenic skinny mouse model or by administering exogenous leptin to the mouse model has shown that it causes accelerated puberty and early sexual maturation.[46-47] However, recent studies in human and rats have shown that leptin is essential to proceed the pubertal events and pubertal maturation but alone cannot accelerate puberty and it has a permissive role.[48-49]

Puberty is a critical event in sexual development and is precisely controlled by complex interactions between endogenous and environmental factor. Leptin plays a crucial role in the development of HPG-axis acting and influencing at each level of HPG axis. The role of leptin in female puberty has been well characterized but there is less evidence of its role in the male puberty. GnRH (gonadotropin releasing hormone) pulse generator consisting of GnRH neuron in the medial basal hypothalamus drives the key events in the pituitary gonadotropin and thus gonadal hormone secretion.[48-50] GnRH pulse generator remain quiescent after few initial years after birth till initiation of puberty. Leptin receptors are not present in the GnRH neurons and it affects GnRH neurons indirectly via the leptin sensitive afferents projecting to these neurons.[51-52]

Kisspeptin a neuropeptide, encoded by KIS-1 gene and synthesized by kisspeptin neurons located in the arcuate nucleus and paraventricular area of third ventricles of the hypothalamus are the key neurotransmitters to initiate and maturation of the pubertal events in the mammals including humans. Kisspeptin acts on the GnRH neurons to initiate the pubertal events. Several studies in the animal models have shown that leptin directly influences the Kisspeptin neurons. mRNA encoding LepR are detected in ARC/Kiss1 neurons in sheep and mouse, leptin directly excites ARC Kiss neurons in guinea pigs, decreased expression of Kiss-1 neurons is seen in leptin deficiency animal models in ARC and periventricular 3 neurons.[53-55] Some studies have also shown that LepR are not present on Kiss1 neurons as well, however Kiss-1 neurons are present in the ARC nucleus and there could be an intermediary pathway of unknown nature by which leptin stimulates the Kiss-1 neurons.[56]

Hypothalamic neuropeptides POMC and CART stimulate GnRH neurons, which are in turn stimulated by leptin, similarly AgRP and NPY inhibits GnRH neurons which are inhibited by leptin, suggesting one of mechanism of hypothalamic control by the leptin on reproduction. These neurons/factors act with upstream regulators of GnRH secretion which arekisspeptin, neurokinin B and dynorphin neurons.[57-59]

Ventral premammilary nucleus (PMV) expresses LepR in high density and neurons from this nucleus innervate kisspeptin neurons, GnRH cells in the preoptic area, and GnRH terminals in the mediobasal hypothalamus. Leptin activates PMV neurons and thus kisspeptin neurons, GnRH neurons. However, the effects of leptin on PMV are sexually dimorphic and role of LepR in male is still not clear.[60]Kisspeptin level positively correlates with

leptin in adolescent girls, however levels of kisspeptin progressively increase while levels of leptin decrease with advancing pubertal stage in boys. Increasing levels of androgens with pubertal advancement is the possible explanation for this effect as androgen inhibits leptin synthesis from adipocytes while estradiol stimulates the leptin synthesis.[61]

GnRH acts on gonadotrophs in the anterior pituitary to secretes gonadotropic hormones LH and FSH; which are key hormones driving reproduction. Secretion of LH and FSH depends on the maturation and pulsatility of the GnRH neurons. Several factors keep the GnRH pulse generator quiescent till the pubertal events starts with the activation of GnRH pulse generator. Leptin promotes pulsed secretion of GnRH in arcuate nucleus neurons of hypothalamus in a dose-dependent manner.[62] LH surge is first seen in the night at the onset of puberty in both males and females. Fast GnRH pulse favors more LH secretion as compared to FSH which is the first change seen in the pituitary gonadotropin secretion i.e., LH and FSH.[63-64]

Leptin receptors are present in human anterior pituitary and direct effects of leptin on gonadotrophs are contradictory.[65]Some studies have shown that leptin has stimulatory effects on LH and FSH secretion while others have shown that leptin have inhibitory effects on LH secretion. Studies have shown that leptin administration in male patients with congenital leptin deficiency increases circulating LH levels and clinical features and hormonal changes consistent with puberty.[66-67]Activation of nitric oxide synthase by leptin directly promotes the release of LH/FSH and growth and differentiation of pituitary cells.[68].LepR are also present on the testes and highlevels of leptin directly inhibits testicular steroidogenesis. Mechanism of leptin inhibition of testicular steroidogenesis are interference in cAMP signaling downregulation of the expression of steroidogenic acute regulatory protein and downregulated STAT transcriptional activity.[69-70] Testosterone inhibits leptin secretion from adipose tissue thus having inverse relationship.[71]

Structural abnormalities of reproductive system are seen in human and rats with leptin gene deficiency and includes reduced weights of prostate &testes, small Leydig cell size and fewer sperm in the seminiferous tubules.[60,72] Leptininhibits division of pre-pubertal Leydig cells via cyclin D1.[73] Leptin is expressed in the germ cells of testes and LepR are predominantly present on the Leydig cells. Seminal fluid contains leptin, and its levels are higher in males with infertility. Low sperm count, decreased sperm motility, higher sperm mitochondrial membrane potential and increased sperm DNA fragmentation are seen in obese males with high leptin levels.[74-75] High seminal levels of leptin negatively affect the sperm motility irrespective of serum leptin levels.[76] Capacitation is a process whereby sperm has the ability to penetrate and fertilize the egg and which is essential for fertility in males. Sperm cell membrane integrity, sperm metabolism, capacitation index and acrosin activity are enhanced by the leptin by enhancing the STAT3 signal transduction pathway and anti-apoptotic protein BCL-2. However, some studies have shown that leptin does not affects sperm motility and capacitation, and further studies are required to delineate the exact role of leptin in these processes.[77]

Alteration in the sperm morphology by leptin are induced by the increase in oxidative stress. Leptin induces the formation reactive oxygen radicles (ROS) by activating nicotinamide adenine dinucleotide phosphate oxidase (NADPH). At physiological levels ROS have positive impact on the sperm development but at pathological level ROS has negative impact on all the parameters of sperm development. Among many of the pathways involved in the oxidative stress like AMPK, PI3K, MAPK, and mTOR leptin has well established role in its mode of action through these pathways.[78-79] The findings that adverse effects of leptin are prevented by powerful antioxidant like melatonin support the fact that induction of ROS by leptin is one of the key factors altering sperm morphology and functions.[80]

Leptin has significant role in male reproduction although less studied for its role in male reproduction as compared to females. At hypothalamus it influences the activity of GnRH pulse generator through kisspeptin by directly or indirectly through other inter-neuronal connections, influences the secretion of pituitary gonadotropic hormones LH and FSH and at gonad level has marked influence on the testicular structure and functions. Understanding of these functions of leptin has clinical significance in the pathogenesis of male reproductive disorders and male infertility, however lot of studies are needed to delineate the exact role of leptin in male reproduction and to design therapies for male factor infertility.[43,63]

LEPTIN AND IMMUNITY

Immune responses in human comprises of innate and adaptive responses. Innate immune responses are the first line, fast responding and nonspecific mechanism of defenses against any external pathogen invasion, while adaptive responses come into play when innate immune responses cannot completely defend or fails to respond to external pathogen invasion and these responses are specific depending upon the type of pathogen. Neutrophil, monocyte–macrophage system, natural killer cells (NK-cells) and acute phase reactants (IL-1, TNF-α) predominantly carries out the innate immune functions while T-cells and B-cell are predominantly involved in the adaptive immune responses. Most of the immune cell types involved in the innate as well as adaptive immunity express leptin receptors, suggesting role of leptin in immune system.[81-84]

Physiological responses to any stress are mediated by complex interaction between stress hormones secreted by hypothalamo-pituitary-adrenal axis, their effects on humoral and cellular immune responses, modulation of activity of mediators of inflammation like IL-1,IL-6 and TNF-α and their negative feedback on their own pro-inflammatory activities. Leptin has been considered a link between neuroendocrine factors and the immune responses.[85-86] Most of the lymphoid organs are associated with adipose tissue such as bone marrow, thymus and lymph nodes. Adipose tissue provides a microenvironment through which adipokines including leptin to have crosstalk for immune and metabolic homeostasis.[87-88]

Leptin has pro-inflammatory properties, and it acts as acute phase reactant along with others like C reactive protein (CRP), Interleukin 1 and 6 in the immune system. TNF-α and IL1

induces leptin expression and also activates human B Cells to secrete TNF-α, IL-6 and IL-10 via JAK2/STAT3, p38, MAPK/ERK1/2 signaling pathway in humans[89-90] Synthesis of acute phase reactants in adipose tissue by leptin continues to maintain a state of low grade inflammation as seen in chronic disorders like obesity, type 2 diabetes mellitus and is a risk factor for many cardiovascular disorders in human.[91]Increased production of leptin is seen in bacterial infections in humans and can be considered a marker of sepsis.[92]

Leptin receptors are present on human hepatic and peripheral blood NK cells and varying effects of leptin on human and animal cell lines are reported.[93] There is conflicting data on leptin impact on cytotoxic and cytokine secretory effect of NK cells. Leptin may negatively affect the functions of NK cell in pathologically elevated leptin states as seen in obesity; however, many studies have observed that leptin has positive effects on NK cells in normal weighted individuals indicating that leptin resistance is one of the crucial factors for normal functioning of NK cells.[94-96]

Leptin stimulates chemotactic, migration and oxidative functions of neutrophils and also has anti-apoptotic effects on neutrophils.[97] Leptin mediates these functions through MAP kinase, m TOR, PI3Kγ, TNF-α and CXCL1 pathways.[98] Leptin activates the eosinophil and basophils and enhances the innate immune responses like chemotaxis, expression of cell surface adhesion molecules, production of pro-inflammatory cytokines and enhanced survival of both of these cells.[12,99]

Leptin promotes production of inflammatory cytokines like IL1 and 6, TNF-α from circulating monocytes and enhances their chemotactic properties.[100] Toll like receptors-2 mediate innate immune responses and human monocytes treated with leptin has shown increased expression of these receptors.[101]Leptin induces the M2 phenotype with M1 secretion pattern in macrophages of adipose tissues, which infiltrates the adipose tissue in obese individuals and cause less adipose tissue inflammation.[102] Dendritic cells are antigen presenting cells and acts as messenger between adaptive and innate immune system. Leptin activates dendritic cells and up regulates TNF-α, IL-1β, IL-6, IL-12, MIP-1α secretion and improves chemotaxis, migration and survival by NF-κβ and PI3K-PKB signaling, increased bcl-2 and bcl-xL gene expression.[103-106]

Long isoforms of LepRs are present on T cells and it activates T-cells through JAK/STAT3 signaling pathways.[107] T and B cell are predominantly secreted from thymus and other lymphoid organs. Leptin promotes thymocyte proliferation particularly promotes double positive $CD4^+$& $CD8^+$ T cells into single positive $CD4^+$ T cells.[108] Secretion of IFN γ and IL-2 which is a feature of Th1 response from$CD4^+$ T cells is promoted by leptin.[109] Leptin promotes proliferation of Th2 lymphocytes and their responses in the form IL-4 secretion.[110]Leptin promotes proliferation of Th17 cells producing IL-17 and have role in autoimmune disorders and maintenance of chronic inflammatory conditions like SLE, lymphocytic arthritis.[111]

Regulatory T cell (T-reg) have role in suppressing autoimmunity, maintaining peripheral tolerance and limiting chronic inflammatory disorders. T-reg mediate their effects by suppression of IL-10, transforming growth factor-β (TGF-β) , IL-35, cytolysis via granzyme-A&B and perforin.[112] Leptin decreases the proliferation of T-reg cells through activation of m-TOR pathway. Th-1 and Th-17 cells functions are related to its metabolism, leptin induces glycolytic metabolism by increasing the expression of GLUT-1(Glucose transporter-1) transporters in these cells thus promotes functions of T cells.[113-114] Higher levels of leptin seen in disorders like SLE has negative impact on the disease severity and anti-leptin therapies can be possible strategies in treating such autoimmune disorders.[113, 115]

B cells express long form of LepR and leptin promotes B cell proliferation and development, induces secretion of pro-inflammatory cytokines TNF, IL-6 and anti-inflammatory cytokines like IL-10 via JAK-STAT and p38MAPK-ERK1/2 signaling pathways.[116] Leptin promotes B cell survival by inhibiting apoptosis via activation of BCL-2 and cyclin D1 expression.[117] Leptin increases mature B cells while decreases pro-B, pre-B and immature B cells.[118]

Leptin has been extensively studied in recent years and has been implicated in various immune metabolic and immune disorders. Obesity, Type 2 DM, insulin resistance states like polycystic ovarian disease, steato-hepatitis and non-alcoholic fatty liver are common conditions which are pro-inflammatory states and leptin is a significant pathological contributor in these disorders. Innate and adaptive immune responses are commonly implicated in the pathogenesis of immune disorders like SLE, Osteoarthritis, and rheumatoid arthritis.[119-120]

FUTURE PERSPECTIVE

Pandemic of obesity has led to increased incidence of T2DM, non-alcoholic fatty liver disease, OA, RA, male infertility and other disorders. Adipokine leptin has emerged as key regulator of energy hemostasis, modulator of immune system and reproductive functions.[12] Treatment of obesity mainly revolves around lifestyle modification and pharmacologic interventions; however, they lack long term efficacy. Drugs targeting the leptin with the use of leptin-binding molecules or miRNAs and antagonists like monoclonal humanized antibodies against LEPRs can be potential therapeutic interventions in the obesity and related immune metabolic disorders.[121-122] Targeting specific immune cell sub-population by specific LEPR isoforms could be a possible novel therapeutic in the immune metabolic and reproductive disorders. Leptin resistance is one the common factor in common obesity and T2DM, development of effective leptin sensitizers can be potential therapeutic approach in these chronic disorders.[123] Use of leptin or its analogues as neurotropic factor can have potential in the treatment neurodegenerative disorders like Alzheimer's disease, Parkinson's disease and age-related dementia. Pathophysiology of depression is incompletely understood however neuronal plasticity plays a significant role in the development of depression. Leptin improves neuronal plasticity and its functions thus have a potential in the treatment of depressive disorders.[124] Chronic inflammation is a hallmark of various chronic disorders; plasma leptin concentration can serve as biological marker of systemic inflammatory status, thus predicting the immune-metabolic stress burden.[125] Leptin has

complex and interrelated effects on energy hemostasis, immune system and reproduction, modifying its actions using various strategies provides novel therapeutic opportunities for treatment of various chronic disorders; however potential side effects is a real challenge while using such therapies due to its varied actions.

CONCLUSION

Discovery of leptin has changed the view of adipose tissue from energy storehouse to an active endocrine and immune organ. Leptin is one of the most studied and important adipokine secreted by the adipose tissue. Besides its conventional role in energy homeostasis, it has emerged as an important modulator of immune system having widespread effects on every cell of immune system. Leptin has emerged as common link between energy homeostasis, reproduction and immune system by modulating common neuronal pathways and cytokine milieu at central and peripheral levels. Leptin is available for the treatment of congenital leptin deficiencies but has not been used in other disorders. Treatment based on modifying the actions of leptin may be possible in future for obesity, type 2 diabetes, chronic inflammatory and immune disorders like SLE, osteoarthritis, psoriasis and male infertility.

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