Review Article

Neuroimmunomodulation in obesity

Venugopal Lalitha, Gopal Krushna Pal[1], Pravati Pal[1], Murugaiyan Sathish Babu[2]

Department of Physiology, Indira Gandhi Medical College and Research Institute, [1]Department of Physiology, Jawaharlal Institute of Post-graduate Medical Education and Research, [2]Department of Biochemistry, Mahatma Gandhi Medical College and Research Institute, Puducherry, India

Abstract

Obesity is the major risk factor for many chronic diseases such as diabetes, hypertension, cardiovascular diseases, and cancer. Obesity has a negative impact on the immune systems. Obesity is associated with chronic low-grade inflammation and altered immune functions. The regulation of body weight is by the interplay of many neuronal circuitries in the brain that control the food intake and energy expenditure. There is a link between the central nervous system (CNS) and immune system. Therefore, in the present review article, we have discussed the immunomodulation in obesity and its interactions with the CNS.

Key words: Immunomodulation, inflammation, neuroendocrine, obesity

Received: 24th April, 2015; ***Revised:*** 28th May, 2015; ***Accepted:*** 5th June, 2015

OBESITY: GENERAL CONCEPT

Obesity is a serious health problem worldwide.[1] According to World Health Organization report, obesity has reached the epidemic proportions globally with 2.8 millions of death occurring every year.[2] Obesity rates were doubled in adults and more than tripled in children.[3] Obesity in adults decreases the life expectancy of about 7 years in both sexes.[4] Obesity is common among children and adolescents.[5] Adolescent obesity is a strong predictor of adulthood obesity.[5] Excessive weight gain during adolescence is unlikely to decrease over time and increases the risk of obesity-related comorbid conditions such as hypertension, atherosclerosis, type 2 diabetes, cardiovascular disorders, and certain types of cancer in adulthood.[5,6] The rising obesity rates have significant consequences on the health of an individual and create a major strain on the health care system.

Access this article online	
Quick Response Code:	Website: www.ijcep.org
	DOI: 10.4103/2348-8093.161530

The old concept of obesity perceived as a symbol of wealth and fertility has become outdated.[6,7] In the present century, obesity is stigmatized, and it is one of the leading preventable causes of death both in adults and children.[6,7] Many of the obese people die from diseases caused by the complications of overweight and obesity.[8] A previous study has reported that severely obese people die 8–10 years sooner than those of normal-weight, and every 15 extra kilograms increases the risk of early death by approximately 30%.[9]

Obesity is influenced by multiple factors like increased dietary intake of energy-dense foods, reduced physical activity, and even genetic factors.[8,10] Obesity is increasing across all socioeconomic groups. The current food environment stimulates a reflexive response that automatically enhances the desire to eat and increase the caloric intake, making it exceedingly difficult for individuals to resist overeating.[11] Energy intake should match with energy expenditure.[12,13] When the energy intake is more than the energy expenditure, the excess of positive energy gets stored in the adipose tissue leading to hypertrophy of the adipocytes.[14,15] The consequences of visceral adiposity and pathogenic fat cell hypertrophy are due to the mechanistic contributions of genetic and environmental predispositions, adipogenesis, adipocyte factors, and inflammation.[14-16] As a result, the excess fat that is not

Address for correspondence: Dr. Gopal Krushna Pal, Department of Physiology, Jawaharlal Institute of Post-graduate Medical Education and Research, Puducherry - 605 006, India. E-mail: drgkpal@gmail.com

burned due to lack of physical activity gets stored and further building up of stored fat contributes to obesity.

IMMUNOMODULATION IN OBESITY

Chronic inflammation in obesity

Obesity affects the immune system both directly and indirectly. Excess adiposity negatively impacts the immune function and host defense in obese individuals.[17,18] Obesity is associated with low-grade inflammation of white adipose tissue (WAT) resulting from chronic activation of the innate immune system.[19] The accumulated adipose tissue produces many secretory bioactive substances, also known as adipocytokines or adipokines, which may directly affect the adjacent or distant organs.[20] Most adipocytokines are pro-inflammatory, thereby promoting obesity-linked disorders.[20,21] Moreover, it is now recognized that dysregulated production or secretion of adipocytokines caused by adipocyte dysfunction leads to the development of obesity-linked complications.[20] Obesity is also characterized by activation of an inflammatory process in metabolically active sites such as adipose tissue, liver, and immune cells. This in turn results in a sharp increase in circulating levels of pro-inflammatory cytokines, adipokines and other inflammatory markers like tumor necrosis factor (TNF), C-reactive protein (CRP), and interleukin-6 (IL-6).[22-25] This activation of the immune response in obesity is mediated by distinct signaling pathways, with Jun N-terminal kinase (JNK) and IκB kinase beta/nuclear factor (NF) kappa-light-chain-enhancer of activated B cells.[26] Inflammatory responses mediated by the adipose tissue in obesity are central to the development of the disease. Once initiated, the chronic inflammation associated with obesity leads to modulation of immune cell function with an influx of macrophages into visceral adipose tissue (VAT), impaired activity of the dendritic cells and macrophages, decreased activity of natural killer cells and dysfunction of lymphocytes and monocytes.[17]

Chronic inflammation characterized by T cell and macrophage infiltration of VAT is a hallmark of obesity-associated insulin resistance and glucose intolerance.[27] Studies have shown that B cells accumulate in VAT of diet-induced obese (DIO) mice, and those DIO mice lacking B cells are protected from the disease despite the weight gain.[27] It was also reported that in nonobese healthy individual, VAT-resident regulatory T-cells and T-helper 2 cells play a beneficial role in reducing VAT inflammation. But in contrast, in a DIO individual, these cells were overwhelmed by a pro-inflammatory cluster of differentiation 8 ($CD8^+$) and T-helper 1 cells, and promote insulin resistance and glucose intolerance.[27] Obesity affects both innate and adaptive immune systems. Previous studies have correlated the obesity indices namely body mass index and waist-hip ratio with immunological parameters like CD4 concentration, and differential leukocyte count.[28-30]

Obesity causes immunosuppression in both humans and mice.[29,31-34] In humans, obesity results in poor wound healing and increases the risk of infection[31,32] and sepsis in burns patients.[35] Obesity also reduces the bacterial killing capacity of polymorphonuclear cells.[36] Obese patients are more prone to nonhealing injuries, infection, and disease.[17] Numerous studies done in genetically obese mice indicate a global impairment of immune function in these mice.[37-42] Furthermore, genetically obese mice have decreased resistance to bacterial and viral infections,[33,40] as well as reduced cell-mediated cytotoxicity.[42,43] The exact reason for immunomodulation in obesity is not known. However, it has been suggested that the pathways that are altered in obesity have significant roles in immune responses. These include nuclear factor kappa B (NF-κB), phosphoinositide-3 kinase, glucocorticoids, catecholamines, and adipokines.[44]

Inflammatory markers associated with obesity

In obesity, WAT is characterized by an increased production and secretion of many inflammatory molecules which has both local and systemic effects. Recent data indicate that obese WAT is infiltrated by macrophages, which is a primary source of locally-produced pro-inflammatory cytokines. In several animal models of obesity, TNF-alpha was overproduced in the adipose tissue, and they play a significant role in the etiopathogenesis of insulin resistance. There is increased production of IL-6 in the human adipose tissue of obese individuals, and this increased IL-6 induces hepatic CRP synthesis and promotes the onset of obesity-related complications. Hence, IL-6 and TNF-alpha are known to alter the insulin sensitivity. Resistin is also known to induce insulin resistance, however; its role in the control of insulin sensitivity in humans remains unclear.

Obesity increases the expression of leptin and decreases adiponectin expression in adipose tissue.[44] Adipokine modulation of immune function, particularly leptin, is the best-characterized link between obesity and immune function.[45] Adiponectin levels were found to be reduced in conditions like obesity-related insulin resistance, diabetes mellitus, and cardiovascular disorders. Adiponectin protects from arteriosclerosis by opposing the pro-inflammatory action of TNF-alpha on the arterial wall. The pro-inflammatory effects of cytokines in obesity are mediated by NF-κB and JNK systems. Any alterations in the pro-inflammatory effectors will result in insulin resistance. Thus, obesity is a sub-clinical inflammatory condition that enhances the production of pro-inflammatory factors that are involved in the pathogenesis of insulin resistance.[19]

NEUROPHYSIOLOGICAL CONTROL OF OBESITY

Food intake and energy expenditure are controlled by a complex, redundant, and distributed neural systems involving thousands of genes reflecting the fundamental biological importance of adequate nutrient supply and energy balance.[15,46] One important fact is that not everybody becomes obese. This shows that individual factors interact with recent environmental changes to predispose some to overeat. It is believed that individual differences in the neural encoding of foods may influence few people to overeat in the presence of an excess of energy-dense food.[15,16,47] Significant portions of the central nervous system (CNS) of animals and humans are concerned with the procurement of food.[46] The hypothalamus, limbic system, cortex, basal ganglia, and the medulla are known to play a role in the control of feeding and adiposity.[16,34,48] The hypothalamus and the brain stem are thought to be the principal homeostatic brain areas responsible for regulating the body weight.[34] The hypothalamus orchestrates the neurophysiological control of energy balance in a complex neural loop.[49] The afferent signals come from the viscera and the brain areas that are concerned with the energy stores, signal transduction occurs in the periventricular nucleus and the lateral hypothalamic area. The efferent signals reach the hypothalamus, mesolimbic areas, and the visceral organs that are concerned with food intake and adiposity.[49]

There are several possible neurophysiological pathways to explain how and why people consume more calories than what they expend.[11] When people were shown different images of food, there was increased secretion of dopamine in the dorsal striatum, which resulted in craving and increased the desire to eat.[11,50] People have preferences for sweet and salt right from their birth; besides, they also prefer fats because they activate the brain's reward system and reduce the physiological satiety signals.[11,51] Humans lack the ability to estimate volume and portion amounts based on appearance.[11] It has been reported that people have a tendency to imitate the food habits of others.[11,52-55] This mimicking behavior continues throughout life, and people tend to mimic the expressions, body language and gestures of others, often without awareness. People imitate the eating behaviors of others, including choices of food and portions.[11,52-55]

NEUROENDOCRINE AXIS OF OBESITY

The regulation of body weight involves the interaction of many neuronal networks in the brain that control food intake and adiposity with the endocrine secretions that regulate the activity of these neurons. The neuronal networks that control food intake and adiposity also modulate the hypothalamic-pituitary-adrenal (HPA) axis. These neurons secrete various neuropeptides like neuropeptide Y (NPY), orexins, endocannabinoids, melanocortins, agouti-related protein, cocaine- and amphetamine-regulated transcript, leptin, peptide YY, corticotrophin releasing hormone, dopamine and growth hormone (GH) releasing hormone. NPY, agouti-related peptide (AgRP), melanin-concentrating hormone, orexins, and endocannabinoids are anabolic peptides. Dopamine, melanin stimulating hormone, cocaine- and amphetamine-regulated transcript, leptin, peptide YY and corticotropin-releasing hormone are catabolic peptides.[56]

The HPA axis plays a significant role in obesity.[57] HPA axis activity is found to be abnormal in obesity, and excessive cortisol exposure has been implicated in metabolic derangements. Hence, there is ample evidence of altered HPA axis function in obesity.[58] Obesity impairs arcuate NPY/AgRP neuronal function and renders these homeostatic neurons unresponsive to the orexigenic hormone ghrelin.[59] Negative energy balance in lean animals and humans consistently inhibits the activity of the hypothalamic-pituitary-thyroid, -gonadotropic and somatotropic axes while concomitantly activating the HPA axis. Animal studies have shown that these neuroendocrine changes may result from the hypothalamic actions of orexigenic and anorexigenic peptides.[60] Ghrelin has many functions in the brain aside from appetite control, including cognitive function, mood regulation, and protection against neurodegenerative diseases. Ghrelin levels were found to be reduced in obesity.[61] The increase in interleukin-1 and IL-6 in the mesenteric fat tissue together with a rise in corticosterone in obese states is associated with obesity-related complications like insulin resistance and hyperlipidemia.[62] The thyrotropin-releasing hormone also plays a significant role in the regulation of energy homeostasis.[63] The thyroid hormone T3 directly stimulates feeding at the level of the hypothalamus. Peripheral administration of T3 doubled the food intake in ad libitum-fed rats. Leptin suppresses thyroid stimulating hormone-induced thyroid function.[64]

Diet-induced obesity is characterized by a reduction in basal and stimulated GH release in humans. Several hypotheses have been put forth regarding how obesity-associated hyperinsulinemia may suppress GH production. Pituitaries of obese mice remain responsive to the acute actions of insulin despite systemic insulin resistance, and the changes in pituitary expression observed in hyperinsulinemic, obese mice can be replicated by insulin administration *in vitro*. These results strongly support the hypothesis that insulin at higher doses is one of the major determinants of suppression of

GH output in the obese state by direct down-regulation of somatotrope function.[7-9]

Long-term high-fat feeding alters the function of the pituitary-testicular axis, resulting in hypogonadotropic hypogonadism. These rats exhibited a metabolic profile compatible with insulin resistance and metabolic syndrome, and they concomitantly showed decreased serum luteinizing hormone concentrations, low serum testosterone levels and elevated serum 17 beta-estradiol concentrations. Hence, the pituitary attempts to counterbalance the effects of long-term obesity on reproductive functions.[65] Studies have shown that the hypothalamic IKKbeta/NF-κB program is a general neural mechanism for energy imbalance underlying obesity. This indicates that suppression of hypothalamic IKKbeta/NF-κB may represent a strategy to combat obesity and its related diseases.[66]

NEUROENDOCRINE AXIS OF IMMUNITY

There is a link between the immune system and CNS.[67] The CNS signals the immune system via hormonal and neuronal pathways and the immune system signals the CNS through immune mediators. Among the hormonal pathway, the most important is the HPA axis [Figure 1]. The autonomic nervous system controls the functions of the immune system primarily via adrenergic neurotransmitters released through neuronal routes.[67] The neuroendocrine control of immune system plays an important role in the emergency and stressful situations. Cortisol plays an essential role in this neuroendocrine system, and it has multiple effects on immune cells.[68] The sex hormones and the hypothalamic-pituitary-gonadal axis also play a significant role in the regulation of immune functions.

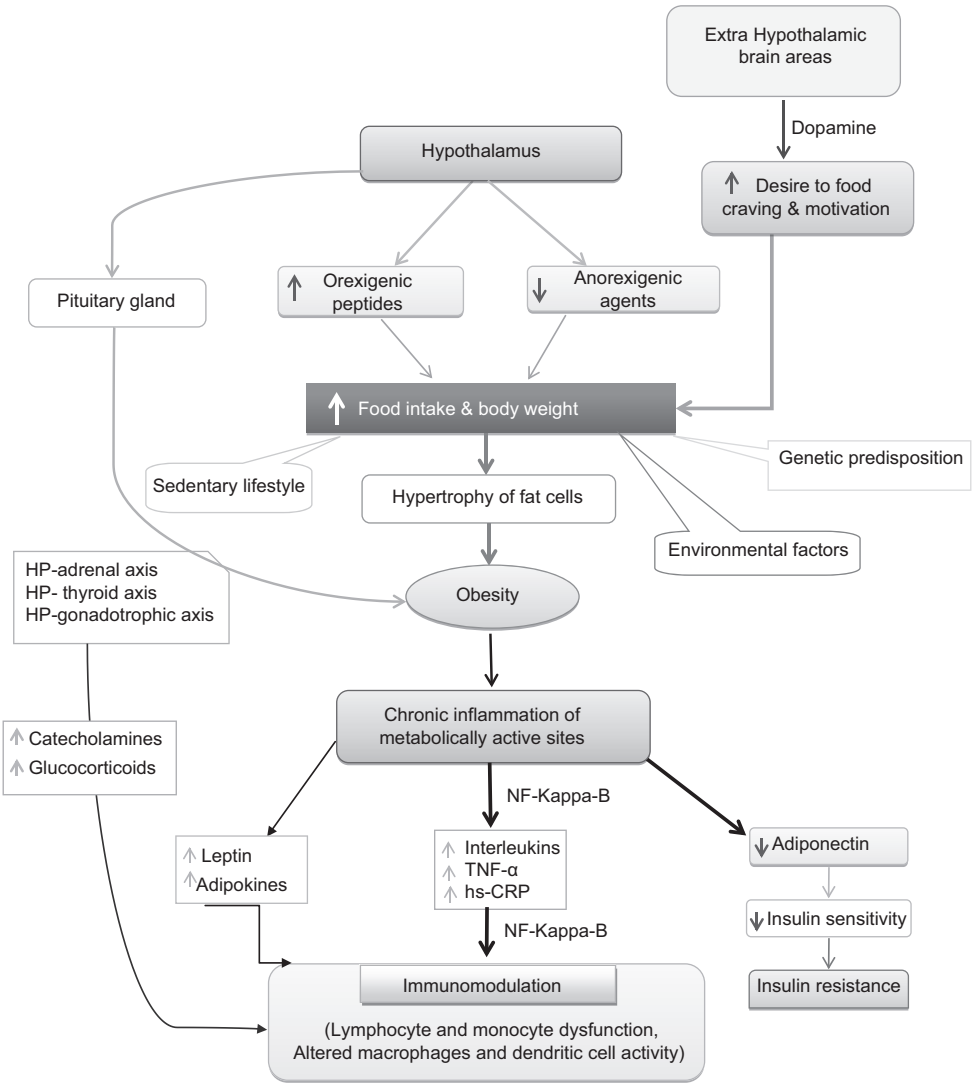

Figure 1: Mechanism of neuroimmunomodulation in obesity. HP-adrenal axis: Hypothalamic -pituitary-adrenal axis, HP-thyroid axis: Hypothalamic-pituitary-thyroid axis, HP-gonadotrophic axis: Hypothalamic-pituitary-gonadotrophic axis, NF-kB: Nuclear factor - kappa B, TNF-α: Tumor necrosis factor-alpha, hs-CRP: High sensitive-C-reactive protein

Hence, inflammation and inflammatory responses are modulated by bidirectional communication between the neuroendocrine and immune system.[69-71]

CONCLUSION

Obesity represents a state of both systemic and vascular inflammation. There is a report of altered immune functions in obesity. There exists an active neural regulation of adiposity and immune functions. However, the gender difference in immunomodulation by the different brain areas in obesity has not been discussed in detail. Hence, future reviews can focus on the gender difference in neuroimmunomodulation in obesity.

REFERENCES

1. González Jiménez E. Obesity: Etiologic and pathophysiological analysis. Endocrinol Nutr 2013;60:17-24.
2. World Health Statistics Report: Report on Global Public Health and Key Statistics, May; 2012.
3. World Health Organisation: Report on Obesity and Overweight, May; 2012. Available from: http://www.who.int/entity/mediacentre/factsheets/fs311/en/index.html. [Last accessed on 2015 May 5]
4. Peeters A, Barendregt JJ, Willekens F, Mackenbach JP, Al Mamun A, Bonneux L, *et al.* Obesity in adulthood and its consequences for life expectancy: A life-table analysis. Ann Intern Med 2003;138:24-32.
5. Ha J, Cohen JI, Tirsi A, Convit A. Association of obesity-mediated insulin resistance and hypothalamic volumes: Possible sex differences. Dis Markers 2013;35:249-59.
6. Haslam DW, James WP. Obesity. Lancet 2005;366:1197-209.
7. Barness LA, Opitz JM, Gilbert-Barness E. Obesity: Genetic, molecular, and environmental aspects. Am J Med Genet A 2007;143A: 3016-34.
8. Dlouhá D, Hubácek JA. FTO gene and his role in genetic determination of obesity. Vnitr Lek 2012;58:208-15.
9. Obesity Update 2014. OECD's Report Obesity and the Economics of Prevention: Fit not Fat Published in 2010. Available from: http://www.oecd.org/health/fitnotfat. [Last accessed on 2015 Apr 25].
10. Smith SR, de Jonge L, Zachwieja JJ, Roy H, Nguyen T, Rood JC, *et al.* Fat and carbohydrate balances during adaptation to a high-fat. Am J Clin Nutr 2000;71:450-7.
11. Cohen DA. Neurophysiological pathways to obesity: Below awareness and beyond individual control. Diabetes 2008;57:1768-73.
12. Jéquier E, Tappy L. Regulation of body weight in humans. Physiol Rev 1999;79:451-80.
13. Katz DL, Rachel SC. Nutrition in Clinical Practice: A Comprehensive, Evidence-Based Manual for the Practitioner. 2nd ed. Baltimore: Lippincott Williams and Wilkins; 2008. p. 49-70.
14. Bays HE, González-Campoy JM, Bray GA, Kitabchi AE, Bergman DA, Schorr AB, *et al.* Pathogenic potential of adipose tissue and metabolic consequences of adipocyte hypertrophy and increased visceral adiposity. Expert Rev Cardiovasc Ther 2008;6:343-68.
15. Dev S, Pal P, Pal GK, Ananthanarayanan PH, Lalitha V, Gaur A, *et al.* Role of ventromedial hypothalamus on energy homeostasis in albino rats: Effect of gender. Indian J Physiol Pharmacol 2012;56:107-16.
16. Dev S, Pal P, Pal GK, Ananthanarayanan PH, Lalitha V, Adithan C. Effect of lesion of nucleus septal medialis on energy homeostasis in Wistar rats. Indian J Physiol Pharmacol 2012;56:314-21.
17. Cheung KP, Taylor KR, Jameson JM. Immunomodulation at epithelial sites by obesity and metabolic disease. Immunol Res 2012;52:182-99.
18. Milner JJ, Beck MA. The impact of obesity on the immune response to infection. Proc Nutr Soc 2012;71:298-306.
19. Bastard JP, Maachi M, Lagathu C, Kim MJ, Caron M, Vidal H, *et al.* Recent advances in the relationship between obesity, inflammation, and insulin resistance. Eur Cytokine Netw 2006;17:4-12.
20. Ouchi N, Ohashi K, Shibata R, Murohara T. Adipocytokines and obesity-linked disorders. Nagoya J Med Sci 2012;74:19-30.
21. Indumathy J, Pal GK, Pal P. Sympathovagal imbalance in obesity: Cardiovascular perspectives. Int J Clin Exp Physiol 2014;1:93-100.
22. Boehm BO, Claudi-Boehm S. The metabolic syndrome. Scand J Clin Lab Invest Suppl 2005;240:3-13.
23. O'Rourke RW, Kay T, Scholz MH, Diggs B, Jobe BA, Lewinsohn DM, *et al.* Alterations in T-cell subset frequency in peripheral blood in obesity. Obes Surg 2005;15:1463-8.
24. Tilg H, Moschen AR. Adipocytokines: Mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol 2006;6:772-83.
25. Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, *et al.* Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med 2002;8:1288-95.
26. Karalis KP, Giannogonas P, Kodela E, Koutmani Y, Zoumakis M, Teli T. Mechanisms of obesity and related pathology: Linking immune responses to metabolic stress. FEBS J 2009;276:5747-54.
27. Daniel AW, Shawn W, Lei S. B Lymphocytes promote insulin resistance through modulation of T Lymphocytes and production of pathogenic IgG antibody. Clin Exp Pharmacol Physiol 2006;33:940-5.
28. Al-Sufyani AA, Mahassni SH. Obesity and immune cells in Saudi females. Innate Immun 2011;17:439-50.
29. Norton A. Immune system may play role in obesity. Health Day Report 2014;13:11-22.
30. Bandaru P, Rajkumar H, Nappanveettil G. The impact of obesity to immune response and vaccine: An insight into plausible mechanisms. Endocrinol Metab Syndr 2013;2:10-2.
31. Massie JB, Heller JG, Abitbol JJ, McPherson D, Garfin SR. Postoperative posterior spinal wound infections. Clin Orthop Relat Res 1992;52:99-108.
32. Norris SO, Provo B, Stotts NA. Physiology of wound healing and risk factors that impede the healing process. AACN Clin Issues Crit Care Nurs 1990;1:545-52.
33. Ikejima S, Sasaki S, Sashinami H, Mori F, Ogawa Y, Nakamura T, *et al.* Impairment of host resistance to *Listeria monocytogenes* infection in liver of db/db and ob/ob mice. Diabetes 2005;54:182-9.
34. Lalitha V, Pal GK, Parija SC, Pal P, Sathish Babu M, Indumathy J. Effect of gender on food intake, adiposity and immunological responses following lesion of ventromedial hypothalamus in albino Wistar rats. Int J Clin Exp Physiol 2014;1:44-50.
35. Gottschlich MM, Mayes T, Khoury JC, Warden GD. Significance of obesity on nutritional, immunologic, hormonal, and clinical outcome parameters in burns. J Am Diet Assoc 1993;93:1261-8.
36. Palmblad J, Hallberg D, Engstedt L. Polymorphonuclear (PMN) function after small intestinal shunt operation for morbid obesity. Br J Haematol 1980;44:101-8.
37. Caspar-Bauguil S, Cousin B, André M, Nibbelink M, Galinier A, Periquet B, *et al.* Weight-dependent changes of immune system in adipose tissue: Importance of leptin. Exp Cell Res 2006;312:2195-202.
38. Hick RW, Gruver AL, Ventevogel MS, Haynes BF, Sempowski GD. Leptin selectively augments thymopoiesis in leptin deficiency and lipopolysaccharide-induced thymic atrophy. J Immunol 2006;177:169-76.

39. Rüter J, Hoffmann T, Demuth HU, Moschansky P, Klapp BF, Hildebrandt M. Evidence for an interaction between leptin, T cell costimulatory antigens CD28, CTLA-4 and CD26 (dipeptidyl peptidase IV) in BCG-induced immune responses of leptin- and leptin receptor-deficient mice. Biol Chem 2004;385:537-41.
40. Webb SR, Loria RM, Madge GE, Kibrick S. Susceptibility of mice to group B coxsackie virus is influenced by the diabetic gene. J Exp Med 1976;143:1239-48.
41. Mancuso P, Canetti C, Gottschalk A, Tithof PK, Peters-Golden M. Leptin augments alveolar macrophage leukotriene synthesis by increasing phospholipase activity and enhancing group IVC iPLA2 (cPLA2gamma) protein expression. Am J Physiol Lung Cell Mol Physiol 2004;287:L497-502.
42. Fernandes G, Handwerger BS, Yunis EJ, Brown DM. Immune response in the mutant diabetic C57BL/Ks-dt mouse. Discrepancies between *in vitro* and *in vivo* immunological assays. J Clin Invest 1978;61:243-50.
43. Meade C, Sheena J, Mertin J. Immunological changes associated with the ob-ob (obese) genotype. Proc Nutr Soc 1978;37:38.
44. Gil A, María Aguilera C, Gil-Campos M, Cañete R. Altered signalling and gene expression associated with the immune system and the inflammatory response in obesity. Br J Nutr 2007;98 Suppl 1:S121-6.
45. La Cava A, Matarese G. The weight of leptin in immunity. Nat Rev Immunol 2004;4:371-9.
46. Lenard NR, Berthoud HR. Central and peripheral regulation of food intake and physical activity: Pathways and genes. Obesity (Silver Spring) 2008;16 Suppl 3:S11-22.
47. Small DM. Individual differences in the neurophysiology of reward and the obesity epidemic. Int J Obes (Lond) 2009;33 Suppl 2:S44-8.
48. Labelle DR, Cox JM, Dunn-Meynell AA, Levin BE, Flanagan-Cato LM. Genetic and dietary effects on dendrites in the rat hypothalamic ventromedial nucleus. Physiol Behav 2009;98:511-6.
49. Isganaitis E, Lustig RH. Fast food, central nervous system insulin resistance, and obesity. Arterioscler Thromb Vasc Biol 2005;25:2451-62.
50. Volkow ND, Wang GJ, Maynard L, Jayne M, Fowler JS, Zhu W, *et al.* Brain dopamine is associated with eating behaviors in humans. Int J Eat Disord 2003;33:136-42.
51. Keskitalo K, Knaapila A, Kallela M, Palotie A, Wessman M, Sammalisto S, *et al.* Sweet taste preferences are partly genetically determined: Identification of a trait locus on chromosome 16. Am J Clin Nutr 2007;86:55-63.
52. Bandura A. Social Foundations of Thought and Action: A Social Cognitive Theory. Englewood Cliffs, NJ: Prentice-Hall; 1986. p. 101-2.
53. Rizzolatti G. The mirror neuron system and its function in humans. Anat Embryol (Berl) 2005;210:419-21.
54. Chartrand TL, Maddux W, Lakin J. Beyond the perception-behavior link: The ubiquitous utility and motivational moderators of nonconscious mimicry. 2nd ed. New York: Oxford University Press; 2005. p. 102-6.
55. Dijksterhuis A, Smith P, van Baaren R, Wigboldus D. The unconscious consumer: Effects of environment on consumer behavior. J Consum Psychol 2005;15:193-202.
56. Richard D, Baraboi D. Circuitries involved in the control of energy homeostasis and the hypothalamic-pituitary-adrenal axis activity. Treat Endocrinol 2004;3:269-77.
57. Pasquali R. The hypothalamic-pituitary-adrenal axis and sex hormones in chronic stress and obesity: Pathophysiological and clinical aspects. Ann N Y Acad Sci 2012;1264:20-35.
58. Tyrka AR, Walters OC, Price LH, Anderson GM, Carpenter LL. Altered response to neuroendocrine challenge linked to indices of the metabolic syndrome in healthy adults. Horm Metab Res 2012;44:543-9.
59. Briggs DI, Lemus MB, Kua E, Andrews ZB. Diet-induced obesity attenuates fasting-induced hyperphagia. J Neuroendocrinol 2011;23:620-6.
60. Sainsbury A, Zhang L. Role of the hypothalamus in the neuroendocrine regulation of body weight and composition during energy deficit. Obes Rev 2012;13:234-57.
61. Briggs DI, Enriori PJ, Lemus MB, Cowley MA, Andrews ZB. Diet-induced obesity causes ghrelin resistance in arcuate NPY/AgRP neurons. Endocrinology 2010;151:4745-55.
62. Guijarro A, Laviano A, Meguid MM. Hypothalamic integration of immune function and metabolism. Prog Brain Res 2006;153:367-405.
63. Lechan RM, Fekete C. The TRH neuron: A hypothalamic integrator of energy metabolism. Prog Brain Res 2006;153:209-35.
64. Isozaki O, Tsushima T, Nozoe Y, Miyakawa M, Takano K. Leptin regulation of the thyroids: Negative regulation on thyroid hormone levels in euthyroid subjects and inhibitory effects on iodide uptake and Na/I- symporter mRNA expression in rat FRTL-5 cells. Endocr J 2004;51:415-23.
65. Olivares A, Méndez JP, Zambrano E. Reproductive axis function and gonadotropin microheterogeneity in a male rat model of diet-induced obesity. Endocrinology 2010;166:356-64.
66. Zhang X, Zhang G, Zhang H, Karin M, Bai H, Cai D. Hypothalamic IKKbeta/NF-kappaB and ER stress link overnutrition to energy imbalance and obesity. Cell 2008;135:61-73.
67. Eskandari F, Sternberg EM. Neural-immune interactions in health and disease. Ann N Y Acad Sci 2002;966:20-7.
68. Webster JI, Tonelli L, Sternberg EM. Neuroendocrine regulation of immunity. Annu Rev Immunol 2002;20:125-63.
69. Eskandari F, Webster JI, Sternberg EM. Neural immune pathways and their connection to inflammatory diseases. Arthritis Res Ther 2003;5:251-65.
70. Ferencík M, Novák M, Rovenský J. Relation and interactions between the immune and neuroendocrine systems. Bratisl Lek Listy 1998;99:454-64.
71. Besedovsky HO, del Rey A. Feed-back interactions between immunological cells and the hypothalamus-pituitary-adrenal axis. Neth J Med 1991;39:274-80.

How to cite this article: Lalitha V, Pal GK, Pal P, Babu MS. Neuroimmunomodulation in obesity. Int J Clin Exp Physiol 2015;2:97-102.

Source of Support: Nil, **Conflict of Interest:** Nil.