Editorial

Obesity and the limbic system

Volume 13 Issue 1 - 2023

Stavros J Baloyannis
Aristotelian University, Research Institute for Alzheimer's disease, Greece

Correspondence: Stavros J Baloyannis, Professor Emeritus, Aristotelia Univesity, Angelaki 5, Thessaloniki 54621, Greece, Tel +302310270434, Fax +302310270434, Email sibh84@otenet.gr

Received: February 23, 2023 | **Published:** February 24, 2023

Keywords: Obesity, limbic system, hypothalamus, amygdala neurotransmitters, BDNF

Editorial

Obesity is a serious multifactorial health problem, which has taken considerable dimensions in countries with a western style of diet.[1,2] It is reasonable, that the etiopathogenetic mechanisms of obesity are subjects for research in many fields of biological sciences in an attempt to improve the quality of life and prolong the viability, given that obesity may become a serious risk factor for several other co-morbidities affecting the life expectancy.[3–6]

Although the genetic background and many environmental conditions may contribute to obesity,[7,8] the limbic system and hypothalamus must play a crucial role in the equilibrium of body weight and food intake,[9–11] since they control energy homeostasis,[12] in close collaboration with the peptides of the alimentary system, harmonizing the deposition of adipose tissue in the body,[13,14] according to food intake and energy consumption.

The hypothalamus, which is located on the floor of the third ventricle,[15] among many other vital capacities,[16–18] is responsible for controlling energy balance and adjusting body weight.[18] Theoretically, a 'hunger center' might exist in the lateral hypothalamus,[19] been counteracted by a 'satiety center' in the ventromedial hypothalamic nucleus (VMN).[20, 21] Nevertheless, many more areas of the brain, such as the amygdala, some hypothalamic nuclei, and mesencephalic neuronal networks are continuously involved in the desire for food intake and the regulation of body weight.[21] However, it must be underlined that a high-lipid diet may increase the level of the inflammatory cytokines, inducing a chronic low-grade inflammatory reaction in the hypothalamus,[22,23] characterized by astrocytic proliferation and activation of microglial cells and macrophages, a fact which was proved at the experimental level.[24,25]

Loss of body weight control coincides, several times, with alterations of the amygdala[26–28] in connexion with the ventromedial hypothalamic nuclei, inducing hyperphagia,[29,30] hypometabolism, change of autonomic balance, and deficiency of growth hormone (GH), resulting eventually in the increase of body weight.[31] The numerous connections of the hypothalamus with most of the cortical and subcortical structures of the brain and the cerebellum play a substantial role in the influence of mental and emotional activities upon the hypothalamic homeostatic regulation,[32] with obvious consequences on the control of the body weight.[33] Besides, many gut hormones and among them cholecystokinin, somatostatins, amylin, ghrelin, oxyntomodulin, glucagon-like peptide-2, and glucose-dependent insulinotropic peptide contribute greatly to the adjustment of body weight,[34] since they play a role of neurotransmitters, which control food intake and energy balance.[35]

The dorsal vagal complex contributes greatly to the interpretation of peripheral signals to the amygdala and the arcuate nucleus of the hypothalamus, which would stimulate or inhibit food intake.[36] Thus, several peptides, such as Peptide YY, pancreatic polypeptide, glucagon-like peptide-1, and oxyntomodulin suppress the desire of feeding,[37] whilst ghrelin increases the appetite.[38,39]

In the amygdala and the arcuate nucleus (ARC), many neurons co-express neuropeptide Y (NPY) and agouti-related peptide (AgRP), stimulating food intake.[40] and increasing adiposity. Besides, the brain-derived neurotrophic factor (BDNF), acting in the ventromedial hypothalamus, decreases food intake, antagonizing the NPY neurons.[41] It is expected, therefore, that the degeneration of the BDNF-sensitive neurons may induce obesity.[42]

In addition, the hypothalamic autophagic pathway[43] is essential for the activation of orexigenic and anorectic neurons, controlling appetite in cases of depression, anxiety, panic reactions, and additional noxious stress conditions.[44,45] Impairments also in the central signaling pathways of insulin,[46] and a decrease in leptin sensitivity are substantial causative factors for obesity[47–50] since insulin and leptin are the main anorectic hormones, activating POMC neurons, which have a high density of leptin receptors.

Intermittent fasting (IF), which is frequently practiced as a popular intervention for the confrontation of obesity[51–54] increases the inflammatory response in the hypothalamus,[55] a fact that plays a crucial role in the resistance to leptin and insulin activity in the brain. The hypothalamic chronic slow inflammation aggravates the problems of food intake,[56,57] provoking overfeeding and obesity,[58] with serious psychological effects, which may stimulate furthermore the overfeeding.[59]

The hypothalamic inflammation due to intermitted feeding may be associated with Endoplasmic Reticulum Stress (ER stress),[60] which may induce changes in neuropeptide gene expression,[61,62] increasing the susceptibility to obesity and insulin resistance.[63,64]

Generally, the investigation of obesity at the clinical and experimental level and the application of any efficient therapeutic regime would alleviate the psychosomatic burden of billion of people on earth, ameliorating the quality of life.

Acknowledgments

None.

Conflicts of interest

The author declare that they have no conflicts of interest.

References

1. Jackson SE, Llewellyn CH, Smith L. The obesity epidemic - nature via nurture: a narrative review of high-income countries. *SAGE Open Med*. 2020;8:2050312120918265.

2. Katzmarzyk PT, Chaput JP, Fogelholm M, et al. International study of childhood obesity, lifestyle and the environment (ISCOLE): contributions to understanding the global obesity epidemic. *Nutrients*. 2019;11(4):848.

3. López-Suárez A. Burden of cancer attributable to obesity, type 2 diabetes and associated risk factors. *Metabolism*. 2019;92:136–146.

4. Saitta C, Pollicino T, Raimondo G. Obesity and liver cancer. *Ann Hepatol*. 2019;18(6):810–815.

5. Peña JE, Rascón-Pacheco RA, Ascencio-Montiel IJ, et al. Hypertension, diabetes and obesity, major risk factors for death in patients with COVID-19 in Mexico. *Arch Med Res*. 2021;52(4):443–449.

6. Sattar N, McInnes IB, McMurray JJV. Obesity is a risk factor for severe COVID-19 infection: multiple potential mechanisms. *circulation*. 2020;142(1):4–6.

7. Rohde K, Keller M, la Cour Poulsen L, et al. Genetics and epigenetics in obesity. *Metabolism*. 2019;92:37–50.

8. Loos RJF, Yeo GSH. The genetics of obesity: from discovery to biology. *Nat Rev Genet*. 2022;23(2):120–133.

9. Lee CH, Suk K, Yu R, et al. Cellular contributors to hypothalamic inflammation in obesity. *Mol Cells*. 2020;43(5):431–437.

10. Obradovic M, Sudar-Milovanovic E, Soskic S, et al. Leptin and obesity: role and clinical implication. *Front Endocrinol (Lausanne)*. 2021;12:585887.

11. Flores Ocampo PM, Esvieta TB, Germán MA, et al. The limbic system as a neuroanatomical link between obesity and depression. Neuroimaging findings. *Journal of Physiotherapy and Medical Technology*. 2021;5(14):18–28.

12. Kuzawa CW, Blair C. A hypothesis linking the energy demand of the brain to obesity risk. *Proc Natl Acad Sci U S A*. 2019;116(27):13266–13275.

13. Schepers J, Gebhardt C, Bracke A, et al. Structural and functional consequences in the amygdala of leptin-deficient mice. *Cell Tissue Res*. 2020;382(2):421–426.

14. Azevedo EP, Ivan VJ, Friedman JM, et al. Higher-Order Inputs Involved in Appetite Control. *Biol Psychiatry*. 2022;91(10):869–878.

15. Dudás B. Anatomy and cytoarchitectonics of the human hypothalamus. *Handb Clin Neurol*. 2021;179:45–66.

16. Schönknecht P, Anwander A, Petzold F, et al. Diffusion imaging-based subdivision of the human hypothalamus: a magnetic resonance study with clinical implications. *Eur Arch Psychiatry Clin Neurosci*. 2013;263(6):497–508.

17. Swaab DF, Hofman MA, Lucassen PJ, et al. Functional neuroanatomy and neuropathology of the human hypothalamus. *Anat Embryol (Berl)*. 1993;187(4):317–330.

18. Roger C, Lasbleiz A, Guye M, et al. The Role of the Human Hypothalamus in Food Intake Networks: An MRI Perspective. *Front Nutr*. 2022;8:760914.

19. Yousefvand S, Hamidi F. Role of Lateral Hypothalamus Area in the Central Regulation of Feeding. *International Journal of Peptide Research and Therapeutics*. 2022;28(3):1–9.

20. Rabin BM. Ventromedial hypothalamic control of food intake and satiety: a reappraisal. *Brain Res*. 1972;43(2):317–342.

21. King BM. The rise, fall, and resurrection of the ventromedial hypothalamus in the regulation of feeding behavior and body weight. *Physiol Behav*. 2006;87(2):221–244.

22. Velloso LA, Araújo EP, de Souza CT. Diet-induced inflammation of the hypothalamus in obesity. *Neuroimmunomodulation.* 2008;15(3):189–193.

23. Guillemot-Legris O, Muccioli GG. Obesity-induced neuroinflammation: beyond the hypothalamus. *Trends Neurosci*. 2017;40(4):237–253.

24. Thaler JP, Yi CX, Schur EA, et al. Obesity is associated with hypothalamic injury in rodents and humans. *J Clin Invest*. 2012;122(1):153–162.

25. Buckman LB, Thompson MM, Moreno HN, et al. Regional astrogliosis in the mouse hypothalamus in response to obesity. *J Comp Neurol*. 2013;521(6):1322–1333.

26. Ip CK, Zhang L, Farzi A, et al. Amygdala NPY circuits promote the development of accelerated obesity under chronic stress conditions. *Cell Metab*. 2019;30(1):111–128.e6.

27. Graff H, Stellar E. Hyperphagia, obesity, and finickiness. *J Comp Physiol Psychol*. 1962;55:418–424.

28. Perlaki G, Molnar D, Smeets PAM, et al. Volumetric gray matter measures of amygdala and accumbens in childhood overweight/obesity. *PLoS One*. 2018;13(10):e0205331.

29. Rollins BL, King BM. Amygdala-lesion obesity: what is the role of the various amygdaloid nuclei? *Am J Physiol Regul Integr Comp Physiol*. 2000;279(4):R1348–1356.

30. Li G, Hu Y, Zhang W, et al. Resting activity of the hippocampus and amygdala in obese individuals predicts their response to food cues. *Addict Biol*. 2021;26(3):e12974.

31. Kim MS, Luo S, Azad A, et al. Prefrontal cortex and amygdala subregion morphology are associated with obesity and dietary self-control in children and adolescents. *Front Hum Neurosci*. 2020;14:563415.

32. Sewards TV, Sewards MA. Representations of motivational drives in mesial cortex, medial thalamus, hypothalamus and midbrain. *Brain Res Bull*. 2003;61(1):25–49.

33. Roger C, Lasbleiz A, Guye M, et al. The Role of the Human Hypothalamus in Food Intake Networks: An MRI Perspective. *Front Nutr*. 2022;8:760914.

34. Strader AD, Woods SC. Gastrointestinal hormones and food intake. *Gastroenterology*. 2005;128(1):175–191.

35. Konturek SJ, Konturek JW, Pawlik T, et al. Brain-gut axis and its role in the control of food intake. *J Physiol Pharmacol*. 2004;55(1 Pt 2):137–154.

36. MacDonald AJ, Holmes FE, Beall C, et al. Regulation of food intake by astrocytes in the brainstem dorsal vagal complex. *Glia*. 2020;68(6):1241–1254.

37. le Roux CW, Bloom SR. Peptide YY, appetite and food intake. *Proc Nutr Soc*. 2005;64(2):213–216.

38. Druce MR, Wren AM, Park AJ, et al. Ghrelin increases food intake in obese as well as lean subjects. *Int J Obes (Lond)*. 2005;29(9):1130–1136.

39. de Guia RM, Hassing AS, Skov LJ, et al. Fasting- and ghrelin-induced food intake is regulated by NAMPT in the hypothalamus. *Acta Physiol (Oxf)*. 2020;228(4):e13437.

40. Marcos P, Coveñas R. Regulation of Homeostasis by Neuropeptide Y: Involvement in Food Intake. *Curr Med Chem*. 2022;29(23):4026–4049.

41. Yousefvand S, Hamidi F. The role of ventromedial hypothalamus receptors in the central regulation of food intake. *International Journal of Peptide Research and Therapeutics*. 2021;27(1):689–702.

42. Podyma B, Parekh K, Güler AD, et al. Metabolic homeostasis via BDNF and its receptors. *Trends Endocrinol Metab*. 2021;32(7):488–499.

43. Dionysopoulou S, Charmandari E, Bargiota A, et al. The role of hypothalamic inflammation in diet-induced obesity and Its association with cognitive and mood disorders. *Nutrients*. 2021;13(2):498.

44. Barson JR. Orexin/hypocretin and dysregulated eating: Promotion of foraging behavior. *Brain Res*. 2020;1731:145915.

45. Mattar P, Uribe-Cerda S, Pezoa C, et al. Brain site-specific regulation of hedonic intake by orexin and DYN peptides: role of the PVN and obesity. *Nutr Neurosci*. 2022;25(5):1105–1114.

46. Kullmann S, Kleinridders A, Small DM, et al. Central nervous pathways of insulin action in the control of metabolism and food intake. *Lancet Diabetes Endocrinol*. 2020;8(6):524–534.

47. Wingrove J, O'Daly O, De Lara Rubio A, et al. The influence of insulin on anticipation and consummatory reward to food intake: A functional imaging study on healthy normal weight and overweight subjects employing intranasal insulin delivery. *Hum Brain Mapp*. 2022;43(18):5432–5451.

48. Lee YH, Hsu HC, Kao PC, et al. Augmented insulin and leptin resistance of high fat diet-fed APPswe/PS1dE9 transgenic mice exacerbate obesity and glycemic dysregulation. *Int J Mol Sci*. 2018;19(8):2333.

49. Niswender KD, Baskin DG, Schwartz MW. Insulin and its evolving partnership with leptin in the hypothalamic control of energy homeostasis. *Trends Endocrinol Metab*. 2004;15(8):362–369.

50. Figlewicz DP. Adiposity signals and food reward: expanding the CNS roles of insulin and leptin. *Am J Physiol Regul Integr Comp Physiol*. 2003;284(4):R882–R892.

51. Michalsen A, Li C. Fasting therapy for treating and preventing disease -current state of evidence. *Forsch Komplementmed*. 2013;20(6):444–453.

52. Yoon G, Song J. Intermittent Fasting: a Promising Approach for Preventing Vascular Dementia. *J Lipid Atheroscler*. 2019;8(1):1–7.

53. Welton S, Minty R, O'Driscoll T, et al. Intermittent fasting and weight loss: Systematic review. *Can Fam Physician*. 2020;66(2):117–125.

54. Halpern B, Mendes TB. Intermittent fasting for obesity and related disorders: unveiling myths, facts, and presumptions. *Arch Endocrinol Metab*. 2021;65(1):14–23.

55. Zenz G, Jačan A, Reichmann F, et al. Intermittent Fasting Exacerbates the Acute Immune and Behavioral Sickness Response to the Viral Mimic Poly(I:C) in Mice. *Front Neurosci*. 2019;13:359.

56. Kälin S, Heppner FL, Bechmann I, et al. Hypothalamic innate immune reaction in obesity. *Nat Rev Endocrinol*. 2015;11(6):339–351.

57. Seong J, Kang JY, Sun JS, et al. Hypothalamic inflammation and obesity: a mechanistic review. *Arch Pharm Res*. 2019;42(5):383–392.

58. Cavadas C, Aveleira CA, Souza GF, et al. The pathophysiology of defective proteostasis in the hypothalamus - from obesity to ageing. *Nat Rev Endocrinol*. 2016;12(12):723–733.

59. Iovino M, Messana T, Lisco G, et al. Neuroendocrine Modulation of Food Intake and Eating Behavior. *Endocr Metab Immune Disord Drug Targets*. 2022;22(13):1252–1262.

60. Liu Y, Yu J, Shi YC, et al. The role of inflammation and endoplasmic reticulum stress in obesity-related cognitive impairment. *Life Sci*. 2019;233:116707.

61. Perner C, Krüger E. Endoplasmic Reticulum Stress and Its Role in Homeostasis and Immunity of Central and Peripheral Neurons. *Front Immunol*. 2022;13:859703.

62. Ozcan L, Ergin AS, Lu A, et al. Endoplasmic reticulum stress plays a central role in development of leptin resistance. *Cell Metab*. 2009;9(1):35–51.

63. Purkayastha S, Zhang H, Zhang G, et al. Neural dysregulation of peripheral insulin action and blood pressure by brain endoplasmic reticulum stress. *Proc Natl Acad Sci U S A*. 2011;108(7):2939–2944.

64. Bánhegyi G, Baumeister P, Benedetti A, et al. Endoplasmic reticulum stress. *Ann N Y Acad Sci*. 2007;1113:58–71.