Obesity and neurodegeneration

Abstract

Obesity has become a major health problem in the last few decades, mainly due to change of society towards sedentary lifestyle, intake of high-calorie diets and reduction in physical activity. Obesity is characterized by excess storage of fat in muscles and adipose tissues. It brings along with it physiological changes to the body such as insulin resistance, hyperinsulinemia, dyslipidemia, adipokine secretion by adipose tissues. These physiological changes have a stark impact on proper brain functioning and may induce oxidative stress, ER stress and mitochondrial dysfunction. Obesity affects the glucose and energy metabolism of the brain cells and through the secretion of pro-inflammatory agents like TNF-α, IL-1, IL-6 induces neuroinflammation mainly in the hypothalamic region of the brain. The overall effect is impairment of neuronal function and its internal molecular machinery, resulting in aberrant protein depositions either intracellularly or extracellularly or both, thus leading to neurodegeneration. Obesity and neurodegenerative diseases (NDDs) are linked by alterations in molecular pathways such as PI3K/Akt signaling pathway and IKKβ/NF-κB pathway, which may change expression profiles of genes or activate or deactivate molecular mediators and thereby drift away from normal cell functioning. Herein, we have discussed (i) Physiological alterations occurring during obesity and their potential link between neurodegenerative diseases. (ii) The signaling pathways affected during obesity and their impact on neurodegeneration and (iii) a list of gene involved in obesity mediated neurodegeneration.

Keywords: obesity, neuronal loss, hyperinsulinemia, signaling, inflammation

Abbreviations: NDD, neurodegenerative disease; AD, alzheimer’s disease; PD, parkinson’s disease; Aβ, amyloid beta; NFTs, neurofibrillary tangles; IKK-β, inhibitor of nuclear factor kappa-b kinase subunit beta; T2D, type 2 diabetes; CVDs, cardiovascular diseases; TNFα, tumor necrosis factor α; APP, amyloid precursor protein; MAP, microtubule associated protein; HD, huntington’s disease; IDE, insulin degrading enzyme

Introduction

Obesity is a health disorder that has been increasing globally at an alarming rate, majorly in developed and developing countries and especially in children.1 This increase is majorly due to a change towards sedentary lifestyle, high-fat, sugar food intake and a less physical activity. Obesity, attributed with excessive calorie intake and storage of fat in adipose tissues in the form of triglycerides, is the major driver of metabolic syndrome and also serves as a risk factor for the development of chronic diseases such as T2D and related cardiovascular diseases (CVDs).2 Obesity has also been associated with the accelerated aging process.3 Various physiological alterations are observed in an obese individual viz. insulin tolerance leading to impairment in glucose homeostasis, central obesity, dyslipidemia, where the latter is termed as ‘metabolic syndrome’. Concomitants with these two systemic alterations are also attributed to obesity and metabolic syndrome, i.e., oxidative damage to cellular components and increased secretion of pro-inflammatory factors such as TNFα (Tumor Necrosis Factor α), cytokines and interleukins.4–6

A growing number of researchers now suggest a link between obesity and pathology of NDD. NDDs are characterized by a progressive loss of memory and cognition, which can ultimately lead to death. This deterioration is majorly a result of inflammation due to aberrant protein deposition, oxidative stress and modification in lipid pathways.7,8 AD and PD are the two most common neurodegenerative diseases.

Alzheimer’s disease is the most common age related neurodegenerative disease affecting ~10% of population above 65years.9 Extracellular Aβ plaques10 and NFTs11 are two hallmark lesions of the disease, which in conjugation with other physiological and structural alterations cause severe neuronal dysfunction and neuronal loss. Aβ derived from the sequential proteolytic cleavage of the Amyloid Precursor Protein (APP) by β-secretase and followed by γ-secretase, is usually of 40–42 amino acids in size.12,13 In an AD brain, tau aggregates are present in the form of NFTs. Tau is a microtubule associated protein (MAP) which binds to microtubules and stabilizes them. When tau becomes ubiquitinated and hyperphosphorylated its affinity for microtubules decreases several such hyperphosphorylated tau aggregate together to form (NFTs).14,15

Parkinson’s disease is the second most common neurodegenerative disease with associated cognition and movement impairments. It is characterized by the pathology of Lewy body. They are cytoplasmic inclusions of 5 to 25μm in diameter containing insoluble synaptic protein α-synuclein aggregates whereas Lewy neurites are dystrophic neuronal processes. These two pathology cause neuronal loss associated with PD in the region pertaining to substantia nigra.16 Various studies now suggest that there is potential link between the occurrence of obesity and the pathology of NDDs such as AD, PD, Huntington’s disease (HD), etc. Although, genetic links between obesity and NDDs are poorly understood, much is now known about the functional changes and mutual impact of the two diseases.

Physiological alterations in obesity contributing to neurodegeneration

Insulin resistance: Insulin is a peptide hormone that plays a critical
role in peripheral glucose homeostasis regulating the balance between glucose production by liver and its uptake by muscle and adipose tissues. Insulin holds important neurotrophic properties in the brain. The hormone is transported to the central nervous system through the blood-brain barrier by a transport mechanism mediated by insulin receptors. These receptors are chiefly localized in hippocampus, entorhinal cortex and frontal which functions in learning, memory and cognition.

It has been observed that visceral adiposity is a major causative of insulin resistance. Visceral fat tissues due to their high metabolic rate act as endocrine organs that secretes adipokines (e.g. leptin) and cytokines (e.g. TNF-α, IL-6, heparin-binding epidermal growth factor). Activation of proinflammatory pathways and secretion of cytokines leads to insulin resistance. In brain insulin deficiency and resistance triggers neuronal death due to the withdrawal of trophic factor, energy metabolism deficits, and inhibition of insulin-responsive gene expression thereby, stimulating neurodegeneration.

In case of Parkinson’s disease insulin negatively regulates the brain dopaminergic activity. Insulin inhibits the firing of dopamine-containing neurons found within the substantia nigra and stops or reverses the increase in discharge rates of dopaminergic cells normally elicited by the dopamine-receptor antagonist haloperidol. Also, the reactive oxygen species produced chronic hyperglycemia can be a mechanism underlying dopaminergic cell loss in hyperglycemic animals. However, chronic hyper-glycemia is only a minor risk factor for Parkinson’s disease in humans.

Glucose intolerance and type 2 diabetes mellitus.

Insulin resistance is a common pathophysiologic characteristic of obesity and glucose intolerance as it affects the membrane cation transport. Glucose intolerance is defined as a pre-diabetic situation of hyperglycemia which is associated with insulin resistance and increased risk of cardiovascular and neurological pathology. Impaired glucose tolerance precedes T2D mellitus which in turn act as a cause of many neurodegenerative disorders. The treatment strategies for the macrovascular and microvascular complications of diabetes mellitus have seen profound improvement. Therefore, people are living for a longer age with diabetes mellitus, which has lead to the emergence of several new complications. Dementia is one example of these emerging new complications. Compared with the general population, the increased risk of dementia is 50%–150% in people with T2DM. T2DM is closely associated with identified risk factors for dementia, including atherosclerotic vascular disease, the APOE-ε4 allele. Several researches have shown that diabetes with the APOE-ε4 allele was associated with increased risk of dementia.

Brain cells are unable to synthesize or store glucose; therefore, it has to be transported across the blood-brain-barrier. This is done by Glucose Transporters like GLUT-1, GLUT-3 and GLUT-4. In condition of glucose dysmetabolism, Advanced Glycation end products (AGEs), which are by products of Maillard reaction may start accumulating within the cells. AGEs glycated Aβ which make these peptides more prone to aggregation, also AGEs play a role in hyperphosphorylation of tau. This modification of Aβ results in formation of senile plaques, tau hyperphosphorylation and subsequent formation of neurofibrillary tangles which are hallmarks for AD pathology.

Hyperinsulinemia- a risk factor for AD

Insulin regulates amyloid precursor protein metabolism by decreasing its intracellular accumulation. At moderate concentrations, Insulin is also associated with the synthesis of essential neurotransmitters like acetylcholine and norepinephrine. Hyperinsulinemia with increased levels of insulin in the brain may be involved with a decline in Aβ clearance due to competition for their major degrading mechanism-the “Insulin-Degrading Enzyme”. IDE is a multifunctional enzyme that degrades insulin and amylin, peptides associated with the pathology of T2D, together with Aβ peptide in the AD brain. Hyperinsulinemia may elevate the levels of Aβ through insulin’s competition with Aβ for IDE. Therefore, IDE is a potential link between hyperinsulinemia and AD. Since IDE is much more selective for insulin than for Aβ, brain hyperinsulinemia may deprive Aβ of its main clearance mechanism, supporting its deposition in the brain, and hence, its subsequent neurotoxic effects.

Dyslipidemia

Dyslipidemia is one of the consequences of obesity and is characterized by an increase in triglycerides and free fatty acids, and decrease in HDL-C and HDE. This increase in free fatty acids along with obesity induced inflammation leads to insulin resistance. Many of the fatty acids are cytotoxic and can cause inflammation by stimulating the synthesis of proinflammatory cytokines like TNF-α, IL-1, IL-6 etc.

Adipokine secretion

Adipokines are soluble mediators mainly produced by adipocytes that act in paracrine, autocrine or systemic manner. Till now, over 50 adipokines have been identified out of which leptin, autotaxin and adiponectin have shown to play predominant role in neurodegeneration.

Leptin (identified in 1994) is a 16KDa protein is translated from obese (ob) gene that regulates obesity by inhibiting hunger. Leptin primarily acts on hypothalamic region and controls appetite. Leptin receptors are also expressed in extra hypothalamic regions like amygdala, brain stem and cerebellum.

Effect adipokine secretion on AD: In a normal cell, leptin act as a neuroprotectant by inhibiting cell death, decreasing cell cytotoxicity and reducing the effects of oxidative stress. From the experiments on Diet-induced obese rodents it has been concluded that activity of blood-brain barrier transport system is reduced leading to failure in leptin circulation to its targets in brain. Thus, leptin signaling is significantly decreased in the arcuate nucleus of the hypothalamus. Leptin expression is negatively correlated with AD pathology as it regulates Aβ levels by suppressing accumulation of intraneuronal lipids and inhibiting GSK-3β thereby reducing tau phosphorylation and formation of neurofibrillary tangles.

Effect adipokine secretion on PD: PD is characterized by loss of dopamine producing neurons in substantia nigra. Leptin have protective effects against 6-OHDA (6-hydroxydopamine) toxicity in dopaminergic neurons and preserves the functioning of the dopamine system. Since the leptin levels are reduced due to obesity hence, leptin signaling is significantly decreased in the arcuate nucleus of the hypothalamus. Leptin expression is negatively correlated with AD pathology as it regulates Aβ levels by suppressing accumulation of intraneuronal lipids and inhibiting GSK-3β thereby reducing tau phosphorylation and formation of neurofibrillary tangles.

Neuroinflammation

Neuroinflammation can be described as activation of innate immune response of brain for protection of CNS against infections, injuries and disease. Neuroinflammation is a complex series of reactions comprising cellular and molecular changes, activation of peripheral immune response, initiation of intracellular signaling pathway, release
of inflammatory mediators leading to neuronal dysfunction and loss.\textsuperscript{36} Neuroinflammation leads to neurodegeneration by activation of IKKβ/NF-κB pathway, dysfunction of Blood brain barrier and accumulation of macrophages (astrocytes and microglia).\textsuperscript{37,38} Obesity leads to accumulation of white adipose tissue which acts as a key site for facilitating systemic inflammation.\textsuperscript{39} Hypertrophied adipocytes and immune cells of adipose tissue cause an increase in circulating levels of proinflammatory cytokines like TNF-α, IL-6, IL-1β etc.\textsuperscript{40–42} out of which IL-6 and IL-1β can destroy neuronal circuits involved in cognition and memory.\textsuperscript{43} Accumulation and activation of macrophages has been observed in adipose tissues in obese humans.\textsuperscript{44} Thus, neuroinflammation can be considered as a consequence of obesity leading to neurodegeneration.

Hypothalamus constitutes the major part of CNS affected by inflammation. Hypothalamic inflammation refers to the cellular and molecular changes in hypothalamus due to physical injuries, trauma, infections, metabolic abnormalities and aging.\textsuperscript{45} Hypothalamus regulates energy balance, governs physiological processes like feeding, energy expenditure, body weight and glucose metabolism. The mediobasal region of hypothalamus (MBH) recognizes various circulating signals and activates downstream signaling pathways to control metabolic physiology.\textsuperscript{46} IKKβ/NF-κb has been reported to trigger hypothalamic inflammation which can cause diabetic changes like glucose intolerance, insulin resistance and impaired insulin secretion.\textsuperscript{47} Activation of IKKβ/NF-κb pathway affects the notch signaling pathway to inhibit the differentiation of neuronal stem cells and impair the survival of these cells causing neurodegeneration which may result in diseases like AD.\textsuperscript{48}

### Alteration in signaling pathways due to obesity

Numerous pathway alterations are evident in obesity that can affect the normal brain functioning. These altered pathways lead to damaging effects on the brain cells such as oxidative stress, ER stress and mitochondrial dysfunction, thereby causing dysfunction of cellular machinery and gradually neuronal loss.

Insulin and Insulin Growth Factor 1 (IGF-1) are important in brain glucose homeostasis and cell survival acting in either paracrine or autocrine way\textsuperscript{49} through the P13K-Akt signaling pathway.\textsuperscript{50} This pathway is sensitive to various metabolic signals and stress conditions and majorly involved in inhibition of tumor formation and apoptosis.\textsuperscript{51} In normal insulin conditions, insulin receptors (IR)/IGF-1Rs are activated in response to oxidative stress, whereas glycogen synthasekinase-3 β (GSK-3β) is inhibited. This is accompanied by increased production of 4-hydroxynonenal (4-HNE) for oxidative protection of neuronal lipids and proteins.\textsuperscript{52} However, impaired insulin/IR and IGF-1/IGF-1R signaling results from altered insulin and/or IGF-1 levels in obese or T2D brains. This altered signaling is associated with APP dysmetabolism and tau hyperphosphorylation stimulation, two hallmark causatives of AD.\textsuperscript{53,54}

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**Figure 1** Linkage between various pathways leading to neurodegeneration under obesity burden. The inflammatory response is mediated by the activation of IKKβ/NF-κB pathway.\textsuperscript{55} Hypothalamic inflammation induced by IKKβ/NF-κB has been shown to cause glucose intolerance and insulin resistance.\textsuperscript{56} In this pathway IKKβ degrades IkB protein and liberates NF-κB that localizes to the nucleus and activates transcription of inflammatory proteins. In case of obesity Toll-like receptors (TLRs) and cytokine receptors have shown to mediate neuroinflammation by activation of IKKβ/NF-κB pathway.\textsuperscript{57,58} Studies have shown that hypothalamic inflammation is achieved by activation of the IKKβ/NF-κB pathway through ER stress and autophagy defects.\textsuperscript{59–74}

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Table 1 Genes that are involved in obesity

| Gene   | Locus   | Function                                                                 | Mutation                                                                                                                                   | References |
|--------|---------|--------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|------------|
| LEP    | 7q31.3  | Regulates body weight; inhibit food intake and/or regulate energy expenditure | Cause severe obesity, and morbid obesity with hypogonadism                                                                             | 33         |
| APOE   | 19q13.2 | Protein encoded binds to a specific liver and peripheral cell receptor; and is essential for the normal catabolism of triglyceride-rich lipoprotein constituents | Results in familial dysbetalipoproteinemia, or type III hyperlipoproteinemia (HLP III) which increases plasma cholesterol and triglycerides as a consequence of impaired clearance of chylomicron and VLDL remnants. | 61         |
| GRN    | 17q21.32| Encodes Progranulin which promotes motor neuron survival and neurite outgrowth, tumor cell growth, wound healing, vascularization, and cell migration | Causes fronto-temporal dementia (FTD)                                                                                                   | 62         |
| ARSG   | 17q24.2 | Encoded protein belongs to sulfatase enzyme family and regulates hormone biosynthesis, modulation of cell signaling, and degradation of acromolecules. | Causes a decline in enzyme activity upto 75% leading to Neuronal ceroidlipofuscinoses (NCL)                                             | 63         |
| FTO    | 16q12.2 | Encodes nuclear protein of the AlkB related non-phaem iron and 2- oxoglutarate-dependent oxygenase super family which oxidativelydemethylates DNA. | Marked by reductions in the volume of frontal lobe, impaired verbal fluency performance, increased AD risk                              | 64         |
| MC4R   | 18q22   | Expressed in cortex, thalamus, hypothalamus, and the spinal cord, involved in melanocortins anti-inflammatory action in the brain | Defects causes of autosomal dominant obesity                                                                                              | 65         |
| IRS-2  | 13q34   | Mediates effects of insulin,insulin like growth factor 1 and other cytokines | Insulin resistance and impaired pancreatic b-cell function, Reduction in brain mass                                                      | 66         |
| SLC2A4 | 17p13   | Encodes a protein that functions as an insulin-regulated facilitative glucose transporter | Increased levels of insulin and glucose, hypertension and impaired glucose tolerance                                                      | 67         |
| PIK3R1 | 5q13.1  | Important role in metabolic actions of insulin by controlling downstream transduction of insulin action pathway | Causes insulin resistance and thus increases susceptibility for T2D                                                                     | 68         |
| PTP1B  | 20q13.1-q13.2 | Negatively regulates the insulin signaling by dephosphorylating the phosphotyrosine residues of insulin receptor kinase | Can lead to insulin resistance                                                                                                          | 69         |
| SOCS3  | 17q25.3 | Encodes STAT-induced STAT inhibitor (SSI) protein that an inhibitory signaling protein that inhibits both leptin and insulin signaling | Upregulation of SOCS3 induces hypothalamic leptin and insulin resistance                                                               | 70         |
| PTPN1  | 20q13.1-13.2 | Encodes Protein tyrosine phosphatases and negatively regulate of insulin signaling | Inhibition counteracts over nutrition-induced leptin resistance and glucose disorders                                                      | 71         |
| MYD88  | 3p22    | Role in the development of obesity, insulin resistance and dyslipidemia | causes early onset obesity                                                                                                              | 72         |
| POMC   | 2p23.3  | Inflammation-induced Pomp activation results in food intake suppression, physical inactivity | Associated with late onset obesity                                                                                                       | 73         |
| AGRP   | 16q22   | Regulates the hypothalamic control of feeding behaviour and thus plays a role in weight homeostasis | Associated with late onset obesity                                                                                                       | 74         |

Conclusion

Obesity is associated with a growing risk for various chronic neurologic diseases. Even if the mechanisms underlying this risk have not been entirely elucidated, it appears that alterations in hormones, metabolites or inflammatory mediators can impose a negative impact on CNS. Researches on obesity and neurodegeneration conducted over the past two decades clearly infer the role of insulin action that prolongs well beyond peripheral glucose metabolism. Insulin is active throughout the CNS in various key pathways of learning and memory.

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Alterations in insulin action have been linked to neurodegenerative processes characteristic of AD, PD and mild cognitive impairments. Various observations suggest that not only is insulin important for normal cognitive functioning, but that impaired insulin action and signaling may promote and/or exacerbate cognitive decline. Also, in extra-hypothalamic sites, leptin has notable effects on neurogenesis, synaptogenesis, axon growth, dendritic morphology, and Aβ regulation. Its effects have been shown to improve cognition. However, a better understanding of these effects will lead to the development of potential therapies against neurodegeneration.

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Conflict of interest

The author declares no conflict of interest.

References

1. Prentice AM. The emerging epidemic of obesity in developing countries. Int J Epidemiol. 2006;35(1):93–99.
2. Haslam DW, James WP. Obesity. Lancet. 2005;366(9492):1197–1209.
3. Tzanetakis JP, Katsilambros NL, Benets A, et al. “Is obesity linked to aging?”: adipose tissue and the role of telomeres. Ageing Res Rev. 2012;11(2):220–229.
4. Grattagliano I, Palmieri VO, Portincasa P, et al. Oxidative stress–induced risk factors associated with the metabolic syndrome: a unifying hypothesis. J Nutr Biochem. 2008;19(8):491–504.
5. Pennathur S, Heinecke JW. Mechanisms for oxidative stress in diabetic cardiovascular disease. Antioxid Redox Signal. 2007;9(7):955–969.
6. Sutherland JP, McKinley B, Eckel RH. The metabolic syndrome and inflammation. Metab Syndr Relat Disord. 2004;2(2):82–104.
7. Mattson MP, Pedersen WA, Duan W, et al. Cellular and molecular mechanisms underlying perturbed energy metabolism and neuronal degeneration in Alzheimer’s and Parkinson’s diseases. Ann NY Acad Sci. 1999;893:154–175.
8. Perl DP, Olanow CW, Calme D. Alzheimer’s disease and Parkinson’s disease: distinct entities or extremes of a spectrum of neurodegeneration? Ann Neurol. 1998;44(3 Suppl 1):S19–S31.
9. Zhang Y, Thompson R, Zhang H, et al. APP processing in Alzheimer’s disease. Mol Brain. 2011;4:3.
10. Masters CL, Simms G, Weinman NA, et al. Amyloid plaque core antigen in Alzheimer disease and Down syndrome. Proc Natl Acad Sci. 1985;82(12):4245–4249.
11. Goedert M, Wischik CM, Crowther RA, et al. Cloning and sequencing of the cDNA encoding a core protein of the paired helical filament of Alzheimer disease: identification as the microtubule–associated protein tau. Proc Natl Acad Sci. 1988;85(11):4051–4055.
12. Masters CL, Cappai R, Barnham KJ, et al. Molecular mechanisms for Alzheimer’s disease: implications for neuroimaging and therapeutics. J Neurochem. 2006;97(6):1700–1725.
13. Murphy MP, LeVine H. Alzheimer’s disease and the amyloid-beta peptide. J Alzheimers Dis. 2010;19(1):311–323.
14. Grundke-Iqbal I, Iqbal K, Quinlan M, et al. Microtubule–associated protein tau. A component of Alzheimer paired helical filaments. J Biol Chem. 1986;261:6084–6089.
15. Grundke-Iqbal I, Iqbal K, Tung YC, et al. Abnormal phosphorylation of the microtubule–associated protein tau (tau) in Alzheimer cytoskeletal pathology. Proc Natl Acad Sci. 1986;83:4913–4917.
16. Spillantini MG, Schmidt ML, Lee VM, et al. Alpha–synuclein in Lewy bodies. Nature. 1997;388(6645):839–840.
17. Barbagallo M, Dominguez LJ. Type 2 diabetes mellitus and Alzheimer’s disease. World Journal of Diabetes. 2014;5(6):889–893.
18. de la Monte SM. Contributions of brain insulin resistance and deficiency in amyloid–related neurodegeneration in Alzheimer’s disease. Drugs. 2012;72(1):49–66.
19. Saller CF, Chiado LA. Glucose suppresses basal firing and haloperidol–induced increases in the firing rate of central dopaminergic neurons. Science. 1980;210(4475):1269–1271.
20. Stranahan AM, Arumugam TV, Cutler RG, et al. Diabetes impairs hippocampal function through glucocorticoid–mediated effects on new and mature neurons. Nat Neurosci. 2008;11(3):309–317.
21. Barr EL, Zimmet PZ, Wellborn TA, et al. Risk of cardiovascular and all–cause mortality in individuals with diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance: the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). Circulation. 2007;116(2):151–157.
22. Strachan MW, Deary IJ, Ewing FM, et al. Is type II diabetes associated with an increased risk of cognitive dysfunction? A critical review of published studies. Diabetes Care. 1997;20(3):438–445.
23. Takeda M, Martinez R, Kudo T, et al. Apolipoprotein E and central nervous system disorders: reviews of clinical findings. Psychiatry Clin Neurosci. 2010;64(6):592–607.
24. Phiel CJ, Wilson CA, Lee VM, et al. GSK-3alpha regulates production of Alzheimer’s disease amyloid–beta peptides. Nature. 2003;423(6938):435–439.
25. Kroner Z. The relationship between Alzheimer’s disease and diabetes: Type 3 diabetes? Aliment Med Rev. 2009;14(4):373–379.
26. Qiu WQ, Folstein MF. Insulin, insulin–degrading enzyme and amyloid–beta peptide in Alzheimer’s disease: review and hypothesis. Neurobiol Aging. 2006;27(2):190–198.
27. Craft S, Watson GS. Insulin and neurodegenerative disease: shared and specific mechanisms. Lancet Neurol. 2004;3(3):169–178.
28. Franssen R, Monajemi H, Stroes ES, et al. Obesity and dyslipidemia. Med Clin North Am. 2011;95(5):893–902.
29. Capurso C, Capurso A. From excess adiposity to insulin resistance: the role of free fatty acids. Int J Mol Sci. 2012;13(4):917–923.
30. Serras B, Ricordi C. Role of fatty acids and polyphenols in inflammatory gene transcription and their impact on obesity, metabolic syndrome and diabetes. Eur Rev Med Pharmacol Sci. 2012;16(9):1137–1154.
31. Tilg H, Moschen AR. Apipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol. 2006;6(10):772–783.
32. Zhang Y, Proenca R, Maffei M, et al. Positional cloning of the obese gene and its human homologue. Nature. 1994;372(6505):425–432.
33. Greco SJ, Sarkar S, Johnston JM, et al. Leptin reduces Alzheimer’s disease–related tau phosphorylation in neuronal cells. Biochem Biophys Res Commun. 2008;376(3):536–541.
34. Weng Z, Signore AP, Gao Y, et al. Leptin protects against 6–hydroxydopamine–induced dopaminergic cell death via mitogen–activated protein kinase signaling. J Biol Chem. 2007;282(47):34479–34491.
35. Spencer JP, Vafeiadiou K, Williams RJ, et al. Neuroinflammation: modulation by flavonoids and mechanisms of action. Mol Aspects Med. 2012;33(1):83–97.
36. McGeer EG, McGeer PL. Neuroinflammation in Alzheimer’s disease and mild cognitive impairment: a field in its infancy. J Alzheimers Dis. 2010;19(1):355–361.
37. Dugan LL, Ali SS, Shektman G, et al. IL-6-mediated degeneration of forebrain GABAergic interneurons and cognitive impairment in aged mice through activation of neuronal NADPH oxidase. PLoS One. 2009;4(5):e5518.

38. Steinman L. Inflammatory cytokines at the summits of pathological signal cascades in brain diseases. Sci Signal. 2013;6(258):ea3.

39. Odegard JI, Chawla A. Pleiotropic actions of insulin resistance and inflammation in metabolic homeostasis. Science. 2013;339(6116):172–177.

40. Ouchi N, Parker JL, Lugus JJ, et al. Adipokines in inflammation and metabolic disease. Nat Rev Immunol. 2011;11(2):85–97.

41. Visser M, Bouter LM, McQuillan GM, et al. Elevated C-reactive protein levels in overweight and obese adults. JAMA. 1999;282(22):2131–2135.

42. Yudkin JS, Stehouwer CD, Emeis JJ, et al. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? Arterioscler Thromb Vasc Biol. 1999;19(4):972–978.

43. Gemma C, Bickford PC. Interleukin-1beta and caspase-1: players in the regulation of age-related cognitive dysfunction. Rev Neurosci. 2007;18(2):137–148.

44. Drake C, Boutin H, Jones MS, et al. Brain inflammation is induced by co-morbidities and risk factors for stroke. Brain Behavior Immunity. 2011;25(6–4):1113–1122.

45. Lam TK, Schwartz GJ, Rossetti L. Hypothalamic sensing of fatty acids. Nat Neurosci. 2005;8(5):579–584.

46. Myers MG, Leibel RL, Seeley RJ, et al. Obesity and leptin resistance: distinguishing cause from effect. Trends Endocrinol Metabol. 2010;21(11):643–651.

47. Posey KA, Clegg DJ, Printz RL, et al. Hypothalamic proinflammatory lipid accumulation, inflammation, and insulin resistance in rats fed a high-fat diet. Am J Physiol Endocrinol Metab. 2009;296(5):E1003–E1012.

48. Li J, Tang Y, Cai D. IKK/J/NF-kB disrupts adult hypothalamic neural stem cells to mediate a neurodegenerative mechanism of dietary obesity and pre-diabetes. Nat Cell Biol. 2012;14(10):999–1012.

49. Hoyer S. Causes and consequences of disturbances of cerebral glucose metabolism in sporadic Alzheimer disease: therapeutic implications. Adv Exp Med Biol. 2004;541:135–152.

50. Bondy CA, Cheng CM. Signaling by insulin-like growth factor 1 in brain. Eur J Pharmacol. 2004;490(1–3):25–31.

51. Martelli AM, Faenza I, Billi AM, et al. Intraneuronal 3'-phosphoinositide metabolism and Akt signaling: new mechanisms for tumorigenesis and protection against apoptosis? Cell Signal. 2006;18(8):1101–1107.

52. Duarte AI, Santos MS, Oliveira CR, et al. Insulin neuroprotection against oxidative stress in cortical neurons—involvement of uric acid and glutathione antioxidant defenses. Free Radic Biol Med. 2005;39(7):876–889.

53. Gasparini L, Gouras GK, Wang R, et al. Stimulation of beta-amyloid precursor protein trafficking by insulin reduces intraneuronal beta-amyloid and requires mitogen-activated protein kinase signaling. J Neurosci. 2001;21(8):2561–2570.

54. Li ZG, Zhang W, Sima AA. Alzheimer-like changes in rat models of spontaneous diabetes. Diabetes. 2007;56(7):1817–1824.

55. Cai D. NFkappaB-mediated metabolic inflammation in peripheral tissues versus central nervous system. Cell Cycle. 2009;8:2542–2548.

56. Arruda AP, Milanski M, CoopeA, et al. Low-grade hypothalamic inflammation leads to defective thermogenesis, insulin resistance, and impaired insulin secretion. Endocrinology. 2011;152(4):1314–1326.

57. Milanski M, Degasperi G, CoopeA, et al. Saturated fatty acids produce an inflammatory response predominantly through the activation ofTLR4 signaling in hypothalamus: implications for the pathogenesis of obesity. J Neurosci. 2009;29(2):359–370.

58. Romannoto T, Roman EA, Arruda AP, et al. Deletion of tumor necrosis factor–alpha receptor 1 (TNFR1) protects against diet–induced obesity by means of increased thermogenesis. J Biol Chem. 2009;284(52):36213–36222.

59. Meng Q, Cai D. Defective hypothalamic autophagy directs the central pathogenesis of obesity via the IkkappaB kinase beta (IKKbeta)/Nf–kappab pathway. J Biol Chem. 2011;286(37):32324–32332.

60. 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. 2011;108(7):2939–2944.

61. Hirschhorn JN, Lohmueller K, Byrne E, et al. A comprehensive review of genetic association studies. Genet Med. 2002;4:45–61.

62. Nguyen AD, Nguyen TA, Martens LH, et al. Programulin: at the interface of neurodegenerative and metabolic diseases. Trends Endocrinol Metab. 2013;24(12):597–606.

63. Abitbol M, Thibaud JL, Olby NJ, et al. A canine Arylsulfatase G (ARSG) mutation leading to a sulfatase deficiency is associated with neuronal ceroid lipofuscinosis. Proc Natl Acad Sci. 2010;107(33):14775–14780.

64. Keller L, Xu W, Wang HX, et al. The obesity related gene, FTO, interacts with APOE, and is associated with Alzheimer’s disease risk: a prospective cohort study. J Alzheimers Dis. 2011;23(3):461–469.

65. Lasaga M, Delbeljuk L, Durand D, et al. Role of alpha–melanocyte stimulating hormone and melanocortin 4 receptor in brain inflammation. Peptides. 2008;29(10):1825–1835.

66. Kubota N, Tohe K, Terauchi Y, et al. Disruption of insulin receptor substrate 2 causes type 2 diabetes because of liver insulin resistance and lack of compensatory beta-cell hyperplasia. Diabetes. 2000;49(11):1880–1889.

67. Stenbit AE, Tsao TS, Li J, et al. GLUT4 heterozygous knockout mice develop muscle insulin resistance and diabetes. Nat Med. 1997;3(10):1096–1101.

68. Barroso I, Luan J, Middelberg RP, et al. Candidate gene association study in type 2 diabetes indicates a role for genes involved in beta–cell function as well as insulin action. PLoS Biol. 2003;1(1):e20.

69. Elchebly M, Payette P, Michaliszyn E, et al. Increased insulin sensitivity and obesity resistance in mice lacking the protein tyrosine phosphatase–1B gene. Science. 1999;283(5407):1544–1548.

70. Howard JK, Flier JS. Attenuation of leptin and insulin signaling by SOCS proteins. Trends Endocrinol Metab. 2006;17(9):365–371.

71. Bence KK, Delibegovic M, Xue B, et al. Neuronal PTP1B regulates body weight, adiposity and leptin action. Nat Med. 2006;12(8):917–924.

72. Kleinridders A, Schenten D, Körner AC, et al. MyD88 signaling in the CNS is required for development of fatty acid–induced leptin resistance and diet–induced obesity. Cell Metab. 2009;10(4):249–259.

73. Shi X, Wang X, Li Q, et al. Nuclear factor kxB (NF–xB) suppresses food intake and energy expenditure in mice by directly activating the Pome promoter. Diabetologia. 2013;56(4):925–936.

74.卡尔纳伊 A, 卡帕 I, 帕加斯 V, et al. Association between a rare SNP in the second intron of human Agouti related protein gene and increased BMI. BMC Med Genet. 2009;10:63.