Review Article

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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 hypothalmic 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 P13K/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

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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 plaques[10] and NFTs[11] 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.[17]

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.[18]

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.[19] Also, the reactive oxygen species produced chronic hyperglycemia can be a mechanism underlying dopaminergic cell loss in hyperglycemic animals. However, chronic hyper-glycaemia is only a minor risk factor for Parkinson's disease in humans.[20]

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.[21] 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.[22] 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.[23]

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.[24] 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.[25]

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.[26] 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.[27]

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 HDL.[28] This increase in free fatty acids along with obesity induced inflammation leads to insulin resistance.[29] 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.[30]

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.[31]

Leptin (identified in 1994) is a 16KDa protein is translated from obese (ob) gene that regulates obesity by inhibiting hunger.[32] 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.[33]

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, Increase in the risk of PD.[34]

Neuroinflammation

Neuroinflammation can be described as activation of innate immune response of brain for protection of CNS against infections, injuries and disease.[35] Neuroinflammation is a complex series of reactions comprising cellular and molecular changes, activation of peripheral immune response, initiation of intracellular signaling pathway, release

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of inflammatory mediators leading to neuronal dysfunction and loss.[36] Neuroinflammation leads to neurodegeneration by activation of IKKβ/NF-κB pathway, dysfunction of Blood brain barrier and accumulation of macrophages (astrocytes and microglia).[37,38] Obesity leads to accumulation of white adipose tissue which acts as a key site for facilitating systemic inflammation.[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.[40–42] out of which IL-6 and IL-1β can destroy neuronal circuits involved in cognition and memory.[43] Accumulation and activation of macrophages has been observed in adipose tissues in obese humans.[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.[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.[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.[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.[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[49] through the P13K-Akt signaling pathway.[50] This pathway is sensitive to various metabolic signals and stress conditions and majorly involved in inhibition of tumor formation and apoptosis.[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.[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.[53,54]

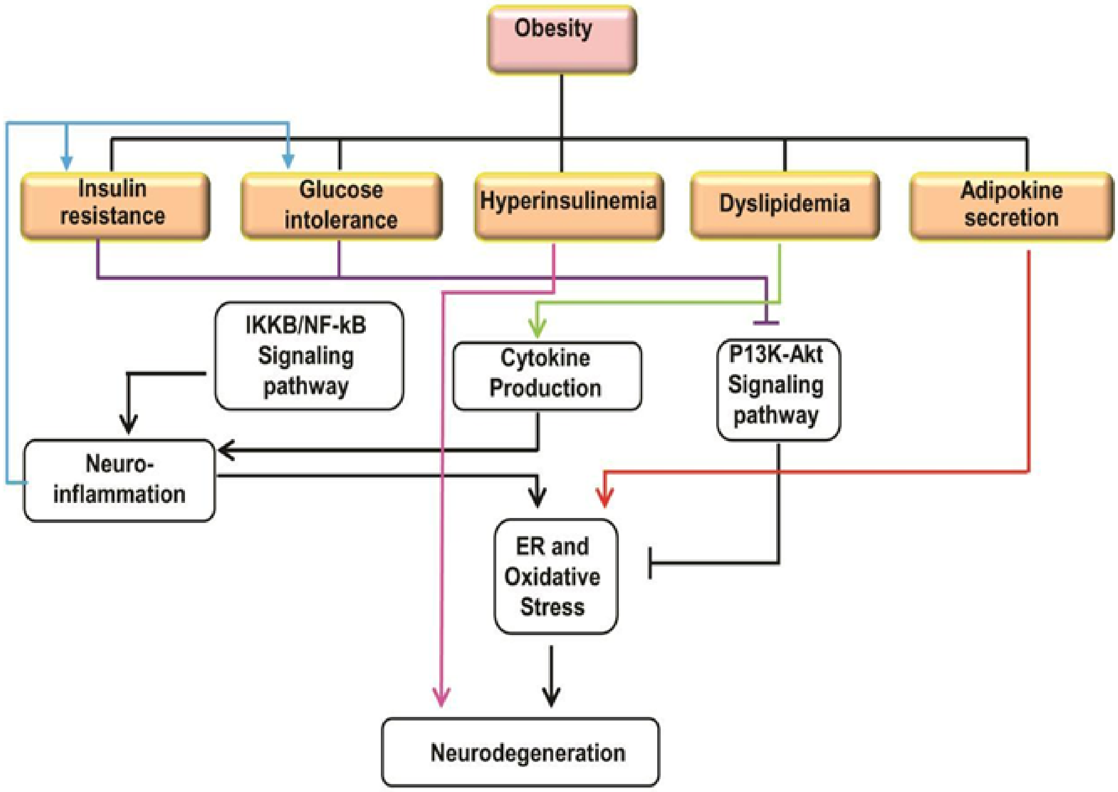

Figure 1 Linkage between various pathways leading to neurodegeneration under obesity burden.

The inflammatory response is mediated by the activation of IKKb/NF-κB pathway.[55] Hypothalmic inflammation induced by IKKb/NF-kB has been shown to cause glucose intolerance and insulin resistance.[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 IKKb/NF-κB pathway.[57,58] Studies have shown that hypothalmic inflammation is achieved by activation of the IKKb/NF-κB pathway through ER stress and autophagy defects.[59–74]

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Table 1 Genes that are involved in obesity

Gene	Locus	Function	Mutation	References
Genes involved in obesity and neurodegeneration				
Adipokine secretion				
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-haem 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
Insulin resistance and glucose intolerance				
IRS-2	13q34	Mediates effects of insulin ,insulin like growth factor I 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 phosphotryosine residues of insulin receptor kinase	Can lead to insulin resistance	69
Neuroinflammation				
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-q13.2	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		72
POMC	2p23.3	Inflammation-induced Pomc activation results in food intake suppression, physical inactivity	causes early 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.

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