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OBESITY PROMOTES ALZHEIMER'S DISEASE IN MIDDLE AGED INDIVIDUALS BY AGGRAVATING NEURODEGENERATION THROUGH VARIOUS MECHANISMS : A REVIEW

Ramya Akoju[1], Sravana Jyothi[1], Anusha Govindula[2], Subba Rao Chamakuri[2], Ashish Suttee[3]* and Md. Sarvar Pasha[4]

[1]Depart. of Pharmacology, Vaagdevi College of Pharmacy, Hanamkonda, Warangal-506001 (Telangana), India.
[2]Department of Pharmacy, Vaageswari College of Pharmacy, Karimnagar-505527 (Telangana), India.
[3*]School of Pharmaceutical Sciences, Lovely Professional University-144411 (Punjab), India
[4]Department of Pharmaceutical Analysis, Vaageswari Institute of Pharmaceutical Sciences, Karimnagar-505527 (Telangana), India.

Abstract

Obesity can be defined as a metabolic chronic disorder resulting due to imbalance in the intake and expenditure of energy which is also linked to several disorders of metabolism, increasing expressions of pro-inflammatory markers, as well as an increase in the risk of different diseases leading to cardiovascular diseases, type-2 diabetes, and various types of cancer. The primary reasons for the present-day issue of obesity are linked with abruptly changing lifestyles, an increase in energy-dense food consumption in saturated sugar and fat as well as a reduction in physical activity. Obesity apart from causing metabolic disorders also accounts for the onset of AD symptoms in middle-aged obese persons and progresses the symptoms in elderly patients already with the disease by aggravating neurodegeneration via various pathways which include an increased generation and deposition of b-amyloid by cholesterol, neuroinflammation, oxidative stress, brain insulin resistance, hyperlipidemia induced cerebral ischemia and also by accelerating the normal process of aging.

Key words: Obesity, Neurodegeneration, Insulin Resistance (IR), Cerebral Ischemia, Neuroinflammation.

Introduction

Neurodegenerative diseases are characterized by progressive, irreversible loss of neurons from specific regions of the brain. Neurodegenerative diseases that can affect cognitive ability include Alzheimer's disease (AD), Pick's disease, Parkinson's disease, Lewy body disease, Huntington's disease, progressive supranuclear palsy and cerebella degeneration (Martha *et al.,* 2007). Learning is the process of acquisition of information and skills, while subsequent retention of that information is called memory. Learning and memory together called as cognition. Cognitive impairment is deficit in the processes by which persons perceive, encode, store, retrieve, and use information. Many processes can lead to cognitive impairment which includes neurodegeneration, strokes, tumors, head trauma, hypoxia, cardiac surgery, malnutrition, attention-deficit disorder, depression, anxiety and the side effects of medication, and normal ageing. Common vascular disorders that affect cognition include stroke, multiple strokes, and cerebral embolic disease (Pattewar *et al.,* 2011). Alzheimer's disease (AD), first identified by Alois Alzheimer's in 1906 is an irreversible, progressive neurodegenerative brain disease that slowly destroys memory and thinking skills and eventually even the ability to carry out the simplest tasks. AD is associated with localized loss of cholinergic neurons, mainly in the hippocampus and frontal cortex of the brain (Rang *et al.,* 2007). AD is the most common cause of dementia among people of age 65 and older. Dementia is the loss of cognitive functioning-thinking, remembering, reasoning and behavioral abilities. The two hallmarks of the disease are Beta amyloid plaques (Aβ), the extracellular amorphous deposits of b-amyloid protein) and Intra-neuronal neurofibrillary tangles (NFTs), comprising filaments of a phosphorylated form of a microtubule-

***Author for correspondence :** E-mail : chamakurisubbarao@gmail.com

associated protein (Tau) build up inside the neuron (Amartya *et al*., 2011).

Alzheimer's disease

AD is a progressive and irreversible kind of neurodegenerative disease-related to the human brain which slowly destroys the thinking skills as well as the memory of the person which ultimately leads to a lack of ability for carrying out some simple chores of daily life (Amartya D *et al.,* 2011). It is associated with localized lack in cholinergic neurons, mainly in both hippocampus as well as the frontal cortex of the brain, and is a usual reason for dementia in people older than the age of 65 (Rang HP *et al.,* 2007). Alzheimer's disease can be prevalent with an exponential increase in age, which occurs after nearly 7% of individual's age from 65 to 74 years, 53% between the ages of 75-84 and 40% among the people of older than 85 years. The onset of the disease is noticed from forty years, which results in an arbitrary classification of the age of 40 to 64 years age under early-onset and 65 years and older under late-onset (Hebert LE *et al.,* 2003). AD is believed to develop in response to a combination of genetic and nongenetic factors, which may be different in different individuals (Claudine F *et al.,* 2002). The Pathophysiological factors responsible for AD include b-Amyloid plaque and neurofibrillary tangle formation, decreased Acetylcholine levels, Glutamate toxicity in neurons, oxidative stress, chronic inflammation, and genetic predisposition. Other risk factors that contribute to AD are Age, Obesity, Unhealthy Eating Habits, Diabetes, Hypertension, High Cholesterol, Insulin Resistance, History of Head Injury, etc(Jana P *et al.,* 2012).

Obesity

In layman, language obesity is often termed as an excessive or abnormal accumulation of fat which can ultimately lead to health risks. Its characterization can be done using the measuring index BMI (Body Mass Index) with weight divided by the square of height with weight measured in Kg and height is measured in meters. A person with BMI greater than 30kg/m^2 is considered obese, with 25-30 kg/m^2 BMI is considered as overweight, and the person with 20-25 kg/m^2BMI is known to have a healthy body weight (Rang HP *et al* 2007). Overweight or obesity is considered as one of the major risk factors when it comes to developing type 2 diabetes, metabolic disorders, atherosclerosis, dyslipidemia, cardiovascular disease, and systemic hypertension (Changhyun R *et al.,* 2012).

Link Between Obesity and Brain Volume

Since the last 10 years, there have been new technologies being invented every day especially in the medical field with newer CT (computer tomography) and MRI (magnetic resonance imaging) Scans being used today which reports major alterations occurring in the morphology of brains among people who are obese. Some latest research specifies that higher waist-to-hip ratio or high BMI in people belonging to the middle-age group are linked to reduced volume of brain in their frontal-temporal brain lobes which is responsible for our judgment and higher-order reasoning, it can affect the hippocampus which processes a person's long-term memories, and anterior cingulate gyrus responsible for our decision making and the key to attention skills. Such conditions might contribute to reasoning with the link formed among the brain and different indicators of obesity like abdominal fat, waist-to-hip ratio, waist circumference, and BMI(Rana A *et al.,* 2013).

Obesity Associated Pathophysiological Processes in Brain

Obesity results in the AD onset and progression by altering the normal physiological processes in the body and thereby promoting various pathophysiological pathways that affect the brain function which include:

Obesity and Amyloid -Production

The term "Altered Cholesterol Homoeostasis" is considered to be a crucial aspect of Alzheimer's disease pathogenesis as per a recent report. Cholesterol is the major influencing factor in the enzyme activities which are required in the production of Aβ and amyloid precursor protein cleavage. Higher cholesterol results in higher APP cleavage and raises the production of Ab where the lower levels of cholesterol inhibit the formation of Ab from APP (Luigi P *et al.,* 2003). An increase in free cholesterol concentrations in a neuronal membrane helps in stimulating the increased production of Ab through the membrane or intracellular effects. Higher levels of membrane cholesterol-induced ACAT: A cholesterol acyltransferase named cellular Acyl Coenzyme for producing more cholesterol eaters in an intracellular granulesm, by a vague body mechanism. This raised activities of ACAT helps in modulating the production of Ab which increases the synthesis (Puglielli L *et al.,* 2001).

Obesity and Insulin Resistance

A principal hormone named Insulin is synthesized in significant quantities by β-cells in the pancreas in case the body is producing higher levels of glucose in the blood. Insulin exerts its effects by binding to IRs: Insulin Receptors and stimulating the influx of glucose in the muscles, deposition of fat and muscle in adipocytes, and synthesis of glycogen in the liver. Other crucial functions

of insulin include the increase in protein synthesis, growth, and survival of cells, preventing catabolism of protein, anabolism, anti-apoptotic and anti-inflammatory functions (Jeevendra JA *et al.,* 2008).

Insulin role in the brain

Glucose is used as a primary fuel by the human brain, secretion of insulin in the pancreas crosses the BBB (Blood Brain Barrier), which reaches to the glial cells and the neurons, as well as exerting the region-specific impact on the metabolism of glucose. Insulin and its Receptors (IR) distributed in the brain having higher concentrations in the cerebral cortex, hippocampus, hypothalamus as well as the olfactory bulb, which are the key elements for memory formation and learning (Neumann KF *et al.,* 2008). The uptake pathway of insulin-mediated glucose which includes synthesis of neuronal insulin and an insulin-dependent transporter of glucose called the GLUT4, present in the tissues of our brain, specifically in the hippocampus. These exist some recent considerable evidence that signals that insulin is important for the optimum functioning of the hippocampus (Yaso E *et al.,* 2013). In CNS, the participation of insulin for regulatory behavior of feeding and neuronal maintenance, energy homeostasis, cell survival, synaptic plasticity neurogenesis, neurotransmitter regulation as well as for controlling the processes related to aging. Besides, Insulin acts like a neuroprotective as well as a neurotrophic factor, as it helps in promoting the survival rates of the neuron and has an important part in cognitive functioning by modulating the concentration of CNS neurotransmitter linked to some important cognition parts like acetylcholine (Karen FN *et al.,* 2008).

Insulin resistance and Alzheimer's Disease

Cognitive damage is recognized increasingly among people with resistance to insulin. The more the fat person carrying around, the more resistant body becomes to insulin, to try to remedy this resistance of insulin (reduction in insulin sensitivity by some mainly targeted organs such as muscle, fat or liver is referred to Insulin Resistance) and to overcome hyperglycemia body makes more insulin, if the cycle continues the result is Hyperinsulinemia (in case there is an increases insulin levels in the blood) and type II Diabetes. Peripheral resistance of insulin results in decreased signaling insulins in the CNC, which leads to alterations in the metabolism of the human brain. Hyperinsulinemia can raise the AD risk by impeding the clearance of beta-amyloid and with stimulation of pro-inflammatory released molecules in the human brain (Karen FN *et al.,* 2008). It can also result in higher DNA damage, oxidative stress, dysfunction of mitochondria and can then also result in cell death (Monte SM *et al.,* 2006). Additionally, the chronic neuron exposure to a higher level of insulin can also have an adverse effect on the memory as per the studies conducted on animal models. Hyperinsulinemia is a chronic disorder that impairs the IR activity and BBB function which further reduced the transport of insulin into the brain. IDE elaborated as Insulin Degrading Enzyme is a primary enzyme that helps in degrading the extra amount of insulin along with other substrates like Aβ, a peptide that implicates in AD pathogenesis. Insulin also helps in regulating the IDE levels and its resistance further reduced the clearance of Aβ by either downregulating the expression of IDE or by competing it to bind the IDE. Reduced activity of IDE may contribute to senile plaques formation as per an inability to degrading the Abβpeptide. Thus, the elevated insulin levels and central insulin resistance are implicated in the brain cell's failure to clear beta-amyloid, increased Abβtoxicity, Tau hyperphosphorylation, oxidative stress, neuroinflammation which finally leads to neurode-generation and AD (Sung MS *et al.,* 2011) Fig. 1.

Obesity and Cerebral Ischemia

Cerebral ischemia is a condition, where the brain becomes deprived of oxygen and glucose with resultant decreased blood supply to the brain due to vascular occlusion. It is a neurological disorder in which the neural cells are diminished because of the occurrence of some pathophysiological events taking place serially known as the "ischemic cascade" such as apoptosis, inflammation, oxidative stress, excitotoxicity, energy failure, etc. All such damaging factors can occur due to blocked or decreased flow of blood. Vascular risk factors for cerebral ischemia are Hyperlipidemia/hypercholesterolemia, Diabetes Mellitus (DM), Hypertension, and other Cardiovascular diseases (CVD) (Ashu A *et al.,* 2010).

Pathophysiological Features

Narrowing/occlusion of extra-cerebral arteries (left carotid and left vertebral arteries) that supplies blood to the brain due to atherosclerosis associated with hypercholesterolemia, decreased myocardial contractility, myocardial infarction, etc (Ernest PS *et al.,* 2010).

Ischemic Cascade

The tissues in the human brain could be deprived of oxygen and glucose within few minutes of vascular occlusion which then leads to the accumulation of acidic by-products. Decreasing pH level and nutrients loss result in the transporting of electron chain activities in the mitochondria which leads to a fact decrease in the concentration of ATP (Lee JM *et al.,* 2000). When the body experience strokes the first event which occurs is

the failure of energy homeostasis. With the loss in ATP, it results in the disruption of systems of the ionic pumps such as Ca^{2}+-H+ATPase, Na+-K+-ATPase, reverse Na+-Ca^{2+} transporter leading to increase in Na^{+}, Ca^{2+}, Cl intracellular concentration as well as K^{+} efflux. Such ion re-distribution in the plasmatic membranes results in depolarization of neurons, resulting in excess neurotransmitter release, in glutamate and generally in the specific areas resulting in neuronal excitotoxicity (Endo H *et al.,* 2006). Glutamate results in increasing the Ca^{2+} concentration in excessive amounts in the nerve cells by overactivation of the receptors which results in triggering numerous processes leading to apoptosis and necrosis (Salinska E *et al.,* 2005). This process also includes overloading of Ca^{2+} in the mitochondrial function, oxygen-free radical activation, and formation of caspases-3, 8, 8, BAX, BAD and calpains which results in apoptosis and oxidative stress (Ivan C *et al.,* 2004) Fig. 2.

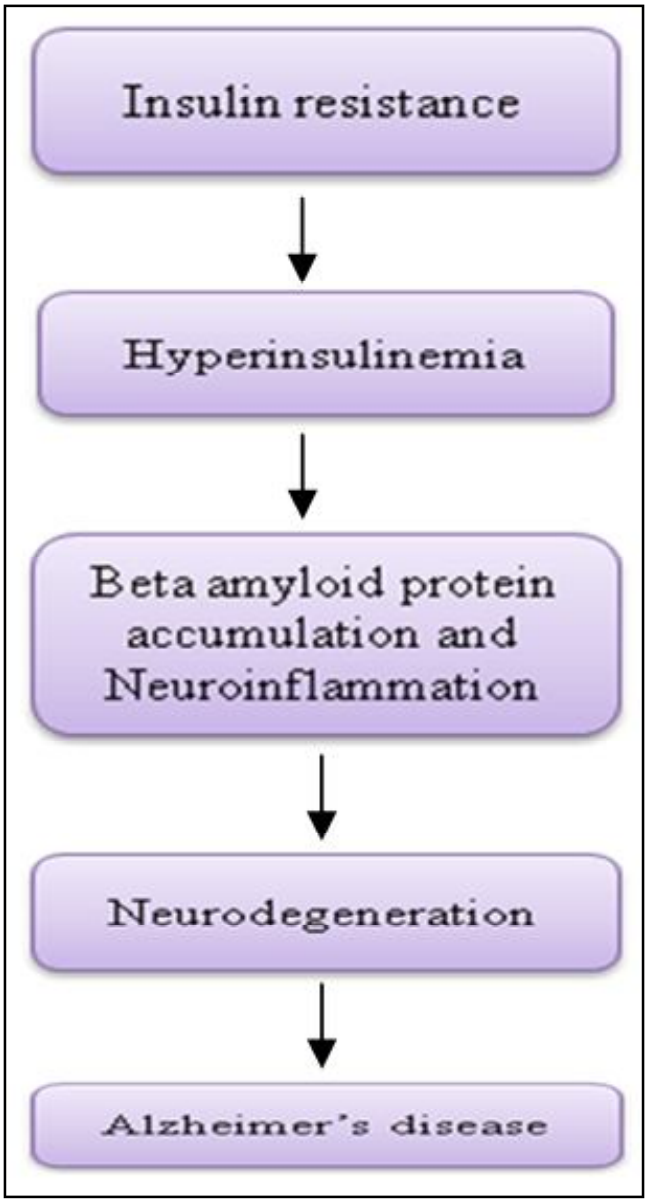

Fig. 1: Insulin resistance and Alzheimer's disease.

After cerebral ischemia, necrotic neuron death in the local ischemic area, microglia of the brain get activated, their morphology is changed, and they start to secrete proinflammatory cytokines like TNF-α (Tumor Necrosis Factor), Interleukin (IL)-1, and IFN- γ (Interferon) and starts the inflammatory cascades (Ashu A *et al.,* 2010).

Obesity and Neuroinflammation

Alzheimer's Disease is quite recently has been researched to be linked to obesity as per the noticed release of the inflammatory cytokines by macrophages activation in the visceral adipose tissues (Rita B *et al.,* 2012). Adipose tissue is the site where the excess fat gets accumulated. Although this can be recognized as endocrine tissues which produced numerous inflammatory-related factors, acting at a physiological level. As obesity takes place, the inflammatory cytokines released by activated macrophages in the visceral adipose tissues become higher (Harwood HJ *et al.,* 2012). Adipose tissues are comprised of different types of cells, like macrophages and adipocytes which produce the cytokines like tumor necrosis factor α, IL-6 (interleukin) and chemo-attractants or chemokines (CCL-2 and MCP-1: Monocyte Chemoattractant Protein) which recruits the monocytes into a white adipose tissue (Fabbrini E *et al.,* 2010). Adipose Tissues which are obese exhibits exhibit raised MCP-1 (Monocyte Chemoattractant Protein) and CCL-2 chemokines expressions with the capability to recruit macrophages (Clement S *et al.,* 2008). There also exist many other chemokines which have a major role in recruiting the macrophages or monocytes in the adipose tissues like MIF (Migration Inhibitory Factor), MCP2, MCP4, MIP-1α, MIP-2α, or MIP2-α known as the

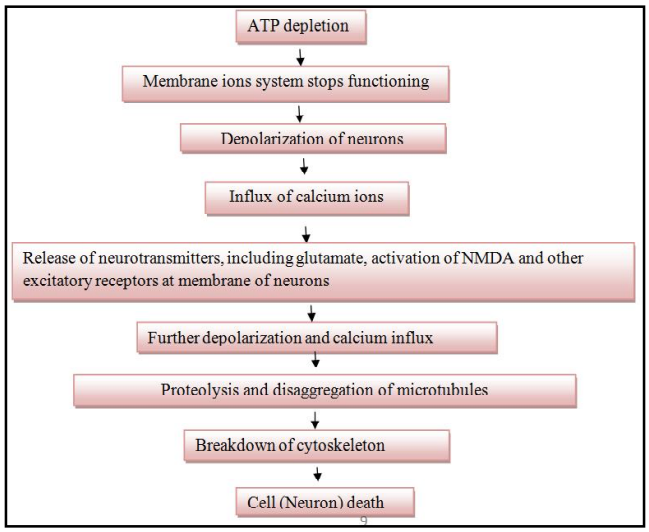

Fig. 2: Flowchart representing Ischemic Cascade in brain.

Macrophage Inflammatory Proteins (Gonzalez CM *et al.,* 2011), which can cause inflammation and insulin resistance. Apart from adipocytes, the amount of macrophages is high in obese environments hence, it provides an extra source of cellular inflammatory factors (Weisberg SP *et al.,* 2003). Many research conducted recently are prospectively assessing the prediction values of high pro-inflammatory cytokines under risk of AD being developed in cognitively intact people or to aggravate the symptoms of AD in people already diagnosed with it (Rita B *et al.,* 2012). Increased levels of plasma in inflammatory marker IL-6 and α1-antichymotrypsin (Engelhart MJ *et al.,* 2004), along with high spontaneous IL-1β or TNF-α production by peripheral blood mononuclear cells (Tzanetakou *et al.,* 2012) and was discovered to be linked with high AD risk in future among other people. Thus, obesity leads to adverse effects the cognitive functioning because of a defect in glucose transport, or defected signaling pathway, impaired insulin metabolism, vascular defects, increased Aβ deposition, oxidative stress with resultant cerebral ischemia and inflammatory cascades in the brain as mentioned earlier, where all together ultimately contribute to AD symptoms onset.

Conclusion

As obesity induces neurodegeneration via weakened insulin metabolism as well as a pathway of signals or flaws in transporting glucose, increased Ab deposition, vascular defects, oxidative stress with resultant cerebral ischemia and inflammatory cascades in the brain, there is a critical need to develop therapeutic interventions applicable to the human population to reverse the obesity mediated pathophysiological processes that occurs in the brain of middle-aged obese individuals and protect their predisposition to early-onset Alzheimer's Disease symptoms rather than disease management.

References

Amartya, D., N. Bala and D.G Pallab (2011). Alzheimer's Disease and its Management. *IJRBS,* **2(4):** 1439-1443.

Ashu, A., A. Parveen, K. Mamta and K. Sunil (2010). Cerebral Ischemic Stroke: Sequels of Cascade. *Int. J. Pharm. Bio. Sci.,* **1(3):** 1-24.

Changhyun, R. and J. Uhee (2012). Screening of Crude Plant Extracts with Anti-Obesity Activity. *Int. J. Mol. Sci.,* **13:** 1710-1719.

Claudine, F., T.H. Mary and R. Rita (2002). Advances in Diagnosis and Treatment of Alzheimer's Disease. Hospital Physician, 47-54.

Clement, S., J.C. Aubry, A. Sgroi, S. Conzelmann, V. Pazienza, C.B. Pittet, *et al*., (2008). Monocyte chemoattractant protein-1 secreted by adipose tissue induces direct lipid accumulation in hepatocytes. *Hepatology,* **48(3):** 799-807.

Endo, H., C. Nito, H. Kamada, F. Yu and P.H. Chan (2006). Akt/GSK3-β Survival Signaling is Involved in Acute Brain Injury After Subarachnoid Hemorrhage in Rats. Stroke, **37:** 2140-2146.

Engelhart, M.J., M.I. Geerlings, J. Meijer, A. Killiaan and A. Ruitenberg (2004). Van SJC Inflammatory proteins in plasma and the risk of dementia: the Rotterdam study. *Arch. Neurol.,* **61(5):** 668-672.

Ernest, P.S. and C.R. Virgina (2010). Epidemiology and Risk Factors of Cerebral Ischemia and Ischemic Heart Diseases: Similarities and Differences. *Curr. Cardiol. Rev.,* **6(3):** 138-149.

Fabbrini, E., S. Sullivan and S. Klein (2010). Obesity and Nonalcoholic Fatty Liver Disease: Biochemical, Metabolic, and Clinical Implications. *Hepatology,* **51(2):** 679-689.

Gonzalez, C.M. and C.A. Rodriguez (2011). Dietary phytochemicals and their potential effects on obesity: a review. *Pharmacology Research,* **64(5):** 438-455.

Harwood, H.J. (2012). The adipocyte as an endocrine organ in the regulation of metabolic homeostasis. *Neuropharmacol,* **63(1):** 57-75.

Hebert, L.E., P.A. Scherr and J.L. Bienias (2003). Alzheimer's disease in the U.S. population Prevalence estimates using the 2000 census. *Arch. Neurol.,* **60(8):** 1119-1122.

Ivan, C., T. Eric (2004). Convergence of atherosclerosis and Alzheimer's disease: inflammation, cholesterol, and misfolded proteins. Riview. *The Lancet,* **363:** 1140-1146.

Jana, P., P. Ambroza, B. Michal, P. Veronika, S. Omar, T. Hana, *et al*., (2012). Epidemiological of and risk factors for Alzheimer's disease: *A review, Biomed. Pap. Med. Fac. Univ Palacky Olomouc. Czech. Repub.,* **156(2):** 108-114.

Jeevendra, J.A., K. Masao and Y. Shingo (2008). Obesity-induced Insulin Resistance and Hyperglycemia. *Anesthesiol,* **109(1):** 137-48.

Karen, F.N., R. Leonel, P.N. Leonardo, F. Gonzalo, R. Paula and B.M. Ricardo (2008). Insulin Resistance and Alzheimer´s Disease: Molecular Links and Clinical Implications. *Curr. Alzheimer Res.,* **5(5):** 1-10.

Lee, J.M., M.C. Grabb, G.J. Zipfel and W.D. Choi (2000). Brain tissue response to ischemia. *J. Clin. Invest.,* **106(6):** 723-730.

Luigi, P., E. Rudolph, Tanzi and M.K. Dora (2003). Alzheimer's disease cholesterol connection. *Nat. Neuro sci.,* **6(4):** 345-351.

Martha, D.B., H. Evelyn, T.C. Victor, H.C. Michael and S. Lynn (2007). Cognitive impairment and pain management: Review of issues and challenges, *Journal of Rehabilitation Research and Development,* **44:** 315-330.

Monte, S.M. and J.R. Wands (2006). Molecular indices of oxidative stress and mitochondrial dysfunction occur early and often progress with severity of Alzheimer's disease. *J. Alzheimers Dis.,* **9(2):** 167-81.

Neumann, K.F., L. Rojo, L.P. Navarrete, G. Farias, P. Reyes and R.B. Maccioni (2008). Insulin resistance and Alzheimer's disease: molecular links and clinical implications. *Curr. Alzheimer Res.,* **5:** 438-47.

Puglielli, L., G. Konopka and E.C. Pack (2001). Acyl-coenzyme A: cholesterol acyltransferase modulates the generation of the amyloid beta-peptide. *Nat. Cell Biol.,* **3:** 905-912.

Rana, A., P. Avinash, L.H. Christian (2013). Influence of Obesity on Neurodegenerative Diseases. In Intech. Neurodegenerative Diseases, p. 382-402.

Rang, H.P., M.M. Dale, J.M. Ritter and R.J. Flower (2007). Rang and Dale's Pharmacology, 6th edition: 514-517.

Rita, B., L. Flora, R. Serafino, C. Nicoletta, F. Andrea (2012). Alzheimer's Disease Promotion by Obesity: Induced Mechanisms-Molecular Links and Perspectives. *Curr. Gerontol. Geriatr. Res.,* **2012:** 1-13.

Salinska, E., W. Danysz, J.W. Lazarewicz (2005). The role of excitotoxicity in neurodegeneration. *Folia Neuropathol,* **43(4):** 322-339.

Strachan, M.W., I.J. Deary, F.M. Ewing and B.M. Frier (1997). Is type II diabetes associated with an increased risk of cognitive dysfunction? A critical review of published studies. *Diabetes Care,* **20:** 438-45.

Sung, M.S., J.S. Hong and M.J. Inhee (2011). Insulin Resistance and Alzheimer's Disease. In Intech: Z. Mark, editor. Topics in the Prevention, Treatment and Complications of Type 2 Diabetes. p. 53-74.

Tzanetakou, I.P., N.L. Katsilambros and A. Benetos, D.P. Mikhailidis and D.N. Perrea (2012). "Is obesity linked to aging?": adipose tissue and the role of telomeres. *Ageing Res. Rev.,* **1(2):** 220-229.

Weisberg, S.P., D. McCann, M. Desai, M. Rosenbaum, R.L. Leibel and A.W. Ferrante (2003). Obesity is associated with macrophage accumulation in adipose tissue. *J. Clin. Invest.,* **112(12):** 1796-808.

Yaso, E., E.C. Lowri, J.T. Damian, A.D. Celeste, A.D. Smith and C. Kieran (2013). Human hippocampal energy metabolism is impaired during cognitive activity in a lipid infusion model of insulin resistance. *Brain and Behavior,* **3(2):** 134-144.