Alzheimer's Disease And Type 2 Diabetes: Exploring The Association To Obesity And Tyrosine Hydroxylase

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Abstract: Alzheimer's disease (AD) and type 2 diabetes mellitus (T2DM) are two debilitating health disorders afflicting millions worldwide. Recent research has revealed similarities between AD and T2DM. Both these protein conformational disorders are associated with obesity, insulin resistance, inflammation and endoplasmic reticulum stress, en-route initiation and/or stage aggravation. In this mini review we have tried to summarize studies describing obesity, insulin resistance and glucocorticoid imbalance as common patho-mechanisms in T2DM and AD. A reduction in tyrosine hydroxylase (TH) in the brain has been found to occur in Parkinson's disease (PD). AD, T2DM and PD share common risk factors like depression. Thus, whether TH is involved in the 'state of cognitive depression' that is the hallmark of AD and often accompanies PD and T2DM is also explored.

GENERAL INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most common metabolic diseases and, according to a report by the World Health Organization, it will impact a total population of 220 million worldwide by the year 2020 [1]. T2DM is considered to be a heterogeneous, multifactorial, polygenic disorder characterized by a defect in the biological actions of insulin (insulin resistance, IR) and in insulin secretion (a β cell secretory defect). Additionally, T2DM has been identified as a risk factor for Alzheimer's disease (AD) [2]. AD, a progressive neurodegenerative disorder, has been described as the pandemic of the 21st century [3]. An estimated 24 million people worldwide have been reported to be afflicted with dementia, the majority of who are thought to have AD [4]. Although T2DM increases the likelihood of AD, the exact mechanisms underpinning this remain to be fully elucidated. Recent research has shown that there are multiple similarities between T2DM and AD [5], and common physiological processes underlie both, including systemic inflammatory conditions, atherosclerosis, oxidative stress, progressive amyloidosis and other ageing-related processes [6]. Most of these processes are components of metabolic syndrome (MetS) [7, 8]. Thus, indirectly in the present review, the links between MetS and AD as well as T2DM have been explored.

OBESITY AND INSULIN RESISTANCE (IR)

Adiposity (obesity), referring to the presence of excess body fat (an increased amount of adipose tissue within the body), does not generally have any normal or ideal threshold value. It can be accurately quantified by underwater weighing and dual-energy X-ray absorption (DXA), and computed tomography as well as magnetic resonance imaging can assess body fat distribution. Such technology, however, is often too time consuming or costly to be routinely in clinical settings, and hence methods such as impedance analysis, skin-fold thickness or the determination of the body mass index (BMI) are commonly applied to estimate the level of obesity.

Adiposity, hyperinsulinemia, glucose intolerance, and T2DM, are related sequentially and often occur simultaneously, and understanding this relationship is fundamental in the study of the role of adiposity, IR, and T2DM in AD [9-12]. Abnormal glucose levels are caused by IR. IR is the resistance of tissues such as skeletal muscle, liver, adipocytes and pancreatic which dispose the glucose according to the actions of insulin. Another factor known to cause abnormal glucose level is the insufficiency in the pancreatic insulin secretion, at a normal level or higher than normal level (hyperinsulinemia) which assists to overcome IR in the tissues [13, 14]. IR is a primary contributory factor in the development of MetS. IR usually increases as a function of age. Continued IR may result in diminished capacity of pancreas to maintain a state of hyperinsulinemia leading either to glucose intolerance and T2DM in certain cases or to persistent hyperinsulinemia in others [14].

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Obesity is one of the most crucial determinants of IR [9, 15]. An elevated BMI has been associated with specific anterior hippocampal atrophy in AD [16] and in middle age with higher dementia risk [17, 18].

Insulin in AD: A strong correlation between hyperinsulinemia and an increased risk of AD has been reported [19-22]. But its mechanistic link to AD has not yet been elucidated fully. Insulin readily crosses the blood-brain barrier and along with insulin growth factor (IGF) exert myriad effects within the brain, epitomized by a modulation of cognition, neuronal growth, survival, differentiation, migration, metabolism, gene expression, protein synthesis, cytoskeletal assembly, synapse formation, and plasticity by binding to IGF receptors, most of which are concentrated in the cerebral cortex, olfactory bulb, hippocampus, cerebellum and hypothalamus [3, 23, 24]. Insulin and IGF-1 also regulate growth, survival and myelin production/ maintenance in oligodendrocytes [3, 23, 25]. Plausibly any impairment in insulin/ IGF-I signaling adversely affects neuronal and glial cell functions [23, 26]. Insulin appears also to be important for learning and memory as well as cognitive function, and abnormalities in insulin sensitivity promote cognitive impairment [24, 27]. The presence of a higher abundance of insulin receptors within the cognition pertinent areas of the brain is clearly indicative of a close association between insulin and cognition [28]. Cognitive impairment and dementia are known complications of diabetes mellitus [29]. Evidently neurotrophic at low concentrations, insulin at high concentrations may compete with amyloid-β peptide (Aβ) for insulin degrading enzyme (IDE) in the brain, including within the hippocampus, resulting in a decreased clearance of Aβ and a higher risk of AD [29]. Also, insulin has been reported to stimulate Aβ secretion, potentially causing excessive Aβ deposition in senile plaques [7].

Insulin and IGF-1 primarily mediate their effects by activating intrinsic receptor tyrosine kinases, which then phosphorylate insulin receptor substrate (IRS) proteins (at tyrosine residues) [26]. Tyrosine phosphorylated IRS interacts with various downstream molecules including the p85 regulatory subunit of phosphatidylinositol-3 kinase (PI3 kinase) [30]. PI3 kinase stimulates glucose transport [31] and inhibits mitochondrial DNA damage and apoptosis [32] by activating Akt/protein kinase B and inhibiting glycogen synthase kinase-3β (GSK-3β) [33]. Defective insulin and IGF signaling consequent to insulin/IGF resistance leads to decreased energy metabolism, manifested by reduced glucose uptake and ATP production [26, 34], which, in turn, adversely impacts active processes involved in cellular homeostasis, membrane permeability, and fundamental mechanisms required for synaptic maintenance and remodeling, which underpin learning and establishing new memory [26]. A decline in expression of insulin/IGF, their receptors and IRS proteins has been reported in AD patients. Such abnormal expression has also been shown to associate with progression of the disease [26]. In addition to a reduced expression of insulin/IGF receptors, AD patients have been described to have less insulin, IGF-1, and IGF-2 receptor binding [26, 35] than non- AD subjects, which may contribute to degenerative processes occurring within the brain and a correction of insulin levels has been correlated with improved cognition [3, 26, 36]. From this, it follows that insulin represents a common thread that links the pathologies of T2DM and AD.

Thus, as suggested by Rivera, EJ [36], the two main pathophysiological mechanisms responsible for brain insulin/IGF resistance in AD are: 1) a progressive loss of insulin/IGF responsive neurons, and 2) impaired insulin/IGF ligand-receptor binding. In this scenario AD can be considered as a brain specific form of diabetes characterized by insulin/IGF deficiency or resistance, and hence has been hailed as, "Type 3 Diabetes" [3, 35].

Insulin has been reported to promote hyper-phosphorylation of tau protein by increased activation of GSK-3β [7, 37]. An inhibition of PI3K/Akt and blocking of the Wnt signaling pathway - the negative regulator of GSK-3β – consequent to impaired insulin signaling, are responsible for pronounced activation of GSK [36]. Insulin/IGF resistance results in oxidative stress which can further activate GSK-3β [38]. Notably, increased oxidative stress is an established feature of both T2DM and AD. Unable to be transported in axons, hyper-phosphorylated *tau* aggregates to form neurofibrillary tangles within the neuronal perikarya, and thereby contributes to neurodegeneration [26, 39]. A very recent study has reported that brain IR (induced by peripheral IR) can mediate events in AD by yet a further unique mechanism: accelerating Aβ fibrillogenesis into toxic oligomers by inducing GM1 ganglioside clustering in the presynaptic membranes [40].

The formation and accumulation of advanced glycation end products (AGEs) (a further consequence of diabetes and adiposity) have also been identified immune-histochemically in senile plaques and neurofibrillary tangles, the pathologic hallmarks of AD [41] further corroborating the presumption of T2DM and AD linkage.

Obesity in AD: Obesity is a key cause of IR. Some 80% of obese people are insulin resistant [42]. Confounding data exists on the relationship between obesity and AD. A high BMI in mid-life has been correlated to a higher risk of dementia, unlike a lower BMI in late life. Hence, obesity or higher BMI in mid life is associated with the occurrence of AD in late life [43]. The elderly obese have a greater likelihood for expression of amyloid aggregates and neurofibrillary tangles [44]. An increased risk of neurodegenerative dementia among diabetic persons has also been reported [43]. In cognitively normal elderly individuals, a high BMI was found to be associated with lower brain volumes in hippocampus, orbital frontal complex and parietal lobes and also with a lower neuronal viability in frontal, parietal and temporal lobes [45, 46]. When this study was extended to patients with mild cognitive impairment and AD, Ho *et al.*, found an association between higher BMI and lower brain volumes in the occipital, frontal, temporal and parietal lobes [44]. Long-term follow up studies have revealed that obesity increases the risk of AD by 1.80 fold [47]. The fat mass and obesity associated (FTO) protein (also known as α-ketoglutarate-dependent dioxygenase) is an enzyme encoded by the *FTO* gene, which is one of the independent genetic loci controlling obesity [48]. It is highly expressed in the brain. Recently, a modest but significant reduction in brain volumes within the frontal and occipital lobes has been reported to be induced by the same FTO allele that predisposes individuals to obesity [48]. Whether

or not any association exists between AD and FTO polymorphisms has yet to be elucidated.

The mechanism(s) *via* which obesity may mediate AD progression are likely complex and remain to be fully clarified. In this regard, free fatty acids (FFA) have been studied as the crucial link between obesity, IR and hence AD [42, 49]. In obesity and IR, an uncontrolled activation of adipocyte hormone-sensitive lipase causes persistently high levels of FFA. Normalizing these FFA levels improves insulin sensitivity in obese individuals and high plasma FFA levels can predict diabetes progression [49]. FFA have been described to impact Aβ clearance by inhibiting IDE activity [50]. *In vitro*, FFA have been reported to stimulate an increased assembly of amyloid and tau filaments [51]. In this scenario, FFA are proinflammatory and are widely considered to mediate their effects through tumor necrosis factor-α (TNF-α). TNF-α is over expressed in adipose tissue, and its levels are inversely related to insulin sensitivity [49]. Elevated brain TNFα levels have been reported patients with AD and mild cognitive impairment [52]. TNFα has additionally been reported to inhibit Aβ blood-brain barrier transport from the brain to the periphery [53]. As reviewed by Frankola *et al.*, [54], the generation and release of TNF-α has been shown to stimulate an enhanced glial cellular expression of amyloid precursor protein (APP), from which Aβ is proteolytically cleaved *via* the action of β- and γ-secretase activities. In addition, the actions of this cytokine have been reported to upregulate the conversion of APP into pathological forms of Aβ peptides by stimulating γ-secretase activity. As microglia and astrocytes can become activated by the presence of amyloid plaques as well as by fibrillar Aβ, *via* a cell surface receptor complex through which microglial cells become activated and further increase their production of TNF-α, these biological actions thereby create the potential for a self-propagating cycle of APP induction, elevated Aβ generation, and further neuroinflam-mation and TNF-α generation with the potential to drive disease progression [54].

Cumulatively, TNF-α appears to increase accumulation of Aβ in the brain contributing to AD pathogenesis. Chronic inflammation has hence been postulated as commonality between AD and obesity by Puig *et al.* [55]. Mutations in the gene coding for APP are associated with an autosomal dominant form of AD. Quite strikingly, adipose tissue and adipocyte cell lines also express APP and increased levels of adipose APP and plasma Aβ (1-40) are found in obese individuals [56, 57]. A recent study evidenced an increased activation of microglial cells and macrophages and elevated neuronal and macrophage/adipocyte APP and TNF-α in adipose tissue and brain in animal model of obesity [55]. Obesity mediated modulations in expression of APP can be coordinated across various tissues. Hence APP plausibly can be considered to mediate pro-inflammatory changes in adipose as well as neuronal tissues contributing to AD [55].

Adipokines (epitomized by leptin and adiponectin produced by adipose tissue) are also correlated with IR and hyperinsulinemia [9]. Leptin is known to have roles in neuroprotection, brain development, cognition, learning and memory [9, 58], the processes affected severely in AD, and known reductions in leptin associated with obesity and IR would likely impact these.

CONTRIBUTION OF GLUCOCORTICOIDS TO IR AND TO AD

Results of multiple studies have revealed an association of adverse chronic stress (and concomitant elevated glucocorticoids) with AD and mood disorders such as depression [59-61]. Stress induces activation of the hypothalamic-pituitary-adrenal (HPA) axis which leads to an increased release of steroid hormones (glucocorticoids - mainly cortisol in man and corticosterone in rodents) from the adrenal cortex [62, 63]. The interrelationship of abnormal glucocorticoid levels and IR is implicated in AD [64]. Glucocorticoid excess results in IR *via* a negative impact on insulin action/sensitivity as well as insulin secretion [65, 66]. The effects of IR in the development of AD have already been summarized in the foregoing discussion. The interdependence of prevailing networks among T2DM, AD, IR and adiposity is depicted in Fig. (**1**). An extensive discussion of supportive experimental and epidemiological studies interrelating AD, T2DM, IR and obesity can be found in Milinois *et al.*, [7], Luchsinger *et al.*, [9], Hildreth *et al.*, [27], and Craft [49].

LINKING T2DM & AD TO PD: EXPLORING THE ROLE OF TH

Parkinson's disease (PD) is the most prevalent neurodegenerative movement disorder affecting more than 0.1% of the population older than 40 years of age [67]. PD is characterized by the accumulation of amyloid-like fibrils of α-synuclein in the form of Lewy body plaques in neurons of the substantia nigra, together with a loss of dopaminergic neurons and a tyrosine hydroxylase (TH) deficiency [68, 69]. The involvement of α-synuclein amyloidogenesis in various neurodegenerative disorders, including dementia associated with Lewy body disease, diffuse Lewy body disease and multiple system atrophy and AD, has been strongly implicated [70, 71].

A number of common risk factors have been suggested for PD, AD as well as T2DM, including but not limited to, oxidative stress, IR and inflammation [72, 73]. How TH integrates the pathology of the three has not been fully explored. TH catalyzes the hydroxylation of L-tyrosine to L-dihydroxyphenylalanine (L-DOPA), the rate-limiting step in the biosynthesis of the catecholamines dopamine, norepinephrine, and epinephrine. This iron-containing mixed function oxidase requires molecular oxygen and the cofactor tetrahydrobiopterin (BH4) for activity. TH is expressed mainly within specific brain areas and the adrenal medulla [74], and a central role for TH has been indicated by the non-viability of TH-knockout mice [75].

Clinical, experimental, genome wide association and transcriptomic studies have indicated a link between PD and T2DM [76, 77]. The substantia nigra genes described to be significantly up regulated in PD have known biological associations with cancer, diabetes and inflammation [78]. In a recent investigation of PD patients with and without dementia for glucose tolerance and IR, a significant correlation was found between impaired glucose tolerance, IR and T2DM in patients who had dementia [79]. The study suggested that PD patients with dementia are two times more likely to have IR than patients with PD [71]. T2DM has been
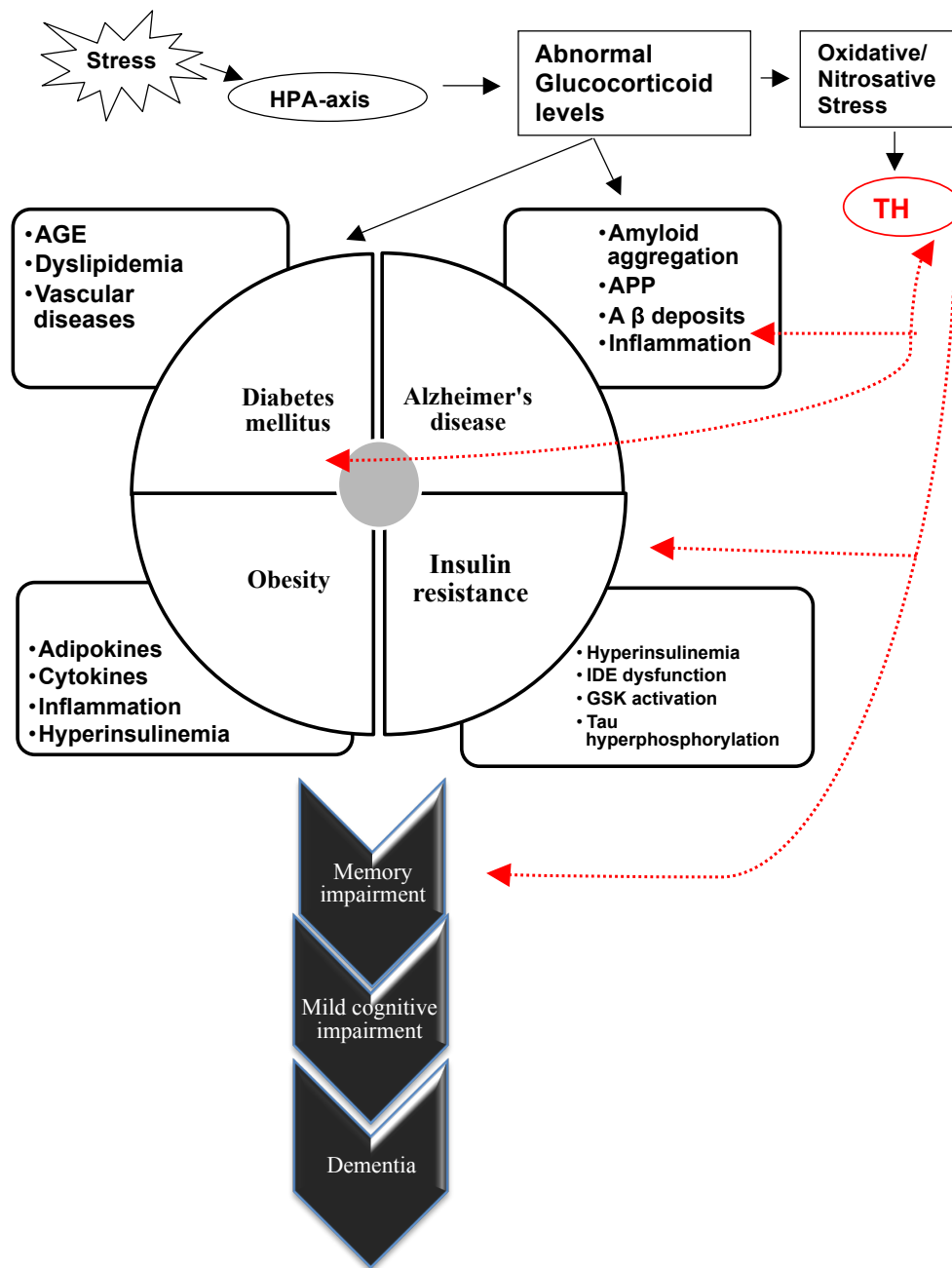
Fig. (1). The vicious circle: interdependence of obesity, IR, AD, T2DM. The most prominent features of each of the individual conditions have been indicated, yet the mechanisms of obesity, IR, diabetes and AD cannot be readily dissected. Eventually, they converge on memory impairment and dementia. The mechanisms by which TH (and hence PD) may be involved in the pathology of type 2 diabetes and Alzheimer's disease are shown by dashed line.

found to be associated with a higher risk of PD although the nature of this association remains unknown [80-83]. T2DM has also been suggested to be a potent risk factor for drug induced Parkinsonism [84]. Interestingly, a high fat diet (providing a model for early stage T2DM) has been described to disrupt nigrostriatal dopamine function, resulting in a decrease in dopamine release and clearance in experimental animals [85]. This suggests that T2DM may accompany a loss of dopamine function.

Albeit there is a lack of an established mechanism linking T2DM to PD, as in AD, both insulin deficiency and IR with

compensatory hyperinsulinemia might play a role [86, 87]. As already discussed, insulin can act as a neurotrophic factor within the brain and can reduce oxidative stress. IR has been shown to result in decreased insulin transport into the brain [28, 72, 77]. Insulin receptors are densely present within the substantia nigra and insulin increases dopamine transporter mRNA in the substantia nigra, thus regulating dopamine concentrations in the brain [28, 72, 77]. Microsatellite poly-morphisms of the TH gene, leading to disturbances in the TH and insulin variable number of tandem repeats (INS –VNTR), have also been found to have strong linkages with IR and depressive disorders [88].

Both IR and PD may be consequences of the aging process [67, 89], albeit the association of T2DM and PD with age remains controversial [80]. Other pathogenic mechanisms shared by diabetes and PD involve the (neuro) inflammatory and mitochondrial dysfunction pathways [90, 91]. Furthermore, recent studies support the hypothesis that the link between these two diseases might relate to the bioenergetic similarity of the midbrain substantia nigra and the pancreatic islet β-cells [28, 72, 77]. Here the oxidative/nirosative damage and inactivation of TH [92] consequent to diabetes as well as PD may provide the common link. Hypertension and cardiovascular factors, like increased blood cholesterol, are risk factors for both T2DM as well as PD [93-96]. However, additional extensive studies are required to substantiate the above reports.

The study of potential interrelations between AD and PD has likewise been an area of intense research [25]. Amyloid deposits, stress, redox imbalance, inflammation, and IR represent some of the common potentiating agents. Whether or not TH, one of the prime targets in PD [97], has some role to play in AD still remains a matter of conjecture. Cholinergic neurons are markedly dysfunctional in AD [98], as they are also in PD [99]. Recent advances have indicated the involvement of other neurotransmitter systems (additional to dysfunctional acetylcholine transmission) in cognitive dysfunction occurring in AD. Among these, the dopaminergic system appears to play a relevant role in the mechanisms involved in learning and memory processes, showing strong synaptic interactions and a neuromodulatory role with the cholinergic system in different brain areas [100-103]. A loss of temporal lobe dopamine D_2 receptors has been reported to correlate with memory dysfunction, and impaired dopamine transport and binding have been reported in several brain areas in AD [104-106]. These studies in large part support the work of Martorana *et al.* [107] in which L-DOPA administration restored considerable consistency in cortical activity in AD patients. An altered expression of receptor subtypes for dopamine in defined brain areas in AD patients has additionally been recently described [108], supporting the concept of a dopamine content deficit during the neurodegenerative process of the disease. A decline in TH activity and/or expression besides the L-DOPA receptor-transporter could also mediate the process, although remaining less explored – a mild loss of TH activity in AD was described in an early report by Torack and Morris [109]. Few studies have reported compensatory increases in TH mRNA expression in the regions of a significant noradrenergic neuronal loss [110]. Furthermore, TH has also been assumed to be linked to cardiovascular disorders through mechanisms common to AD (as well as T2DM); this possibility however still requires grounding in firm data [111]. Various possible points where TH may exert influence in AD and T2DM are illustrated in Fig. (**1**).

CONCLUSION

The contributory roles of IR, hyperinsulinemia, obesity and glucocorticoid imbalance and their interactions to T2DM and AD have begun to be defined. There is substantive evidence supporting a connection between the two disorders that is based upon findings from a diversity of studies.

Diabetes has also been suggested to be a risk factor for PD. An AD-PD link occurring through the dopaminergic neurotransmitter system has been hypothesized. However, there remains a lack of conclusive evidence on the association of AD-PD-T2DM. Certain biochemical cascades, like the involvement of TH, impaired HPA axis function, AGEs, and insulin regulated acetylcholine synthesis, remain to be further resolved. Nevertheless, it appears that the multiple pathways leading to these three disorders are likely interwoven *via* at least several common threads (such as insulin, IGF-1 and TH) yielding an overlapping network of alterations, and providing novel targets for therapy and biomarkers. The convergence of research into the arenas of AD, PD and T2DM, all individually important diseases, is providing a rich vein to mine and warrants significant further research.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

ABBREVIATIONS

AD	=	Alzheimer's disease
AGEs	=	Advanced glycosylation end products
APP	=	Amyloid-β precursor protein
Aβ	=	Amyloid-β peptide
BMI	=	Body mass index
CVD	=	Cardiovascular diseases
CNS	=	Central nervous system
FFA	=	Free fatty acids
FTO	=	Fat mass and obesity associated (FTO) protein or gene
GSK-3β	=	Glycogen synthase kinase-3β
HPA axis	=	Hypothalamic-pituitary-adrenal axis
IDE	=	Insulin degrading enzyme
IR	=	Insulin resistance
L-DOPA	=	L-dihydroxyphenylalanine
PD	=	Parkinson's disease
TH	=	Tyrosine hydroxylase
T2DM	=	Type 2 diabetes mellitus
TNFα	=	Tumor necrosis factor α

REFERENCES

[1]   Kumar, S.; Singh, R.; Vasudeva, N.; Sharma, S. Acute and chronic animal models for the evaluation of anti-diabetic agents. *Cardiovasc. Diabetol.*, **2012**, *11*(1), 9.

[2]   Kroner, Z. The relationship between alzheimer's disease and diabetes: type 3 diabetes? *Altern. Med. Rev.*, **2009**, *14*(4), 373-379.

[3]   Jellinger, K.A. Alzheimer 100 – highlights in the history of Alzheimer research. *J. Neural Transm.*, **2006**, *113*, 1603-23.

[4]   Ballard, C.; Gauthier, S.; Corbett, A.; Brayne, C.; Aarsland, D.; Jones, E. Alzheimer's disease. *Lancet*, **2011**, *377*(9770), 1019-1031.

[5]   Li, L.; Holscher, C. Common pathological processes in Alzheimer disease and type 2 diabetes. A review. *Brain Res. Rev.*, **2007**, *56*, 384-402.

[6]   Ahmed, I.; Goldstein, B.J. Cardiovascular risk in the spectrum of type 2 diabetes mellitus. *Mt. Sinai J. Med.*, **2006**, *73*, 759-768.

[7]   Milionis, H.J.; Florentin, M.; Giannopoulos, S. Metabolic Syndrome and Alzheimer's disease: A link to a vascular hypothesis? *CNS Spectr.*, **2008**, *13*(7), 606-613.

[8]   Banu, S.; Jabir, N.R.; Manjunath, C.N.; Shakil, S.; Kamal, M.A. C-peptide and itscorrelation to parameters of insulin resistance in the metabolic syndrome. *CNS Neurol. Disord. Drug Targets*, **2011**, *10*(8), 921-927.

[9]   Luchsinger J.A.; Gustafson D.R. Adiposity, type 2 diabetes and Alzheimer's disease. *J. Alzheimers Dis.*, **2009**, *16*(4), 693–704.

[10]   Poirier, P.; Giles, T.D.; Bray, G.A.; Hong, Y.; Stern, J.S.; Pi-Sunyer, F.X.; Eckel, R.H. Obesity and cardiovascular disease: Pathophysiology, evaluation, and effect of weight loss: An update of the 1997 American Heart Association scientific statement on obesity and heart disease from the Obesity Committee of the Council on Nutrition, PhysicalActivity, and Metabolism. *Circulation*, **2006**, *113*, 898–918.

[11]   Pi-Sunyer, F.X. The obesity epidemic: Pathophysiology and consequences of obesity. *Obes. Res.*, **2002**, *10*, 97-104.

[12]   Naderali, E.K.; Ratcliffe, S.H.; Dale, M.C. Obesity and Alzheimer's disease: a link between body weight and cognitive function in old age. *Am. J. Alzheimers Dis. Other Demen.*, **2010**, *24*(6), 445-449.

[13]   DeFronzo, R.A. Pharmacologic therapy for type 2 diabetes mellitus. *Ann. Intern. Med.*, **2000**, *133*, 73-74.

[14]   Festa, A.; Williams, K.; D'Agostino, R. Jr.; Wagenknecht, L.E.; Haffner, S.M. The Natural course of {beta}- cell function in nondiabetic and diabetic individuals: The insulin resistance atherosclerosis study. *Diabetes*, **2006**, *55*, 1114-1120.

[15]   Reaven, G. Insulin resistance, type 2 diabetes mellitus, and cardiovascular disease: the end of the beginning. *Circulation*, **2005**, *112*, 3030-3032.

[16]   Hoa, A.J.; Rajib C.A.; Saharana, P.; DeGiorgioa, A.; Madsena, S.K.; Hibara, D.P.; Steina, J.L.; Beckerd, J.T.; Lopezf, O.L.; Togaa, A.W.; Thompsona, P.M.; The Alzheimer's Disease Neuroimaging Initiative (ADNI). Hippocampal volume is related to body mass index in Alzheimer's disease. *Neuroreport*, **2011**, *22*(1), 10-14.

[17]   Whitmer, R.A.; Gunderson, E.P.; Barrett-Connor, E.; Quesenberry, C.P., Jr.; Yaffe, K. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. *BMJ*, **2005**, *330*(7504), 1360.

[18]   Anstey, K.J.; Cherbuin, N.; Budge, M.; Young, J. Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies. *Obes. Rev.*, **2011**, *12*(5), e426-e437.

[19]   Razay, G.; Wilcock, G.K. Hyperinsulinaemia and Alzheimer's disease. *Age Ageing.*, **1994**, *23*, 396-399.

[20]   Stolk, R.P.; Breteler, M.M.; Ott, A.; Pols, H.A.; Lamberts, S.W.; Grobbee, D.E.; Hofman, A. Insulin and cognitive function in an elderly population. The Rotterdam Study. *Diabetes Care*, **1997**, *20*, 792-795.

[21]   Ott, A.; Stolk, R.P.; van Harskamp, F.; Pols, H.A.; Hofman, A.; Breteler, M.M. Diabetes mellitus and the risk of dementia: The Rotterdam Study. *Neurology*, **1999**, *53*, 1937-1942.

[22]   Arvanitakis, Z.; Wilson, R.S.; Bienias, J.L.; Evans, D.A.; Bennett, D.A. Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. *Arch. Neurol.*, **2004**, *61*, 661-666.

[23]   D'Ercole, A.J.; Ye, P.; Calikoglu, A.S.; Gutierrez-Ospina, G. The role of the insulin- like growth factors in the central nervous system. *Mol. Neurobiol.*, **1996**, *13*, 227-255.

[24]   Martin, E.D.; Sa´nchez-Perez, A.; Trejo, J.L.; Martin-Aldana, J.A.; Cano Jaimez, M.; Pons, S.; Umanzor, C.A.; Menes, L.; White

[25]   M.F.; Burks, D.J. IRS-2 Deficiency impairs NMDA receptor-dependent long-term potentiation. *Cerebr. Cortex*, **2011**, doi:10.1093/cercor/bhr216.

[25]   Riederer, P.; Bartl J.; Laux, G.; Grunblatt, E. Diabetes type II: risk factor for depression-Parkinson-Alzheimer? *Neurotox. Res.*, **2011**, *19*, 253-265.

[26]   de la Monte, S.M. Insulin resistance and Alzheimer's disease. *BMB Rep.*, **2009**, *42*, 475-481.

[27]   Hildreth, K.L.; Van Pelt, R.E.; Schwartz, R.S. Obesity, Insulin resistance and Alzheimer's Disease. *Obesity* (*Silver Spring*), **2012**, doi: 10.1038/oby.2012.19.

[28]   Craft, S.; Watson, G.S. Insulin and neurodegenerative disease: shared and specific mechanisms. *Lancet Neurol.*, **2004**, *3*, 169-178.

[29]   Roriz-Filho, J.S.; Sá-Roriz, T.M.; Rosset, I.; Camozzato, A.L.; Santos, A.C.; Chaves, M.L.; Moriguti, J.C.; Roriz-Cruz, M. (Pre) diabetes, brain aging, and cognition. *Biochim. Biophys. Acta*, **2009**, *1792*(5), 432-443.

[30]   Sun, X.J.; Crimmins, D.L.; Myers, M.J.; Miralpeix, M.; White, M.F. Pleiotropic insulin signals are enInsulin resistance and AD Suzanne M. de la Monte 480 BMB *reports* http://bmbreports.org gaged by multisite phosphorylation of IRS-1. *Mol. Cell. Biol.*, **1993**, *13*, 7418-7428.

[31]   Lam, K.; Carpenter, C.L.; Ruderman, N.B.; Friel, J.C.; Kelly, K.L. The phosphatidylinositol 3-kinase serine kinase phosphorylates IRS-1. Stimulation by insulin and inhibition by Wortmannin. *J. Biol. Chem.*, **1994**, *269*, 20648-20652.

[32]   Halestrap, A.P.; Doran, E.; Gillespie, J.P.; O'Toole, A. Mitochondria and cell death. *Biochem. Soc. Trans.*, **2000**, *28*, 170-177.

[33]   Dudek, H.; Datta, S.R.; Franke, T.F.; Birnbaum, M.J.; Yao, R.; Cooper, G.M.; Segal, R.A.; Kaplan, D.R.; Greenberg, M.E. Regulation of neuronal survival by the serine- threonine protein kinase Akt [see comments]. *Science*, **1997**, *275*, 661-665.

[34]   de la Monte, S.M.; Wands J.R. Review of insulin and insulin-like growth factor expression, signaling, and malfunction in the central nervous system: relevance to Alzheimer's disease. *J. Alzheimers Dis.*, **2005**, *7*, 45-61.

[35]   Steen, E.; Terry, B.M.; Rivera, E.J.; Cannon, J.L.; Neely, T.R.; Tavares, R.; Xu, X.J.; Wands, J.R.; de la Monte, S.M. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease is this type 3 diabetes? *J. Alzheimers Dis.*, **2005**, *7*, 63-80.

[36]   Rivera, E.J.; Goldin, A.; Fulmer, N.; Tavares, R.; Wands, J.R.; de la Monte, S.M. Insulin and insulin-like growth factor expression and function deteriorate with progression of Alzheimer's disease: link to brain reductions in acetylcholine. *J. Alzheimers Dis.*, **2005**, *8*, 247-268.

[37]   Li, L., Holscher, C. Common pathological processes in Alzheimer disease and type 2 diabetes: a review. *Brain Res. Rev.*, **2007**, *56*, 384-402.

[38]   Chen, G.J.; Xu, J.; Lahousse, S.A.; Caggiano, N.L.; de la Monte, S.M. Transient hypoxia causes Alzheimer-type molecular and biochemical abnormalities in cortical neurons: potential strategies for neuroprotection. *J. Alzheimers Dis.*, **2003**, *5*, 209- 228.

[39]   Mandelkow, E.M.; Stamer, K.; Vogel, R.; Thies, E.; Mandelkow, E. Clogging of axons by tau, inhibition of axonal traffic and starvation of synapses. *Neurobiol. Aging*, **2003**, *24*, 1079-1085.

[40]   Yamamoto, N.; Matsubara, T.; Sobue, K.; Tanida, M.; Kasahara, R.; Naruse, K.; Taniura, H.; Sato, T.; Suzuki, K. Brain insulin resistance accelerates Aß fibrillogenesis by inducing GM1 ganglioside clustering in the presynaptic membranes. *J. Neurochem.*, **2012**, *121*(4), 619-628.

[41]   Yamagishi, S.; Nakamura, K.; Inoue, H.; Kikuchi, S.; Takeuchi, M. Serum or cerebrospinal fluid levels of glyceraldehyde-derived advanced glycation end products (AGEs) may be a promising biomarker for early detection of Alzheimer's disease. *Med. Hypotheses*, **2005**, *64*, 1205-1207.

[42]   Cornier, M.A.; Dabelea, D.; Hernandez, T.L.; Lindstrom, R.C.; Steig, A.J.; Stob, N.R.; Van Pelt, R.E.; Wang, H.; Eckel, R.H. The metabolic syndrome. *Endocr. Rev.*, **2008**, *29*(7), 777-822.

[43]   Qiu, C.; Kivipelto, M.; von Strauss, E. Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. *Dialogues Clin. Neurosci.*, **2009**, *11*, 111-128.

[44]   Ho, A.J.; Raji, C.A.; Becker, J.T.; Lopez, O.L.; Kuller, L.H.; Hua, X.; Lee, S.; Hibar, D.; Dinov, I.D.; Stein, J.L.; Jack Jr, C.R.; Weiner, M.W.; Toga, A.W.; Thompson, P.M.; The Cardiovascular

Health Study; The ADNI. Obesity is linked with lower brain volume in 700 AD and MCI Patients. *Neurobiol. Aging*, **2010**, *31*(8), 1326-1339.

[45]   Raji, C.A.; Ho, A.J.; Parikshak, N.N.; Becker, J.T.; Lopez, O.L.; Kuller, L.H.; Hua, X.; Leow, A.D.; Toga, A.W.; Thompson, P.M. Brain structure and obesity. *Hum. Brain Mapp.*, **2010**, *31*(3), 353-364.

[46]   Gazdzinski, S.; Millin, R.; Kaiser, L.G.; Durazzo, T.C.; Mueller, S.G.; Weiner, M.W.; Meyerhoff, D.J. BMI and neuronal integrity in healthy, cognitively normal elderly: a proton magnetic resonance spectroscopy study. *Obesity (Silver Spring)*, **2010**, *18*(4), 743-748.

[47]   Beydoun, M.A.; Beydoun, H.A.; Wang, Y. Obesity and central obesity as risk factors for incident dementia and its subtypes: a systematic review and meta-analysis. *Obes. Rev.*, **2008**, *9*, 204-218.

[48]   Bertram, L.; Heekeren, H. Obesity and the brain: a possible genetic link. *Alzheimer's Res. Ther.*, **2010**, *2*, 27.

[49]   Craft, S. The role of metabolic disorders in alzheimer disease and vascular dementia. *Arch. Neurol.*, **2009**, *66*(3), 300-305.

[50]   Bravata, D.M.; Wells, C.K.; Concato, J.; Kernan, W.N.; Brass, L.M.; Gulanski, B. I. Two measures of insulin sensitivity provided similar information in a US population. *J. Clin. Epidemiol.*, **2004**, *57*(11), 1214-1217.

[51]   Bray, G.A.; Lovejoy, J.C.; Smith, S.R.; DeLany, J.P.; Lefevre, M.; Hwang, D.; Ryan, D.H.; York, D.A. The influence of different fats and fatty acids on obesity, insulin resistance and inflammation. *J. Nutr.*, **2002**, *132*(9), 2488-2491.

[52]   Vessby, B.; Unsitupa, M.; Hermansen, K.; Riccardi, G.; Rivellese, A.A.; Tapsell, L.C.; Nälsén, C.; Berglund, L.; Louheranta, A.; Rasmussen, B.M.; Calvert, G.D.; Maffetone, A.; Pedersen, E.; Gustafsson, I.B.; Storlien, L.H.; KANWU Study. Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women: the KANWU Study. *Diabetologia*, **2001**, *44*(3), 312-319.

[53]   Lopez, S.; Bermu´dez, B.; Pacheco, Y.M.; Villar, J.; Abia, R.; Muriana, F.J. Distinctive postprandial modulation of beta cell function and insulin sensitivity by dietary fats: monounsaturated compared with saturated fatty acids. *Am. J. Clin. Nutr.*, **2008**, *88*(3), 638-644.

[54]   Frankola, K.A.; Greig, N.H.; Luo, W.; Tweedie, D. Targeting TNF-α to elucidate and ameliorate neuroinflammation in neurodegenerative diseases. *CNS Neurol. Disord. Drug Targets*. **2011**, *10*(3), 391-403.

[55]   Puig, K.L.; Floden, A.M.; Adhikari, R.; Golovko, M.Y.; Combs, C.K. Amyloid precursor protein and proinflammatory changes are regulated in brain and adipose tissue in a murine model of high fat diet-induced obesity. *PLoS ONE*, **2012**, *7*(1), e30378.

[56]   Lee, Y.H.; Martin, J.M.; Maple, R.L.; Tharp, W.G.; Pratley, R.E. Plasma amyloid- beta peptide levels correlate with adipocyte amyloid precursor protein gene expression in obese individuals. *Neuroendocrinology*, **2009**, *90*, 383-390.

[57]   Sommer, G.; Kralisch, S.; Lipfert, J.; Weise, S.; Krause, K.; Jessnitzer, B.; Lössner, U.; Blüher, M.; Stumvoll, M.; Fasshauer, M. Amyloid precursor protein expression is induced by tumor necrosis factor alpha in 3T3- L1 adipocytes. *J. Cell Biochem.*, **2009**, *108*, 1418-1422.

[58]   Johnston, J.M.; Greco, S.J.; Hamzelou, A.; Ashford, J.W.; Tezapsidis, N. Repositioning leptin as a therapy for Alzheimer's disease. *Therapy*, **2011**, *8*(5), 481- 490.

[59]   Rothman, S.M.; Mark, P. Mattson. Adverse stress, hippocampal networks, and alzheimer's disease. *Neuromol. Med.*, **2010**, *12*(1), 56-70.

[60]   Solas, M.; Aisa, B.; Mugueta, M.C.; Del Rio, J.; Tordera, R.M.; Ramirez, M.J. Interactions between age, stress and insulin on cognition: implications for alzheimer's disease. *Neuropsychopharmacology*, **2010**, *35*, 1664-1673.

[61]   Sotiropoulos, I.; Cerqueira, J.J.; Catania, C.; Takashima, A.; Sousa, N.; Almeida, O.F.X. Stress and glucocorticoid footprints in the brain- the path from depression to Alzheimer's disease. *Neurosci. Biobehav. Rev.*, **2008**, *32*, 1161-1173.

[62]   Nelson, D.H. Regulation of glucocorticoid release. *Am. J. Med.*, **1972**, *53*, 590-594.

[63]   Berton, O.; Nestler, E.J. New approaches to antidepressant drug discovery: beyond monoamines. *Nat. Rev. Neurosci.*, **2006**, *7*, 137-151.

[64]   Dhikav, V.; Anand, K.S. Glucocorticoids may initiate Alzheimer's disease: a potential therapeutic role for mifepristone (RU-486). *Med. Hypotheses*, **2007**, *68*, 1088-1092.

[65]   Amatruda, J.M.; Livingston, J.N.; Lockwood, D.H. Cellular mechanisms in selected states of insulin resistance: human obesity, glucocorticoid excess and chronic renal failure. *Diabetes Metab. Rev.*, **1985**, *1*, 293-317.

[66]   Delaunay, F.; Khan, A.; Cintra, A.; Davani, B.; Ling, Z.C.; Andersson, A.; Ostenson, C.G.; Gustafsson, J.; Efendic, S.; Okret, S. Pancreatic beta cells are important targets for the diabetogenic effects of glucocorticoids. *J. Clin. Invest.*, **1997**, *100*, 2094-2098.

[67]   Lees, A.J.; Hardy, J.; Revesz, T. Parkinson's disease. *Lancet*, **2009**, *373*, 2055-2066.

[68]   Nagatsu, T.; Sawada, M. Biochemistry of postmortem brains in Parkinson's disease: historical overview and future prospects. *J. Neural Transm.*, **2007**, *72*, 113-120.

[69]   Zafeiriou, D.I.; Willemsen, M.A.; Verbeek, M.M.; Vargiami, E.; Ververi, A.; Wevers, R. Tyrosine hydroxylase deficiency with severe clinical course. *Mol. Genet. Metab.*, **2009**, *97*(1), 18-20.

[70]   Spillantini, M.G.; Goedert, M. The a-Synucleinopathies: Parkinson's disease, dementia with lewy bodies, and multiple system atrophy. *Ann. NY Acad. Sci.*, **2000**, *920*, 16-27.

[71]   Hamilton, R.L. Lewy bodies in Alzheimer's disease: Aneuropathological review of 145 cases using a-Synuclein immunohistochemistry. *Brain Pathol.*, **2000**, *10*, 378- 384.

[72]   Cardoso, S.; Correia, S.; Santos, R.X.; Carvalho, C.; Santos, M.S.; Oliveira, C.R.; Perry, G.; Smith, M.A.; Zhu, X.; Moreira, P.I. Insulin is a two-edged knife on the brain. *J. Alzheimers Dis.*, **2009**, *18*(3), 483-507.

[73]   Reale, M.; Greig, N.H.; Kamal, M.A. Peripheral chemo-cytokine profiles in Alzheimer's and Parkinson's diseases. *Mini Rev. Med. Chem.*, **2009**, *9*(10), 1229-1241.

[74]   Cooper, J.R.; Bloom, F.E.; Roth, R.H. In: *The Biochemical Basis Of Neuropharmacology*; Oxford University Press: New York, **1996**, p. 230.

[75]   Zhou, Q-Y.; Qualfe, C.J.; Palmiter, R.D. Targeted disruption of the tyrosine hydroxylase gene reveals that catecholamines are required for mouse fetal development. *Nature*, **1995**, *374*, 640-643.

[76]   Moran, L.B.; Graeber, M.B. Towards a pathway definition of Parkinson´s disease: a complex disorder with links to cancer, diabetes and inflammation. *Neurogenetics*, **2008**, *9*, 1-13.

[77]   Cereda, E.; Barichella, M.; Pedrolli, C.; Klersy, C.; Cassani, E.; Caccialanza, R.; Pezzoli, G. Diabetes and risk of parkinson's disease: a systematic review and meta- analysis. *Diabetes Care*, **2011**, *34*, 2614-2623.

[78]   Loscalzo, J.; Kohane, I.; Barabasi, A.L. Human disease classification in the postgenomic era: a complex systems approach to human pathobiology. *Mol. Syst. Biol.*, **2007**, *3*, 124.

[79]   Bosco, D.; Plastino, M.; Cristiano, D.; Colica, C.; Ermiom C.; De Bartolom M.; Mungari, P.; Fonte, G.; Consoli, D.; Consoli, A.; Fava, A. Dementia is associated with Insulin Resistance in patients with Parkinson's Disease. *J. Neurol. Sci.*, **2012**, *315*(1-2), 39-43.

[80]   Xu, Q.; Park, Y.; Huang, X.; Hollenbeck, A.; Blair, A.; Schatzkin, A.; Chen, H. Diabetes and risk of Parkinson's disease. *Diabetes Care*, **2011**, *34*(4), 910-915.

[81]   Driver, J.A.; Smith, A.; Buring, J.E.; Gaziano, J.M.; Kurth, T.; Logroscino, G. Prospective cohort study of type 2 diabetes and the risk of Parkinson's disease. *Diabetes Care*, **2008**, *31*(10), 2003-2005.

[82]   D'Amelio, M.; Ragonese, P.; Callari, G.; Di Benedetto, N.; Palmeri, B.; Terruso, V.; Salemi, G.; Famoso, G.; Aridon, P.; Savettieri, G. Diabetes preceding Parkinson's disease onset. A case-control study. *Parkinsonism Relat. Disord.*, **2009**, *15*(9), 660-664.

[83]   Hu, G.; Jousilahti, P.; Bidel, S.; Antikainen, R.; Tuomilehto, J. Type 2 Diabetes and the Risk of Parkinson's Disease. *Diabetes Care*, **2007**, *30*(4), 842-847.

[84]   Ma, H.I.; Kim, J.H.; Chu, M.K.; Oh, M.S.; Yu, K.H.; Kim, J.; Hahm, W.; Kim, Y.J.; Lee, B.C. Diabetes mellitus and drug-induced Parkinsonism: a case-control study. *J. Neurol. Sci.*, **2009**, *284*(1-2), 140-143.

[85]   Morris, J.K.; Bomhoff, G.L.; Gorres, B.K.; Davis, V.A.; Kim, J.; Lee, P.P.; Brooks, W.M.; Gerhardt, G.A.; Geiger, P.C.; Stanford, J.A. Insulin resistance impairs nigrostriatal dopamine function. *Exp. Neurol.*, **2011**, *231*(1), 171-180.

[86]   Rönnemaa, E.; Zethelius, B.; Sundelöf, J.; Sundström, J.; Degerman-Gunnarsson, M.; Lannfelt, L.; Berne, C.; Kilander, L. Glucose metabolism and the risk of Alzheimer's disease and dementia: a population-based 12 year follow-up study in 71- year-old men. *Diabetologia*, **2009**, *52*, 1504-1510.

[87]   Rönnemaa, E.; Zethelius, B.; Sundelöf, J.; Sundström, J.; Degerman-Gunnarsson, M.; Lannfelt, L.; Berne, C.; Kilander, L. Impaired insulin secretion increases the risk of Alzheimer disease. *Neurology*, **2008**, *71*, 1065-1071.

[88]   Karakelides, H.; Irving, B.A.; Short, K.R.; O'Brien, P.; Nair, K.S. Age, obesity, and sex effects on insulin sensitivity and skeletal muscle mitochondrial function. *Diabetes*, **2010**, *59*, 89-97.

[89]   Chen, H.; O'Reilly, E.J.; Schwarzschild, M.A.; Ascherio, A. Peripheral inflammatory biomarkers and risk of Parkinson's disease. *Am. J. Epidemiol.*, **2008**, *167*, 90-95.

[90]   Chiba, M.; Suzuki, S.; Hinokio, Y.; Hirai, M.; Satoh, Y.; Tashiro, A.; Utsumi, A.; Awata, T.; Hongo, M.; Toyota, T. Tyrosine hydroxylase gene microsatellite polymorphism associated with insulin resistance in depressive disorder. *Metabolism*, **2000**, *49*(9), 1145-1149.

[91]   Song, I.U.; Kim, J.S.; Chung, S.W.; Lee, K.S. Is there an association between the level of highsensitivity C-reactive protein and idiopathic Parkinson's disease? A comparison of Parkinson's disease patients, disease controls and healthy individuals. *Eur. Neurol.*, **2009**, *62*, 99-104.

[92]   Blanchard-Fillion, B.; Souza, J.M.; Friel, T.; Jiang, G.C.T.; Vrana, K.; Sharov, V.; Barron, L.; Schoneich, C.; Quijano, C.; Alvarez, B.; Radi, R.; Przedborski, S.; Fernando, G.S.; Horwitz, J.; Ischiropoulos, H. Nitration and inactivation of tyrosine hydroxylase by peroxynitrite. *J. Biol. Chem.*, **2001**, *276*(49-7), 46017-46023.

[93]   Goldstein, L.B.; Gorelick, P.B.; Howard, G.; Kittner, S.J.; Manolio, T.A.; Whisnant, J.P.; Wolf, P.A. American Heart Association Prevention Conference. IV. Prevention and Rehabilitation of Stroke. Risk factors. *Stroke*, **1997**, *28*, 1507-1517.

[94]   Vermeer, S.E.; Prins, N.D.; den Heijer, T.; Hofman, A.; Koudstaal, P.J.; Breteler, M.M. Silent brain infarcts and the risk of dementia and cognitive decline. *N. Engl. J. Med.*, **2003**, *348*, 1215-1222.

[95]   Qiu, C.; Hu, G.; Kivipelto, M.; Laatikainen, T.; Antikainen, R.; Fratiglioni, L.; Jousilahti, P.; Tuomilehto, J. Association of blood pressure and hypertension with the risk of Parkinson disease: the National FINRISK Study. *Hypertension*, **2011**, *57*, 1094-1100.

[96]   Hu, G.; Antikainen, R.; Jousilahti, P.; Kivipelto, M.; Tuomilehto, J. Total cholesterol and the risk of Parkinson disease. *Neurology*, **2008**, *70*, 1972-1979.

[97]   Tabrez, S.; Jabir, N.R.; Shakil, S.; Greig, N.H.; Alam, Q.; Abuzenadah, A.M.; Damanhouri, G.A.; Kamal, M.A. A synopsis on the role of tyrosine hydroxylase in parkinson's disease. *CNS Neurol. Disord. Drug Targets,* **2012**, *11*(2). XX-XX.

[98]   Martorana, A.; Mori, F.; Esposito, Z.; Kusayanagi, H.; Monteleone, F.; Codeca, C.; Sancesario, G.; Bernardi, G.; Koch, G. Dopamine modulates cholinergic cortical excitability in alzheimer's disease patients. *Neuropsychopharmacology*, **2009**, *34*, 2323-2328.

[99]   Bohnen, N.I.; Albin, R.L. The cholinergic system and Parkinson disease. *Behav. Brain Res.*, **2011**, *221*(2), 564-673.

[100]   Blokland, A. Acetylcholine: a neurotransmitter for learning and memory? *Brain Res. Brain Res. Rev.*, **1995**, *21*, 285-300.

[101]   Cao, Y.J.; Surowy, C.S.; Puttfarcken, P.S. Different nicotinic acetylcholine receptor subtypes mediating striatal and prefrontal cortical [3H]dopamine release. *Neuropharmacology*, **2005**, *48*, 72-79.

[102]   Di Cara, B.; Panayi, F.; Gobert, A.; Dekeyne, A.; Sicard, D.; De Groote, L.; Millan, M.J. Activation of dopamine D1 receptors enhances cholinergic transmission and social cognition: a parallel dialysis and behavioural study in rats. *Int. J. Neuropsychopharmacol.*, **2007**, *10*, 383-399.

[103]   Millan, M.J.; Di Cara, B.; Dekeyne, A.; Panayi, F.; De Groote, L.; Sicard, D.; Cistarelli, L.; Billiras, R.; Gobert, A. Selective blockade of dopamine D(3) versus D(2) receptors enhances frontocortical cholinergic transmission and social memory in rats: a parallel neurochemical and behavioural analysis. *J. Neurochem.*, **2007**, *100*, 1047-1061.

[104]   Murray, A.M.; Weihmueller, F.B.; Marshall, J.F.; Hurtig, H.I.; Gottleib, G.L.; J Joyce, J.N. Damage to dopamine systems differs between Parkinson's disease and Alzheimer's disease with parkinsonism. *Ann. Neurol.*, **1995**, *37*, 300-312.

[105]   Pizzolato, G.; Chierichetti, F.; Fabbri, M.; Cagnin, A.; Dam, M.; Ferlin, G.; Battistin, L. Reduced striatal dopamine receptors in Alzheimer's disease: single photon emission tomography study with the D2 tracer [123I]-IBZM. *Neurology*, **1996**, *47*, 1065-1068.

[106]   Kemppainen, N.; Laine, M.; Laakso, M.P.; Kaasinen, V.; Nagren, K.; Vahlberg, T. Hippocampal dopamine D2 receptors correlate with memory functions in Alzheimer's disease. *Eur. J. Neurosci.*, **2003**, *18*, 149-154.

[107]   Martorana, A.; Stefani, A.; Palmieri, M.G.; Esposito, Z.; Bernardi, G.; Sancesario, G.; Pierantozzi, M. L-: dopa modulates motor cortex excitability in Alzheimer's disease patients. *J. Neural Transm.* **2008**, *115*, 1313-1319.

[108]   Kumar, U.; Patel, S.C. Immunohistochemical localization of dopamine receptor subtypes (D1R-D5R) in Alzheimer's disease brain. *Brain Res.*, **2007**, *1131*, 187- 196.

[109]   Torack, R.M.; Morris, J.C. Tyrosine hydroxylase-like (TH) immunoreactivity in Parkinson's disease and Alzheimer's disease. *J. Neural Transm. Park. Dis. Dement. Sect.*, **1992**, *4*(2), 165-171.

[110]   McMillan, P.J.; White, S.S.; Franklin, A.; Greenup, J.L.; Leverenz, J.B.; Raskin, A.M.; Szot, P. Differential response of the central noradrenergic nervous system to the loss of locus coeruleus neurons in Parkinson's disease and Alzheimer's disease. *Brain Res.*, **2011**, *10*(1373), 240-252.

[111]   Rao, F.; Zhang, L.; Wessel, J.; Zhang, K.; Wen, G.; Kennedy, B.P.; Rana, B.K.; Das, M.; Rodriguez-Flores, J.L.; Smith, D.W.; Cadman, P.E.; Salem, R.M.; Mahata, S.K.; Schork, N.J.;Taupenot, L.; Ziegler, M.G.; O'Connor, D.T. Tyrosine hydroxylase, the rate-limiting enzyme in catecholamine biosynthesis discovery of common human genetic variants governing transcription, autonomic activity, and blood pressure *in vivo. Circulation*, **2007**, *116*(9), 993- 1006.