REVIEW

Synopsis on the Linkage of Alzheimer's and Parkinson's Disease with Chronic Diseases

Nasimudeen R. Jabir,¹ Chelapram K. Firoz,¹ Saleh S. Baeesa,² Ghulam Md Ashraf,¹ Suhail Akhtar,³ Warda Kamal,⁴ Mohammad A. Kamal¹ & Shams Tabrez¹

¹ King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia

² Division of Neurosurgery, College of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

³ Center for Intestinal and Liver Inflammation Research, Stanley Manne Children's Research Institute, Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University, Chicago, IL, USA

⁴ Biomediotronics, Enzymoic, Hebersham, NSW, Australia

Keywords

Alzheimer's disease; Cancer; Cardiovascular disease; Neurodegenerative disorders; Parkinson's disease.

Correspondence

Dr. Shams Tabrez, King Fahd Medical Research Center, King Abdulaziz University, P. O. Box 80216, Jeddah 21589, Saudi Arabia.
Tel.: +966-2640-1000/2-5185;
Fax: +966-2695-2076;

E-mail: shamstabrez1@gmail.com

Received 4 June 2014; revision 25 September 2014; accepted 26 September 2014

SUMMARY

Neurodegeneration is the progressive loss of neuronal structure and function, which ultimately leads to neurological disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis, and Huntington's disease. Even after the recent significant advances in neurobiology, the above-mentioned disorders continue to haunt the global population. Several studies have suggested the role of specific environmental and genetic risk factors associated with these disorders. However, the exact mechanism associated with the progression of these disorders still needs to be elucidated. In the recent years, sophisticated research has revealed interesting association of prominent neurodegenerative disorders such as AD and PD with chronic diseases such as cancer, diabetes, and cardiovascular diseases. Several common molecular mechanisms such as generation of free radicals, oxidative DNA damage, aberrations in mitochondrial DNA, and dysregulation of apoptosis have been highlighted as possible points of connection. The present review summarizes the possible mechanism of coexistence of AD and PD with other chronic diseases.

doi: 10.1111/cns.12344

Introduction

Neurodegeneration and associated progressive loss of neuronal structure and function are the key causatives factors for some of the devastating neurological disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis, and Huntington's disease [1,2]. Despite the significant advances in neurobiology research, the above-mentioned disorders continue to rise with higher prevalence because of the lack of effective treatments till date [3,4]. Although several studies suggested the role of specific environmental and genetic risk factors, the exact mechanism(s) associated with the progression of these disorders still needs to be elucidated.

Aging and age-related disorders negatively impact health and the quality of life in humans. Biological aging is a complex multifactorial process proposed as the most important risk factor in the development of degenerative diseases such as AD, PD, cancer, diabetes, and cardiovascular diseases (CVD) [5]. Several physiological, genetic, and environmental factors that promote the aging process have been reported in the scientific literature [6]. However, the exact mechanism of aging is still obscure.

Several contributing pathways that control aging and longevity have been suggested previously. Among those biological pathways, fatty acid oxidation [7], γ -tocotrienol pathway [8], DNA repair [9], centrosome amplification [10], and PARP1 regulation [11] have been proposed to have significant effect on the longevity and aging process. In addition, the effect of environmental changes has also been reported as an important contributing factor toward aging [12]. Several studies have revealed the role of reactive oxygen species (ROS) in the regulation of aging [13–15]. Altogether, the above-mentioned pathological features also contribute to various disease conditions such as AD, PD, cancer, diabetes, and CVD.

In the recent years, sophisticated research has revealed interesting association of prominent neurodegenerative disorders (NDDs) such as AD and PD with other chronic diseases [16–18]. Several prevalent comorbid medical conditions such as cancer, diabetes, CVD, stroke, stress, seizures, osteoporosis, and renal disease have been also associated with AD and PD [19–22]. The increasing occurrence of comorbid conditions further worsens the neuropathological complications and significantly contributes to enhanced mortality [21,23]. The management of comorbid

medical conditions gained, recently in the development of novel strategies for the treatment of AD and PD.

Several common molecular mechanisms such as generation of free radicals, oxidative DNA damage, aberrations in mitochondrial DNA, dysregulation of apoptosis, and metabolism of co-enzyme Q10 have been highlighted in the scientific literature, which facilitate the association between NDDs and chronic diseases [24–29]. It is expected that these common mediators will significantly accelerate an universal common novel mechanism-based treatment strategy of NDDs and associated health issues. Although there are quite a few literatures evidences available linking individual NDDs with some other health issues and vice versa, the knowledge pertaining to various prominent NDDs with other important diseases is still not published. We have therefore compiled a comprehensive correlation of AD and PD with diabetes, cancer and CVD in the present manuscript, which we believe will aid in valuable development of common novel therapeutics.

Linkage between NDDs and Diabetes

Oxidative damage has been reported as the major causative factor for the two most prominent NDDs, AD and PD [26,30]. Several evidence such as increase in the levels of heavy metals, lipid peroxidation, certain proteins, and DNA oxidation has been reported that confirms the role of ROS in AD pathology [24]. The advanced glycation end products (AGEs) and decreased cytochrome c oxidase content in patients with AD have also supported the above observation [26]. A number of studies have suggested the association of ROS with PD, especially in dopamine cell degeneration—an important hallmark of PD [30,31]. There have been reports on two-way linkage between oxidative stress-induced hyperglycemia and vice versa. Some *in vivo* studies reported the appearance of oxidative stress-induced hyperglycemia even before the clinically apparent diabetic complications [32–34]. Hyperglycemia-induced diabetic complications have also been proposed to involve oxidative stress [35,36]. Hyperglycemia may activate other biochemical pathways associated with oxidative imbalance such as NF- κ B, NH₂-terminal Jun kinases/stress-activated protein kinases, p38 mitogen-activated protein (MAP) kinase, and hexosamine [34]. In addition, hyperglycemia could also cause overproduction of superoxides, the activation of AGEs, polyol pathway flux, and the activation of protein kinase C [32,37]. In one study, Simone *et al.* [38] suggested oxidative DNA damage in diabetes *via* tuberlin inactivation and downregulation of DNA repair enzyme 8-hydroxy-7,8-deoxyguanine (8-oxodG). They suggested 8-oxodG as a sensitive marker of ROS-induced DNA damage.

The role of apoptotic pathway has also been suggested in the scientific literature. Chronic hyperglycemia observed in diabetes promotes β -cell apoptosis either via Fas-mediated activation or modulation of the expression of multiple Bcl family proteins and the activation of the misfolded protein [39,40].

A number of cohort studies have been conducted to evaluate the risk of type 2 diabetes mellitus (T2DM) in the development of PD [41–46]. Most studies reported the absence of any preceding evidence of T2DM to PD. However, in many cases, both T2DM and PD have been diagnosed relatively at the same instance, thus suggesting a shared mechanism between both the diseases [42,43]. Moreover, certain cohorts also reported that T2DM

increases the risk of PD, but there is still no irrefutable evidence to prove it [44–46].

In a recent work on molecular mapping and functional analysis within human functional linkage network, a set of seven genes have been identified which were found to be affected in both PD and T2DM [47]. The upregulation of amyloid precursor protein (APP) gene could lead into neurodegenerative incidents in T2DM patients [47]. Recent studies on the reciprocal insulin and dopamine regulation sheds light on the comorbidity of T2DM and PD [18]. Peroxisome proliferator-activated receptor gamma co-activator 1- α (PGC-1 α) is a regulatory enzyme, which has a role in insulin resistance and mitochondrial respiration and could be targeted for an early intervention in PD cases. Their activation can prevent the dopaminergic neuron destruction caused by mutant α -synuclein [48,49]. Moreover, certain medications already in use for insulin resistance were found to be effective as PD-modifying agents, which also suggests a possible link between PD and T2DM [48].

The presence of AD and T2DM is reported to be prevalent in aged population. While AD is characterized by cerebral accumulation of amyloid β [50,51], T2DM is typified by the deposition of extracellular amylin in the pancreas, especially in β -cells [52,53]. Insulin resistance and deficits in the insulin signaling have been reported to be causative factor for T2DM and scientific literatures also support their role in AD pathology [33,54–56]. Two studies reported exaggerated AD pathologies such as tau phosphorylation and A β plaques in mice constructs designed with insulin deficient diabetes accompanied with APP overexpression [57,58]. These studies suggest that T1DM arising due to deregulated insulin-signaling cascades and can be a reason for AD development. In another study, Jolival *et al.* [59] studied the peripheral neuropathy as well as insulin signaling in sciatic nerve, keeping insulin deficiency and APP overexpression as two different traits. They noticed resembling pathological indices with accumulation of A β -immunoreactive protein in nerves of both models, which highlights the role of insulin signaling in neurodegenerative disease.

The presence of insulin and its receptors have been identified in human brain, and an alteration in their related action has been linked with approximately 20% of NDDs [60]. Moreover, high prevalence of diabetes in NDDs patients clearly indicates the link between insulin signaling and neuropathology [61]. In addition, remarkable similarity between insulin receptor (IRS) and insulin-like growth factor-1 receptor (IGF-1R) at several regions of brain could overlap signal transduction pathways and lead to same neuronal effects [62]. Altered insulin/insulin-like growth factor-1 (IGF-1) signaling has been also reported in postmortem AD brains [63,64], which leads to several pathological consequences such as reduction of IRS and receptor kinase activity markers, localization of both IRs and IGF-1Rs in AD neurons, and reduced levels of IRS-1 and IRS-2 (key adaptors for both IR and IGF-1R signaling) [62].

A β and its equilibrium states such as A β monomers and A β oligomers are well known as a pathologic triggering factor for AD. Recently, there has been report on association of insulin/IGF-1 receptor signaling with these monomers and oligomers [62]. A β oligomers are responsible for the downregulation of neuronal IRs and its monomers are responsible for the activation of insulin/IGF-1 signaling [65]. It has been reported in the scientific literature that IGF-1 regulates the process of A β clearance by enhancing

transport of A β carrier proteins into the brain [66]. In addition, insulin and IGF-1 have an indirect role in A β oligomerization by altering systemic conditions [62]. Stimulation of a receptor of the insulin/IGF-1 system promotes the reduction of oligomers to monomers via insulin degrading enzyme and results into the survival of developing neurons along with the protection of mature neurons against excitotoxic death [33,51,65]. Early defects in insulin/IGF-1 receptor signaling could lead to the depletion of A β monomers and ultimately lead to the pathological A β aggregation in the preclinical phase of AD. The above-mentioned facts related to the association between A β and insulin/IGF-1 receptor signaling clearly indicate the molecular link between AD and diabetes.

Linkage between NDDs and Cancer

In different types of cancer, oxidative stress-induced cellular redox imbalance has been reported as an important pathogenic mechanism [67–70]. The commencing step of carcinogenesis has been suggested via ROS-mediated permanent damage to DNA. Oxidative damage to DNA stimulates the cancer-associated biochemical events such as impaired cellular signal transduction, unregulated transcription, impaired DNA replication, and genomic instability [25,68,69]. Moreover, the cellular redox imbalance could also generate oxidized DNA products and lead to both mutagenic and carcinogenic effects [25,71]. Several modification in the bases and sugar backbone has been reported, and 8-oxodG have gained special attention in this case [26]. Recently, human Abelson murine leukemia viral oncogene homolog 1 (c-Abl) has been reported to be associated with ROS signaling by Gonfloni *et al.* [72]. They highlighted the linkage between c-Abl signaling and DNA damage. Moreover, the aberrant c-Abl activation is linked to many neurodegenerative disorders and cancer.

Apoptotic cell death has been considered as the key pathological feature of several chronic disorders [73]. During apoptosis, biochemical cascades are activated and secrete proteases which results into destruction of the cell. Several studies reported neuronal cell death as an important pathologic feature of human neurological disorders, including AD and PD [27,74,75]. Significant loss of neurons in AD is suggested due to the activation of apoptotic pathway [27]. Aberrant caspase activation could also play an important role in apoptosis, leading to progressive pathologic complications present in the different neurodegenerative disorder [76]. There have been many scientific reports on the predominant expression of apoptotic regulatory proteins such as p53, p16, and cyclin-dependent kinase 4 in AD neurons [28,77]. Apoptosis has also been proposed as one of the insulting signals for the neuronal loss observed in PD [78]. Increased levels of apoptosis promoting proteins such as BAX, cytochrome *c*, and pro-caspase 9 have also been reported in postmortem PD neurons [78]. It is well-known fact that cancer involves an unprogrammed cell death, with various reputable scientific reviews already available on the role of apoptotic pathway in cancer. Keeping this in our mind, we are skipping this part in the present manuscript.

Epidemiological study on the association between AD and cancer is limited. However, there are accumulating evidences that points toward some common molecular mechanisms which could lead to the development of both AD and cancer [16,79,80]. Amyloid precursor protein (APP)-mediated generation of A β peptides

are the key pathological mechanism of AD [81]. The upregulation of APP in solid tumors points its potential role in cancer cell growth as well [17]. In one study, Takagi *et al.* [82] reported the activation of androgen-induced gene by APP, which promotes proliferation of breast carcinoma cells. We believe that the mechanisms of tumor genesis by APP could be a potential area of research in future studies. In addition, Luo *et al.* [83] reported similar role of heat shock protein 90 (Hsp90) in both cancer and neurodegeneration. They suggested that the process of normal to malignant cellular transformation includes several dysregulated processes (via binding with aberrant proteins) along with different signaling molecules viz. chaperones. They also suggested Hsp90 as an important pathologic contributor of accumulation and progression of dysregulated events observed in AD [83].

Common pathogenic mechanisms observed in PD and cancer have renewed the interest of scientific community toward the linkage between these disorders. Some well-designed epidemiological studies reported the association of PD and melanoma [84,85]. There are already reports on some common genetic pattern between PD and cancer [86,87]. PD-associated genes such as PARK1, PARK2 and α -synuclein have been reported to be associated with human cancer [87]. Similarly, mutation of tumor-suppressor gene PTEN has also been reported be associated with PD [88]. Recently, Kareus *et al.* [89] reported a significantly increased risk of prostate cancer in the patients with PD and their relatives. These observations further confirm genetic association between PD and prostate cancer.

Cell cycle events and its regulation have been attributed to several chronic disorders such as CVD, AD, and cancer. The strong neurobiological linkage between AD and cancer has been reported via cell cycle activation [90,91]. Even though neurons do not enter into the replicating phase of cell cycle, it eventually leads to the process of apoptosis through neuronal cell cycle reentry. AD leads to dysfunction in the neuronal cell cycle reentry. In the cultured neurons, synthetic A β reproduces the neuronal cell cycle reentry in transgenic AD model [92,93]. The ectopic reactivation of cell cycle in AD neurons could also lead to synaptic failure, which ensures cognitive deficits and precede neuronal death [92,93].

The expression of cell cycle proteins (viz. p16, p27, CDK4, histone H3) and aberrant replicative DNA synthesis has been observed in neuronal populations fated to degenerate in the AD brain [94,95]. Aberrant neuronal growth via mitogenic pathways is activated during early AD and has been also proposed as one of the pathologic mechanism of AD [96–98]. Cell cycle disturbances through inappropriate reactivation of the cell cycle have also been suggested as an early and important event in the development of AD [99]. Localization of various cell cycle control elements such as cyclins, cyclin-dependent kinases, and cyclin inhibitors in neurons could lead to cell cycle dysregulation and ultimately results into neurodegeneration. The above-mentioned mechanism is also an important hallmark of cancer, early cell cycle pathophysiology in AD may recruit oncogenic signal transduction mechanisms, which suggests the linkage between cancer and AD [100].

A therapeutic agent, bexarotene has been reported in the literature for its promising chemopreventive efficacy via cell cycle progression blockage and apoptosis induction [101]. Bexarotene is a retinoid X receptor agonists approved by the US Food and Drug

Administration [102,103]. Cell cycle regulating activity and blood–brain barrier permeability of bexarotene make it as an excellent drug candidate for the CNS disorders as well. Recently, Cramer *et al.* [104] reported an enhanced clearance rate of A β within hours after oral administration of bexarotene in mouse model of AD, which clearly indicate its potential as an antineoplastic as well as neuroprotecting agents. Inhibition of cell cycle regulating agents such as cyclin-dependent kinase (CDK) has been suggested for the treatment of cancer in the literature. Flavopiridol (CDK inhibitor) has been reported as an important antiproliferative agent for the treatment of cancer [105]. The same flavopiridol has also been reported for its role in the inhibition of CDK5, which is active only in neuronal cells [106]. As CDK5 activity and its regulation have been associated with neurodegenerative diseases such as AD and PD, CDK5 inhibitors could play an important role in the development of novel therapeutic agent against both AD and cancer [107].

Linkage between NDDs and CVD

Reactive oxygen species-mediated cardiovascular tissue injury in cardiac and vascular myocytes is suggested as a key causative agent of CVD and associated conditions such as atherosclerosis, ischemic heart disease, hypertension, and congestive heart failure [108,109]. Some studies have reported that ROS-mediated endothelial dysfunction that leads to the disruption of vascular wall microenvironment is one of the significant pathological factors for CVD [110–112]. The destruction of nitric oxide by ROS and blockage of associated pathways have been suggested as the possible reason behind endothelial dysfunction [113]. The decline in endothelium-dependent vaso-relaxation promotes platelet adhesion and deposition of platelets on the endothelial surface and ultimately leads to cardiovascular complications [113].

Apoptotic pathways also play a role in cardiac diseases and have been considered as a novel treatment target to inhibit heart failure [114]. Previously, human and animal studies suggested cardiomyocyte apoptosis-mediated heart failure via downregulation of apoptosis protein inhibitors [114–116].

The association of CVD and vascular dementia is an area of research since long [117–119]. Certain lifestyle risk factors such as smoking have a profounding effect on CVD and are suspected to have a role in AD as well [120–122]. Hypertension is another proven risk factor for CVD and is reported to accelerate the tau-related pathology in neurodegenerative disorders [123]. Similarly, other common risk factors for CVD viz. hypercholesterolemia, hyperglycemia, inflammatory responses, and oxidative stress are also thought to be related to AD pathology [51,124]. Modifications of CVD risk factors, proper management, and nutritional strategies could limit future AD incidence [33,125]. A possible linkage between AD and PD with other diseases such as cancer, T2DM, and CVD has been demonstrated in Figure 1.

Cardiac failure is often associated with the elderly onset of PD and its prevalence has been suggested twice compared with the normal population [126]. Although brain and heart tissues vary significantly in their structure and function, their unique high-energy demand makes them rely heavily on mitochondrial energy packs [127]. Recent findings depicted the association of mitofusin 2 (Mfn2), a key functional element in heart mitophagy with two

Figure 1 Diagram for possible presentation of linkage between Alzheimer's disease (AD) and Parkinson's disease (PD) with other chronic diseases such as cancer, type 2 diabetes mellitus (T2DM), and cardiovascular diseases (CVD). ERF, GRF, CCA, and mDNA represent for environmental risk factors, genetic risk factors, cell cycle activation, and mitochondrial DNA, respectively.

other PD-associated factors, PINK1 and Parkin [128]. The mitophagy in heart tissue is naturally programmed to keep up with the demand of unique energy system [129]. The phosphorylation of Mfn2 by PINK1 on the mitochondrial walls facilitates Parkin-induced ubiquitination and clears the ailing mitochondria [130]. Chances of mutation in either PINK1 or Parkin or both might result into mitophagy impairment and associated consequences [131].

Another cardinal feature in PD is orthostatic hypotension (OH), which is referred as consistent fall in both systolic and diastolic blood pressures upon postural variation [132]. Approximately 30–40% of patients with PD exhibit these phenomena and most of them have been observed with cardiac noradrenergic denervation [133]. These autonomic nervous defects precede other motor manifestations in PD and can be identified early using proper neuroimaging techniques as well as by measuring low baroreflex-cardiovascular gain [134].

Future Prospective and Conclusion

Based on our manuscript, it can be easily stated that there are indeed some linkage between neurological disorders and chronic diseases. Keeping in mind, the previously suggested mechanistic association by the researchers, extensive research works are required to decipher the exact mechanistic aspects of these associations to develop a common treatment targets against these devastating diseases.

Acknowledgments

This work was supported by the NSTIP Strategic Technologies Program in the Kingdom of Saudi Arabia—Project No (11-BIO-2020-03). The authors also acknowledge with thanks Science and Technology Unit, King Abdulaziz University for technical support.

Conflict of Interest

The authors declare no conflict of interest.

References

- Cannon JR, Greenamyre JT. The role of environmental exposures in neurodegeneration and neurodegenerative diseases. *Toxicol Sci* 2011;**124**:225–250.
- Son JH, Shim JH, Kim K-H, Ha J-Y, Han JY. Neuronal autophagy and neurodegenerative diseases. *Exp Mol Med* 2012;**44**:89–98.
- Robillard JM, Federico CA, Tairyan K, Ivanson AJ, Illes J. Untapped ethical resources for neurodegeneration research. *BMC Med Ethics* 2011;**12**:9.
- Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer's disease. *Lancet* 2011;**377**:1019–1031.
- Ergin V, Hariry RE, Karasu C. Carbonyl stress in aging process: Role of vitamins and phytochemicals as redox regulators. *Aging Dis* 2013;**4**:276–294.
- Tosato M, Zamboni V, Ferrini A, Cesari M. The aging process and potential interventions to extend life expectancy. *Clin Interv Aging* 2007;**2**:401–412.
- Lee SH, Lee SK, Paik D, Min KJ. Overexpression of fatty-acid- β -oxidation-related genes extends the lifespan of drosophila melanogaster. *Oxid Med Cell Longev* 2012;**2012**:854502.
- Makpol S, Zainuddin A, Chua KH, Mohd Yusof YA, Ngah WZW. Gamma-Tocotrienol modulated gene expression in senescent human diploid fibroblasts as revealed by microarray analysis. *Oxid Med Cell Longev* 2013;**2013**:454328.
- Leclère R, Torregrosa-Muñumer R, Kireev R, et al. Effect of estrogens on base excision repair in brain and liver mitochondria of aged female rats. *Biogerontology* 2013;**14**:383–394.
- Ohshima S. Centrosome aberrations associated with cellular senescence and p53 localization at supernumerary centrosomes. *Oxid Med Cell Longev* 2012;**2012**:217594.
- Mangerich A, Bürkle A. Pleiotropic cellular functions of PARP1 in longevity and aging: Genome maintenance meets inflammation. *Oxid Med Cell Longev* 2012;**2012**:321653.
- de Magalhães JP, Wuttke D, Wood SH, Plank M, Vora C. Genome-environment interactions that modulate aging: Powerful targets for drug discovery. *Pharmacol Rev* 2012;**64**:88–101.
- Reid MB, Durham WJ. Generation of reactive oxygen and nitrogen species in contracting skeletal muscle: Potential impact on aging. *Ann N Y Acad Sci* 2002;**959**:108–116.
- Jackson MJ. Interactions between reactive oxygen species generated by contractile activity and aging in skeletal muscle? *Antioxid Redox Signal* 2013;**19**:804–812.
- Jackson MJ, McArdle A. Age-related changes in skeletal muscle reactive oxygen species generation and adaptive responses to reactive oxygen species. *J Physiol* 2011;**589**:2139–2145.
- Roe CM, Fitzpatrick AL, Xiong C, et al. Cancer linked to Alzheimer disease but not vascular dementia. *Neurology* 2010;**74**:106–112.
- Venkataramani V, Rossner C, Iffland L, et al. Histone deacetylase inhibitor valproic acid inhibits cancer cell proliferation via down-regulation of the Alzheimer amyloid precursor protein. *J Biol Chem* 2010;**285**:10678–10689.
- Lima MMS, Targa ADS, Noseda ACD, et al. Does Parkinson's disease and type-2 diabetes mellitus present common pathophysiological mechanisms and treatments? *CNS Neurol Disord Drug Targets* 2014;**13**:418–428.
- Doraiswamy PM, Leon J, Cummings JL, Marin D, Neumann PJ. Prevalence and impact of medical comorbidity in Alzheimer's disease. *J Gerontol A Biol Sci Med Sci* 2002;**57**:M173–M177.
- Zamrini E, Parrish JA, Parsons D, Harrell LE. Medical comorbidity in black and white patients with Alzheimer's disease. *South Med J* 2004;**97**:2–6.
- Qiu C, Hu G, Kivipelto M, et al. Association of blood pressure and hypertension with the risk of Parkinson disease: The National FINRISK Study. *Hypertension* 2011;**57**:1094–1100.
- Duthie A, Chew D, Soiza RL. Non-psychiatric comorbidity associated with Alzheimer's disease. *QJM* 2011;**104**:913–920.
- Larson EB, Shadlen M-F, Wang L, et al. Survival after initial diagnosis of Alzheimer disease. *Ann Intern Med* 2004;**140**:501–509.
- Uttara B, Singh AV, Zamboni P, Mahajan RT. Oxidative stress and neurodegenerative diseases: A review of upstream and downstream antioxidant therapeutic options. *Curr Neuroparmacol* 2009;**7**:65–74.
- Acharya A, Das I, Chandhok D, Saha T. Redox regulation in cancer. *Oxid Med Cell Longev* 2010;**3**:23–34.
- Pala FS, Gürkan H. The role of free radicals in ethiopathogenesis of diseases. *Adv Mol Biol* 2008;**1**:1–9.
- Friedlander RM. Apoptosis and caspases in neurodegenerative diseases. *N Engl J Med* 2003;**348**:1365–1375.
- Kitamura Y, Shimohama S, Kamoshima W, Matsuoka Y, Nomura Y, Taniguchi T. Changes of p53 in the brains of patients with Alzheimer's disease. *Biochem Biophys Res Commun* 1997;**232**:418–421.
- Dhanasekaran M, Ren J. The emerging role of coenzyme Q-10 in aging, neurodegeneration, cardiovascular disease, cancer and diabetes mellitus. *Curr Neurovasc Res* 2005;**2**:447–459.
- Khan MS, Tabrez S, Priyadarshini M, Priyamvada S, Khan MM. Targeting Parkinson's – tyrosine hydroxylase and oxidative stress as points of interventions. *CNS Neurol Disord Drug Targets* 2012;**11**:369–380.
- Thomas B, Beal MF. Parkinson's disease. *Hum Mol Genet* 2007;**16**:R183–R194.
- Evans JL, Goldfine ID, Maddux BA, Grodsky GM. Are oxidative stress-activated signaling pathways mediators of insulin resistance and β -cell dysfunction? *Diabetes* 2003;**52**:1–8.
- Rösen P, Nawroth PP, King G, Möller W, Tritschler HJ, Packer L. The role of oxidative stress in the onset and progression of diabetes and its complications: A summary of a Congress Series sponsored by UNESCO-MCBN, the American Diabetes Association and the German Diabetes Society. *Diabetes Metab Res Rev* 2001;**17**:189–212.
- Koya D, King GL. Protein kinase C activation and the development of diabetic complications. *Diabetes* 1998;**47**:859–866.
- Giacco F, Brownlee M. Oxidative stress and diabetic complications. *Circ Res* 2010;**107**:1058–1070.
- Kamal MA, Priyamvada S, Anbazhagan AN, Jabir NR, Tabrez S, Greig NH. Linking Alzheimer's disease and type 2 diabetes mellitus via aberrant insulin signaling and inflammation. *CNS Neurol Disord Drug Targets* 2014;**13**:338–346.
- Folli F, Corradi D, Fanti P, et al. The role of oxidative stress in the pathogenesis of type 2 diabetes mellitus micro- and macrovascular complications: Avenues for a mechanistic-based therapeutic approach. *Curr Diabetes Rev* 2011;**7**:313–324.
- Simone S, Gorin Y, Velagapudi C, Abboud HE, Habib SL. Mechanism of oxidative DNA damage in diabetes. *Diabetes* 2008;**57**:2626–2636.
- Johnson JD, Luciani DS. Mechanisms of pancreatic beta-cell apoptosis in diabetes and its therapies. *Adv Exp Med Biol* 2010;**654**:447–462.
- Maedler K, Donath MY. Beta-cells in type 2 diabetes: A loss of function and mass. *Horm Res* 2004;**62**:67–73.
- Palacios N, Gao X, McCullough ML, et al. Obesity, diabetes, and risk of Parkinson's disease. *Mov Disord* 2011;**26**:2253–2259.
- Sun Y, Chang Y-H, Chen H-F, Su Y-H, Su H-F, Li C-Y. Risk of Parkinson disease onset in patients with diabetes: A 9-year population-based cohort study with age and sex stratifications. *Diabetes Care* 2012;**35**:1047–1049.
- Driver JA, Smith A, Buring JE, Gaziano JM, Kurth T, Logroscino G. Prospective cohort study of type 2 diabetes and the risk of Parkinson's disease. *Diabetes Care* 2008;**31**:2003–2005.
- Hu G, Jousilahti P, Bidel S, Antikainen R, Tuomilehto J. Type 2 diabetes and the risk of Parkinson's disease. *Diabetes Care* 2007;**30**:842–847.
- Cereda E, Barichella M, Pedrollo C, et al. Diabetes and risk of Parkinson's disease: A systematic review and meta-analysis. *Diabetes Care* 2011;**34**:2614–2623.
- Xu Q, Park Y, Huang X, et al. Diabetes and risk of Parkinson's disease. *Diabetes Care* 2011;**34**:910–915.
- Santiago JA, Potashkin JA. Integrative network analysis unveils convergent molecular pathways in Parkinson's disease and diabetes. *PLoS One* 2013;**8**:e83940.
- Aviles-Olmos I, Limousin P, Lees A, Foltynic T. Parkinson's disease, insulin resistance and novel agents of neuroprotection. *Brain* 2013;**136**:374–384.
- Zheng B, Liao Z, Locascio JJ, et al. PGC-1 α , a potential therapeutic target for early intervention in Parkinson's disease. *Sci Transl Med* 2010;**2**:52ra73.
- Upadhya AR, Kosterin I, Kumar S, et al. Biochemical stages of amyloid- β peptide aggregation and accumulation in the human brain and their association with symptomatic and pathologically preclinical Alzheimer's disease. *Brain* 2014;**137**:887–903.
- Jabir NR, Kamal MA, Abuzenadah AM, et al. Alzheimer's and type 2 diabetes treatment via common enzyme targeting. *CNS Neurol Disord Drug Targets* 2014;**13**:299–304.
- Mushtaq G, Khan JA, Kumosani TA, Kamal MA. Alzheimer's disease and type 2 diabetes via chronic inflammatory mechanisms. *Saudi J Biol Sci* 2014. In Press: DOI: 10.1016/j.sjbs.2014.05.1003.
- Costes S, Langen R, Gurlo T, Matveyenko AV, Butler PC. β -cell failure in type 2 diabetes: A case of asking too much of too few? *Diabetes* 2013;**62**:327–335.
- Bomfim TR, Forgy-Germano L, Sathler LB, et al. An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease-associated A β oligomers. *J Clin Invest* 2012;**122**:1339–1353.
- Devi L, Alldred MJ, Ginsberg SD, Ohno M. Mechanisms underlying insulin deficiency-induced acceleration of β -amyloidosis in a mouse model of Alzheimer's disease. *PLoS One* 2012;**7**:e32792.
- Ho L, Qin W, Pompl PN, et al. Diet-induced insulin resistance promotes amyloidosis in a transgenic mouse model of Alzheimer's disease. *FASEB J* 2004;**18**:902–904.
- Jolival CG, Hurford R, Lee CA, Dumaop W, Rockenstein E, Masliah E. Type 1 diabetes exaggerates features of Alzheimer's disease in APP transgenic mice. *Exp Neurol* 2010;**223**:422–431.

58. Wang X, Zheng W, Xie J-W, et al. Insulin deficiency exacerbates cerebral amyloidosis and behavioral deficits in an Alzheimer transgenic mouse model. *Mol Neurodegener* 2010;**5**:46.
59. Jolivald CG, Calcott NA, Masliah E. Similar pattern of peripheral neuropathy in mouse models of type 1 diabetes and Alzheimer's disease. *Neuroscience* 2012;**202**:405–412.
60. Candeias E, Duarte AI, Carvalho C, et al. The impairment of insulin signaling in Alzheimer's disease. *IUBMB Life* 2012;**64**:951–957.
61. Janson J, Laedike T, Parisi JE, O'Brien P, Petersen RC, Butler PC. Increased risk of type 2 diabetes in Alzheimer disease. *Diabetes* 2004;**53**:474–481.
62. Giuffrida ML, Tomasello F, Caraci F, Chiechio S, Nicoletti F, Copani A. Beta-amyloid monomer and insulin/IGF-1 signaling in Alzheimer's disease. *Mol Neurobiol* 2012;**46**:605–613.
63. Frölich L, Blum-Degen D, Bernstein HG, et al. Brain insulin and insulin receptors in aging and sporadic Alzheimer's disease. *J Neural Transm* 1998;**105**:423–438.
64. Steen E, Terry BM, Rivera EJ, et al. 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.
65. Zhao W-Q, Lacor PN, Chen H, et al. Insulin receptor dysfunction impairs cellular clearance of neurotoxic oligomeric A β . *J Biol Chem* 2009;**284**:18742–18753.
66. Carro E, Trejo JL, Gomez-Isla T, LeRoith D, Torres-Aleman I. Serum insulin-like growth factor I regulates brain amyloid-beta levels. *Nat Med* 2002;**8**:1390–1397.
67. Tabrez S, Priyadarshini M, Priyamvada S, Khan MS, Na A, Zaidi SK. Gene-environment interactions in heavy metal and pesticide carcinogenesis. *Mutat Res* 2014;**760**:1–9.
68. Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. *Chem Biol Interact* 2006;**160**:1–40.
69. Cooke MS, Evans MD, Dizdaroğlu M, Lunec J. Oxidative DNA damage: Mechanisms, mutation, and disease. *FASEB J* 2003;**17**:1195–1214.
70. Persé M. Oxidative stress in the pathogenesis of colorectal cancer: Cause or consequence? *Biomed Res Int* 2013;**2013**:725710.
71. Bailey DT, DeFedericis H-CC, Greene KF, et al. A novel approach to DNA damage assessments: Measurement of the thymine glycol lesion. *Radiat Res* 2006;**165**:438–444.
72. Gonfloni S, Maiani E, Di Bartolomeo C, Diederich M, Cesareni G. Oxidative stress, DNA damage, and c-Abl signaling: At the crossroad in neurodegenerative diseases? *Int J Cell Biol* 2012;**2012**:683097.
73. Favaloro B, Allocati N, Graziano V, Di Ilio C, De Laurenzi V. Role of apoptosis in disease. *Aging (Albany NY)* 2012;**4**:330–349.
74. Shimohama S. Apoptosis in Alzheimer's disease—an update. *Apoptosis* 2000;**5**:9–16.
75. Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. *Cold Spring Harb Perspect Med* 2011;**1**:a006189.
76. Loo DT, Copani A, Pike CJ, Whittemore ER, Walencewicz AJ, Cotman CW. Apoptosis is induced by beta-amyloid in cultured central nervous system neurons. *Proc Natl Acad Sci U S A* 1993;**90**:7951–7955.
77. McShea A, Harris PL, Webster KR, Wahl AF, Smith MA. Abnormal expression of the cell cycle regulators P16 and CDK4 in Alzheimer's disease. *Am J Pathol* 1997;**150**:1933–1939.
78. Tatton WG, Chalmers-Redman R, Brown D, Tatton N. Apoptosis in Parkinson's disease: Signals for neuronal degradation. *Ann Neurol* 2003;**53**:S61–S70.
79. Jope RS, Yuskaitis CJ, Beurel E. Glycogen synthase kinase-3 (GSK3): Inflammation, diseases, and therapeutics. *Neurochem Res* 2007;**32**:577–595.
80. Li T, Wen H, Brayton C, et al. Moderate reduction of gamma-secretase attenuates amyloid burden and limits mechanism-based liabilities. *J Neurosci* 2007;**27**:10849–10859.
81. Zheng H, Koo EH. Biology and pathophysiology of the amyloid precursor protein. *Mol Neurodegener* 2011;**6**:27.
82. Takagi K, Ito S, Miyazaki T, et al. Amyloid precursor protein in human breast cancer: An androgen-induced gene associated with cell proliferation. *Cancer Sci* 2013;**104**:1532–1538.
83. Luo W, Rodina A, Chiosis G. Heat shock protein 90: Translation from cancer to Alzheimer's disease treatment? *BMC Neurosci* 2008;**9**:57.
84. Driver JA, Logroscino G, Buring JE, Gaziano JM, Kurth T. A prospective cohort study of cancer incidence following the diagnosis of Parkinson's disease. *Cancer Epidemiol Biomarkers Prev* 2007;**16**:1260–1265.
85. Pan T, Li X, Jankovic J. The association between Parkinson's disease and melanoma. *Int J Cancer* 2011;**128**:2251–2260.
86. Plun-Favreau H, Lewis PA, Hardy J, Martins LM, Wood NW. Cancer and neurodegeneration: Between the devil and the deep blue sea. *PLoS Genet* 2010;**6**:e1001257.
87. West AB, Dawson VL, Dawson TM. To die or grow: Parkinson's disease and cancer. *Trends Neurosci* 2005;**28**:348–352.
88. Kim RH, Mak TW. Tumours and tremors: How PTEN regulation underlies both. *Br J Cancer* 2006;**94**:620–624.
89. Kareus SA, Figueroa KP, Cannon-Albright LA, Pulst SM. Shared predispositions of Parkinsonism and cancer: A population-based pedigree-linked study. *Arch Neurol* 2012;**69**:1572–1577.
90. Raina AK, Monteiro MJ, McShea A, Smith MA. The role of cell cycle-mediated events in Alzheimer's disease. *Int J Exp Pathol* 1999;**80**:71–76.
91. Aliev G, Obrenovich ME, Tabrez S, et al. Link between cancer and Alzheimer disease via oxidative stress induced by nitric oxide-dependent mitochondrial DNA overproliferation and deletion. *Oxid Med Cell Longev* 2013;**2013**:962984.
92. Herrup K, Neve R, Ackerman SL, Copani A. Divide and die: Cell cycle events as triggers of nerve cell death. *J Neurosci* 2004;**24**:9232–9239.
93. Arendt T, Brückner MK. Linking cell-cycle dysfunction in Alzheimer's disease to a failure of synaptic plasticity. *Biochim Biophys Acta* 2007;**1772**:413–421.
94. Ogawa O, Zhu X, Lee H-G, et al. Ectopic localization of phosphorylated histone H3 in Alzheimer's disease: A mitotic catastrophe? *Acta Neuropathol* 2003;**105**:524–528.
95. Ogawa O, Lee H-g, Zhu X, et al. Increased p27, an essential component of cell cycle control, in Alzheimer's disease. *Aging Cell* 2003;**2**:105–110.
96. Arendt T. Neuronal dedifferentiation and degeneration in Alzheimer's disease. *Biol Chem Hoppe Seyler* 1993;**374**:911–912.
97. Saitoh T, Horsburgh K, Masliah E. Hyperactivation of signal transduction systems in Alzheimer's disease. *Ann N Y Acad Sci* 1993;**695**:34–41.
98. Gärtner U, Holzer M, Heumann R, Arendt T. Induction of p21ras in Alzheimer pathology. *NeuroReport* 1995;**6**:1441–1444.
99. McShea A, Lee H-g, Petersen RB, et al. Neuronal cell cycle re-entry mediates Alzheimer disease-type changes. *Biochim Biophys Acta* 2007;**1772**:467–472.
100. Raina AK, Zhu X, Rottkamp CA, Monteiro M, Takeda A, Smith MA. Cyclin' toward dementia: Cell cycle abnormalities and abortive oncogenesis in Alzheimer disease. *J Neurosci Res* 2000;**61**:128–133.
101. Qu L, Tang X. Bexarotene: A promising anticancer agent. *Cancer Chemother Pharmacol* 2010;**65**:201–205.
102. USFDA. www.accessdata.fda.gov/drugsatfda_docs/nda/99/21055_Targretin.cfm, 1999.
103. Farol LT, Hymes KB. Bexarotene: A clinical review. *Expert Rev Anticancer Ther* 2004;**4**:180–188.
104. Cramer PE, Cirrito JR, Wesson DW, et al. ApoE-directed therapeutics rapidly clear β -amyloid and reverse deficits in AD mouse models. *Science* 2012;**335**:1503–1506.
105. Park JW, Baek NS, Lee SC, et al. Preclinical efficacy testing for stomach and liver cancers. *Cancer Res Treat* 2014;**46**:186–193.
106. Senderowicz AM. The cell cycle as a target for cancer therapy: Basic and clinical findings with the small molecule inhibitors flavopiridol and UCN-01. *Oncologist* 2002;**7**:12–19.
107. Malumbres M, Pevarillo P, Barbacid M, Bischoff JR. CDK inhibitors in cancer therapy: What is next? *Trends Pharmacol Sci* 2008;**29**:16–21.
108. Dhalla NS, Temsah RM, Netticadan T. Role of oxidative stress in cardiovascular diseases. *J Hypertens* 2000;**18**:655–673.
109. Kukreja RC, Hess ML. The oxygen free radical system: From equations through membrane-protein interactions to cardiovascular injury and protection. *Cardiovasc Res* 1992;**26**:641–655.
110. Manea A, Manea SA, Gafencu AV, Raicu M, Simionescu M. AP-1-dependent transcriptional regulation of NADPH oxidase in human aortic smooth muscle cells: Role of p22phox subunit. *Arterioscler Thromb Vasc Biol* 2008;**28**:878–885.
111. Elahi MM, Kong YX, Matata BM. Oxidative stress as a mediator of cardiovascular disease. *Oxid Med Cell Longev* 2009;**2**:259–269.
112. Simionescu M. Implications of early structural-functional changes in the endothelium for vascular disease. *Arterioscler Thromb Vasc Biol* 2007;**27**:266–274.
113. Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: The role of oxidant stress. *Circ Res* 2000;**87**:840–844.
114. van Empel VPM, Bertrand ATA, Hofstra L, Crijns HJ, Doevendans PA, De Windt LJ. Myocyte apoptosis in heart failure. *Cardiovasc Res* 2005;**67**:21–29.
115. Ottaviani G, Lavezzi AM, Rossi L, Matturri L. Proliferating cell nuclear antigen (PCNA) and apoptosis in hyperacute and acute myocardial infarction. *Eur J Histochem* 1999;**43**:7–14.
116. Scheubel RJ, Bartling B, Simm A, et al. Apoptotic pathway activation from mitochondria and death receptors without caspase-3 cleavage in failing human myocardium: Fragile balance of myocyte survival? *J Am Coll Cardiol* 2002;**39**:481–488.
117. Strand BH, Langballe EM, Hjellevik V, et al. Midlife vascular risk factors and their association with dementia deaths: Results from a Norwegian prospective study followed up for 35 years. *J Neurol Sci* 2013;**324**:124–130.
118. Alonso A, Jacobs DR Jr, Menotti A, et al. Cardiovascular risk factors and dementia mortality: 40 years of follow-up in the Seven Countries Study. *J Neurol Sci* 2009;**280**:79–83.
119. Newman AB, Fitzpatrick AL, Lopez O, et al. Dementia and Alzheimer's disease incidence in relationship to cardiovascular disease in the Cardiovascular Health Study cohort. *J Am Geriatr Soc* 2005;**53**:1101–1107.
120. Barnes DE, Haight TJ, Mehta KM, Carlson MC, Kuller LH, Tager IB. Secondhand smoke, vascular disease, and dementia incidence: Findings from the cardiovascular health cognition study. *Am J Epidemiol* 2010;**171**:292–302.
121. Low L-F, Yap MHW, Brodaty H. Will testing for apolipoprotein E assist in tailoring dementia risk reduction? A review *Neurosci Biobehav Rev* 2010;**34**:408–437.
122. Bachman DL, Green RC, Benke KS, Cupples LA, Farrer LA, Group MS. Comparison of Alzheimer's disease risk factors in white and African American families. *Neurology* 2003;**60**:1372–1374.
123. Díaz-Ruiz C, Wang J, Ksiazek-Reding H, et al. Role of hypertension in aggravating abeta neuropathology of AD

- type and Tau-mediated motor impairment. *Cardiovasc Psychiatry Neurol* 2009;**2009**:107286.
124. Humpel C. Chronic mild cerebrovascular dysfunction as a cause for Alzheimer's disease? *Exp Gerontol* 2011;**46**:225–232.
 125. Muqtaadar H, Testai FD, Gorelick PB. The dementia of cardiac disease. *Curr Cardiol Rep* 2012;**14**:732–740.
 126. Zesiewicz TA, Strom JA, Borenstein AR, et al. Heart failure in Parkinson's disease: Analysis of the United States medicare current beneficiary survey. *Parkinsonism Relat Disord* 2004;**10**:417–420.
 127. Richards BJ. Q10 Boosts Energy, Nerves, Muscles & Metabolism, <http://www.wellnessresources.com>, 2014.
 128. Chen Y, Dorn GW. PINK1- phosphorylated mitofusin 2 is a Parkin receptor for culling damaged mitochondria. *Science* 2013;**340**:471–475.
 129. Weckman A, Di Ieva A, Rotondo F, et al. Autophagy in the endocrine glands. *J Mol Endocrinol* 2014;**52**:R151–R163.
 130. Friedman JR, Nunnari J. Mitochondrial form and function. *Nature* 2014;**505**:335–343.
 131. Scarffe LA, Stevens DA, Dawson VL, Dawson TM. Parkin and PINK1: Much more than mitophagy. *Trends Neurosci* 2014;**37**:315–324.
 132. Stuebner E, Vichayanrat E, Low DA, Mathias CJ, Isenmann S, Haensch C-A. Twenty-four hour non-invasive ambulatory blood pressure and heart rate monitoring in Parkinson's disease. *Front Neurol* 2013;**4**:49.
 133. Ziemssen T, Reichmann H. Treatment of dysautonomia in extrapyramidal disorders. *Ther Adv Neurol Disord* 2010;**3**:53–67.
 134. Iodice FG, Thomas M, Walker I, Garside V, Elliott MJ. Analgesia in fast-track paediatric cardiac patients. *Eur J Cardiothorac Surg* 2011;**40**:610–613.