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Review Article

Role of Vitamin D in Parkinson's Disease

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Parkinson's disease (PD) is the second most common form of neurodegeneration in the elderly population. Clinically, it is characterized by tremor, rigidity, slowness of movement, and postural imbalance. A significant association between low serum vitamin D and PD has been demonstrated, suggesting that elevated vitamin D levels might provide protection against PD. Genetic studies have helped identify a number of proteins linking vitamin D to PD pathology, including the major histocompatibility complex (MHC) class II, the vitamin D receptor (VDR), cytochrome P450 2D6 (CYP2D6), chromosome 22, the renin-angiotensin system (RAS), heme oxygenase-1 (HO-1), poly(ADP-ribose) polymerase-1 gene (*PARP-1*), neurotrophic factor (NTF), and Sp1 transcription factor. Vitamin D has also been implicated in PD through its effects on L-type voltage-sensitive calcium channels (L-VSCC), nerve growth factor (NGF), matrix metalloproteinases (MMPs), prostaglandins (PGs) and cyclooxygenase-2 (COX-2), reactive oxygen species (ROS), and nitric oxide synthase (NOS). A growing body of evidence suggests that vitamin D supplementation may be beneficial for PD patients. Among the different forms of vitamin D, calcitriol (1,25-dihydroxyvitamin D_3) is best indicated for PD, because it is a highly active vitamin D_3 metabolite with an appropriate receptor in the central nervous system (CNS).

1. Introduction

Parkinson's disease (PD) is a movement disorder characterized by tremor, rigidity, slowness of movement, and postural imbalance. There is evidence of abnormalities in the vitamin D-endocrine system in PD patients, including low bone mineral density (BMD), decreased vitamin D levels, and increased bone turnover makers (bone alkaline phosphatase and urinary N-terminal telopeptide of type I collagen) compared to controls [1]. These factors, combined with balance problems, are the probable reasons for the high incidence of fractures, especially of the hip, reported in elderly women with PD [2]. Sunlight exposure can increase the BMD of PD by increasing serum 25-hydroxyvitamin D_3 (25OHD) levels [3]. In another study, serum 25OHD and BMD were reported to be reduced in PD patients. The BMD Z-score of the trochanter was directly correlated to the degree of physical activity and total body BMD Z-score correlated to the degree of rigidity [4]. Osteoporosis and osteopenia are common findings in PD patients, affecting up to 91% of women and 61% of men [5]. Decreased BMD, low concentrations of serum ionized calcium, and compensatory hyperparathyroidism increase the risk of hip fracture in PD patients [1]. Despite an abundance of correlational studies, it is unknown whether vitamin D deficiency is a cause or consequence of PD. In the present paper, we review the hypothesized roles of vitamin D in PD pathogenesis.

2. Genomic Factors Associated with Vitamin D in Parkinson's Disease

2.1. Major Histocompatibility Complex (MHC). Studies have suggested that several genes in the MHC region promote susceptibility to PD. Significantly increased levels of MHC class II expressions were detected in the cerebrospinal fluid (CSF) monocytes of PD patients [6]. Human leukocyte antigen (HLA) genes have also been implicated in PD, and large numbers of HLA-DR-positive reactive microglia were detected in the substantia nigra (SN) and the nigrostriatal tract in PD patients [7, 8]. HLA-DR-positive microglia have also been found in these regions in a case of Parkinson's-associated dementia in Guam [8]. Conversely, calcitriol

(1,25-dihydroxyvitamin D_3) is known to stimulate phagocytosis but suppress MHC class II antigen expression in human mononuclear phagocytes [9, 10]. Calcitriol also decreases interferon-gamma-induced HLA-DR antigen expression on normal and transformed human keratinocytes [11, 12]. These findings suggested that vitamin D may modulate MHC class II antigen expression in PD.

2.2. Vitamin D Receptor (VDR). There is ample evidence for vitamin D involvement in mammalian brain function. VDR and 1α-hydroxylase, the enzyme responsible for the formation of active vitamin D in the human brain, are found in the large neurons of the SN, as well as in neurons and glial cells in the hypothalamus [13]. VDR, a nuclear receptor, is restricted to the nucleus but 1α-hydroxylase is distributed throughout the cytoplasm. The presence of these proteins in the CNS suggests that vitamin D is active within the brain. VDR knockout mice have muscular and motor impairment [14]. Genetic studies provide an opportunity to link molecular variations with epidemiological data, DNA sequence variations, such as polymorphisms, exert subtle biological effects on the expression and functionality of proteins. VDR mRNA was identified as a potential blood marker for PD [15]. In a Korean population, the VDR BsmI genotype is reported to be associated with PD [16]. Butler et al. [17] reported that the VDR gene is a potential susceptibility gene for PD in the Caucasian population. These reports suggested a role of vitamin D in PD.

2.3. The Cytochrome P_{450} (CYP). CYP superfamily of enzymes is responsible for the oxidation, peroxidation, and/or reduction of vitamins, steroids, and xenobiotics, as well as the metabolism of drugs. CYP2D6, an important member of this superfamily, is expressed in neurons in the brain and gut and may be influenced by polymorphic expression. There is a higher prevalence of the poor-metabolizing CYP2D6*4 allele in PD patients compared with controls (20.7% versus 11.0%) [18]. In case-control and meta-analysis studies, the CYP2D polymorphism was found to be associated with PD [19, 20]. Other studies, however, did not find an association between the CYP2D6 polymorphism and PD in an Asian population [21, 22]. Although the poor metabolizer genotype has a small but highly significant association with PD, it would be easily missed in studies with modest numbers of subjects. CYP2D6 protein and enzymatic activity are completely absent in less than 1% of Asian people and in up to 10% of Caucasians with two null alleles [23]. Singh et al. reported the expression of CYP2D22, an ortholog of human CYP2D6, in mouse striatum and its modulation in MPTP-induced PD phenotype and nicotine-mediated neuroprotection [24]. CYP2D6 is a potential 25-hydroxylase, which converts vitamin D_3 into 25OHD, and vitamin D 25-hydroxylase deficiency resulted in vitamin D deficiency [25]. Moreover, the CYP2D and PD loci are located on the same chromosome 22 [26, 27]. Deletion of chromosome 22q11 syndrome was reported to be associated with PD [28, 29]. Interestingly, patients with a deletion of chromosome 22q11 showed a reduced BMD, serum calcium, and PTH levels; 11% and 8% of these patients had serum 25OHD levels under 20 ng/ml and abnormal serum 1,25OHD levels, respectively [30].

2.4. The Renin-Angiotensin System (RAS). The primary function of the RAS is to maintain fluid homeostasis and regulate blood pressure. Several components of the RAS and its receptors are found in the CNS [31–34], suggesting that RAS is important in the brain. CSF levels of angiotensin-converting enzyme (ACE) activity were reported to be decreased in PD patients and increased with dopaminergic treatment [35, 36]. In addition, the ACE inhibitor perindopril has been shown to exert beneficial effects on the dopaminergic system [37, 38]. After four weeks of treatment with perindopril, patients with PD had faster improvement in motor response after L-dopa and a reduction in "on phase" peak dyskinesia [39]. The frequency of the homozygous DD genotype of the ACE gene was significantly increased in patients with PD, and is also higher in PD patients with L-dopa-induced psychosis versus without psychosis [40, 41]. However, other studies did not reveal any associations between ACE polymorphisms, PD, and of L-dopa-induced adverse effects [42, 43]. The dissimilar findings may be attributable to differences between Chinese and Caucasian populations. Interestingly, there is also an interaction between vitamin D and the RAS. The use of ACE inhibitors by the ACE DD genotype has been shown to decrease the level of calcitriol [44]. In addition, genetic disruption of the VDR resulted in overstimulation of the RAS with increased production of renin and angiotensin II, thereby leading to high blood pressure and cardiac hypertrophy. Treatment with captopril reduced cardiac hypertrophy in VDR knockout mice [45], suggesting that calcitriol may function as an endocrine suppressor of renin biosynthesis. Vitamin D has also been reported to decrease ACE activity in bovine endothelial cells [46]. The findings suggested that vitamin D might affect ACE activity in PD.

2.5. Heme Oxygenase-1 (HO-1). HO-1 is a stress protein that may confer cytoprotection by enhancing catabolism of pro-oxidant heme to the radical scavenging bile pigments, biliverdin, and bilirubin. The HO-1 gene can be upregulated by a host of noxious stimuli and is induced in CNS tissues affected by neurological diseases [47]. In the normal brain, basal HO-1 expression is low and restricted to small groups of scattered neurons and neuroglia [48]. In the brains of PD patients, the HO-1 is highly overexpressed in astrocytes within the SN and in Lewy bodies found in affected dopaminergic neurons [49]. Serum HO-1 levels are increased in PD patients but not in patients with Alzheimer's disease (AD) [50], suggesting a systemic antioxidant reaction to a chronic oxidative stress state that is unique to PD. Similarly, calcitriol delayed of HO-1 immunoreactivity after the postlesional survival time of 12 hours concomitant with a reduction in glial fibrillary acidic protein immunoreactivity in remote cortical regions affected by a secondary spread of injury in glial cells of the focal cerebral ischemic [51], thereby supporting the protective role of calcitriol in postcellular injury.

2.6. Poly(ADP-Ribose) Polymerase-1 (PARP-1). PARP-1 is a nuclear protein that can promote either neuronal death or survival under certain stress conditions. Overexpression of PARP-1 has been reported in the dopaminergic neurons of the SN in PD [52]. PARP-1 is also implicated in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine- (MPTP-) induced neurotoxicity *in vivo* [53]. MPTP is a neurotoxin that induces parkinsonian symptoms in human and animals, but mice lacking PARP gene are spared from MPTP neurotoxicity [54]. Therefore, PARP inhibitors have proved to be valuable tools in PD model [55, 56]. PARP-1 variants are reported to be protective against PD [57]. In addition, increased levels of vitamin D seem to downregulate PARP-1 expression; PARP-1 levels decrease following calcitriol treatment in NB4 cells, which represent an acute promyelocytic leukemia cells [58]. Vitamin D exerts a concentration-dependent inhibitory effect on PARP-1 in the human keratinocyte cells [59]. Vitamin D-induced downregulation of PARP is further enhanced by nicotinamide in human myeloblastic leukemia cells [60]. Furthermore, PARP is attenuated in the hippocampus of rats that received dexamethasone and vitamin D [61], suggesting that the anti-inflammatory effects of dexamethasone and vitamin D derives from their ability to downregulate microglial activation. These findings suggested that vitamin D may have a protective role in PD by downregulating PARP.

2.7. Neurotrophic Factors (NTFs). NTFs are keys to surviving various neuronal insults and promote neuronal regeneration following injury [62]. NTFs can exert protective or even restorative effects on PD animal models and dopaminergic cell cultures; key examples include brain-derived neurotrophic factor (BDNF) [63], glial-derived neurotrophic factor (GDNF) [64], mesencephalic-astrocyte-derived neurotrophic factor (MANF) [65], and cerebral dopamine neurotropic factor (CDNF) [66]. Receptors for these NTFs are expressed in the striatum and SN [67, 68]. NTF expression is reduced in the SN of patients with PD [69–71]. Moreover, the C allele of an inotropic CDNF single nucleotide polymorphism (rs7094179) has been suggested to infer susceptibility to PD in a Korean population [72], and A allele of BDNF is associated with PD in a Chinese Han population [73]. Interestingly, calcitriol regulates the expression of the low-affinity neurotrophic receptor [74] and increases striatal GDNF mRNA and protein expression in adult rats [75]. *In vivo*, calcitriol is also a potent inducer of GDNF in rat glioma cells [76]. The brains of offspring from vitamin D-deficient dams are characterized by diminished expression of neurotrophic factors [77]. Furthermore, calcitriol protects against dopamine loss from 6-hydroxydopamine- (6-OHDA-) lesioned rats by increasing GDNF and partially restores tyrosine hydroxylase expression in SN and striatum [78, 79].

2.8. Sp1 Transcription Factor. Sp1 transcription factor is a member of an extended family of DNA-binding proteins that is acetylated in response to oxidative stress in neurons [80]. The Sp1 family of proteins plays an important role in controlling the expression of the dopamine transporter gene within dopaminergic neurons [81] and also regulates expression of rat dopamine receptor gene [82]. On the other hand, binding sites for the transcription factor Sp1 have been implicated in the transcription of several genes by hormones. In cultured human fibroblasts, the level of CYP24 (25-OHD 24-hydroxylase) mRNA plays a key role in the metabolism of 1,25OHD and increases up to 20,000-fold in response to calcitriol. Two vitamin D-responsive elements (VDREs) located upstream of the CYP24 gene are primarily responsible for the increased mRNA levels, and Sp1 acted synergistically with these VDREs for the induction [72]. The mVDR promoter is controlled by Sp1 sites [73] and functions as the transactivation component of the VDR/Sp1 complex to trigger gene expression [74]. Moreover, the genes encoding Sp1 and VDR were mapped to human chromosome 12q [75, 76].

3. Nongenomic Role of Vitamin D in Parkinson's Disease

3.1. Diabetes Mellitus (DM). Glucose is the molecule necessary to produce energy in the brain. A link between DM and PD has been suggested in several reports, but the results have been inconsistent. Insulin receptors and their mRNAs are localized in the SN [83, 84]. A high incidence of abnormal glucose tolerance has been reported in PD and seems to be exacerbated by L-dopa treatment [85]. DM has been associated with the risk of developing PD [86, 87] whereas others reported from protective to no associations with PD [88–90]. Human and experimental animal studies, however, demonstrated neurodegeneration associated with peripheral insulin resistance [91]. In a 6-OHDA model of PD, striatal insulin resistance was observed in the striatum [92], and patients with PD exhibited increased autoimmune reactivity to insulin [93]. Individuals newly diagnosed with PD display reduced insulin-mediated glucose uptake [94], which is hypothesized to be due to inhibit early insulin secretion and hyperglycemia after glucose loading [95]. Furthermore, chronic hyperglycemia decreased limbic extracellular dopamine concentrations and striatal dopaminergic transmission in streptozotocin-induced diabetic rats [96, 97]. Vitamin D levels may provide a link between the diseases; serum 1,25OHD and 25OHD levels are low in diabetic patients [98, 99], and diabetic rats had an increased metabolic clearance rate of 1,25OHD [100]. Interestingly, a significant high prevalence of vitamin D insufficiency is reported in patients with PD [101, 102]. A significant inverse association between serum vitamin D and PD was demonstrated [103] and suggested that high vitamin D status might provide protection against PD. In diabetic-induced rats, vitamin D and insulin treatment markedly recovered the levels of altered gene (cholinergic, dopaminergic, and insulin receptors) expression and its binding parameters nearly to those of the control rats [104]. Maternal vitamin D deficiency was reported to alter the expression of genes involved in dopamine specification in the developing rat mesencephalon [105]. Calcitriol has been shown to protect dopamine neuronal toxicity induced by 6-OHDA and the combination of L-buthionine sulfoximine and MPTP,

thereby restoring motor activity in the lesioned animals [106, 107]. Furthermore, vitamin D was reported to improve rigidity and akinesia and reduce levodopa dosage in a patient with PD [108].

3.2. L-Type Voltage-Sensitive Calcium Channels (L-VSCC). Unlike most neurons in the brain, dopaminergic neurons function as autonomous pacemakers that rely on L-VSCC to generate action potentials at a clock-like 2–4 Hz in the absence of synaptic input [109]. L-VSCC activity during autonomous pacemaking increased the sensitivity of dopaminergic neurons to mitochondrial toxins in an animal model of PD [110]. Epidemiological data supports a link between L-VSCC functioning and the risk of developing PD [111–113]. Pretreatment with the calcium channel antagonist nimodipine has been shown to block the development of MPTP-induced neurotoxicity in animal models [114, 115]. Israpidine, another L-VSCC antagonist, caused a dose-dependent reduction in L-dopa-induced rotational behavior and abnormal involuntary movements in the 6-OHDA-lesioned rat model of PD [116]. With respect to AD, amyloid-β protein was reported to promote neurodegeneration by inducing L-VSCC expression and suppressing VDR expression; subsequent treatment with vitamin D protected neurons by preventing cytotoxicity and apoptosis, probably by downregulating L-VSCC and upregulating VDR [117]. Calcitriol decreased L-VSCC activity in aged rats and in neuronal vulnerability with particular impact on reducing age-related changes associated with Ca^{2+} dysregulation [118, 119]. Treatment with 24R, 25 dihydroxyvitamin D_3 also reduced L-VSCC activity in vascular smooth muscle in rats [120].

3.3. Nerve Growth Factor (NGF). NGF is a small secreted protein that is important for the growth, maintenance, and survival of certain target neurons. NGF has been implicated in maintaining and regulating the septohippocampal pathway, which is involved in learning and memory [121–123]. NGF is also present in the human SN [124] and in the adrenal gland [125]. NGF concentrations are decreased in the SN of the PD and in a rat model of PD [69, 126]. NGF levels showed greater reductions in early states of the disease compared with advanced stages [126], implying that decreased NGF may be involved in the pathogenesis of PD. NGF is reported to protect dopamine neurotoxicity induced by MPTP, rotenone, and 6-OHDA via different pathways [127–129]. The chronic infusion of NGF into the rat striatum resulted in cholinergic hyperinnervation and reduced spontaneous activity of striatal neurons [130]. Moreover, NGF increases survival of dopaminergic grafts, rescues nigral dopaminergic neurons, and restores motor dysfunction in a rat model of PD [131, 132]. In addition, the brains of newborn rats from vitamin D-deficient dams showed reduced expression of NGF [77]. *In vitro*, calcitriol regulated the expression of the VDR gene and stimulated the expression of the NGF gene in Schwann cells [133]. In mouse fibroblasts, calcitriol and vitamin D analogs are reported to enhance NGF induction by increasing AP-1 binding activity to the NGF promoter [134, 135]. These findings suggest a protective role for vitamin D in the CNS.

3.4. Matrix Metalloproteinases (MMPs). MMPs are proteolytic enzymes responsible for extracellular matrix (ECM) remodeling and the regulation of leukocyte migration through the ECM, which is an important step for inflammatory processes. Neuroinflammation is known to contribute significantly to progressive dopaminergic neurodegeneration in PD. MMP involvement has been reported in the degeneration of dopaminergic neurons. MMP-3 expression is increased during lipopolysaccharide- (LPS-) induced dopamine neurotoxicity [136]. MMP-9 is also elevated in MPTP-induced parkinsonism in mice [137]. Application of dopaminergic neurotoxins to two human neuroblastoma cell lines downregulates the transcription and translation of tissue inhibitor of metalloproteinase- (TIMP-) 2 effectively enhancing MMP activity [138]. Exendin-4, which is an analogue of glucagon-like peptide 1 (GLP-1), significantly attenuates the loss of SN neurons and the striatal dopaminergic fibers in the MPTP-induced PD model, and inhibits the expression of MMP-3 [139]. Conversely, the VDR TaqI polymorphism is associated with decreased production of TIMP-1, a natural inhibitor of MMP-9 [140]. Calcitriol modulates tissue MMP expression under experimental conditions [141]. Calcitriol downregulates MMP-9 levels in keratinocytes and may attenuate deleterious effects due to excessive TNF-α-induced proteolytic activity associated with cutaneous inflammation [142]. In addition, a vitamin D analogue was reported to reduce the expression of MMP-2, MMP-9, VEGF, and parathyroid hormone-related protein in Lewis lung carcinoma cells [143]. These findings suggested that vitamin D plays a role in modulating MMP activation in PD.

3.5. Prostaglandins (PGs). PGs play a role in inflammatory processes [144]. Cyclooxygenase (COX) participates in the conversion of arachidonic acid into PGs. PGE_2 is a key product of COX-2 and is increased in the SN of patients with PD and MPTP-induced PD in an animal model [145, 146]. PGE_2 is also directly and selectively toxic to dopaminergic neurons [147]. PGE_2 receptors are found on dopaminergic neurons in the rat SN [147]. Overexpression of COX-2 is reported in PD and an MPTP-animal model [148, 149]. COX inhibitors provide neuroprotection in the MPTP-mouse model of PD [150]. Similarly, regular use of COX-2 inhibiting nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, has been associated with a decreased incidence of PD [151]. Calcitriol, which reportedly regulates the expression of several key genes involved in PG pathways, decreases PG synthesis [152]. Calcitriol and its analogues have also been shown to inhibit selectively the activity of COX-2 [153]. These findings suggested that vitamin D has a role in anti-inflammatory processes in PD.

3.6. Oxidative Stress. Oxidative stress has been suggested to contribute to the pathogenesis of PD. Lymphocytes from untreated PD patients have increase oxidative stress [154]. Analyses of postmortembrains from PD reveal evidence

of increased lipid peroxidation in PD SN [155, 156]. A selective superoxide dismutase (SOD) is also increased in the SN of PD patients [157]. Calcitriol administration has been reported to exert a receptor-mediated effect on the secretion of hydrogen peroxide by human monocytes [158]. *In vitro,* monocytes gradually lose their ability to produce superoxide when stimulated; the addition of calcitriol, lipopolysaccharide, or lipoteichoic acid (LTA) restored the ability of stimulated monocytes to produce superoxide and increases the oxidative capacity compared with unstimulated monocytes [159]. Calcitriol can also protect nonmalignant prostate cells from oxidative stress-induced cell death by preventing ROS-induced cellular injuries [160]. Vitamin D metabolites and analogues were reported to induce lipoxygenase mRNA expression, lipoxygenase activity, and ROS production in a human bone cell line [161]. Vitamin D can also reduce lipid peroxidation and induce SOD activity in the rat hepatic antioxidant system [162]. These findings suggested a role of vitamin D in oxidative stress in PD.

3.7. Nitric Oxide Synthase (NOS). NOS is an enzyme involved in the synthesis of nitric oxide (NO), which has also been implicated in PD. In postmortem brains of PD, high levels of NOS expression were found in the nigrostriatal region and basal ganglia [163]. A significant increase in the nitrite content was reported in polymorphonuclear leukocytes of PD patients [164]. Inducible and neuronal NO are increased in both 6-OHDA and MPTP animal models [165, 166]. Moreover, studies with NOS inhibitors and NOS knock-out animals have also confirmed the role of NOS in neurodegeneration [167, 168]. Reduced and oxidized glutathione (GSH) were demonstrated in the SN of patients with PD [169]. Conversely, the activation of 1α-hydroxylase in macrophages increases in 1,25OHD, which inhibits inducible NOS (iNOS) expression and reduces NO production by lipopolysaccharide- (LPS-) stimulated macrophages [170]. Thus, calcitriol production by macrophages may provide protection against oxidative injuries caused by the NO burst. Calcitriol is known to inhibit LPS-induced immune activation in human endothelial cells [171]. In experimental allergic encephalomyelitis, calcitriol inhibits the expression of iNOS in the rat CNS [172]. Astrocytes play a pivotal role in CNS detoxification pathways where glutathione (GSH) is involved in the elimination of oxygen and nitrogen reactive species, such as nitric oxide. Calcitriol affects this pathway by enhancing intracellular GSH pools and significantly reduces nitrite production induced by LPS [173].

4. Conclusion

Recent studies have highlighted a possible relationship between vitamin D and PD. Vitamin D may be beneficial in PD patients, as one patient showed improved rigidity and akinesia and was able to decrease their levodopa dosage after vitamin D therapy. Genetic studies have provided opportunities to determine what proteins may link vitamin D to PD pathology. Vitamin D can also act through a number of nongenomic mechanisms, including effects on protein expression, oxidative stress, inflammation, and cellular metabolism. Among the many forms of vitamin D, calcitriol (1,25-dihydroxyvitamin D_3) is an attractive therapeutic candidate, because it is a particularly active metabolite, and its receptor is expressed in the CNS.

Conflict of Interests

The authors declare that they have no conflict of interests.

References

[1] S. Abou-Raya, M. Helmii, and A. Abou-Raya, "Bone and mineral metabolism in older adults with Parkinson's disease," *Age and Ageing*, vol. 38, no. 6, pp. 675–680, 2009.

[2] Y. Sato, M. Kaji, T. Tsuru, and K. Oizumi, "Risk factors for hip fracture among elderly patients with Parkinson's disease," *Journal of the Neurological Sciences*, vol. 182, no. 2, pp. 89–93, 2001.

[3] Y. Sato, J. Iwamoto, and Y. Honda, "Amelioration of osteoporosis and hypovitaminosis D by sunlight exposure in Parkinson's disease," *Parkinsonism and Related Disorders*, 2010.

[4] B. Lorefält, G. Toss, and A.-K. Granérus, "Bone mass in elderly patients with Parkinson's disease," *Acta Neurologica Scandinavica*, vol. 116, no. 4, pp. 248–254, 2007.

[5] M. Invernizzi, S. Carda, G. S. Viscontini, and C. Cisari, "Osteoporosis in Parkinson's disease," *Parkinsonism and Related Disorders*, vol. 15, no. 5, pp. 339–346, 2009.

[6] U. Fiszer, E. Mix, S. Fredrikson, V. Kostulas, and H. Link, "Parkinson's disease and immunological abnormalities: increase of HLA-DR expression on monocytes in cerebrospinal fluid and of $CD45RO^+$ T cells in peripheral blood," *Acta Neurologica Scandinavica*, vol. 90, no. 3, pp. 160–166, 1994.

[7] P. L. McGeer, S. Itagaki, B. E. Boyes, and E. G. McGeer, "Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains," *Neurology*, vol. 38, no. 8, pp. 1285–1291, 1988.

[8] P. L. McGeer and S. E. G. Itagaki McGeer, "Expression of the histocompatibility glycoprotein HLA-DR in neurological disease," *Acta Neuropathologica*, vol. 76, no. 6, pp. 550–557, 1988.

[9] N. Tokuda and R. B. Levy, "1,25-Dihydroxyvitamin D_3 stimulates phagocytosis but suppresses HLA-DR and CD13 antigen expression in human mononuclear phagocytes," *Proceedings of the Society for Experimental Biology and Medicine*, vol. 211, no. 3, pp. 244–250, 1996.

[10] N. Tokuda, N. Mizuki, M. Kasahara, and R. B. Levy, "1,25-dihydroxyvitamin D_3 down-regulation of HLA-DR on human peripheral blood monocytes," *Immunology*, vol. 75, no. 2, pp. 349–354, 1992.

[11] K. Tamaki, A. Saitoh, and Y. Kubota, "1,25-Dihydroxyvitamin D_3 decreases the interferon-γ (IFN-γ) induced HLA-DR expression but not intercellular adhesion molecule 1 (ICAM-1) on human keratinocytes," *Regional Immunology*, vol. 3, no. 5, pp. 223–227, 1990.

[12] T. Tone, H. Eto, K. Katsuoka, K. Nishioka, and S. Nishiyama, "Suppression of gamma-interferon induced HLA-DR antigen expression on normal and transformed keratinocytes by 1,25 $(OH)_2$ vitamin D_3," *The Japanese Journal of Dermatology*, vol. 101, no. 5, pp. 519–525, 1991.

[13] D. W. Eyles, S. Smith, R. Kinobe, M. Hewison, and J. J. McGrath, "Distribution of the Vitamin D receptor and

1α-hydroxylase in human brain," *Journal of Chemical Neuroanatomy*, vol. 29, no. 1, pp. 21–30, 2005.

[14] T. H. J. Burne, J. J. McGrath, D. W. Eyles, and A. Mackay-Sim, "Behavioural characterization of Vitamin D receptor knockout mice," *Behavioural Brain Research*, vol. 157, no. 2, pp. 299–308, 2005.

[15] C. R. Scherzer, A. C. Eklund, L. J. Morse et al., "Molecular markers of early Parkinson's disease based on gene expression in blood," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 104, no. 3, pp. 955–960, 2007.

[16] J. S. Kim, Y. I. Kim, C. Song et al., "Association of vitamin D receptor gene polymorphism and Parkinson's disease in Koreans," *Journal of Korean Medical Science*, vol. 20, no. 3, pp. 495–498, 2005.

[17] M. W. Butler, A. Burt, T. L. Edwards et al., "Vitamin D receptor gene as a candidate gene for Parkinson disease," *Annals of Human Genetics*, vol. 75, no. 2, pp. 201–210, 2011.

[18] M. Stefanovic, E. Topic, A. M. Ivanisevic, M. Relja, and M. Korsic, "Genotyping of CYP2D6 in Parkinson's disease," *Clinical Chemistry and Laboratory Medicine*, vol. 38, no. 9, pp. 929–934, 2000.

[19] M. Singh, V. K. Khanna, R. Shukla, and D. Parmar, "Association of polymorphism in cytochrome P450 2D6 and N-acetyltransferase-2 with Parkinson's disease," *Disease Markers*, vol. 28, no. 2, pp. 87–93, 2010.

[20] S. J. McCann, S. M. Pond, K. M. James, and D. G. Le Couteur, "The association between polymorphisms in the cytochrome P-450 2D6 gene and Parkinson's disease: a case-control study and meta-analysis," *Journal of the Neurological Sciences*, vol. 153, no. 1, pp. 50–53, 1997.

[21] S. L. Ho, M. H. W. Kung, L. S. W. Li, I. J. Lauder, and D. B. Ramsden, "Cytochrome P4502D6 (debrisoquine 4-hydroxylase) and Parkinson's disease in Chinese and Caucasians," *European Journal of Neurology*, vol. 6, no. 3, pp. 323–329, 1999.

[22] S. I. Woo, J. W. Kim, H. G. Seo et al., "CYP2D6*4 polymorphism is not associated with Parkinson's disease and has no protective role against Alzheimer's disease in the Korean population," *Psychiatry and Clinical Neurosciences*, vol. 55, no. 4, pp. 373–377, 2001.

[23] U. M. Zanger, S. Raimundo, and M. Eichelbaum, "Cytochrome P450 2D6: overview and update on pharmacology, genetics, biochemistry," *Naunyn-Schmiedeberg's Archives of Pharmacology*, vol. 369, no. 1, pp. 23–37, 2004.

[24] S. Singh, K. Singh, D. K. Patel et al., "The expression of cyp2d22, an ortholog of human cyp2d6, in mouse striatum and its modulation in 1-methyl 4-phenyl-1,2,3, 6-tetrahydropyridine-induced parkinson's disease phenotype and nicotine-mediated neuroprotection," *Rejuvenation Research*, vol. 12, no. 3, pp. 185–197, 2009.

[25] C. J. Lin, A. Dardis, S. D. Wijesuriya, M. A. Abdullah, S. J. Casella, and W. L. Miller, "Lack of mutations in CYP2D6 and CYP27 in patients with apparent deficiency of vitamin D 25-hydroxylase," *Molecular Genetics and Metabolism*, vol. 80, no. 4, pp. 469–472, 2003.

[26] S. Shojaee, F. Sina, S. S. Banihosseini et al., "Genome-wide linkage analysis of a parkinsonian-pyramidal syndrome pedigree by 500 K SNP arrays," *American Journal of Human Genetics*, vol. 82, no. 6, pp. 1375–1384, 2008.

[27] K. Wilhelmsen, D. Mirel, K. Marder et al., "Is there a genetic susceptibility locus for Parkinson's disease on chromosome 22q13?" *Annals of Neurology*, vol. 41, no. 6, pp. 813–817, 1997.

[28] C. Zaleski, A. S. Bassett, K. Tam, A. L. Shugar, E. W. C. Chow, and E. McPherson, "The Co-occurrence of early onset Parkinson disease and 22q11.2 deletion syndrome," *American Journal of Medical Genetics, Part A*, vol. 149, no. 3, pp. 525–528, 2009.

[29] J. Booij, T. Van Amelsvoort, and E. Boot, "Co-occurrence of early-onset Parkinson disease and 22q11.2 deletion syndrome: potential role for dopamine transporter imaging," *American Journal of Medical Genetics A*, vol. 152, no. 11, pp. 2937–2938, 2010.

[30] S. Stagi, E. Lapi, E. Gambineri et al., "Bone density and metabolism in subjects with microdeletion of chromosome 22q11 (del22q11)," *European Journal of Endocrinology*, vol. 163, no. 2, pp. 329–337, 2010.

[31] D. G. Changaris, L. C. Keil, and W. B. Severs, "Angiotensin II immunohistochemistry of the rat brain," *Neuroendocrinology*, vol. 25, no. 5, pp. 257–274, 1978.

[32] D. P. Healy and M. P. Printz, "Distribution of immunoreactive angiotensin II, angiotensin I, angiotensinogen, and renin in the central nervous system of intact and nephrectomized rats," *Hypertension*, vol. 6, supplement 2, pp. 130–136, 1984.

[33] D. Ganten, K. Hermann, and C. Bayer, "Angiotensin synthesis in the brain and increased turnover in hypertensive rats," *Science*, vol. 221, no. 4613, pp. 869–871, 1983.

[34] V. J. Dzau, J. Ingelfinger, R. E. Pratt, and K. E. Ellison, "Identification of renin and angiotensinogen messenger RNA sequences in mouse and rat brains," *Hypertension*, vol. 8, no. 6, pp. 544–548, 1986.

[35] G. S. Zubenko, L. Volicer, and L. K. Direnfeld, "Cerebrospinal fluid levels of angiotensin-converting enzyme in Alzheimer's disease, Parkinson's disease and progressive supranuclear palsy," *Brain Research*, vol. 328, no. 2, pp. 215–221, 1985.

[36] C. H. Konings, M. A. Kuiper, P. L. M. Bergmans, A. M. Grijpma, G. J. van Kamp, and C. E. Wolters, "Increased angiotensin-eonverting enzyme activity in cerebrospinal fluid of treated patients with Parkinson's disease," *Clinica Chimica Acta*, vol. 231, no. 1, pp. 101–106, 1994.

[37] R. Kurosaki, Y. Muramatsu, H. Kato et al., "Effect of angiotensin-converting enzyme inhibitor perindopril on interneurons in MPTP-treated mice," *European Neuropsychopharmacology*, vol. 15, no. 1, pp. 57–67, 2005.

[38] T. A. Jenkins, J. Y. F. Wong, D. W. Howells, F. A. O. Mendelsohn, and S. Y. Chai, "Effect of chronic angiotensin-converting enzyme inhibition on striatal dopamine content in the MPTP-treated mouse," *Journal of Neurochemistry*, vol. 73, no. 1, pp. 214–219, 1999.

[39] K. A. Reardon, F. A. O. Mendelsohn, S. Y. Chai, and M. K. Horne, "The angiotensin converting enzyme (ACE) inhibitor, perindopril, modifies the clinical features of Parkinson's disease," *Australian and New Zealand Journal of Medicine*, vol. 30, no. 1, pp. 48–53, 2000.

[40] J. J. Lin, K. C. Yueh, D. C. Chang, and S. Z. Lin, "Association between genetic polymorphism of angiotensin-converting enzyme gene and Parkinson's disease," *Journal of the Neurological Sciences*, vol. 199, no. 1-2, pp. 25–29, 2002.

[41] J. J. Lin, K. C. Yueh, S. Z. Lin, H. J. Harn, and J. T. Liu, "Genetic polymorphism of the angiotensin converting enzyme and l-dopa-induced adverse effects in Parkinson's disease," *Journal of the Neurological Sciences*, vol. 252, no. 2, pp. 130–134, 2007.

[42] G. Mellick, D. D. Buchanan, S. J. McCann et al., "The ACE deletion Polymorphism is not associated with Parkinson's disease," *European Neurology*, vol. 41, no. 2, pp. 103–106, 1999.

[43] E. Pascale, C. Purcaro, E. Passarelli et al., "Genetic polymorphism of Angiotensin-Converting Enzyme is not associated with the development of Parkinson's disease and of l-dopa-induced adverse effects," *Journal of the Neurological Sciences*, vol. 276, no. 1-2, pp. 18–21, 2009.

[44] J. L. Pérez-Castrillón, I. Justo, A. Sanz, D. De Luis, and A. Dueñas, "Effect of angiotensin converting enzyme inhibitors on 1.25-$(OH)_2$ D levels of hypertensive patients. Relationship with ACE polymorphisms," *Hormone and Metabolic Research*, vol. 38, no. 12, pp. 812–816, 2006.

[45] W. Xiang, J. Kong, S. Chen et al., "Cardiac hypertrophy in vitamin D receptor knockout mice: role of the systemic and cardiac renin-angiotensin systems," *American Journal of Physiology*, vol. 288, no. 1, pp. E125–E132, 2005.

[46] H. Hagiwara, H. Furuhashi, K. Nakaya, and Y. Nakamura, "Effects of vitamin D_3 and related compounds on angiotensin converting enzyme activity of endothelial cells and on release of plasminogen activator from them," *Chemical and Pharmaceutical Bulletin*, vol. 36, no. 12, pp. 4858–4864, 1988.

[47] J. R. Hascalovici, J. Vaya, S. Khatib et al., "Brain sterol dysregulation in sporadic AD and MCI: relationship to heme oxygenase-1," *Journal of Neurochemistry*, vol. 110, no. 4, pp. 1241–1253, 2009.

[48] D. E. Barañano and S. H. Snyder, "Neural roles for heme oxygenase: contrasts to nitric oxide synthase," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 98, no. 20, pp. 10996–11002, 2001.

[49] R. Castellani, M. A. Smith, P. L. Richey, and G. Perry, "Glycoxidation and oxidative stress in Parkinson disease and diffuse Lewy body disease," *Brain Research*, vol. 737, no. 1-2, pp. 195–200, 1996.

[50] I. Mateo, J. Infante, P. Sánchez-Juan et al., "Serum heme oxygenase-1 levels are increased in Parkinson's disease but not in Alzheimer's disease," *Acta Neurologica Scandinavica*, vol. 121, no. 2, pp. 136–138, 2010.

[51] E. Oermann, H. J. Bidmon, O. W. Witte, and K. Zilles, "Effects of 1α,25 dihydroxyvitamin D_3 on the expression of HO-1 and GFAP in glial cells of the photothrombotically lesioned cerebral cortex," *Journal of Chemical Neuroanatomy*, vol. 28, no. 4, pp. 225–238, 2004.

[52] J. Soós, J. I. Engelhardt, L. Siklós, L. Havas, and K. Majtényi, "The expression of PARP, NF-κB and parvalbumin is increased in Parkinson disease," *NeuroReport*, vol. 15, no. 11, pp. 1715–1718, 2004.

[53] H. Wang, M. Shimoji, S. W. Yu, T. M. Dawson, and V. L. Dawson, "Apoptosis inducing factor and PARP-mediated injury in the MPTP mouse model of Parkinson's disease," *Annals of the New York Academy of Sciences*, vol. 991, pp. 132–139, 2003.

[54] A. S. Mandir, S. Przedborski, V. Jackson-Lewis et al., "Poly (ADP-ribose) polymerase activation mediates 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 96, no. 10, pp. 5774–5779, 1999.

[55] A. Iwashita, K. Mihara, S. Yamazaki et al., "A new poly (ADP-ribose) polymerase inhibitor, FR261529 [2-(4-chlorophenyl)-5-quinoxalinecarboxamide], ameliorates methamphetamine-induced dopaminergic neurotoxicity in mice," *Journal of Pharmacology and Experimental Therapeutics*, vol. 310, no. 3, pp. 1114–1124, 2004.

[56] H. Yokoyama, H. Kuroiwa, T. Tsukada, H. Uchida, H. Kato, and T. Araki, "Poly(ADP-ribose)polymerase inhibitor can attenuate the neuronal death after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced neurotoxicity in mice," *Journal of Neuroscience Research*, vol. 88, no. 7, pp. 1522–1536, 2010.

[57] J. Infante, P. Sánchez-Juan, I. Mateo et al., "Poly (ADP-ribose) polymerase-1 (PARP-1) genetic variants are protective against Parkinson's disease," *Journal of the Neurological Sciences*, vol. 256, no. 1-2, pp. 68–70, 2007.

[58] M. Bhatia, J. B. Kirkland, and K. A. Mecking-Gill, "Modulation of poly(ADP-ribose) polymerase during neurophilic and monocytic differentiation of promyelocytic (NB4) and myelocytic (HL-60) leakaemia cells," *Biochemical Journal*, vol. 308, pp. 131–137, 1995.

[59] J. G. Mabley, R. Wallace, P. Pacher, K. Murphy, and C. Szabó, "Inhibition of poly(adenosine diphosphate-ribose) polymerase by the active form of vitamin D," *International Journal of Molecular Medicine*, vol. 19, no. 6, pp. 947–952, 2007.

[60] M. Shen and A. Yen, "Nicotinamide cooperates with retinoic acid and 1,25-dihydroxyvitamin D_3 to regulate cell differentiation and cell cycle arrest of human myeloblastic leukemia cells," *Oncology*, vol. 76, no. 2, pp. 91–100, 2009.

[61] M. Moore, A. Piazza, Y. Nolan, and M. A. Lynch, "Treatment with dexamethasone and vitamin D_3 attenuates neuroinflammatory age-related changes in rat hippocampus," *Synapse*, vol. 61, no. 10, pp. 851–861, 2007.

[62] A. K. McAllister, "Neurotrophins and neuronal differentiation in the central nervous system," *Cellular and Molecular Life Sciences*, vol. 58, no. 8, pp. 1054–1060, 2001.

[63] T. Numakawa, T. Matsumoto, M. Numakawa, M. Richards, S. Yamawaki, and H. Kunugi, "Protection action of neurotrophic factors and estrogen against oxidative stress-mediated neurodegeneration," *Journal of Toxicology*, vol. 2011, Article ID 405194, 12 pages, 2011.

[64] E. Garbayo, E. Ansorena, J. L. Lanciego, M. J. Blanco-Prieto, and M. S. Aymerich, "Long-term neuroprotection and neurorestoration by glial cell-derived neurotrophic factor microspheres for the treatment of Parkinson's disease," *Movement Disorders*, vol. 26, no. 10, pp. 1943–1947, 2011.

[65] M. H. Voutilainen, S. Bäck, E. Pörsti et al., "Mesencephalic astrocyte-derived neurotrophic factor is neurorestorative in rat model of Parkinson's disease," *Journal of Neuroscience*, vol. 29, no. 30, pp. 9651–9659, 2009.

[66] Z.-P. Sun, L. Gong, S.-H. Huang, Z. Geng, L. Cheng, and Z.-Y. Chen, "Intracellular trafficking and secretion of cerebral dopamine neurotrophic factor in neurosecretory cells," *Journal of Neurochemistry*, vol. 117, no. 1, pp. 121–132, 2011.

[67] Q. Yan, M. J. Radeke, C. R. Matheson, J. Talvenheimo, A. A. Welcher, and S. C. Feinstein, "Immunocytochemical localization of TrkB in the central nervous system of the adult rat," *Journal of Comparative Neurology*, vol. 378, no. 1, pp. 135–157, 1997.

[68] S. Marco, J. Saura, E. Prez-Navarro, M. J. Mart, E. Tolosa, and J. Alberch, "Regulation of c-Ret, GFRα1, and GFRα2 in the substantia nigra pars compacta in a rat model of Parkinson's disease," *Journal of Neurobiology*, vol. 52, no. 4, pp. 343–351, 2002.

[69] M. Mogi, A. Togari, T. Kondo et al., "Brain-derived growth factor and nerve growth factor concentrations are decreased in the substantia nigra in Parkinson's disease," *Neuroscience Letters*, vol. 270, no. 1, pp. 45–48, 1999.

[70] D. W. Howells, M. J. Porritt, J. Y. F. Wong et al., "Reduced BDNF mRNA expression in the Parkinson's disease

substantia nigra," *Experimental Neurology*, vol. 166, no. 1, pp. 127–135, 2000.

[71] P. Scalzo, A. Kümmer, T. L. Bretas, F. Cardoso, and A. L. Teixeira, "Serum levels of brain-derived neurotrophic factor correlate with motor impairment in Parkinson's disease," *Journal of Neurology*, vol. 257, no. 4, pp. 540–545, 2010.

[72] J.-M. Choi, J.-H. Hong, M.-J. Chae et al., "Analysis of mutations and the association between polymorphisms in the cerebral dopamine neurotrophic factor (CDNF) gene and Parkinson disease," *Neuroscience Letters*, vol. 493, no. 3, pp. 97–101, 2011.

[73] L. Chen, Y. Wang, H. Xiao et al., "The 712A/G polymorphism of Brain-derived neurotrophic factor is associated with Parkinson's disease but not Major Depressive Disorder in a Chinese Han population," *Biochemical and Biophysical Research Communications*, vol. 408, no. 2, pp. 318–321, 2011.

[74] P. Naveilhan, I. Neveu, C. Baudet et al., "1,25-dihydroxyvitamin D_3 regulates the expression of the low-affinity neurotrophin receptor," *Molecular Brain Research*, vol. 41, no. 1-2, pp. 259–268, 1996.

[75] B. Sanchez, E. Lopez-Martin, C. Segura, J. L. Labandeira-Garcia, and R. Perez-Fernandez, "1,25-Dihydroxyvitamin D_3 increases striatal GDNF mRNA and protein expression in adult rats," *Molecular Brain Research*, vol. 108, no. 1-2, pp. 143–146, 2002.

[76] P. Naveilhan, I. Neveu, D. Wion, and P. Brachet, "1,25-Dihydroxyvitamin D_3, an inducer of glial cell line-derived neurotrophic factor," *NeuroReport*, vol. 7, no. 13, pp. 2171–2175, 1996.

[77] F. Féron, T. H. J. Burne, J. Brown et al., "Developmental Vitamin D_3 deficiency alters the adult rat brain," *Brain Research Bulletin*, vol. 65, no. 2, pp. 141–148, 2005.

[78] M. P. Smith, A. Fletcher-Turner, D. M. Yurek, and W. A. Cass, "Calcitriol protection against dopamine loss induced by intracerebroventricular administration of 6-hydroxydopamine," *Neurochemical Research*, vol. 31, no. 4, pp. 533–539, 2006.

[79] B. Sanchez, J. L. Relova, R. Gallego, I. Ben-Batalla, and R. Perez-Fernandez, "1,25-Dihydroxyvitamin D_3 administration to 6-hydroxydopamine-lesioned rats increases glial cell line-derived neurotrophic factor and partially restores tyrosine hydroxylase expression in substantia nigra and striatum," *Journal of Neuroscience Research*, vol. 87, no. 3, pp. 723–732, 2009.

[80] H. Ryu, J. Lee, K. Zaman et al., "Sp1 and Sp3 are oxidative stress-inducible, antideath transcription factors in cortical neurons," *Journal of Neuroscience*, vol. 23, no. 9, pp. 3597–3606, 2003.

[81] J. Wang and M. J. Bannon, "Sp1 and Sp3 activate transcription of the human dopamine transporter gene," *Journal of Neurochemistry*, vol. 93, no. 2, pp. 474–482, 2005.

[82] S. Yajima, S. H. Lee, T. Minowa, and M. M. Mouradian, "Sp family transcription factors regulate expression of rat D2 dopamine receptor gene," *DNA and Cell Biology*, vol. 17, no. 5, pp. 471–479, 1998.

[83] D. P. Figlewicz, S. B. Evans, J. Murphy, M. Hoen, and D. G. Baskin, "Expression of receptors for insulin and leptin inthe ventral tegmental area/substantia nigra (VTA/SN) of the rat," *Brain Research*, vol. 964, no. 1, pp. 107–115, 2003.

[84] M. Takahashi, T. Yamada, I. Tooyama et al., "Insulin receptor mRNA in the substantia nigra in Parkinson's disease," *Neuroscience Letters*, vol. 204, no. 3, pp. 201–204, 1996.

[85] R. Sandyk, "The relationship between diabetes mellitus and Parkinson's disease," *International Journal of Neuroscience*, vol. 69, no. 1–4, pp. 125–130, 1993.

[86] M. D'Amelio, P. Ragonese, G. Callari et al., "Diabetes preceding Parkinson's disease onset. A case-control study," *Parkinsonism and Related Disorders*, vol. 15, no. 9, pp. 660–664, 2009.

[87] Q. Xu, Y. Park, X. Huang et al., "Diabetes and risk of Parkinson's disease," *Diabetes Care*, vol. 34, no. 4, pp. 910–915, 2011.

[88] E. Schernhammer, J. Hansen, K. Rugbjerg, L. Wermuth, and B. Ritz, "Diabetes and the risk of developing Parkinson's disease in Denmark," *Diabetes Care*, vol. 34, no. 5, pp. 1102–1108, 2011.

[89] K. M. Powers, T. Smith-Weller, G. M. Franklin, W. T. Longstreth, P. D. Swanson, and H. Checkoway, "Diabetes, smoking, and other medical conditions in relation to Parkinson's disease risk," *Parkinsonism and Related Disorders*, vol. 12, no. 3, pp. 185–189, 2006.

[90] C. Becker, G. P. Brobert, S. Johansson, S. S. Jick, and C. R. Meier, "Diabetes in patients with idiopathic parkinson's disease," *Diabetes Care*, vol. 31, no. 9, pp. 1808–1812, 2008.

[91] M. A. Fishel, G. S. Watson, T. J. Montine et al., "Hyperinsulinemia provokes synchronous increases in central inflammation and β-amyloid in normal adults," *Archives of Neurology*, vol. 62, no. 10, pp. 1539–1544, 2005.

[92] J. K. Morris, H. Zhang, A. A. Gupte, G. L. Bomhoff, J. A. Stanford, and P. C. Geiger, "Measures of striatal insulin resistance in a 6-hydroxydopamine model of Parkinson's disease," *Brain Research*, vol. 1240, no. C, pp. 185–195, 2008.

[93] K. R. Wilhelm, K. Yanamandra, M. A. Gruden et al., "Immune reactivity towards insulin, its amyloid and protein S100B in blood sera of Parkinson's disease patients," *European Journal of Neurology*, vol. 14, no. 3, pp. 327–334, 2007.

[94] M. H. Van Woert and P. S. Mueller, "Glucose, insulin, and free fatty acid metabolism in Parkinson's disease treated with levodopa," *Clinical Pharmacology and Therapeutics*, vol. 12, no. 2, pp. 360–367, 1971.

[95] A. E. Boyd 3rd. A.E., H. E. Lebovitz, and J. M. Feldman, "Endocrine function and glucose metabolism in patients with Parkinson's disease and their alternation by L-Dopa," *Journal of Clinical Endocrinology and Metabolism*, vol. 33, no. 5, pp. 829–837, 1971.

[96] E. Murzi, Q. Contreras, L. Teneud et al., "Diabetes decreases limbic extracellular dopamine in rats," *Neuroscience Letters*, vol. 202, no. 3, pp. 141–144, 1996.

[97] H. Shimizu, Y. Shimomura, M. Takahashi, I. Kobayashi, and S. Kobayashi, "Dopamine receptor in the streptozotocin-induced diabetic rats," *Experimental and Clinical Endocrinology*, vol. 95, no. 2, pp. 263–266, 1990.

[98] H. Kaur, K. C. Donaghue, A. K. Chan et al., "Vitamin D deficiency is associated with retinopathy in children and adolescents with type 1 diabetes," *Diabetes Care*, vol. 34, no. 6, pp. 1400–1402, 2011.

[99] Y.-F. Yiu, Y.-H. Chan, K.-H. Yiu et al., "Vitamin D deficiency is associated with depletion of circulating endothelial progenitor cells and endothelial dysfunction in patients with type 2 diabetes," *Journal of Clinical Endocrinology and Metabolism*, vol. 96, no. 5, pp. E830–E835, 2011.

[100] J. Verhaeghe, A. M. H. Suiker, R. Van Bree et al., "Increased clearance of $1,25(OH)_2D_3$ and tissue-specific responsiveness to $1,25(OH)_2D_3$ in diabetic rats," *American Journal of Physiology*, vol. 265, no. 2, pp. E215–E223, 1993.

[101] Y. Sato, M. Kikuyama, and K. Oizumi, "High prevalence of vitamin D deficiency and reduced bone mass in Parkinson's disease," *Neurology*, vol. 49, no. 5, pp. 1273–1278, 1997.

[102] M. L. Evatt, M. R. DeLong, M. Kumari, P. Auinger, M. P. McDermott, and V. Tangpricha, "High prevalence of hypovitaminosis D status in patients with early Parkinson disease," *Archives of Neurology*, vol. 68, no. 3, pp. 314–319, 2011.

[103] P. Knekt, A. Kilkkinen, H. Rissanen, J. Marniemi, K. Sääksjärvi, and M. Heliövaara, "Serum vitamin D and the risk of Parkinson disease," *Archives of Neurology*, vol. 67, no. 7, pp. 808–811, 2010.

[104] K. T. Peeyush, B. Savitha, A. Sherin, T. R. Anju, P. Jes, and C. S. Paulose, "Cholinergic, dopaminergic and insulin receptors gene expression in the cerebellum of streptozotocin-induced diabetic rats: functional regulation with Vitamin D_3 supplementation," *Pharmacology Biochemistry and Behavior*, vol. 95, no. 2, pp. 216–222, 2010.

[105] X. Cui, M. Pelekanos, T. H. J. Burne, J. J. McGrath, and D. W. Eyles, "Maternal vitamin D deficiency alters the expression of genes involved in dopamine specification in the developing rat mesencephalon," *Neuroscience Letters*, vol. 486, no. 3, pp. 220–223, 2010.

[106] J. Y. Wang, J. N. Wu, T. L. Cherng et al., "Vitamin D_3 attenuates 6-hydroxydopamine-induced neurotoxicity in rats," *Brain Research*, vol. 904, no. 1, pp. 67–75, 2001.

[107] K. Shinpo, S. Kikuchi, H. Sasaki, F. Moriwaka, and K. Tashiro, "Effect of 1,25-dihydroxyvitamin D_3 on cultured mesencephalic dopaminergic neurons to the combined toxicity caused by L-buthionine sulfoximine and 1-methyl-4-phenylpyridine," *Journal of Neuroscience Research*, vol. 62, no. 3, pp. 374–382, 2000.

[108] L. Derex and P. Trouillas, "Reversible Parkinsonism, hypophosphoremia, and hypocalcemia under vitamin D therapy: case report," *Movement Disorders*, vol. 12, no. 4, pp. 612–613, 1997.

[109] D. J. Surmeier, "Calcium, ageing, and neuronal vulnerability in Parkinson's disease," *Lancet Neurology*, vol. 6, no. 10, pp. 933–938, 2007.

[110] G. Martella, G. Madeo, T. Schirinzi et al., "Altered profile and D_2-dopamine receptor modulation of high voltage-activated calcium current in striatal medium spiny neurons from animal models of Parkinson's disease," *Neuroscience*, vol. 177, pp. 240–251, 2011.

[111] C. R. Lee and J. M. Tepper, "A calcium-activated nonselective cation conductance underlies the plateau potential in rat substantia nigra GABAergic neurons," *Journal of Neuroscience*, vol. 27, no. 24, pp. 6531–6541, 2007.

[112] C. S. Chan, T. S. Gertler, and D. J. Surmeier, "A molecular basis for the increased vulnerability of substantia nigra dopamine neurons in aging and Parkinson's disease," *Movement Disorders*, vol. 25, no. 1, pp. S63–S70, 2010.

[113] C. S. Chan, T. S. Gertler, and D. J. Surmeier, "Calcium homeostasis, selective vulnerability and Parkinson's disease," *Trends in Neurosciences*, vol. 32, no. 5, pp. 249–256, 2009.

[114] A. Kupsch, M. Gerlach, S. C. Pupeter et al., "Pretreatment with nimodipine prevents MPTP-induced neurotoxicity at the nigral, but not at the striatal level in mice," *NeuroReport*, vol. 6, no. 4, pp. 621–625, 1995.

[115] A. Kupsch, J. Sautter, J. Schwarz, P. Riederer, M. Gerlach, and W. H. Oertel, "1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced neurotoxicity in non-human primates is antagonized by pretreatment with nimodipine at the nigral, but not at the striatal level," *Brain Research*, vol. 741, no. 1-2, pp. 185–196, 1996.

[116] S. Schuster, E. Doudnikoff, D. Rylander et al., "Antagonizing L-type Ca^{2+} Channel Reduces Development of Abnormal Involuntary Movement in the Rat Model of L-3,4-Dihydroxyphenylalanine-Induced Dyskinesia," *Biological Psychiatry*, vol. 65, no. 6, pp. 518–526, 2009.

[117] E. Dursun, D. Gezen-Ak, and S. Yilmazer, "A novel perspective for Alzheimer's disease: vitamin D receptor suppression by amyloid-β and preventing the amyloid-β induced alterations by vitamin D in cortical neurons," *Journal of Alzheimer's Disease*, vol. 23, no. 2, pp. 207–219, 2011.

[118] L. D. Brewer, N. M. Porter, D. S. Kerr, P. W. Landfield, and O. Thibault, "Chronic 1α,25-$(OH)_2$vitamin D_3 treatment reduces Ca^{2+}-mediated hippocampal biomarkers of aging," *Cell Calcium*, vol. 40, no. 3, pp. 277–286, 2006.

[119] L. D. Brewer, V. Thibault, K. C. Chen, M. C. Langub, P. W. Landfield, and N. M. Porter, "Vitamin D hormone confers neuroprotection in parallel with downregulation of L-type calcium channel expression in hippocampal neurons," *Journal of Neuroscience*, vol. 21, no. 1, pp. 98–108, 2001.

[120] J. J. Shan, B. Li, N. Taniguchi, and P. K. T. Pang, "Inhibition of membrane L-type calcium channel activity and intracellular calcium concentration by 24R,25-dihydroxyvitamin D_3 in vascular smooth muscle," *Steroids*, vol. 61, no. 11, pp. 657–663, 1996.

[121] C. W. K. Wu and H. H. Yeh, "Nerve growth factor rapidly increases muscarinic tone in mouse medial septum/diagonal band of Broca," *Journal of Neuroscience*, vol. 25, no. 17, pp. 4232–4242, 2005.

[122] B. Poucet and T. Herrmann, "Septum and medial frontal cortex contribution to spatial problem-solving," *Behavioural Brain Research*, vol. 37, no. 3, pp. 269–280, 1990.

[123] D. S. Olton, J. A. Walker, and F. H. Gage, "Hippocampal connections and spatial discrimination," *Brain Research*, vol. 139, no. 2, pp. 295–308, 1978.

[124] T. Nishio, S. Furukawa, I. Akiguchi, and N. Sunohara, "Medial nigral dopamine neurons have rich neurotrophin support in humans," *NeuroReport*, vol. 9, no. 12, pp. 2847–2851, 1998.

[125] V. Silani, A. Pizzuti, A. Falini et al., "β-Nerve growth factor (β-NGF) mRNA expression in the Parkinsonian adrenal gland," *Experimental Neurology*, vol. 113, no. 2, pp. 166–170, 1991.

[126] L. Lorigados Pedre, N. Pavón Fuentes, L. Alvarez González et al., "Nerve growth factor levels in parkinson disease and experimental parkinsonian rats," *Brain Research*, vol. 952, no. 1, pp. 122–127, 2002.

[127] K. Shimoke and H. Chiba, "Nerve growth factor prevents 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced cell death via the Akt pathway by suppressing caspase-3-like activity using PC12 cells: relevance to therapeutical application for Parkinson's disease," *Journal of Neuroscience Research*, vol. 63, no. 5, pp. 402–409, 2001.

[128] Y. Hirata, T. Meguro, and K. Kiuchi, "Differential effect of nerve growth factor on dopaminergic neurotoxin-induced apoptosis," *Journal of Neurochemistry*, vol. 99, no. 2, pp. 416–425, 2006.

[129] M. Salinas, R. Diaz, N. G. Abraham, C. M. R. De Galarreta, and A. Cuadrado, "Nerve growth factor protects against 6-hydroxydopamine-induced oxidative stress by increasing expression of heme oxygenase-1 in a phosphatidylinositol

3-kinase-dependent manner," *Journal of Biological Chemistry*, vol. 278, no. 16, pp. 13898–13904, 2003.

[130] P. Forander, S. Soderstrom, C. Humpel, and I. Strömberg, "Chronic infusion of nerve growth factor into rat striatum increases cholinergic markers and inhibits striatal neuronal discharge rate," *European Journal of Neuroscience*, vol. 8, no. 9, pp. 1822–1832, 1996.

[131] R. K. Chaturvedi, S. Shukla, K. Seth, and A. K. Agrawal, "Nerve growth factor increases survival of dopaminergic graft, rescue nigral dopaminergic neurons and restores functional deficits in rat model of Parkinson's disease," *Neuroscience Letters*, vol. 398, no. 1-2, pp. 44–49, 2006.

[132] M. Li, S. Z. Zhang, Y. W. Guo et al., "Human umbilical vein-derived dopaminergic-like cell transplantation with nerve growth factor ameliorates motor dysfunction in a rat model of parkinson's disease," *Neurochemical Research*, vol. 35, no. 10, pp. 1522–1529, 2010.

[133] A. Cornet, C. Baudet, I. Neveu, A. Baron-Van Evercooren, P. Brachet, and P. Naveilhan, "1,25-Dihydroxyvitamin D_3 regulates the expression of VDR and NGF gene in Schwann cells in vitro," *Journal of Neuroscience Research*, vol. 53, no. 6, pp. 742–746, 1998.

[134] I. M. Musiol and D. Feldman, "1,25-dihydroxyvitamin D_3 induction of nerve growth factor in L929 mouse fibroblasts: effect of vitamin D receptor regulation and potency of vitamin D_3 analogs," *Endocrinology*, vol. 138, no. 1, pp. 12–18, 1997.

[135] T. D. Veenstra, M. Fahnestock, and R. Kumar, "An AP-1 site in the nerve growth factor promoter is essential for 1,25-dihydroxyvitamin D_3-mediated nerve growth factor expression in osteoblasts," *Biochemistry*, vol. 37, no. 17, pp. 5988–5994, 1998.

[136] J. A. McClain, L. L. Phillips, and H. L. Fillmore, "Increased MMP-3 and CTGF expression during lipopolysaccharide-induced dopaminergic neurodegeneration," *Neuroscience Letters*, vol. 460, no. 1, pp. 27–31, 2009.

[137] S. Lorenzl, N. Calingasan, L. Yang et al., "Matrix metalloproteinase-9 is elevated in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonism in mice," *Neuro-Molecular Medicine*, vol. 5, no. 2, pp. 119–131, 2004.

[138] S. Y. Kim, M. S. Woo, J. S. Park, J. W. Hyun, Y. S. Kim, and H. S. Kim, "The neuroprotective role of tissue inhibitor of metalloproteinase-2 in MPP^+- or 6-OHDA-treated SK-N-BE(2)C and SH-SY5Y human neuroblastoma cells," *Neuroscience Letters*, vol. 468, no. 2, pp. 136–140, 2010.

[139] S. Kim, M. Moon, and S. Park, "Exendin-4 protects dopaminergic neurons by inhibition of microglial activation and matrix metalloproteinase-3 expression in an animal model of Parkinson's disease," *Journal of Endocrinology*, vol. 202, no. 3, pp. 431–439, 2009.

[140] P. M. Timms, N. Mannan, G. A. Hitman et al., "Circulating MMP9, vitamin D and variation in the TIMP-1 response with VDR genotype: mechanisms for inflammatory damage in chronic disorders?" *Monthly Journal of the Association of Physicians*, vol. 95, no. 12, pp. 787–796, 2002.

[141] D. D. Dean, Z. Schwartz, J. Schmitz et al., "Vitamin D regulation of metalloproteinase activity in matrix vesicles," *Connective Tissue Research*, vol. 35, no. 1–4, pp. 331–336, 1996.

[142] K. Bahar-Shany, A. Ravid, and R. Koren, "Upregulation of MMP-9 production by TNFα in keratinocytes and its attenuation by vitamin D," *Journal of Cellular Physiology*, vol. 222, no. 3, pp. 729–737, 2010.

[143] K. Nakagawa, Y. Sasaki, S. Kato, N. Kubodera, and T. Okano, "22-Oxa-1α,25-dihydroxyvitamin D_3 inhibits metastasis and angiogenesis in lung cancer," *Carcinogenesis*, vol. 26, no. 6, pp. 1044–1054, 2005.

[144] E. Ricciotti and G. A. Fitzgerald, "Prostaglandins and inflammation," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 31, no. 5, pp. 986–1000, 2011.

[145] M. B. Mattammal, R. Strong, V. M. Lakshmi, H. D. Chung, and A. H. Stephenson, "Prostaglandin H synthetase-mediated metabolism of dopamine: implication for Parkinson's disease," *Journal of Neurochemistry*, vol. 64, no. 4, pp. 1645–1654, 1995.

[146] T. Wang, Z. Pei, W. Zhang et al., "MPP^+-induced COX-2 activation and subsequent dopaminergic neurodegeneration," *FASEB Journal*, vol. 19, no. 9, pp. 1134–1136, 2005.

[147] E. Carrasco, D. Casper, and P. Werner, "PGE_2 receptor EP1 renders dopaminergic neurons selectively vulnerable to low-level oxidative stress and direct PGE_2 neurotoxicity," *Journal of Neuroscience Research*, vol. 85, no. 14, pp. 3109–3117, 2007.

[148] C. Knott, G. Stern, and G. P. Wilkin, "Inflammatory regulators in Parkinson's disease: iNOS, lipocortin-1, and cyclooxygenases-1 and -2," *Molecular and Cellular Neuroscience*, vol. 16, no. 6, pp. 724–739, 2000.

[149] P. Teismann, K. Tieu, D. K. Choi et al., "Cyclooxygenase-2 is instrumental in Parkinson's disease neurodegeneration," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 100, no. 9, pp. 5473–5478, 2003.

[150] P. Teismann and B. Ferger, "Inhibition of the cyclooxygenase isoenzymes COX-1 and COX-2 provide neuroprotection in the MPTP-mouse model of Parkinson's disease," *Synapse*, vol. 39, no. 2, pp. 167–174, 2001.

[151] H. Chen, S. M. Zhang, M. A. Hernán et al., "Nonsteroidal anti-inflammatory drugs and the risk of Parkinson disease," *Archives of Neurology*, vol. 60, no. 8, pp. 1059–1064, 2003.

[152] J. Moreno, A. V. Krishnan, S. Swami, L. Nonn, D. M. Peehl, and D. Feldman, "Regulation of prostaglandin metabolism by calcitriol attenuates growth stimulation in prostate cancer cells," *Cancer Research*, vol. 65, no. 17, pp. 7917–7925, 2005.

[153] R. Aparna, J. Subhashini, K. R. Roy et al., "Selective inhibition of cyclooxygenase-2 (COX-2) by 1 α,25-dihydroxy- 16-ene-23-yne-vitamin D_3, a less calcemic vitamin D analog," *Journal of Cellular Biochemistry*, vol. 104, no. 5, pp. 1832–1842, 2008.

[154] A. Prigione, I. U. Isaias, A. Galbussera et al., "Increased oxidative stress in lymphocytes from untreated Parkinson's disease patients," *Parkinsonism and Related Disorders*, vol. 15, no. 4, pp. 327–328, 2009.

[155] D. T. Dexter, C. J. Carter, F. R. Wells et al., "Basal lipid peroxidation in substantia nigra is increased in Parkinson's disease," *Journal of Neurochemistry*, vol. 52, no. 2, pp. 381–389, 1989.

[156] D. T. Dexter, A. E. Holley, W. D. Flitter et al., "Increased levels of lipid hydroperoxides in the Parkinsonian Substantia nigra: an HPLC and ESR study," *Movement Disorders*, vol. 9, no. 1, pp. 92–97, 1994.

[157] H. Saggu, J. Cooksey, D. Dexter et al., "A selective increase in particulate superoxide dismutase activity in parkinsonian substantia nigra," *Journal of Neurochemistry*, vol. 53, no. 3, pp. 692–697, 1989.

[158] G. Tesco, S. Latorraca, P. Piersanti, S. Sorbi, S. Piacentini, and L. Amaducci, "Free radical injury in skin cultured fibroblasts from Alzheimer's disease patients," *Annals of the New York Academy of Sciences*, vol. 673, pp. 149–153, 1992.

[159] M. S. Cohen, D. E. Mesler, R. G. Snipes, and T. K. Gray, "1,25-Dihydroxyvitamin D_3 activates secretion of hydrogen peroxide by human monocytes," *Journal of Immunology*, vol. 136, no. 3, pp. 1049–1053, 1986.

[160] R. Levy and H. L. Malech, "Effect of 1,25-dihydroxyvitamin D_3, lipopolysaccharide, or lipoteichoic acid on the expression of NADPH oxidase components in cultured human monocytes," *Journal of Immunology*, vol. 147, no. 9, pp. 3066–3071, 1991.

[161] B. Y. Bao, H. J. Ting, J. W. Hsu, and Y. F. Lee, "Protective role of 1α, 25-dihydroxyvitamin D_3 against oxidative stress in nonmalignant human prostate epithelial cells," *International Journal of Cancer*, vol. 122, no. 12, pp. 2699–2706, 2008.

[162] D. Somjen, S. Katzburg, M. Grafi-Cohen, E. Knoll, O. Sharon, and G. H. Posner, "Vitamin D metabolites and analogs induce lipoxygenase mRNA expression and activity as well as reactive oxygen species (ROS) production in human bone cell line," *Journal of Steroid Biochemistry and Molecular Biology*, vol. 123, no. 1-2, pp. 85–89, 2011.

[163] S. Hunot, F. Boissière, B. Faucheux et al., "Nitric oxide synthase and neuronal vulnerability in Parkinson's disease," *Neuroscience*, vol. 72, no. 2, pp. 355–363, 1996.

[164] M. K. Barthwal, N. Srivastava, R. Shukla et al., "Polymorphonuclear leukocyte nitrite content and antioxidant enzymes in Parkinson's disease patients," *Acta Neurologica Scandinavica*, vol. 100, no. 5, pp. 300–304, 1999.

[165] S. Singh, T. Das, A. Ravindran et al., "Involvement of nitric oxide in neurodegeneration: a study on the experimental models of Parkinson's disease," *Redox Report*, vol. 10, no. 2, pp. 103–109, 2005.

[166] Y. Muramatsu, R. Kurosaki, H. Watanabe et al., "Cerebral alterations in a MPTP-mouse model of Parkinson's disease—an immunocytochemical study," *Journal of Neural Transmission*, vol. 110, no. 10, pp. 1129–1144, 2003.

[167] J. B. Schulz, R. T. Matthews, M. M.K. Muqit, S. E. Browne, and M. F. Beal, "Inhibition of neuronal nitric oxide synthase by 7-nitroindazole protects against MPTP-induced neurotoxicity in mice," *Journal of Neurochemistry*, vol. 64, no. 2, pp. 936–939, 1995.

[168] T. Dehmer, J. Lindenau, S. Haid, J. Dichgans, and J. B. Schulz, "Deficiency of inducible nitric oxide synthase protects against MPTP toxicity in vivo," *Journal of Neurochemistry*, vol. 74, no. 5, pp. 2213–2216, 2000.

[169] D. Kaur, D. Lee, S. Ragapolan, and J. K. Andersen, "Glutathione depletion in immortalized midbrain-derived dopaminergic neurons results in increases in the labile iron pool: implications for Parkinson's disease," *Free Radical Biology and Medicine*, vol. 46, no. 5, pp. 593–598, 2009.

[170] J. M. Chang, M. C. Kuo, H. T. Kuo et al., "1-α,25-Dihydroxyvitamin D_3 regulates inducible nitric oxide synthase messenger RNA expression and nitric oxide release in macrophage-like RAW 264.7 cells," *Journal of Laboratory and Clinical Medicine*, vol. 143, no. 1, pp. 14–22, 2004.

[171] E. Garcion, S. Nataf, A. Berod, F. Darcy, and P. Brachet, "1,25-Dihydroxyvitamin D_3 inhibits the expression of inducible nitric oxide synthase in rat central nervous system during experimental allergic encephalomyelitis," *Molecular Brain Research*, vol. 45, no. 2, pp. 255–267, 1997.

[172] O. Equils, Y. Naiki, A. M. Shapiro et al., "1,25-Dihydroxyvitamin D_3 inhibits lipopolysaccharide-induced immune activation in human endothelial cells," *Clinical and Experimental Immunology*, vol. 143, no. 1, pp. 58–64, 2006.

[173] E. Garcion, L. Sindji, G. Leblondel, P. Brachet, and F. Darcy, "1,25-dihydroxyvitamin D_3 regulates the synthesis of γ-glutamyl transpeptidase and glutathione levels in rat primary astrocytes," *Journal of Neurochemistry*, vol. 73, no. 2, pp. 859–866, 1999.