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Environmental Factors in Alzheimer's and Parkinson's Diseases

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Abstract

Environmental factors can contribute to the pathogenesis of neurodegenerative diseases, including Alzheimer's Diseases (AD) and Parkinson's Diseases (PD). For instance, traumatic brain injury has been suggested to be a chronic health condition. One progressive tauopathy, chronic traumatic encephalopathy, is believed to stem from repeated traumas to the brain. In addition, genetic studies have helped identify a number of factors that link nutrition and medication to the pathogenesis of AD and PD. Nutrition can also contribute to AD and PD via a number of non-genomic mechanisms, including protein expression, oxidative stress, inflammation, and cellular metabolism. Additionally, there is an association between exposure to electromagnetic fields and the development of neurodegenerative diseases. However, there is also a potential therapeutic use for static magnetic fields in the preservation of cognitive performance and motor behavior. Evidence from epidemiological, animal, and cell models suggests that gene-environment interactions can also produce selective neurodegenerative diseases, including AD and PD. In summary, environmental factors (such as trauma, nutrition, medication, and the electromagnetic fields) and the interaction between genes and these environmental factors may play a role in the pathogenesis of AD and PD. Therefore, an understanding of these factors and interactions could provide information on how to intervene, such as correction of poor nutrition, and could prevent the onset of AD and PD or slow their progression, thus contributing to an improvement of health status and quality of life in older age.

Keywords: Parkinson's disease; Environment; Alzheimer's disease; Dementia

Introduction

The two most common neurodegenerative diseases are Alzheimer's Diseases (AD) and Parkinson's Diseases (PD). Their symptoms are initially caused by the selective degeneration of neuronal subpopulations involved in memory or movement control, respectively. The underlying cause of both diseases is usually unknown; however, aging is an inevitable risk factor. Several environmental factors contribute significantly to the risk of developing AD or PD. Studies have demonstrated associations between neurodegenerative diseases, including AD and PD, and environmental factors, such as pesticides, metals, and chemicals. For instance, exposure to heavy metals early in development can precondition the brain to develop a neurodegenerative disease later in life. The effects of lead and mercury were tested in aggregating brain-cell cultures of fetal rat telencephalon, a three-dimensional brain-cell culture system. Both mercury and lead increase the expression of Amyloid Precursor Protein (APP); mercury also stimulates the formation of insoluble β-amyloid, which plays a crucial role in the pathogenesis of AD, and causes oxidative stress and neurotoxicity *in vitro* [1]. These results suggest that the heavy metals lead and mercury contribute to the pathogenesis of neurodegenerative diseases. PD involves the aggregation of α-synuclein into fibrils, which are the major constituent of intracellular protein inclusions (Lewy bodies and Lewy neurites) in dopaminergic neurons of the Substantia Nigra (SN). Several di- and trivalent metal ions caused significant accelerations in the rate of α-synuclein fibril formation. Aluminum was the most effective, along with copper (II), iron (III), cobalt (III), and manganese (II) [2]. Chronic occupational exposure to manganese or copper individually or to dual combinations of lead, iron, and copper is associated with the development of PD [3]. In a prospective cohort study, lower cognitive performance was observed in subjects who had been occupationally exposed to pesticides. In men, the relative risks of developing PD or AD increased to 5.63 and 2.39, respectively, when there was occupational exposure to these metals, as assessed by a job exposure matrix after confounding factors were taken into account [4]. Polychlorinated Biphenyls (PCBs) are synthetic chemicals primarily used as coolants and insulators in electrical equipment. Dementia was reported as a neuropsychological consequence of chronic occupational exposure to PCBs [5]. Epidemiological and laboratory studies also reported a link between PCB exposure and an increased risk for PD; these studies also reported greater susceptibility for females [6]. Exposure to the polybrominated diphenyl ether mixture DE-71, used for its flame retardant properties, was reported to damage the nigrostriatal dopamine system [7]. Oxidative stress and apoptosis have been actively investigated as neurotoxic mechanisms over the past two decades, which has resulted in the increased understanding of neurotoxic processes [8]. Some of these mechanisms may already be active during early stages of life, and some may interact with other genetic factors. In this paper, we review the environmental factors (such as trauma, electromagnetic fields, medication-namely, β-adrenergic receptor blockers-and nutrition, including vitamin D, thiamine, and homocysteine) and the interactions between genes and environmental factors that are involved in the pathogenesis of neurodegenerative diseases, including AD and PD.

The Role of Environmental Factors in Alzheimer's and Parkinson's Diseases

Trauma

In the Central Nervous System (CNS), neurons are highly sensitive to the availability of oxygen. In conditions where oxygen availability is decreased, neuronal function can be altered, leading to injury and

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cell death. It has been suggested that Traumatic Brain Injury (TBI) is a chronic health condition. One progressive tauopathy, Chronic Traumatic Encephalopathy (CTE), is believed to stem from repeated traumas to the brain. CTE has been linked to participation in contact sports such as boxing and American football. CTE results in progressive declines of memory and cognition, depression, suicidal behavior, poor impulse control, aggressiveness, Parkinsonism, and, eventually, dementia [9]. Higher neurodegenerative mortality was observed among players retired from the National Football League in speed positions compared to players in non-speed positions. The mortality from neurodegenerative disease of this cohort is 3 times higher than that of the general US population [10].

AD: The frequent association of CTE with other neurodegenerative disorders suggests that repetitive brain trauma and the deposition of hyperphosphorylated tau protein promote the accumulation of other abnormally aggregated proteins, including TAR DNA-binding protein 43, amyloid β (Aβ) protein, and α-synuclein [11]. Aβ plaques, a hallmark of AD, are found in up to 30% of patients who die acutely following TBI [12,13]. Several case-control studies have suggested that head injury can be a risk factor for AD. The incidence of AD was significantly associated with head injury that occurred within the preceding 30 years [14]. Additionally, there was a statistically significant association between head trauma and AD [15-17]. The associated molecular changes (i.e., altered total tau, Aβ, neurofilament light protein, glial fibrillary acidic protein, and neuron-specific enolase) demonstrate that neuronal and glial injuries are correlated with the number and severity of blows to the head. The risk of punch-drunk syndrome (boxer's dementia or dementia pugilistica) as a late effect of chronic TBI is associated with both the duration of a boxer's career and his earlier stamina [18].

PD: In a population based case-control study, an overall 50% increase in the prevalence of hospital visits for head injury was observed before the first registration of PD [19]. In a case-control study, the frequency of head trauma preceding PD cases was significantly higher than in control cases; additionally, this association between head trauma and the later development of PD varied with severity [20]. Boxing is believed to be a frequent cause for Parkinsonism caused by chronic repetitive head injury. Lolekha et al. [21] revealed in retired traditional Thai boxers that repetitive head trauma may pose an additional risk to certain individuals who are already susceptible to PD. The Parkinsonism of these boxers involved dopaminergic dysfunction with a lesser degree of severity, despite the comparable clinical profile [22]. A systematic review and meta-analysis revealed that a history of head trauma resulting in concussion is associated with a higher risk of developing PD [23]. However, in an analysis of the Swedish National Patient Register, Fang et al. [24] did not find convincing evidence for a causal relationship between head injury later in life and PD, especially for trauma that occurred within the year prior to PD ascertainment. A nationwide population study of severe head injury and PD also failed to support their association [25]. The widely conflicted results found in head injury and PD literature may reflect the fact that many factors, including severity, chronicity, and individual susceptibility, influence the ultimate clinical outcome.

Nutrition

Epidemiological analysis of the relationship between nutrient consumption and degenerative disease is complex. A growing body of evidence suggests there is an association between neurodegenerative diseases and micronutrient status.

Vitamin D: There is ample evidence for vitamin D involvement in mammalian brain function. Vitamin D Receptor (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 and in neurons and glial cells in the hypothalamus [26]. 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 both muscular and motor impairments [27].

AD: A significantly high prevalence of vitamin D insufficiency has been reported in patients with AD [28]. Elderly women who have AD also have an increased prevalence of vitamin D deficiency [29]. Additionally, vitamin D deficiency is associated with low mood and impaired cognitive performance in older adults [30]. Further, there is an association between Mini-Mental State Examination (MMSE) test scores and serum 25-Hydroxyvitamin D_3 (25OHD) levels: patients who had sufficient vitamin D levels had significantly higher MMSE scores compared to patients who had insufficient vitamin D levels [31]. In another study, vitamin D deficiency was associated with increased odds of cognitive impairment in an elderly population in the United States [32]. A vitamin D-free regimen exacerbated the spatial learning deficit in Alzheimer's animal models [33]. Conversely, a vitamin D_3-enriched diet was correlated with a decrease in the number of amyloid plaques, a decrease in Aβ peptides, a decrease in inflammation, and an increase in nerve growth factor in the brains of APP transgenic mice [34]. In a 7-year follow-up study, higher vitamin D dietary intake was associated with a lower risk of developing AD among older women [35]. Furthermore, long-term treatment with calcitriol resulted in a higher density of CA1 neurons in the middle regions of the hippocampus in aging rats [36], suggesting that vitamin D can decrease signs of brain aging. The Membrane-Associated Rapid Response Steroid-Binding Receptor (Calcitriol-MARRS) was reported to be expressed on the cell surface and to mediate the rapid response of calcitriol [37]. Diosgenin derivative, a plant-derived steroidal sapogenin, significantly reduced amyloid deposits and reduced the amount of memory dysfunction in Aβ-infused AD model rats [38]. Diosgenin also exhibited significantly improved performance of object recognition memory in AD model mice and significantly reduced amyloid plaques and neurofibrillary tangles in the cerebral cortex and hippocampus [39]. Calcitriol-MARRS was shown to be a target of diosgenin; knockdown of calcitriol-MARRS completely inhibited diosgenin-induced axonal growth in cortical neurons, and treatment with a neutralizing antibody against calcitriol-MARRS diminished the axonal regeneration effect of diosgenin in Aβ-induced axonal atrophy [39]. These reports suggest that the exogenous stimulator diosgenin activates the calcitriol-MARRS pathway, which may be a critical signaling target for anti-AD therapy. Vitamin D could also exert its effect on AD through nongenomic factors, including L-Type Voltage-Sensitive Calcium Channels (LVSC), Nerve Growth Factor (NGF), the Prostaglandins (PGs), Cyclooxygenase-2 (COX-2), Reactive Oxygen Species (ROS) and Nitric Oxide Synthase (NOS) [40]. Additionally, vitamin D can exert its effects on AD by regulating calcium-sensing receptor expression, enhancing clearance of Aβ peptides, increasing Interleukin-10 (IL-10), down regulating Matrix Metalloproteinases (MMPs), up regulating Heme Oxygenase-1 (HO-1) and suppressing expression of the reduced form of Nicotinamide Adenine Dinucleotide Phosphate (NADP) [41]. Taken together, these results suggest that vitamin D has a beneficial role in AD and could improve cognitive function in some patients with AD.

PD: PD patients have lower 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 control patients [42]. Exposure to sunlight can increase the BMD of PD patients by increasing their serum 25OHD levels [43]. In another study, serum 25OHD and BMD were reported to be reduced in PD patients [44]. There is evidence for abnormalities in vitamin D and the endocrine system in patients with PD, and a high prevalence of vitamin D deficiency has also been reported [28,45,46]. Interestingly, individuals with higher concentrations of serum vitamin D show a reduced risk of PD [47]. In addition, men working outdoors who are exposed to more Ultraviolet (UV) radiation have a lower risk of PD [48]. Interestingly, vitamin D has been reported to improve rigidity and akinesia and to reduce the necessary levodopa dose in a patient with PD [49]. In addition, calcitriol has been shown to protect mesencephalic dopaminergic neurons against a mixture of L-Buthionine Sufimine (BSO) and 1-methyl-4-phenylpyridium ions, which deplete glutathione content [50]. Calcitriol also protects against 6-Hydroxydopamine (6-OHDA)-induced neurotoxicity in rats [51] by upregulating glial cell line-derived neurotrophic factor [52] and partially restores tyrosine hydroxylase expression in the SN and striatum [53]. Calcitriol has also been shown to protect against the dopamine- and serotonin-depleting effects of neurotoxic doses of methamphetamine [54]. Additionally, vitamin D has been implicated in PD through its effects on LVSC, NGF, MMPs, PGs, COX-2, ROS, NOS, bacillus Calmette-Guerin vaccination, IL-10, Wntβ-catenin signaling pathways, Mitogen-Activated Protein Kinase (MAPK) pathways and NADP [55-56]. Taken together, these results suggest that vitamin D may have beneficial role in PD patients.

Thiamine: Thiamine is an essential vitamin that plays an important role in the cellular production of energy from ingested food and enhances normal neuronal actives. Emerging evidence suggests that thiamine deficiency produces alterations in brain function and structural damage that closely models a number of diseases in which neurodegeneration is a characteristic feature, including AD and PD. Thus, thiamine may have a role in AD and PD.

AD: In the neuronal metabolism of glucose, Thiamine Diphosphate (TDP) is an essential coenzyme for mitochondrial pyruvate, α-Ketoglutarate Dehydrogenase (KGD) complexes, and cytosolic transketolase [57,58]. In thiamine deficiency, the levels of thiamine-dependent and non-thiamine-dependent enzymes (succinate and malate dehydrogenase) in the tricarboxylic acid cycle are reduced in the mouse brain [59]. Low plasma thiamine levels have also been reported in patients who have AD [60-62]. In AD patient brains, KGD activities were reduced by more than 75% and those of transketolase were reduced by more than 45% in addition, significant abnormalities of transketolase were identified in red blood cells and cultured fibroblasts from patients with AD [63]. Thiamine is a coenzyme required for the synthesis of acetylcholine, which is the neurotransmitter that is most commonly deficient in AD. In addition, in the neocortex, impaired coupling of muscarinic M1 receptors to G-proteins has been shown to be associated with the severity of dementia in AD [64]. Moreover, it has been shown that the synthesis of acetylcholine is impaired in the brains of thiamine-deficient rats [65], which leads to a significant reduction of neuronal acetylcholine levels [66]. Animal studies have also suggested that thiamine is involved in the presynaptic release of acetylcholine. For instance, it has been shown that thiamine binds to nicotinic receptors and can exhibit anticholinesterase activity [67]. In addition, thiamine deficiency has been shown to induce an early central muscarinic cholinergic lesion [68]. In patients with AD, fursultiamine, a derivative of thiamine, was found to have a mild beneficial effect at an oral dose of 100 mg/d in a 12-week trial [69]. In a short-term trial, Blass et al. [70] demonstrated that using 3 g/day of oral thiamine improved the global cognitive rating determined by the MMSE in AD patients. In another study using 3 to 8 g/d of oral thiamine, Meador et al. [67] reported a mild beneficial effect of thiamine in patients with AD. The long-term oral administration of thiamine at 3 g/d however, did not slow the progression of AD [71]. Eight weeks benfotiamine treatment was found to improve the cognitive function and to reduce both the number of amyloid plaques and the level of phosphorylated tau via a thiamine-independent mechanism in an animal model of AD [72]. However, these effects were not observed using fursultiamine. Interestingly, benfotiamine was unable to raise the levels of intracerebral thiamine phosphate derivatives [73]. In addition, benfotiamine does not easily cross neuroblastoma cell membranes in cultured cells [74]. Sulbutiamine, a lipid-soluble thiamine disulfide derivative, which increases thiamine derivatives in the brain and in cultured cells, can be used as a CNS drug. In rats, chronic treatment with sulbutiamine was shown to improve memory in an object recognition task and to reduce the amnesic effects of dizocilpine, a blocker of N-methyl-D-aspartate glutamate receptors [74,75]. Furthermore, sulbutiamine has been shown to act synergistically with acetylcholinesterase inhibitors in patients who have early-stage AD or moderate-stage AD [76]. Furthermore, genetic studies have provided the opportunity to determine what proteins link thiamine to AD pathology, including transketolase, apolipoprotein E, α-1-antitrypsin, pyruvate dehydrogenase complex, transcription factor *p53*, glycogen synthetase kinase-3β, *c-Fos* gene, the *Sp1*gene promoter, and the *poly*(*ADP-ribosyl*) *polymerase-1* (*PARP-1*) gene [77]. These findings suggest that thiamine may have a role in the pathogenesis of AD.

PD: Dopamine has been reported to suppress the Mouse-Killing Aggression (muricide) that is induced with a Thiamine-Deficient (TD) diet [78]. This suppressive effect can be potentiated with carbidopa [79]. Patients with PD who have undergone levodopa therapy show significantly higher Cerebrospinal Fluid (CSF) levels of TDP and total thiamine than those patients who are not treated with this drug [80]. Moreover, thiamine deficiency can decrease the concentration of dopamine in the striatum, whereas animals fed a diet containing 5% ethanol show increased dopamine turnover [81]. In an experimental TD study, a region-specific vesicular dysfunction, i.e., decreased levels of dopaminergic metabolites, was observed [82]. Intrastriatal administration of Thiamine Triphosphate (TTP) or TDP induces dopamine release [83]. These findings suggest a relationship between thiamine and dopamine. Moreover, thiamine derivatives are present in the human SN at high concentrations [84]. With intrastriatal TTP or TDP administration, dopamine release is increased up to 1400% and 249% of basal levels, respectively; reduced dopamine in the striatum may occur with a thiamine deficiency [83]. Lower CSF-free thiamine levels were noted in PD patients compared to control patients [80]. In parkinsonism-dementia patients, thiamine pyrophosphatase activity was significantly lower in the frontal cortex [85]. In addition, Gold et al. [86] reported that 70% of their PD patients had low plasma thiamine levels and that 33% had low RBC thiamine levels. Starvation TD encephalopathy may also induce symmetrical lesions in the SN [87]. These findings suggest that thiamine could have a role in the activity of dopaminergic neurons. Interestingly, parenteral thiamine administration was used successfully in 9 non-alcoholic patients who presented with acute neurological disorders [88]. The combined administration of thiamine and acetazolamide was reported to reduce scores on the Abnormal Involuntary Movement Scale (AIMS) and the Simpson-Angus Neurological Rating Scale (ANRS) in patients who had tardive dyskinesia and Parkinsonism symptoms [89]. Genetic studies have helped identify a number of factors that link thiamine to PD pathology, including the *DJ-1* gene, Excitatory Amino Acid Transporters (EAATs), the A-Ketoglutarate Dehydrogenase Complex

(KGDHC), Coenzyme Q10 (CoQ_{10} or Ubiquinone), Lipoamide Dehydrogenase (LAD), chromosome 7, transcription factor p53, the Renin–Angiotensin System (RAS), HO-1, and *PARP-1*. Thiamine has also been implicated in PD because of its effects on LVSC, MMPs, PGs, COX-2, ROS, and NOS [90]. Taken together, these findings suggest that thiamine may be beneficial in PD patients.

Homocysteine: Homocysteine is an important intermediate involved in the biosynthesis of methionine and cysteine. Intracellular homocysteine has an integral role in the methylation of biological molecules. Low concentrations of methionine activate the transmethylation of homocysteine, which is the donor of the methyl groups that are necessary for the synthesis of proteins, DNA, RNA, phospholipids, myelin, and catecholamines. Hyperhomocysteinemia is a risk factor for a number of neurodegenerative diseases. Toxic effects of homocysteine and the product of its spontaneous oxidation, homocysteic acid, are based on their capacity to activate N-Methyl-D-Aspartate (NMDA) receptors, which increase intracellular ionized calcium and ROS levels. Even a short-term exposure of cells to homocysteic acid at concentrations characteristic of hyperhomocysteinemia induces their apoptotic transformation [91]. Homocysteine also promoted the activity of NADPH oxidases, resulting in the generation of ROS [92].

AD: Serum homocysteine levels are markedly elevated both in AD and vascular dementia subjects compared to control subjects [93]. Homocysteine concentrations at the upper end of the normal range among the elderly strongly relate to the rate of global cognitive decline in AD patients [94]. Homocysteine reduced Cu (II) more effectively than cysteine or methionine but did not reduce Fe (III) to Fe (II). Homocysteine also generated high levels of hydrogen peroxide in the presence of Cu (II) and promoted Aβ/Cu-mediated hydrogen peroxide production and neurotoxicity in primary neuronal cultures [95], suggesting that increased copper and/or homocysteine levels in the elderly could promote significant oxidant damage to neurons and may represent additional risk factor pathways that conspire to produce AD or other related neurodegenerative conditions. Sudduth et al. [96] developed a model of vascular dementia by inducing hyperhomocysteinemia in wild-type mice. By placing wild-type mice on a diet deficient in folate, vitamin B6, and B12 and supplemented with excess methionine, they induced moderate hyperhomocysteinemia. After 11 weeks on this diet, the hyperhomocysteinemic mice had spatial memory deficits, as assessed by the 2-day radial-arm water maze. The hyperhomocysteinemia-inducing diet worsened pathology [97] and increased Aβ formation and deposition in the transgenic mice [98]. Hyperhomocysteinemia increased Aβ production by enhancing the expression of γ-secretase and the phosphorylation of amyloid precursor protein, which in turn caused memory deficits that, could be rescued with folate and vitamin-B_{12} treatment in rat brains [99]. Mendoza-Oliva et al. [100] demonstrated that the combined effect of cholesterol and homocysteine in the presence of copper significantly increases ROS levels and may render neurons more vulnerable to Aβ in human neuroblastoma cells. This finding suggests interplay between cholesterol and homocysteine in the exacerbation of Aβ toxicity. Homocysteine induces apoptosis of rat hippocampal neurons by inhibiting 14-3-3ε expression and activating calcineurin in a dose-dependent manner [101]. 14-3-3 is involved in the regulation of apoptosis, and 14-3-3 depletion can lead to activation of pro-apoptotic factors [102]. The administration of folates and vitamins is able to reduce serum homocysteine levels and to antagonize some mechanisms that favor neurodegenerative impairments, such as mild cognitive impairment, AD, and dementia [103].

PD: Elevated plasma homocysteine levels were reported in L-dopa-treated PD patients who had cognitive dysfunctions [104] and dyskinesias [105]. In a meta-analysis, PD patients treated with L-dopa plus Catechol-O-Methyltransferase Inhibitor (COMT-I) had lower plasma homocysteine concentrations compared to L-dopa-treated patients. L-dopa treatment is associated with increased plasma homocysteine levels in patients who have PD [106]. Entacapone increases the bioavailability of levodopa and simultaneously partially alleviates the resulting hyperhomocysteinemia [107]. L-dopa treatment increased the release of homocysteine into the media of cultured astrocytes and into the plasma and brains of PD animals. Increased homocysteine from levodopa treatment led to increased apoptosis of neural progenitor cells as a result of activation of the NMDA receptor-dependent Extracellular Signal-Regulated Kinase (ERK) signaling pathways. The administration of an NMDA antagonist significantly attenuated apoptotic cell death in levodopa-treated neural progenitor cells and markedly increased the number of BrdU-positive cells in the sub ventricular zone of L-dopa-treated PD animals [108]. Homocysteine enhanced the toxicity of 1-methyl-4-phenylpyridinium (MPP+) for dopaminergic neurons in a primary mesencephalic culture [109]. Homocysteine acts as an allosteric dopamine D_2 receptor antagonist by selectively reducing the affinity of dopamine D_2 receptors for agonists but not for antagonists [110].

Medications-beta-adrenergic receptor blockers

β-adrenergic receptors are widely distributed in different regions in the brain, including the frontal, parietal, piriform, and retrosplenial cortices; medial septal nuclei; olfactory tubercle; midbrain; striatum; hippocampus and thalamic nuclei [111,112]. These adrenergic receptors (or adrenoceptors) constitute a class of G protein-coupled receptors that are targets of catecholamines, especially Norepinephrine (NE or Noradrenaline) and epinephrine (adrenaline). Many cells possess adrenergic receptors, and the binding of a catecholamine to these receptors will generally stimulate the sympathetic nervous system. There are two main groups of adrenergic receptors, α and β. β receptors have the subtypes β_1, β_2, and β_3. All three β subtype receptors are linked to G_s proteins (although β_2 also couples to G_i), which in turn are linked to adenylate cyclase. Agonist binding thus causes a rise in the intracellular concentration of the second messenger cAMP. Downstream effectors of cAMP include Camp-Dependent Protein Kinase A (PKA), which mediates some of the intracellular events that follow hormone binding.

AD: β_2-adrenergic receptors play an important role in AD. Aβ peptide induces subtle alterations in synaptic function in AD patients. Aβ interacts with β_2 adrenergic receptors in the central noradrenergic system to regulate synaptic functions in the prefrontal cortical neurons and induces the internalization and degradation of the β_2-adrenergic receptor, which results in the impairment of adrenergic and glutamatergic activities [113,114]. Compared to the thalamus in control brains, the thalamus in brains from patients who had dementia had lower total concentrations of β-adrenergic receptors. Compared to the control brains, dementia brains also had significantly lower concentrations of β_1-adrenergic receptor in the hippocampus and higher concentrations in the Nucleus basalis Of Meynert (NbM) and cerebellar hemisphere, whereas dementia brains have lower concentrations of β_2-adrenergic receptor in the thalamus, NbM, and cerebellar hemispheres and higher concentrations in the hippocampus and putamen [115]. Compared to non-AD patients, AD patients have lymphocytes that express lower levels of β_2-adrenergic receptor and lower levels of β_2-adrenergic-stimulated cAMP [116]. Fibroblasts isolated from AD patients exhibit a reduced β_2-adrenergic receptor

response [117]. Karczewski et al. [118] demonstrated the presence of agonistic auto-antibodies that were directed at adrenergic receptors in the circulation of patients with mild to moderate AD and vascular dementia. β-adrenoceptors mediate the capacity of NE to differentially modulate $A\beta_{1\text{-}42}$-induced immune responses. NE suppresses $A\beta_{1\text{-}42}$-mediated cytotoxicity and monocytic chemotactic protein-1 secretion but enhances Aβ-mediated IL-1β secretion via β-adrenoceptor activity combined with the activation of the cAMP/protein kinase A pathway and cAMP Response Element Binding (CREB) in human microglia-like THP-1 cells [119]. In addition, reduced levels of NE are associated with behavioral phenotypes observed in a TgCRND8 mouse model of AD [120]. NE promotes murine microglial uptake and degradation of Aβ [121]. Moreover, the β_3-adrenergic receptor agonist (CL316243), but not the β_2-adrenergic receptor agonist, rescued this Aβ-induced memory loss [122]. The β_2-adrenergic agonist clenbuterol improved the performance of many of the young and aged rats and monkeys that had performed poorly under control conditions [123]. The degeneration of Locus Ceruleus (LC) neurons and reduced levels of NE potentiated Aβ-induced cortical inflammation [124]. Moreover, patients with cognitive impairment who were on β_2-adrenergic receptor blockers had poorer delayed memory retrieval [125]. However, compared to both non-aggressive AD patients and control subjects, aggressive AD subjects had small but significant increases (approximately 25%) in β_1- and β_2-adrenergic receptors of the cerebellar cortex [126]. AD patients have larger total numbers of β_2- and β_1-adrenoceptors in the hippocampus. In contrast, in AD patient putamina, where β_1-receptors are highly expressed, the total numbers of β-$_2$ and β_1-receptors were significantly reduced with no consistent change in the number of β_2-receptors [127]. Furthermore, compared to either cerebellar tissue from AD patients or control tissues, AD patient hippocampi have higher total β-adrenoceptor density [128]. AD patients have a significantly higher total number of β-receptors in the cerebral micro-vessels and increased numbers of β_2-receptors, the type that is predominately expressed in micro-vessels [129]. Activation of the β_2-adrenergic receptor stimulates γ-secretase activity and accelerates amyloid plaque formation. The β_2-adrenergic receptor-selective antagonist ICI 118,551 reduced Aβ peptide production, suggesting that blockade of β_2-adrenergic receptor function might be effective in the prevention and treatment of AD [130,131]. The use of β_2-adrenergic receptor antagonists correlated with a decreased incidence of AD among hypertensive patients [132-134]. Propranolol reduced aggression and agitation in patients with senile dementia [135-138]. Propranolol also restored cognitive deficits and improved amyloid and tau pathologies in a senescence-accelerated mouse model [139-140]. Carvedilol, a nonselective β-adrenergic receptor blocker, demonstrated a neuro-protective effect in colchicine- and aluminum chloride- induced cognitive dysfunction and oxidative damage [141,142]. Carvedilol also significantly attenuated brain oligomeric Aβ content and cognitive deterioration in two independent AD mouse models [143]. In addition, nebivolol is highly tolerable and safe and can significantly reduce amyloid neuropathology in the brain, which could be one of the most important parameters for primary prevention of AD [144]. These findings suggest that β-adrenergic receptor blockade may play a role in AD. Genetic studies have identified proteins that link β-adrenergic receptor antagonism to the pathogenesis of AD, including *human leukocyte antigen* (*HLA*) genes, trace amines, RAS, PARP-1, NGF, Vascular Endothelial Growth Factor (VEGF), and the reduced form of NADP. β-adrenergic receptor inhibition also affects AD pathogenesis via non-genomic mechanisms, including MMPs, MAPK pathways, PGs, COX-2, and NOS [145]. The role of β-adrenergic receptor blockade in AD is still controversial. It is still unclear whether behavioral symptoms, sex, or genetic factors, including *β_2-adrenergic receptor* variants, *apoliporotein E* (*apoE*), and cytochrome P_{450}*CYP2D6*, participate in the β-adrenergic receptor blockade modulation in AD. Various behavioral abnormalities appear to be present in subgroups of AD patients [146-147]. Compared with both non-aggressive AD patients and control subjects, aggressive AD subjects had small but significant (approximately 25%) increases in concentrations of β_1- and β_2-adrenergic receptors in the cerebellar cortex [126]. There was also an apparent sex difference in cerebral amyloid plaque formation. Compared to the males, transgenic female *Tg2576* mice had more $A\beta_{40}$ and $A\beta_{42}$ in their brains [148]. Ni et al. [130] reported that female mice had more amyloid plaques than age-matched males among the control mice. These authors also revealed that female mice appeared to be more sensitive to chronic treatment with a β-adrenergic receptor agonist than the male mice. *β_2-adrenergic receptor* polymorphisms have also been shown to contribute to AD pathology [149-150]. Apo-E is a major cholesterol carrier that supports lipid transport and injury repair in the brain. *ApoE* polymorphic alleles are the main genetic determinants of AD risk; individuals carrying the ε4 allele are at an increased risk of developing AD compared to those carrying the more common *ε3* allele, whereas the *ε2* allele decreases risk [151]. The frequency of the *apoE* ε4 allele was significantly higher in the AD group compared to the control group [152]. Carvedilol reduces the severity of atherosclerosis in apoE-deficient mice by reducing superoxide production [153]. The *CYP2D6B* allele has also been shown to be associated with AD [154-155]. The frequency of the *CYP2D6* allele is known to vary among racial/ethnic groups. In general, the frequency of the functional group of predominant alleles in European Caucasians is 71%. In Asians, the functional alleles represent only ~ 50% of *CYP2D6* alleles [156]. Moreover, genetic polymorphism of *CYP2D6* results in altered pharmacokinetics of β-adrenergic receptor antagonistic medications [157-160]. However, substantial reservation regarding these findings needs to be noted. It is not entirely clear whether the direct action of β-adrenergic receptor antagonists in the brain has been separated from the impact of beta drugs on the cardiovascular system, which, in turn, affects AD. Thus, further studies on the relationship between β-adrenergic receptor antagonists and AD are warranted.

PD: Micro-iontophoretic administration of the non-selective β-adrenergic receptor agonist isoproterenol significantly decreased the firing rate in response to superior cerebellar peduncle stimulation in 82% of studied neurons in a dose-dependent manner. Similar changes were induced by ejection of the selective β_1-adrenergic receptor agonist dobutamine, while fenoterol (selective β_2-adrenergic receptors) increased or reduced the firing rate in 32% and 19% of rat primary motor cortices (M1), respectively. The non-selective β-adrenergic receptor antagonist propranolol enhanced both the background and evoked activity in 84% of tested neurons [161]. The Subthalamic Nucleus (STN) is one of the key structures in idiopathic PD [162]. During the course of the disease, the nucleus develops a bursting firing pattern of 25-45 Hz that is associated with the development of clinical motor symptoms, including akinesia and rigidity. The spiking activity of the STN was temporarily suppressed after the application of the β-adrenergic blocker metoprolol. A transient reduction in PD symptoms (i.e., rigidity) was detected during the suppression of STN spiking activity in PD patients [163]. Akathisia improved in 4 patients with idiopathic PD after low-dose propranolol treatment [164]. NE has been suggested to modulate the expression of L-3,4-Dihydroxyphenylalanine (L-Dopa)-Induced Dyskinesia (LID). Targeting the NE system may provide relief from both PD and LID. Barnum et al. [165] demonstrated that moderate NE loss reduced the development and expression of abnormal involuntary movements and rotations in hemiparkinsonian rats. These authors also reported that

a β-adrenergic receptor blocker maintained its anti-dyskinetic effects in dopamine-treated NE-lesioned rats. The non-selective β-adrenergic receptor blocker, propranolol, significantly attenuated established LID in PD patients [166]. The aberrant striatal signaling associated with LID was normalized after propranolol co-treatment, and intrastriatal propranolol acutely reduced LID in a 6-OHDA-lesioned rat model [167]. Tremor improvement was observed within 2 to 4 weeks after the initiation of β-adrenergic receptor nipradilol therapy; the efficacy rate tended to be higher in the essential tremor group than in the PD group [168]. Arotinolol, a peripheral β-adrenergic receptor blocker, significantly suppressed postural tremor in a dose-dependent manner in monkeys that had 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP)-induced parkinsonism [169]. Nadolol, another peripheral β-adrenergic receptor blocker, yielded a 34% reduction in tremor distance but no change in tremor frequency in idiopathic PD [170]. However, a Cochran Collaboration review revealed that it is impossible to determine whether β-adrenergic receptor blocker therapy is effective and safe for tremor treatment in PD [171]. Genetic studies have identified numerous factors linking β-adrenergic blockade to PD, including *HLA* genes, trace amines, RAS, PARP-1, NGF, VEGF and the reduced form of NADP. β-adrenergic blockade has also been implicated in PD via its effects on MMPs, MAPK pathways, PGs, COX-2 and NOS [172]. These findings suggest that β-adrenergic receptor blockade may play a role in PD.

Electromagnetic Fields (EMF)

Epidemiologic evidence for an association of EMF and neurodegenerative diseases.

AD: The epidemiological evidence for an association between occupational exposure to low-frequency EMF and the risk of dementia has increased during the last five years [173]. Huss et al. [174] studied a population of Swiss patients who resided near power lines and assessed their mortality from neurodegenerative diseases. The authors reported that the adjusted hazard ratio for the development of AD in persons living within 50 m of a 220-380 kV power line was 1.24 compared with persons who lived at a distance of 600 m or more. There was a dose-response relationship with respect to years of residence in the immediate vicinity of power lines and AD: persons living within 50 m for at least 5 years had an adjusted hazard ratio of 1.51, which increased to 1.78 with at least 10 years and to 2.00 with at least 15 years. From 31 years of observations on Swiss railway employees, a link was identified between exposure to Extremely Low-Frequency Electric and Magnetic Fields (ELF-MFs) and the development of AD [175]. Study from the California AD Diagnosis and Treatment Centers suggested that elevated occupational magnetic field exposure was associated with an increased risk of AD [176]. In another study, long-term occupational exposure to a higher ELF-MF level was suggested to increase the risk of AD and dementia in men [177]. Furthermore, a meta-analysis suggested an association between occupational exposure to ELF-MF and the development of AD [178]. Overnight exposure to ELF-MF induced a significant increase of Aβ secretion, including the isoform $A\beta^{1-42}$, without affecting cell survival in cultured human neuroglioma cells [179]. However, Transcranial Electromagnetic Treatment (TEMT) was reported to reduce the risk of developing AD. In AD Transgenic Mice (Tg), long-term TEMT prevented and reversed Aβ deposition, modified cerebral blood flow and provided a select cognitive benefit; TEMT even improved cognitive performance in normal mice [180-182]. Long-term EMF treatment enhanced mitochondrial function in the brains of both Tg and normal mice. The EMF-induced enhancement of brain mitochondrial function in Tg mice was accompanied by 5- to 10-fold increases in soluble $A\beta_{1-40}$within the same mitochondrial preparation [183].

PD: Positive associations for the development of PD were observed with all of the methods for magnetic field exposure assessment, including a dichotomous grouping of electrical versus nonelectrical occupations, a three-tiered grouping of potential magnetic-field exposure based on a combination of job title and industry, and categories of exposure based on the means of the magnetic fields estimated from a job-exposure matrix [184]. Rats exposed to a magnetic field that also had chemically induced dopamine neuronal damage exhibited reductions in irritability and oral activity when stimulated with SKF 38393 (an agonist of central dopamine D_1 receptors) and some increase in catalepsy after administration of SCH 23390 (an antagonist of central dopamine D_1 receptors) [185]. These results indicate that ELF-MF reduced the reactivity of central dopamine D_1 receptors in rats. However, there is no convincing evidence that electricity generation and transmission workers in the United Kingdom have suffered an increased risk for neurodegenerative disease as a consequence of exposure to magnetic fields [186]. In addition, combined therapy that included application of transcranial pulsed electrostimulation and an alternating electrostatic field produced a highly beneficial effect in "restless legs" syndrome in PD patients [187]. A potential therapeutic use of static magnetic fields for the preservation of motor behavior and brain morphology was shown in the SN after 14 days with 6-OHDA lesions [188]. Börnke et al. [189] demonstrated short-term beneficial effects of 10-Hz transcranial magnetic stimulation on motor symptoms in PD patients. Short-term motor improvement was demonstrated after sub-threshold 5-Hz repetitive transcranial magnetic stimulation of the primary motor hand area in PD [190]. The activities of daily living and motor scores from the Unified PD Rating Scale (UPDRS), pronation-supination movements, and buttoning up significantly improved after frontal repetitive transcranial magnetic stimulation as compared to before treatment [191]. An ^{11C}raclopride positron emission tomography study in anesthetized macaque monkeys revealed that endogenous dopamine release was induced by repetitive transcranial magnetic stimulation over the primary motor cortex [192]. Repetitive transcranial magnetic stimulation also increased the release of dopamine in the mesolimbic and mesostriatal systems [193].

Interaction between genes and the environment

AD: The presence of the *eNOSTT894* genotype is more strongly associated with increased plasma homocysteine levels in patients who had experienced cognitive decline as compared to control patients [194]. The influence of the *Glu298Asp* polymorphism of NOS_3 on homocysteine levels at the age of onset was demonstrated in AD patients [195]. The dimerization of $apoE_3$ by disulfide bonds between cysteine residues enhances the capacity of $apoE_3$ to generate High-Density Lipoprotein (HDL). Hyperhomocysteinemia induced by subcutaneous injection of homocysteine in *apolipoprotein* E_3 (*apo E*) knock-in mice decreased $apoE_3$ dimer levels in their brain homogenates [196], which could accelerate the pathogenesis of AD by reducing HDL generation. Total plasma homocysteine concentrations were increased in elderly patients who had mental illness and vascular disease and were carriers of $apoE_4$ [197]. AD subjects had significantly more $apoE_4$ alleles than did control subjects [198].The frequency of the *TT* homozygote of *Methylene Tetrahydrofolate Reductase* (*MTHFR*) was higher in AD patients than in control patients. *TT* homozygotes showed the lowest serum folate and the highest serum homocysteine levels (250% of control) and the lowest MMSE scores among all of the genotypes [199]. The early prevention of AD with monoglutamyl

folate intake (400 mcg per day) is recommended, especially in the *TT* homozygote of *MTHFR*. The *TT677MTHFR* genotype promotes a plasma homocysteine increase, which in turn may favor intima-media thickening in patients with cognitive impairment [200]. High serum concentrations of homocysteine, cholesterol, and uric acid and low concentrations of estradiol and vitamin B_{12}, along with the *MTHFR 1298A→C* mutation, are simultaneously associated with AD-type dementia [201]. Plasma total homocysteine is increased in AD patients and dependent on the *MTHFR T/T* genotype in the presence of low folate levels [202]. Furthermore, the association of homocysteine with AD was strengthened by *MTHFR 677T* and $apoE_4$ alleles [203].

PD: Homocysteine elevation was caused by L-dopa administration and was further promoted by *677C/T* and *T/T* genotypes of the *MTHFR* gene, but not by A1298C genotypes [204]. There is an inverse association between smoking and the risk of developing PD, which is dependent on a polymorphism of the *inducible NOS* gene [205]. The cytochrome P_{450} *2D6* gene could have a modifying effect on the risk of developing PD among persons exposed to pesticides [205-206]. Subjects who had experienced pesticide exposure and had at least 1 copy of the *CYP 2D6 29B* allele had an 83% predicted probability of developing PD with dementia [207]. The distribution of the *Glutathione Transferase* (*GSTP1*) genotypes differed significantly between PD patients and control patients who had been exposed to pesticides [208-209]. Susceptible variants of *Manganese-Containing Superoxide Dismutase* (*MnSOD*) and *NADPH:Quinone Oxidoreductase 1* (*NQO1*) genes may interact with occupational pesticide exposure to increase PD risk in southwestern Taiwanese [210]. Dopamine transporter genetic variants and pesticide exposure were reported to interact to increase PD risk [211-212]. A genetic polymorphism of *Monoamine Oxidase B* (*MAO-B*) modified the association of cigarette smoking and PD [213-214]. Susceptibility to pesticides may be modified by genetic variants of xenobiotic enzymes, such as *Paraoxonase* (*PON*), that play roles in metabolizing some organophosphates. Carriers of the variant *MMPON1-55* genotype exposed to organophosphates exhibited a greater than 2-fold increase in PD risk compared with persons who had the wildtype or heterozygous genotype and no exposure [215]. In MPTP animal models of PD, caffeine protects neurons by blocking the adenosine receptor A2A (ADORA2A). Caffeine is primarily metabolized by *CYP P450 1A2* (*CYP1A2*). Two *ADORA2A* polymorphisms were inversely associated with PD risk, but there was weak evidence of an interaction with coffee consumption. In contrast, the coffee-PD association was strongest among slow metabolizers of caffeine who were homozygous carriers of the *CYP1A2* polymorphism [216]. A genome-wide gene-environment interaction study identified the *glutamate receptor* gene *GRIN2A* as a PD modifier gene that interacts with coffee [217]. The frequency of the homozygous *DD* genotype of the *ACE* gene is significantly increased in patients who have PD compared to control patients, an effect that is also seen in PD patients who have L-dopa-induced psychosis [218-219]. In PD, Manganese (Mn) exposure was associated with significantly higher ROS generation in subjects who have biallelic loss-of-function mutations in *PARK2* compared to control subjects who had no known PD genetic risk factors, despite significantly less intracellular Mn accumulation [220]. Polymorphisms in the Parkinson-related gene *ATPase* type *13A2* are also risk markers for the neurotoxic effects of Mn in humans [221]. Taken together, these findings suggest that there are pathogenic interactions between known genetic and environmental risk factors for PD.

Conclusions

In this paper, we review the environmental factors that can contribute to the pathogenesis of neurodegenerative diseases, including AD and PD. It should be noted that a single environmental factor accounting for a significant number of cases has not been identified. Environmental factors (such as trauma, nutrition, medication, and exposure to electromagnetic fields) and the interaction between genes and environmental factors can play a role in the pathogenesis of AD and PD. Genetic studies have helped identify a number of factors that link nutrition and medication to AD and PD pathologies. Nutrition can also act on AD and PD through a number of non-genomic mechanisms, including protein expression, oxidative stress, inflammation, and cellular metabolism. An association between EMF and neurodegenerative diseases was demonstrated. However, a potential therapeutic use of static magnetic fields for the preservation of cognitive performance and motor behavior was also shown. Evidence from epidemiological, animal, and cell models suggests that gene-environment interactions can also contribute to the development of neurodegenerative diseases, including AD and PD. Data for AD and PD suggest that a number of insults occurring early in life can lead to or contribute to these diseases. Preventing the onset of AD and PD or slowing its progression by correcting or supplementing nutrition and understanding the interaction between genetic and environmental factors could lead to consequent improvements in health status and quality of life in older age.

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