AN UPDATE ON THE ROLE OF ENVIRONMENTAL FACTORS IN PARKINSON'S DISEASE

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Abstract

Parkinson's disease (PD) is an idiopathic, progressive and degenerative disorder of the central nervous system, characterized by slow and reduced movement, muscular rigidity, tremor and postural abnormality. It is second most common neurodegenerative disorder with the prevalence of 1-2 percent after the age of 50 years. PD is a multi-factorial disease, caused by the combination of age, genetic and environmental factors. Environmental exposures to pesticides, herbicides and heavy metals play a critical role in the onset and progression of PD. The susceptibility of individuals for PD depends on the metabolic enzymes involved in the detoxification of selected environmental chemicals and toxicants. Inherited differences in metabolic enzymes are mainly responsible for the neuronal degeneration. Genetic polymorphisms in the toxicant responsive genes greatly alter the susceptibility of chemically induced PD. Evidences obtained from genome wide analysis and biochemical, molecular and epidemiological studies have concluded the significant contribution of environmental factors in the onset of PD. In this article, an update on the role of environmental factors in the onset and progression of Parkinson's disease has been discussed.

Key Words: Parkinson's disease (PD), Environmental Factors, Toxicants, Metals and Pesticides

Introduction

Parkinson's disease (PD) is named after British physician James Parkinson who gave the first cogent description of the syndrome in 1817. Marshall Hall in 1941 referred PD as paralysis agitans. Idiopathic PD is characterized by the progressive degeneration of dopamine-producing cells in the substantia nigra pars compacta region of the mid brain. The main phenotypic symptoms of PD are trembling in hands, legs, jaws and face, stiffness in the limbs and trunk, slowness of the involuntary and emotional movements and postural abnormality. PD is second most common neurodegenerative disorder after Alzheimer's disease. It seems to develop from the interaction of the inherited genetic susceptibility, environmental exposures and age of an individual. Role of environmental factors has acquired attention only when the use of a synthetic heroin was found to elicit severe Parkinsonism in addicts. Following this discovery, an initiating agent 1-methyl-4-phenyl-1, 2, 5, 6-tetrahydropyridine (MPTP) was identified as contaminant in synthetic heroin. Since, MPTP possess structural similarities with some herbicides and pesticides, therefore, the involvement of these pesticides and herbicides in the onset of PD has been predicted. During the last two decades very limited studies have been conducted worldwide on the identification of various environmental factors responsible for the onset of PD, however, studies have also shown increased incidence of PD associated with exposure to pesticides, heavy metals, solvents and viral infections such as encephalitis and head injuries. Advancement in molecular biology has already shown clear-cut involvement of environmental chemicals and toxicants in PD. In the present article, the role of environmental factors in the onset and progression of Parkinson's disease has been discussed along with the evidences obtained from epidemiological, biochemical and molecular studies.

Prevalence

PD is a common disease in the aged individuals that affects about 0.4% of the population over the age of 50 years and 1% of the population over the age of 65 years (1-4). Prevalence of PD has been reported up to 280 individuals per million in North America, 59 individuals per million in Africa, 44 individuals per million in China, 19 individuals per million in India and 150 individuals per million in Western Europe (1-4). In the North America and Western Europe the incidence may reach up to 1 individual per 40 individuals in the aged population (4). Parsis are the most affected population in India and up to 328 cases per million have been reported. However, the incidence of the disease begins at the age of 50 years but the severity of the disease may increase throughout the life (5, 6). PD is more common in men than in women (7) and seems to be more widespread in northern countries than the southern ones; however, reports are also available in literature mentioning the lack of gender preference (8).

Modifying Factors

PD is a multi-factorial disease and contributed by a combination of age, genetic and environmental factors (9 -11). PD is not a disease of childhood; however, some cases of the disease have been found to be associated with exposures to environmental toxicants throughout life, beginning in the childhood or in utero (12). Many researchers believe that several modifying factors in combination are involved in the manifestation of PD that include Caucasian ancestry (13), environmental toxins, herbicide/pesticide exposure (14-16), rural residence, metal exposure (17-23), higher intake of dietary fats, genetic predisposition, free radicals, accelerated aging, male gender (7), conservative pre-Parkinson's personality and family history. Many investigators have reported the involvement of both chemical toxins and genetic mutations (24-27). Scientists are actively involved from the last several decades, in unraveling the molecular mechanism of the death of brain cells and ultimately the rigidity, tremors and other symptoms of PD. The toxic effects resulting from the oxidative stress

combined with environmental exposures could act synergistically to cause PD (28). PD has been associated with drinking well-water, farming, and the exposure to certain wood preservatives (29, 30, 31, 32, 33, 34). The late onset and slow-progressing nature of PD has prompted the consideration of environmental exposure to agrochemicals, including pesticides, as a risk factor (35). It is also reported that head trauma and several neurotoxicants, including MPTP, paraquat, dieldrin, manganese (Mn) and salsolinol may lead to PD (36). The consumption of Cycas circinalis seed in the Japanese population has been found to induce PD like syndrome (37). Single nucleotide polymorphisms (SNPs) in the detoxification genes determine the susceptibility of an individual towards the onset of a disease. SNPs in cytochrome P-450 (CYP), glutathione S-transferase (GST), paraoxanase (PON), nitric oxide synthase (NOS) and several other genes have been extensively studied in many populations and have been correlated with the onset of PD. Genetic factors mainly contribute in the early onset of the disease; however, several studies of twin pairs have shown that genetic factors do not play a critical role in PD (38) until the environmental factors acts on the genetically susceptible individuals.

Environmental Factors

Parkinson's disease can originate from long-term exposure of the central nervous system to environmental chemicals. It is also reported that the workers exposed to industrial solvents might develop PD. It is reported that individuals with familial PD possesses much lover level of detoxifying enzymes than healthy one and accumulation of toxic chemicals is higher in such individuals compared with unexposed one. Heavy metals help in catalyzing free radical reactions that destroy the dopamine-producing cells and have therefore been implicated as the causative agents in the onset and progression of PD (15, 17-21, 23). Individuals exposed to high environmental levels of Mn, which include miners, welders, and those living near ferroalloy processing plants, display a syndrome known as manganism, that is best characterized by debilitating symptoms resembling those of PD (39). Manganese decreases monoamine oxidase (MAO) activity and inhibits the respiratory chain that accumulates in mitochondria and inhibits efflux of calcium (40). The essential metal iron has long been implicated in the neuronal damage associated with PD due to dopamine and motor disturbances (41). Populations exposed to aluminum contamination in the drinking water have high risk of developing PD (42, 43). Aluminium facilitates the passage of toxic chemicals into the brain; however, the brain is normally protected from undesirable chemicals by the blood-brain barrier (44). Aluminum has neurotoxic properties and inhibits the synthesis of important brain chemicals that has the potential to block nucleic acid metabolism within nerve cells. Aluminium interferes with magnesium in the regulation of neurotransmitter receptors (45). Aluminum overload induces clinical symptoms of Encephalopathy (46). Many researchers agree that aluminum is an important factor in dementia and have also demonstrated a positive relationship between aluminum in drinking water and neurological conditions. A unique occurrence of Parkinson's disease in the indigenous population of Guam in the Western Pacific has been reported where the soil and drinking water have high levels of aluminum and low levels of magnesium and calcium (47).

Accumulation of heavy metals, such as cadmium, lead and mercury are known to deteriorate the brain. Mercury is considered to be the most hazardous metal to the brain (48). Organic mercury compounds have been reported to destroy the nerve cells and resulting tremors. A link between dental amalgam and PD has been reported and the amalgam dental material in tooth fillings have been projected as the major source of the introduction of mercury into the bloodstream (49). The essential metal iron has long been implicated in the neuronal damage associated with dopamine and motor disturbances (41). Iron overload is known to aggravate Parkinson's disease as evidenced by the presence of high levels of iron in the substantia nigra (50). Iron tends to catalyze free-radical reactions that destroy dopamine-producing cells (21). Copper levels have been reported to be significantly higher in the cerebrospinal fluid of PD patients and the higher level is probably due to copper dependent enzyme required to convert tyrosine into levodopa. Undesirable changes in the composition of the intestinal flora and the resulting overgrowth in small intestine are known to induce PD (51). Drugs and allergic inflammation of the intestinal wall allow partly digested food fragments and bacterial endotoxins to reach into the brain and act as neurotoxins (52).

Epidemiological, Biochemical and Molecular Approaches of PD and Environmental Factors

In the last few decades, the environmental theory on the etiology of Parkinson disease has acquired significant importance. From an experimental point of view, several new models of PD induced by pesticides have been proposed. In vitro studies have also provided clues that several pesticides stimulate the formation of alpha-synuclein fibrils. A meta-analysis of all case-control studies so far performed have shown a positive, statistically significant association between pesticide exposure and PD (53). Epidemiological studies have identified exposure to agricultural chemicals as potential environmental risk factors for PD (30, 42) in aged individuals and cannot be explained by genetic factors (54). Variation in PD mortality by geographical regions, as reported in several countries, has also been found consistent with an environmental exposure etiology (55-57). It is reported that chronic exposure to a common pesticide can reproduce the anatomical, neurochemical, behavioral and neuropathological features of PD. The use of a synthetic heroin called MPTP (1-methyl-4-phenyl-1, 2, 5, 6-tetrahydropyridine) causes severe, irreversible Parkinsonism, a syndrome, closely related to PD (37). These examples have shown that a PD-like disorder can be caused directly by a chemical in the environment. Chronic subcutaneous exposure to low doses of rotenone causes highly selective nigrostriatal dopaminergic lesions. Dithiocarbamate pesticides potentiate the toxicity of both 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine and paraquat in mouse models of PD and several studies have suggested selective dithiocarbamates may

alter the kinetics of different endogenous and exogenous compounds and enhance their neurotoxicity. The herbicide N, N'-dimethyl-4, 4'-bipyridylium (paraquat) acts as a modifying factor in the onset of PD due to its structural similarity to MPP+ (1-methyl-4-phenylpyridinium ion), (58). Higher paraquat (PQ) levels are evident at 24 h after its administration thereby indicating its involvement in brain toxicity (59). Direct injection of paraquat into brain alters dopamine level, personal behavior and induces neuronal loss (60-62), however, systemic administration does not yield consistent evidence of neurotoxicity in rodents (61, 63, 64). Repeated intraperitoneal paraquat injections killed dopaminergic neurons in the substantia nigra (SN) pars compacta, as assessed by the dose- and age-dependent stereological counting of tyrosine hydroxylase (TH)-immunoreactive, Nissl-stained neurons and the cell loss (65). Several lines of evidence have indicated selective vulnerability of dopaminergic neurons to paraquat (65). The numbers of GABAergic cells are reported to remain unchanged in the SN pars reticulata and counting of Nissl-stained neurons in the hippocampus did not reveal any change in paraquat-treated mice (65). Degenerating cell bodies have been observed by silver staining in the SN pars compacta, and glial response has been known to present in the ventral mesencephalon but not in the frontal cortex and cerebellum (65) following paraquat administration however, no significant depletion of striatal dopamine has been reported (65). On the other hand, enhanced dopamine synthesis has been suggested by an increase in TH activity (65). These findings unequivocally showed selective dopaminergic degeneration, one of the pathological hallmarks of PD. The apparent discrepancy between neurodegenerative and neurochemical effects represents an important feature of the paraquat model and is probably a reflection of compensatory mechanisms by which neurons that survive damage, are capable of restoring neurotransmitter tissue levels (65).

Dithiocarbamate fungicides also possess potent dopaminergic activity and diethyldithiocarbamates, a class of dithiocarbamates, augmented the neurotoxicity of MPTP (66, 67). Several studies have suggested that dithiocarbamates alter the kinetics of different endogenous and exogenous compounds thereby enhancing their neurotoxicity (68). Acute intraperitoneal administration of manganese ethylenebisdithiocarbamate (maneb or MB) exacerbated attenuation in locomotor activity and augmentation in catalepsy produced by MPTP in mice. Maneb itself inhibited locomotor activity and augments aloperidol-induced catatonia (68, 69). Neurological impairments resembling those of PD have also been reported in individuals exposed to MB (70, 71). Residual levels of organochlorine pesticide dieldrin have been found in brains of one third of the PD patients as compared with controls (72, 73). Mancozeb (manganese-zinc-ethylenebisdithiocarbamate) and zineb (zinc-ethylenebisdithiocarbamate) dose-dependently attenuate high affinity dopamine uptake and tyrosine hydroxylase (TH) positive neurons and increase cytotoxicity in mesencephalic striatal primary co-cultures (72). Triadimefon, a triazole fungicide blocks dopamine transporter and produces behavioral effects resembling those of cocaine and d-amphetamine (74- 78).

The combined pesticide exposures may act as important environmental risk factor for Parkinsonism (79). Paraquat (PQ) and maneb (MB) exposure during critical periods of development could permanently change the nigrostriatal dopamine (DA) system and enhance its vulnerability to subsequent neurotoxicant challenges (67). These findings indicate that exposure to pesticides during the prenatal period can produce permanent and progressive lesions of the nigrostriatal dopaminergic system. An enhanced adult susceptibility to these pesticides has suggested that developmental exposure to neurotoxicants may be involved in the induction of neurodegenerative disorders (67); however, such pesticide exposure is irrelevant for medico-legal considerations (66). A consistent pattern of high Parkinson's disease morbidity has been found among occupational groups employed in agriculture and horticulture in Denmark (80). Although, the risk of PD is proportional to pesticide exposure time, no significant dose-response relationship has yet been established (53) and no specific group of pesticide has been identified. PD is also associated with a systemic defect in mitochondrial complex I activity (81) by the environmental toxicants. Animal models have also shown that exposure to the inhibitors of mitochondrial complex I including pesticides, is sufficient to reproduce the features of PD. Complex I defects result in oxidative stress that increases the susceptibility of neurons to excitotoxic death (28). Betarbet and his associates (82) have reported that chronic and systemic inhibition of mitochondrial complex I enzyme by the lipophilic pesticide rotenone, causes highly selective nigrostriatal dopaminergic degeneration and associated behaviorally with hypokinesia and rigidity. Nigral neurons in rotenone-treated rats accumulate fibrillar cytoplasmic inclusions that contain ubiquitin and alpha-synuclein (82). Striatal neurons containing DARPP-32 (dopamine and cAMP-regulated phosphoprotein) and neurons of the globus pallidus and subthalamic nucleus remain intact with normal morphology following rotenone treatment (83).

Gene Expression Based Approaches of PD and Environmental Factors

Recent developments in molecular technologies have made it possible to study and identify the mechanisms of neurodegeneration using DNA microarrays, those were not feasible with conventional biochemical procedures. Microarray based analysis has also provided a number of evidences for the involvement of environmental factors in the onset of PD. The array data of 6-OHDA mediated PD are already available that have suggested that dopamine (DA) denervation of the striatum results in an impairment in the DA-protein kinase A-cyclin dependent kinase 5-protein phosphatases cascade that regulates the state of phosphorylation and activity of DARPP-32 (84). Most of the gene alterations have been reversed by D1 and D2 receptor antagonist R-apomorphine that prevents MPTP induced neurotoxicity in mice (85). An interesting finding has also been reported in which 6-OHDA induced denervation resulted in modulation of the expression of genes encoding for components of dopamine signaling network. PKA and CD5 are known to regulate DARPP-32, a mediator of dopamine signaling, by phosphorylating specific sites at thr-34 and thr-75. A target of PKA-induced thr-34 phosphorylated DARPP-32 has been reported

as protein phosphatase PP1 (86) and PP2A that play a pivotal role in the dephosphorylation of phospho-DARPP-32 at the thr-75 site and denervation modulates the expression of genes that target DARPP-32 as an integration crossroad for intracellular dopamine signaling. A dose-dependent protective effect of PD in coffee and tea drinkers and smokers in an ethnic Chinese population is reported (87). Dopamine (DA), R-apomorphine (R-APO), polyphenol (-)-epigallocatechine-3-gallate (EGCG) and melatonin have also been reported as neuroprotective and free radical scavengers in PD patients (88). A concentration and time-dependent correlation between R-APO, DA, EGCG, and melatonin in modulation of cell survival/cell death-related gene pathways has also been confirmed by quantitative real-time PCR and protein profiles.

The cDNA microarray gene expression has indicated that the mechanism of neurodegeneration by MPTP (N-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine) and 6-hydroxydopamine is a complex cascade of vicious circles (89). Alteration of genes associated with iron metabolism has supported oxidative stress induced neurodegeneration and iron deposition in substantia nigra pars compacta (SNPC) (89). MPTP and R-apomorphine induced alterations in 49 different genes involved in oxidative stress and inflammation (90). It may be hypothesized that an additional cascade might act in parallel to oxidative stress and inflammation to converge into a common pathway leading to neurodegeneration. R-apomorphine is known to prevent the over expression of several genes participating in cell death (90). The concept has been supported by recent complementary DNA (cDNA) microarray gene expression studies, which show the existence of a gene cascade of events occurring in the nigrostriatal pathway of MPTP, 6-OHDA and methamphetamine animal models of PD (91). Genetic correlates of the alterations produced by 6-hydroxydopamine-induced denervation in the nucleus of striatum (92) have shown the modulation of 50 different genes involved in various cellular functions. In particular, products of the genes modulated by this experimental manipulation are involved both in the intracellular transduction of dopamine signal and in the regulation of glutamate transmission in striatal neurons, providing some information on the possible neuronal events which lead to the reorganization of glutamate transmission in the striatum of Parkinsonian rats (92). It is also possible to develop effective neuroprotective drugs using microarray technology (84, 85, 88, 93-95).

Toxicant Responsive Gene Polymorphism Based Approaches of PD and Environmental Factors

After the human genome sequencing, the polymorphism in the genes have shown an important clue to verify the involvement of toxicant responsive genes in the onset of PD. SNP based studies have shown many evidences of the contribution of environmental factors in the onset of the disease. Many enzymes including the cytochrome P-450 system, the flavin monooxygenase system, esterases, paraoxonases and glutathione transferases metabolize pesticides and are involved in the metabolism of pesticides leading to either activation or inactivation (96, 97). Polymorphism in enzymes would be expected to alter the risk of PD by influencing the deposition of pesticides. Genetic susceptibility to neurotoxins has been reported as one of the major causes of PD and polymorphisms in various forms of cytochrome P-450 genes such as CYP1A2, CYP2C9, CYP2C19, CYP2E1, CYP2D6 and CYP3A4 have been extensively studied (98). CYP1A1 gene polymorphisms have been found as a genetic susceptible factor for early-onset of PD, however, CYP2E1 RsaI and PstI polymorphisms are not found to be genetic susceptible factors for both early- and late-onset of PD in the Chinese population (99). CYP2D6 is involved in the detoxification of environmental chemicals and toxicants (97, 100). A significant association between the polymorphisms of this gene and PD has already been reported in Australian population (14). A significant association of PD has been found with drugs and toxins metabolism regulatory gene CYP2D6 (98) in several studies: however, association results of these studies have been inconsistent (98). Genotyping of cytochrome P-450 genes such as CYP2D6 (101), CYP3A4, CYP2C9, and NAD (P) H: ubiquinone oxido-reductase gene (NQO1) indicated their involvement in chemically induced PD and helped in understanding the mechanism of pathogenesis of PD. Deprenyl metabolizing cytochrome P450 system in monkey (Cercopithecus aethiops) liver microsomes has been recently reported (102). Genetic polymorphism of the CYP2E1 gene and susceptibility to PD in Taiwanese population was not found to be significantly related (103). A role of environmental factors in the frequency of CYP2D6-deficient alleles in the patients with PD in European population has also been suggested (8). Investigators have also supported the hypothesis that the CYP2D6 gene is not a major gene responsible for PD. The association of CYP2D6*4 allele was not found with earlier PD onset; however, its association with survival (98) was projected. Remarkable and significant genetic polymorphisms in CYP2D6 genes in Indian population have been reported (99, 104), however, evidences are needed to support their role in the onset and progression of PD. Association between polymorphism in the pi class glutathione transferase and PD in the subjects reported with pesticides exposure is of particular interest because diminished glutathione in the substantia nigra is an early finding in PD (105, 106, 107). An association between PON1 gene and PD has been reported in Asians (108); however, in Caucasians no significant association was found in PD and PON1 (109). PON1 gene is involved in the metabolism of oxidized lipids and plays a major role in the metabolism and detoxification of insecticides processed through the cytochrome P450/PON1 pathway (110). Studies conducted by various investigators have also demonstrated population specific allele frequencies in PON1 gene (111) and its association with the onset of PD. Association between polymorphisms in NOS genes and PD in a community based case control study have also elucidated the role of genetic polymorphisms in PD (112).

Conclusion

PD is a multi-factorial disease and caused by age, genetic and environmental factors. Epidemiologcal, biochemical and molecular studies conducted worldwide have shown significant contribution of environmental factors in the onset of PD. Age is

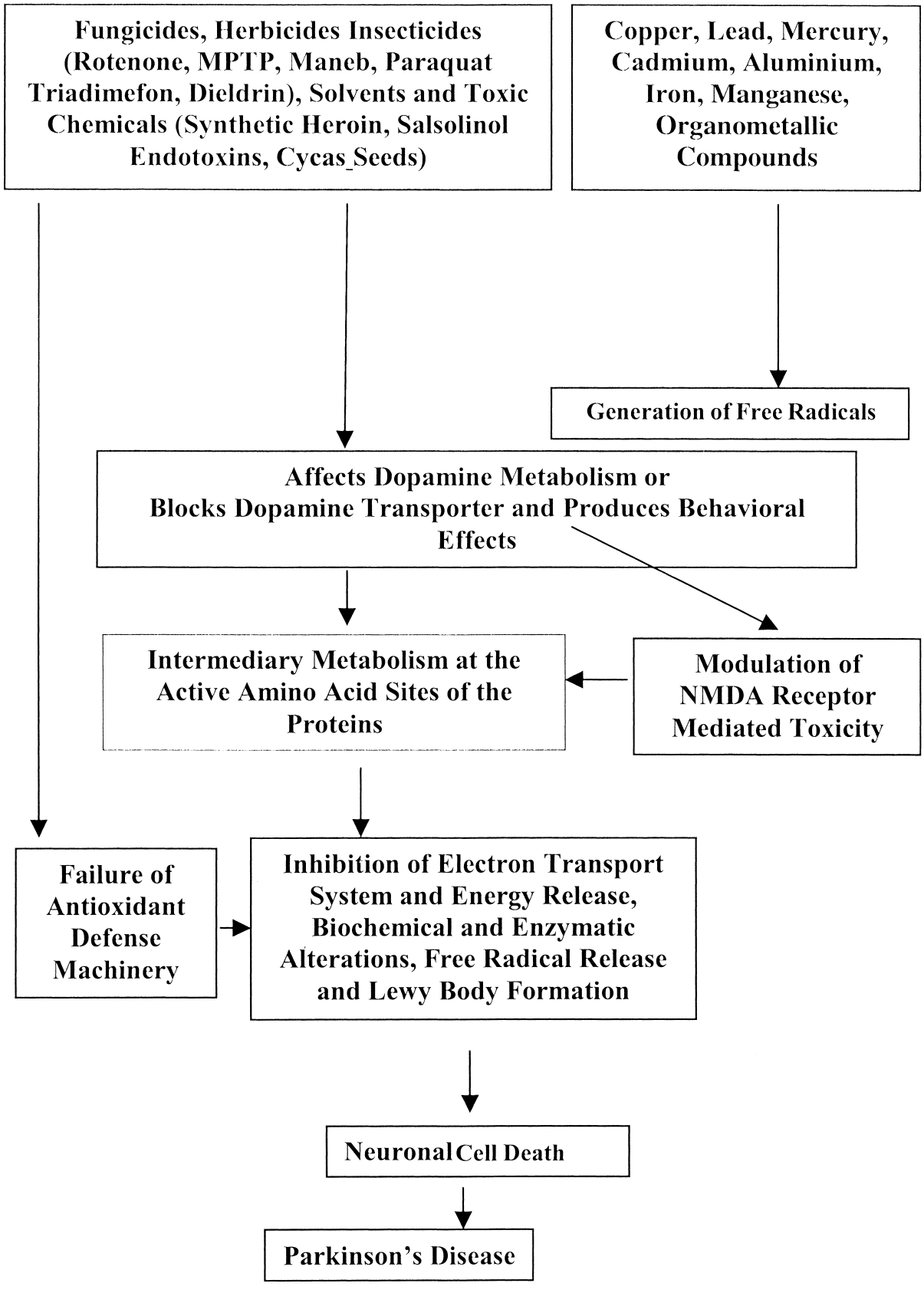

Fig. 1. A diagrammatic representation on the role of environmental factors in the onset and progression of Parkinson's disease. Environmental factors either modulate the antioxidant defense system or generate free radicals or reduce dopamine metabolism and block dopamine transporter. Modulation in any of these parameters may block energy release and thereby induce neuronal cell death in the *susbstantia nigra pars compacta* region of the mid brain.

a consistent risk factor of PD, however, an age-dependent cumulative insult of toxicants on the genetically susceptible individuals have been found to be mainly responsible for the selective degeneration of nigrostriatal dopaminergic neurons.

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