Current Topics in Toxicology
Vol. 12, 2016

Review

A critical review of the interrelationships between genetics, neurotoxicant exposure, and age at onset of neurodegenerative diseases

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ABSTRACT

This review looks at the complex interrelationship between neurotoxicant exposure, chemical metabolism, genetics and age at onset of Parkinson's disease (PD), Alzheimer's disease (AD) and Amyotrophic Lateral Sclerosis (ALS). While the major factors influencing the onset of these age-related neurodegenerative diseases remain genetics and age per se, the role of neurotoxicant exposure as a disease modifying factor is increasingly difficult to ignore. The magnitude and duration of the exposure are the two most important factors that must be considered when investigating the relationship between neurotoxicant exposure and age at onset of neurodegenerative disease. Exposures to high concentrations readily overwhelm the ability of the body to detoxify and eliminate neurotoxicants, while chronic exposures to lower concentrations are associated with insidious cumulative effects on nervous system function. This relationship is further modified by genetic polymorphisms and factors that regulate induction of metabolic enzyme synthesis implicated in the detoxification process. With these thoughts in mind, this review explores the interactions between neurotoxicant exposure and those genetic factors that have the inherent ability to modify chemical metabolism and interaction with mechanisms implicated in the subclinical progression and age at onset of neurodegenerative disease. This review of the literature suggests that there is sufficient evidence, based on data from numerous reliable sources, to conclude that age at onset and lifetime risk for developing overt symptoms of neurodegenerative disease are modified by exposure to chemicals including neurotoxicants found in the workplace and environment and, that this relationship is further altered by genetic factors that influence pharmacokinetic and pharmacodynamics processes implicated in these diseases.

KEYWORDS: Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, neurotoxic, age at onset, exposure

INTRODUCTION

Much has changed in the decade and a half since my late colleague and mentor Bob Feldman and I first wrote a review on this topic [1]. Since then, various genetic factors have been associated with familial as well as some early and late onset forms of neurodegenerative disease and yet, the role of environmental factors in the pathogenesis of these debilitating disorders has never been completely excluded. Researchers involved in the discovery of novel therapeutics aimed at slowing the progression of neurodegenerative disease as well as those who seek to identify specific chemicals as "causative" agents both continue to remain constrained by the ironic observations of Paracelsus who aptly noted that, "Poison is in everything, and there is no thing that is without poison; the dosage makes it either a poison or a remedy". Although the quest for an environmental or occupational chemical hazard has implicated various neurotoxic chemicals with equally

varied mechanisms of action, it has not been possible to identify a single chemical with a definable mechanism of action, that also shows a consistent dose response relationship to disease onset and progression as would be expected if in fact a specific neurotoxic chemical were "the causative agent". This observation has led to the obvious logical conclusion that genetics and environmental factors must all play a collective role in the subclinical and as well as the clinical course of these diseases and most likely in age at onset [2-6]. This review looks at studies of Parkinson's disease (PD), Alzheimer's disease (AD) and Amyotrophic Lateral Sclerosis (ALS) published between 1966 and 2016 available through the Unites States National Library of Medicine via PubMed. It explores the genetic factors that regulate the pharmacokinetics and pharmacodynamics of neurotoxicant exposures implicated in age-related neurodegenerative diseases and attempts to create a path forward for investigating the complex relationships between genetic factors that influence the responses of cells, tissues, organs, and individuals to their environment.

1. Pharmacokinetics and neurodegenerative disease

1.1. Absorption and distribution

The effects of neurotoxic chemicals are mediated in part by tissue distribution which is influenced by the lipophilicity of the chemical and the affinity it has for various transporters and other cellular macromolecules. For example, the distribution of manganese and iron within the brain is influenced in part by the divalent metal ion transporter, while the distribution of mercury is influenced to a greater extent by its affinity for sulfhydryl groups. Factors that influence absorption and distribution must always be considered when evaluating the role of neurotoxic chemicals in disease progression. Most chemicals encountered in the workplace or environment are absorbed via the gastrointestinal, pulmonary, or dermal routes. Lipophilic neurotoxic solvents are readily absorbed across cell membranes of the gastrointestinal tract, lungs, and skin and such compounds also readily cross the blood brain barrier. Exposure to carbon monoxide (CO), which is transported by hemoglobin has been associated with parkinsonism. It has been suggested that anemia could exacerbate the adverse effects of chronic CO exposure and that anemia may even be a risk factor for PD [7-11]. Patients with Sickle Cell Anemia have increased blood levels of carboxyhemoglobin at baseline but the association between this observation and an increased risk for earlier onset of PD among subjects exposed to carbon monoxide is unclear [10, 12].

Absorption and distribution of heavy metals implicated in neurodegenerative disease is mediated in part by transporters such as transferrin and ceruloplasmin. Thus, genetic factors that influence absorption and distribution of neurotoxic metals can include those that regulate the expression of metal ion transporters [13-17]. Not too surprisingly, expression of these transporters has been shown to be influenced by dietary exposure to metals [18]. Genetic mutations coding for these transporters have been implicated in human health and development [19]. Thus, studies looking at the role of heavy metals in neurodegenerative disease should also consider how diet and concomitant exposure to other metals that induce expression of relevant transporters influences absorption and tissue distribution [20].

1.2. Metabolism

Phase I and Phase II enzymes play an important role in the enzymatic metabolic activation and detoxification of neurotoxicants. The oxidation/ reduction reactions that occur in Phase I facilitate the addition of functional groups while those that occur in Phase II catalyze the conjugation of these products with substrates such as glucuronic acid and glutathione. Genetic factors that influence Phase I and/or Phase II of metabolism of neurotoxicants implicated in neurodegenerative disease can influence individual susceptibility and age at onset.

Brain levels of the Phase I enzyme cytochrome P450 have been shown to increase with age but are lower in patients with PD as compared with healthy controls [21]. Chronic exposure to neurotoxicants can induce expression of CYP 450. The cytochrome P450 2D6 mutant allele has been implicated in the Lewy body variant of Alzheimer's disease [22]. Cytochrome P450-dependent metabolism of neurotoxicants such as trichloroethylene has been shown to generate mitochondrial toxicants implicated in PD [23]. Mitochondrial cytochrome P450 2D6 catalyzes the metabolism of 1-methyl-1,2,3,6-

tetrahydropyridine (MPTP) to MPP^+ but this reaction can be prevented by 2D6 inhibitors such as quinidine [24]. Although the relationship between PD and cytochrome P450 2D6 mutations implicated in poor metabolism of xenobiotics has not been established, it is important to realize that many neurotoxic chemicals are metabolically activated during Phase I by CYP 450 enzymes and thus, poor metabolizers may ironically be protected from the effects of exposure to certain neurotoxicants [25]. In fact, this change in susceptibility to neurotoxicant effects could explain conflicting reports of associations in some studies.

Aldehyde dehydrogenase (ALDH) is another Phase I enzyme that plays an important role in oxidation and protection from neurotoxic insults. Aldehyde dehydrogenase plays an important role in the metabolism of dopamine. It has been suggested that decreased ALDH activity, and buildup of the dopamine (DA) metabolite 3,4-dihydroxy-phenylacetaldehyde (DOPAL) plays a role in catecholamine-mediated neuronal death in PD [26]. MAO-mediated oxidative deamination of dopamine leads to the formation of DOPAL which reacts with α-synuclein [27]. DOPAL is oxidized to 3,4-dihydroxyphenylacetic acid (DOPAC) via ALDH. Thus, chemicals that promote or interfere with the activity of ALDH-mediated dopamine metabolism may contribute toward increasing oxidative stress and dicatechol pyrrole lysine adduct formation [26-28].

Genetic polymorphisms result in biosynthesis of an inactive form of ALDH-2, which has been implicated in individual sensitivity to exogenous as well as endogenous chemicals metabolized to aldehydes. The mitochondrial toxicant trichloroethylene which has been implicated in PD is metabolized to the aldehyde choral hydrate [23, 29-30]. The pesticide rotenone which inhibits complex I, has been shown to decrease intracellular ALDH-2 activity [26]. Complex I has been shown to regulate mitochondrial ALDH-2 activity [31]. This enzyme is inserted into mitochondria, where NADH-ubiquinone oxidoreductase (complex I) regenerates NAD^+ [32]. Thus, ALDH-2 plays an important role in the detoxification of aldehydes within mitochondria. The metabolism of aldehydes depends in part on the ability of mitochondrial complex I to reoxidize NADH to NAD^+. Mitochondrial ALDH-2 activity is significantly increased in the putamen of patients with PD compared to controls [33], suggesting that the synthesis of the enzyme may be upregulated in an attempt to provide neuroprotection against endogenously generated aldehydes such as 4-hydroxy-2-nonenal and malondialdehyde. Exposures to neurotoxicants may overwhelm this already taxed system and thereby contribute to the lifetime risk and progression of neurodegenerative diseases such as PD [34]. While mechanistically intriguing, the relationship between this mutation, chemical exposure history and age at onset of neurodegenerative disease remains to be determined.

Genetic polymorphisms that influence expression of Phase I enzymes involved in hydrolysis such as butyrylcholinesterase and paraoxonase can influence individual susceptibility to organophosphate (OP) pesticides. There does not appear to be an association between the PON-1 polymorphisms and age at onset of neurodegenerative diseases such as Amyotrophic Lateral Sclerosis (ALS) among subjects who have not been stratified by chemical exposure history. However, the observation that PON genotype is an important determinant of susceptibility to chronic pesticide poisoning indicates that future studies looking at age at onset of ALS should include stratification of subjects by their history of exposure to OPs [35-37].

Epoxide hydrolases catalyze the metabolism of epoxides formed during CYP 450-mediated oxidation of chlorinated alkenes such as trichloroethylene, exposure to which has been implicated as a risk factor for PD. Expression of epoxide hydrolase is also induced by exposure to neurotoxicants such as trichloroethylene. Exposure to ethylene oxide has been implicated in parkinsonism but not in PD per se [38]. A low activity isoform of epoxide hydrolase (H-113) has been found to be more common in patients with PD [39].

DT-diaphorase (also known as NAD(P)H:quinone oxidoreductase) is an oxidoreductase that catalyzes the two-electron reduction of quinones. This enzyme plays an important role in both the bioactivation and detoxificaiton of quinones. Manganese (Mn) exposure promotes the oxidation of dopamine to its cyclized o-quinone (cDAoQ). Reduction of cDAoQ to the hydroquinone is catalyzed by DT-diaphorase [40]. Conjugation of cDAoQ with glucuronic acid

depends on it being in the fully reduced state. In the presence of Mn^{3+}, the rate of autoxidation of DA is increased and cDAoQ is no longer fully reduced [40]. The ratio of hydroquinone to o-quinone is dependent on the amount of active DT-diaphorase present with low levels of the enzyme being implicated in increased oxidative stress and even cell death. Genetic polymorphisms have been associated with an inactive form of the enzyme. Although studies have found no association between PD risk and polymorphisms of the quinone oxidoreductase genes, future studies that consider interactions between these genes and exposures to chemicals that influence dopamine metabolism such a Mn are warranted [41].

Monoamine oxidase (MAO) catalyzes deamination of dopamine and exogenous amines. MAO-mediated oxidative deamination of dopamine leads to the formation of the reactive aldehyde DOPAL which can interact with α-synuclein [27]. MAO-B plays a role in metabolism of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). MAO-B polymorphisms have been implicated in the risk for PD [42-43] Inhibition of MAO-B provides protection against MPTP neurotoxicity by preventing metabolism of MPTP to the neurotoxic metabolite MPP^+ [44], thus providing evidence of another metabolic point of interaction capable of modifying the effects of neurotoxicants on processes implicated in the pathogenesis of PD. While MPTP readily crosses the blood brain barrier, its charged metabolites $MPDP^+$ and MPP^+ do not and thus, MAO-B-mediated metabolism of MPTP to MPP^+ prior to the parent compound entering the central nervous system is neuroprotective [45]. Estrogen receptors and estrogen-related receptors have been shown to regulate MAO-B promotor activity [46]. Although smoking has repeatedly been shown to be neuroprotective in PD, the MAO-B single nucleotide polymorphism at intron 13 does not appear to modify disease risk among smokers but it may modify risk among women [47-48].

Glutathione conjugation is an important Phase II reaction that is catalyzed by the enzyme glutathione-S-transferase (GST). GST is involved in the detoxification of electrophilic compounds and peroxides. The genetic polymorphisms of GSTM1 and GSTT1 lead to expression of functionally inactive forms of the enzyme while GSTP1 polymorphisms induce functional changes that modify enzymatic activity but do not abolish it [49]. All three of these GST isozymes have been implicated in the risk of neurodegenerative diseases such as PD and Alzheimer's disease (AD) among persons exposed to neurotoxicants including pesticide [50-52]. The risk for PD was found to be higher among those pesticide applicators exposed to the herbicide paraquat who also lacked functional GSTT1, suggesting that the null form of this isozyme may increase risk for PD among subjects exposed to oxidative stressors [53]. GST polymorphisms have been shown to modulate the protective effect of tobacco smoking in PD [54]. GSTP1 single nucleotide polymorphisms have been implicated in the onset of PD at a younger age among male subjects exposed to herbicides [2], indicating that stratification of subjects by exposure history is necessary to detect such associations particularly in subjects with genetic polymorphisms of GSTP1 which can modify enzymatic activity without abolishing it [55].

GST polymorphisms have also been implicated in cognitive deficits associated with lead (Pb) exposure suggesting a point of interaction between genetics and exposure history whereby those at risk for AD may be impacted as well [51, 56].

Although GST polymorphisms have been implicated in the risk for ALS and, have even been shown to modify the association between ALS and biomarkers of Pb exposure, the relationship between these mutations and age at onset of ALS among those exposed to neurotoxicants such a Pb has not been explored due to the difficulty of establishing adequate statistical power to test for such relationships [57-61].

1.3. Elimination

Studies evaluating the relationship between exposure history and age at onset of neurodegenerative disease should also consider factors involved in the clearance and bioaccumulation of neurotoxicants. Elimination of neurotoxicants is dependent in part on their metabolism to water soluble metabolites for excretion in the urine and thus, genetic factors as well as direct toxic effect on hepatic and renal function that interfere with this process can contribute to bioaccumulation of toxic metabolites and increased risk for neurotoxicity [23]. By contrast, elimination of chemicals such as heavy metals that do not undergo biotransformation is less prone to being influenced by genetic differences in enzymatic activity.

Increased serum levels of iron and decreased levels of copper have been implicated in PD suggesting altered clearance is a factor in this neurodegenerative disease [62]. Heritable genetic conditions which influence transport and clearance of neurotoxic metals such as hemochromatosis have been implicated in neurodegenerative disease. Iron has been found to be negatively correlated with age at onset in PD with higher iron levels being found in patients younger than 55 years [62]. Age at onset of PD has also been associated with serum ceruloplasmin levels [63]. Genes involved in iron transport and clearance have been implicated in an earlier age at onset of AD and PD [13, 64].

2. Pharmacodynamics

Neurotoxicants and the neurotoxic products of chemical metabolism can exert effects by interacting with: (1) neurotransmitter receptors, (2) transporters involved in the reuptake of neurotransmitters, (3) cellular macromolecules, and, (4) promoters and repressors of transcription. Interactions of neurotoxic chemicals with receptors and transporters induce immediate changes in neuronal function through modulation of inhibitory and excitatory neurotransmission. These acute changes in neural activity are often associated with symptoms of acute intoxication such as those associated with the use of benzodiazepines and psychostimulants. Although such acute changes typically resolve upon cessation of exposure and are not associated with any measurable residual sequelae in healthy subjects, persistent neurological changes can occur during acute exposures to high concentrations of neurotoxic compounds. Chronic exposure to sufficiently high concentrations of neurotoxic chemicals is associated with the insidious development of neurological symptoms in previously healthy individuals. By contrast, chronic exposure to concentrations of neurotoxicants that would not produce symptoms in healthy individuals can contribute to symptom onset and progression in those with neurodegenerative diseases especially if the mechanism of action implicated in the disease is shared with that of the offending neurotoxicant. The interactions between neurotoxicants and neurodegenerative disease may also be additive or synergistic depending on the mechanism involved.

2.1. Glutamatergic excitotoxicity

Glutamatergic excitotoxicity is one of neurotoxic mechanisms of action consistently implicated in the pathogenesis of neurodegenerative disease. The toxic effects of β-methylamino-L-alanine which is associated with the ALS/PD complex of Guam has been attributed to glutamatergic excitotoxicity [65]. It logically follows that acute exposure to sufficiently high concentrations of chemicals to promote glutamatergic excitotoxicity would be expected to hasten the course of neurodegenerative disease while by contrast, those that attenuate this process would be expected to slow disease progression. This argument is supported by the observation that riluzole provides neuroprotection against glutamatergic excitotoxicity in a non-human primate model of PD induced by MPTP [66] and in animal models of ALS [65].

Chronic exposure to chemicals at lower concentrations can induce changes in gene expression and protein synthesis associated with the insidious onset of persistent alterations in neuronal function and vulnerability to glutamatergic excitotoxicity [67]. In keeping with this logic, chronic treatment of aged rats with riluzole has been shown to prevent many of the changes in hippocampal gene expression implicated in age-related memory deficits [68]. The hyperactivity implicated in the progression of age-related amnestic mild cognitive impairment to AD can also be attenuated with antiepileptic agents such as levetiracetam and valproic acid [69]. Estrone, which is the primary form of estrogen used in hormone replacement therapy, has been shown to attenuate apoptosis mediated by glutamate, in an age- and tissue-dependent manner [60-71]. This observation of neuroprotection by estrone may account in part for the observed differences in age at onset and risk of developing ALS among men and women [72]. Glutamatergic excitotoxicity can also lead to an increase in oxidative stress providing a link between these two mechanisms of neurotoxic action implicated in ALS [73-74].

2.2. Oxidative stress

The formation of reactive oxygen species has been implicated in AD and ALS [75-75]. The reaction of ferrous iron with hydrogen peroxide (H_2O_2) generates hydroxyl radicals implicated in Parkinson's disease [76]; this reaction is prevented by ferritin.

Oxidative stress can disrupt cell membrane integrity, promote the release of cytochrome c from mitochondria, and induce cell death via apoptosis. Higher serum levels of uric acid, which has antioxidant properties, have been associated with a slower rate of clinical decline in PD and ALS [77-78]. In the case of PD, metabolism of dopamine contributes to the formation of reactive oxygen species. Sequestration of dopamine within synaptic vesicles prevents further oxidation. Thus, neurotoxic chemicals that block reuptake of dopamine such as methamphetamine and/or promote the release of dopamine (e.g., manganese) can contribute to oxidative stress [79]. That said, many of the neurotoxicants used to induce parkinsonism in animal models of disease such as MPTP do so specifically by promoting the formation of radicals and increasing oxidative stress. The neurotoxic effects of reactive oxygen species are prevented by DT-diaphorase and superoxide dismutase [40]. Aldehyde products of oxidative stress such as 4-hydroxynonenal and malondialdehyde compete for ALDH and inhibit oxidation of DOPAL thereby contributing to DOPAL-induced crosslinking of α-synuclein [27, 80].

Not too surprisingly, methods to reduce oxidative stress via administration of antioxidants such coenzyme Q10, N-acetyl cysteine, and edaravone have been suggested as therapeutic approaches to slowing disease onset and progression [81-84]. Although the preclinical studies of these antioxidants have often been promising, unfortunately most of the clinical trials have involved patients who are already symptomatic and as a result the effect on age at onset has been impossible to ascertain. On the contrary, exposure to chemicals known to increase oxidative stress such as paraquat, especially under occupational circumstances in which higher levels of exposure are likely to occur, has provided evidence for an association between exposure and increased lifetime risk for developing overt symptoms of PD [85]. While this observation does not allow one to conclude that paraguat exposure causes PD in humans, when it is considered in terms of other data looking at age at onset and genetic polymorphisms implicated in the scavenging of free radicals it does however provide sufficient evidence to conclude that this mechanism of action plays a role in subclinical disease progression [2, 28, 85-88].

CONCLUSION

In conclusion, this review of the literature indicates that age at onset and lifetime risk for developing overt symptoms of neurodegenerative disease is modified by exposure to chemicals including neurotoxicants and, that this relationship is further modified by genetic factors that influence pharmacokinetic and pharmacodynamics processes. This review of the literature provides sufficient evidence, based on data from numerous reliable sources, to conclude that there is an association between exposures to various neurotoxicants and subclinical progression of neurodegenerative disease in humans and animals. This review also indicates that there is sufficient evidence from reliable sources to conclude that there is an association between various genetic polymorphisms that regulate the expression of enzymes involved in neurotoxicant metabolism and lifetime risk for neurodegenerative disease and that this relationship likely plays a role in disease progression as well. There is a limited amount of evidence to suggest that there is an association between the use of therapeutics aimed at reducing oxidative stress and/or glutamatergic excitotoxicity and slowing of neurodegenerative disease progression in humans. This review does not however provide sufficient evidence of a causal relationship between exposure to any specific neurotoxicant and the development of neurodegenerative disease in humans. The data reviewed here also do not provide sufficient evidence to ascertain the specific effect sizes of these disease modifying factors.

Several limitations of human studies due to penetrance, sample size, and stratification that are difficult to overcome were revealed in this review. Due to the limitations of human studies, the continued use of animal models to investigate these relationships remains warranted. Well-documented case studies will also contribute to our understanding of these relationships. Despite these limitations, adoption of improved industrial hygienic practices and the continued pursuit of dietary and pharmacological interventions aimed at slowing subclinical and clinical disease progression through attenuation of oxidative stress and glutamatergic excitotoxicity appears prudent.

ACKNOWLEDGEMENTS

This review is dedicated to the memory of the late Robert G. Feldman, MD, Former Chairman of the Department of Neurology, at the Boston University School of Medicine. Bob's life work and his incredible influence on the fields of clinical neurotoxicology and neurodegenerative disease inspired me to write this review.

AUTHOR CONTRIBUTIONS

Marcia H. Ratner wrote the manuscript.

CONFLICT OF INTEREST STATEMENT

None.

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