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Review

Gene–environment interactions in Parkinson's disease: Specific evidence in humans and mammalian models

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ABSTRACT

Interactions between genetic factors and environmental exposures are thought to be major contributors to the etiology of Parkinson's disease. While such interactions are poorly defined and incompletely understood, recent epidemiological studies have identified specific interactions of potential importance to human PD. In this review, the most current data on gene–environment interactions in PD from human studies are critically discussed. Animal models have also highlighted the importance of genetic susceptibility to toxicant exposure and data of potential relevance to human PD are discussed. Goals and needs for the future of the field are proposed.

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Introduction

Parkinson's disease (PD) affects roughly 5 million individuals world-wide (Dorsey et al., 2007). The primary motor phenotype is typically characterized by a combination of slowed movement (bradykinesia), resting tremor, postural instability, and rigidity—and many of the motor symptoms likely arise from the loss of nigral dopamine neurons and resultant striatal dopamine depletion that occurs in the disease (Cannon and Greenamyre, 2010; Shulman et al., 2011). The formation of intracellular aggregates in surviving dopamine neurons, of which a major component is the protein α-synuclein, is a pathological hallmark (Forno, 1996; Spillantini et al., 1997). Psychiatric, cognitive and autonomic symptoms are also common in PD patients. Currently, curative, or disease modifying treatments are unavailable. Given the prevalence, impact of symptoms on the patient, and lack of suitable treatment options, there are two major areas of focus for much of

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current PD research: 1) the identification of causative factors; and 2) the development of new therapeutic options that delay or halt disease progression. These two areas are not mutually exclusive. The identification of causative factors provides information on pathogenic pathways that may be therapeutic targets. Conversely, neuroprotective regimens, identified in humans or animals may be found to target previously unsuspected pathogenic pathways and provide information on causative factors. Unfortunately, major breakthroughs in either of these areas have been extremely elusive.

The single most important risk factor for PD is aging (Collier et al., 2011). The likelihood of developing PD increases significantly with aging and a sharp rise in incidence curve is observed after the fifth decade of life (Hofman et al., 1989; Mayeux et al., 1995; Morens et al., 1996; Van Den Eeden et al., 2003). However, whether PD is simply 'accelerated' aging or not has been disputed. Much evidence from human neuroanatomical studies indicates that while nigral dopaminergic cell loss and striatal dopamine depletion are part of normal aging, the pattern of cell loss is different from that which occurs in PD. In humans, striatal dopamine depletion naturally occurs with aging. However, subregional analysis indicates that the pattern of aging-associated dopamine loss differs from idiopathic Parkinson's disease (Kish et al., 1992). Nigral dopamine neuron loss in aging (greater in dorsal tier) also differs from that observed in PD (greater loss in ventral tier) (Fearnley and Lees, 1991). Therefore, it is unlikely that human PD simply arises from accelerated aging, but from the interaction between aging and other factors. Thus, the actual causes of most cases of PD are unknown and are termed 'sporadic'. This group typically accounts for ~90% of total cases. Purely inherited 'genetic' forms of PD account for ~10% of total cases. The current view held by many PD researchers is that most PD cases likely arise from a combination of environmental exposures and genetic susceptibility. The goals of this review are to critically assess what is known about gene–environment interactions in human PD and to discuss data relevant to these interactions that has been produced in mammalian models. The depth of the human data on specific gene–environment interactions is highly variable and dependent on the specific interaction. We discuss the key gaps in the literature and address why it is imperative to increase our understanding of such interactions.

Environmental exposures and PD

A role for environmental exposures in PD has received attention for several decades with numerous studies published and several recent reviews (Elbaz and Tranchant, 2007; Wirdefeldt et al., 2011). While a variety of environmental compounds in many 'use' and structural classes have been linked to PD, no single causative agent that contributes to a large number of cases has been identified. Further, occupational exposures to a wide variety of compounds including metals and solvents have been investigated for a role in PD (Cannon and Greenamyre, 2011; Wirdefeldt et al., 2011). Multiple meta-analyses examining 19–39 studies on a role for pesticide exposures in PD have come to the conclusion that exposure potentially increases PD risk on average ~1.5–3-fold (odds ratio, OR) (Priyadarshi et al., 2000; van der Mark et al., 2011).

Examination of any single study on environmental factors and PD typically reveals some major limitations in the field. First, assigning risk to a single compound is extremely difficult. Second, reaching statistical significance for specific classes of compounds is a major challenge as well. Humans are not exposed to single compounds, but mixtures, with great variability in exposure doses and the temporal aspects of the exposure. Thus, assigning risk to a specific compound will always be a challenge. However, there is optimism in the field. Many regions of the U.S., for example, now have advanced pesticide use tracking systems that allow for detailed exposure estimates. Researchers have developed innovative techniques to use this data to identify risk factors. In a recent case–control study examining the risk of developing PD based on exposure to 31 specific pesticides, 2 were found to increase risk (Tanner et al., 2011). The two pesticides found to be significant were paraquat and rotenone (OR ~2–3). While preliminary studies have previously suggested a risk for these compounds (Dhillon et al., 2008; Firestone et al., 2005; Hertzman et al., 1990; Liou et al., 1997), this study was by far the most rigorous. Of major importance is that the two pesticides in this study, which were linked to PD have long been used in the laboratory to model the disease (Betarbet et al., 2000; Brooks et al., 1999; Cannon et al., 2009; McCormack et al., 2002). Paraquat in combination with the fungicide maneb has also been epidemiologically linked to PD and used to model the disease in animals (Thiruchelvam et al., 2000a, 2000b). The importance of this correlation is twofold. First, the epidemiological results validate the use of these models as relevant to human PD. Second, the fact that animal models utilizing these toxicants recapitulate the key PD pathological features supports the relevance of the epidemiological findings to human health.

While many pesticides have been weakly linked to PD by epidemiological studies, few have also been shown to reproduce the key features of PD in laboratory animals. Conversely, there are numerous neurotoxicant-based models of PD, but few are environmentally relevant. The 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) models have been utilized for decades and continue to provide invaluable data on disease pathogenesis and evaluation of potential therapeutics. However, they have limited environmental relevance. 6-OHDA does not cross the blood–brain-barrier (BBB) and must be infused directly into the parenchyma and human MPTP exposure has been mostly limited to a small cohort of intravenous drug users in the 1980s (Langston et al., 1983). Thus, the current data emerging from both animal models and epidemiological studies suggest that toxicants with environmental relevance should be targeted for examination as a causative factor. This is clearly a two-way street. An environmentally relevant compound shown to reproduce the key pathological features of PD can prompt epidemiological research (the case for rotenone). Alternatively, the widespread use of a compound such as paraquat, with structural similarities to MPTP, and epidemiological links can prompt researchers to devise a new environmentally relevant animal model. An ultimate goal of such environmentally relevant models is to better understand causative factors. These models are most likely best suited to examine 'real-world' gene–environment interactions that bear relevance to human health.

Genetics of Parkinson's disease

A brief introduction to genetic factors implicated in environmental interactions

The number and diversity of the function of genes linked to PD is ever expanding. The genetics of PD have been extensively reviewed recently (Bekris et al., 2010; Shulman et al., 2011). It is readily apparent from the history of the field that the link between genetics and PD is continually being built-up. While early twin studies suggested a very limited role of genetics in PD, the link has continued to strengthen with advances in genetic techniques (de Lau and Breteler, 2006). Indeed, the general belief in the field remains that monogenic forms of PD account for a small number of the total cases, 10–30% of PD subjects in a recent study reported a family history and first-degree relatives of PD patients were found to have a two to seven-fold increased relative risk for developing PD (Marder et al., 2003; Shulman et al., 2011; Sveinbjornsdottir et al., 2000).

A thorough discussion on the genetics of PD, is outside the scope of this review. However, a brief examination of the genes with human data on important environmental interactions is fruitful. Much data on gene–environment interactions is derived from α-synuclein genetics. The protein α-synuclein is a pivotal protein in PD. Several mutations

and wildtype gene dupli- and triplications cause highly penetrant forms of PD (Shulman et al., 2011). α-Synuclein was also identified as a major component of the pathological hallmark, the Lewy body in sporadic PD cases (Spillantini et al., 1997). Thus, the protein is important in sporadic and genetic forms of PD. The normal function of α-synuclein is unknown, though it is thought to play a role in synapse development and presynaptic function (Roy, 2009). Several highly penetrant, yet extremely rare mutations in the protein have been found to cause PD (Polymeropoulos et al., 1997; Zarranz et al., 2004). Additionally, within the α-synuclein gene there are genetic variants associated with PD, but with incomplete penetrance—bearing a small increase in risk (odds ratios 1.2-1.4, depending on allele) but being present in very high percentages of certain populations (10–50%, depending on allele and population) (Shulman et al., 2011).

There are many other genes that have been linked to PD with a wide variety of functions. The highly penetrant monogenic forms provide useful information on causative factors, but account for a small number of cases. Thus, in the context of interactions, these forms may be primarily useful to study mechanisms in animals and *in vitro*. Such mutations with extensive data in mammalian models, include: *Parkin*, an E3 ubiquitin ligase where, loss-of-function mutations cause early onset PD (Kitada et al., 1998; Lucking et al., 2000; Periquet et al., 2003); and loss-of-function in DJ-1, which is thought to be involved in the oxidative stress response, cause PD (Bonifati et al., 2003).

A key question is on the role of genetic susceptibility that is not completely penetrant but present in a large portion of the population. A prominent example, currently receiving much attention is the leucine-rich-repeat kinase 2 (LRRK2) protein. It is currently the most common genetic cause of PD, exhibiting variable and incomplete penetrance (Bras et al., 2005; Lesage et al., 2005; Ozelius et al., 2006). There are number of other risk factors that have been identified. While the odds ratios might be low for such factors, the prevalence of these genetic factors can lead to a significant risk. There simply must be other factors influencing penetrance in these cases. The remainder of the review is focused on what we have learned on deleterious gene–environment interactions in both human PD studies and lessons from mammalian models.

Gene–environment-interactions in human Parkinson's disease

While many researchers postulate that the majority of cases are influenced by both genetic predisposition and environmental exposures, the specifics of these interactions are not well understood. Nevertheless, there are some data pointing to specific interactions (Table 1A). The number and diversity of gene–environment interactions that could bear pathogenic relevance to PD is very large, but the current discussion is limited to those interactions with supporting or suggestive data (Table 1B).

Toxicant disposition

Absorption, distribution, metabolism, and excretion are key factors in how the human body deals with xenobiotic exposures. Genetic predispositions may affect toxicant disposition in a number of ways relevant to PD, including increased toxicant accumulation in sensitive brain regions and alterations in metabolism that produce more toxic species. There are indeed some data to support these predispositions.

To have a direct effect on the nigrostriatal dopamine system, a toxicant must first be able to cross the blood–brain-barrier (BBB). Many toxicants are unlikely to cross the BBB due to size or polarity constraints (Pardridge, 2005). Genetic alterations that alter BBB permeability could increase toxicant accumulation into the brain or allow entry of toxicants that are typically excluded. Human data supports the potential of such an interaction. P-glycoprotein is the product of the multidrug resistance (MDR1) and contributes to the function of the BBB. Interestingly, distribution of the 3435T/T genotype, which has previously been associated with decreased P-glycoprotein expression and function, was highest in early-onset PD patients, second-highest in late-onset PD patients, and lowest in controls (Furuno et al., 2002). Additional reports have suggested that ethnicity, polymorphisms, and haplotype expression, relevant to MDR1 may modulate PD risk (Drozdzik et al., 2003; Lee et al., 2004; Tan et al., 2005). Alterations in P-glycoprotein expression, may indeed be important to toxicant uptake. A positron emission tomography measuring brain uptake of [(11)C]-verapamil, which is normally extruded from the brain by P-glycoprotein showed increased absorption in the midbrain of PD patients (Kortekaas et al., 2005). This study suggests that both that P-glycoprotein and a dysfunctional BBB could have a role in PD. An additional imaging study did not find dysfunction in P-glycoprotein in early-onset PD cases, although variability was high (Bartels et al., 2008). In postmortem tissue the level of MDR1 mRNA in the striatum was reduced in PD patients compared to controls (Westerlund et al., 2008). These studies suggest that reduced expression or function may have a pathogenic role in PD. MDR1 −/− mice have been shown to accumulate anticancer drugs, narcotics, and pesticides (Schinkel et al., 1994; Schinkel et al., 1996). Depending on the compound, accumulation may occur at much higher levels than in control, or compounds that are typically completely excluded may gain access in MDR1 −/− mice. The direct relevance to dopaminergic toxicants has not yet been established and it may be that altered brain entry of normally excluded endogenous factors is much more important than environmental exposures in modulating PD risk.

Dopamine metabolism has been linked to PD. While the loss of dopamine in PD causes much of the motor phenotype, dopamine itself likely contributes to the selective susceptibility of dopamine neurons. The molecule is highly reactive and its metabolism can produce oxidative stress and oxidative protein modification (Hastings and Zigmond, 1994). Both dopamine and MPTP are metabolized by monoamine oxidase B (MAO-B) and it is possible that other environmentally relevant neurotoxicants are metabolized by this enzyme (Chiba et al., 1984; Javitch et al., 1985; Kopin, 1992). Polymorphisms in MAO-B have been linked to PD and may influence neurotoxicant metabolism and hydrogen peroxide production (Kurth et al., 1993). Many follow-up studies were conducted shortly after this initial report with mixed results (Costa et al., 1997; Ho et al., 1995; Hotamisligil et al., 1994; Mellick et al., 1999; Morimoto et al., 1995; Nanko et al., 1996; Tan et al., 2000). There are significant variations between studies in sample sizes and methods. Several of these studies do, however, suggest a potential link. A very interesting gene–environment interaction that has emerged out of this line of research is between MAO-B polymorphisms, smoking, and PD. Smoking in humans and nicotine in animal models of PD, for reasons not fully understood, have been repeatedly shown to be protective in PD (Quik et al., 2009). Specific polymorphisms in MAO-B have been found to ameliorate this protective effect, increasing risk (Checkoway et al., 1998). Again, follow-up studies did not always support this finding (Hernan et al., 2002). A major variable in many epidemiological studies is the ethnicity of the cohort, which may have an influence. Such discrepancies also illustrate the difficulty in identifying disease-modifying factors. Nonetheless, the potential removal of an environmentally-induced protective factor through expression of a specific polymorphism is of interest. While the effects of smoking are rarely beneficial, the mechanisms of the interaction are worth understanding.

While the primary lesion responsible for the motor phenotype in PD is the loss of nigral dopamine neurons and striatal dopamine depletion, other neuronal populations and neurotransmitter systems are affected (Rub et al., 2002). The role the other neurotransmitter systems such as serotonin and acetylcholine play in PD is undetermined. However, some specific gene–environment interactions have been proposed. Organophosphates are degraded by paroxonase 1 (PON1) and exhibit much of their toxicity through acetylcholinesterase (AChE) inhibition (Akhmedova et al., 2001; Brophy et al., 2001; Shapira et al., 2000). Epidemiological studies have recently linked some organophosphates to PD (Gatto et al., 2009). Case reports also have suggested that acute

Table 1A
Gene–environment interactions linked to human PD. Gene–environment interactions in human Parkinson's disease. Published human data implicating an interaction between a specific genetic factor and an environmentally relevant toxicant or class of compounds.

Gene/protein	Alteration	Toxicant	Potential mechanism (s)	References
Monoamine oxidase-B	Polymorphisms	None yet identified, certain expression profiles remove the protective effect of smoking	Oxidative stress production, altered dopamine neurotransmission; toxicant metabolism	(Checkoway et al., 1998; Kurth and Kurth, 1993)
Paraoxonase I	Polymorphisms resulting in altered expression profiles	Organophosphates	Alterations in toxicant metabolism; neurotransmission imbalance (acetylcholine)	(Benmoyal-Segal et al., 2005; Gatto et al., 2009)
Manganese-containing superoxide dismutase and NAD(P)H: quinone reductase	Polymorphisms	Pesticides	Reduced ability to metabolize pesticides; altered metabolic pathways resulting in increase formation of more toxic metabolites	(Fong et al., 2007)
CYP2D6	Polymorphisms, mutations	Pesticides, solvents	Reduced ability to metabolize toxicants; altered metabolic pathways resulting in increase formation of more toxic metabolites	(Agundez et al., 1995; Armstrong et al., 1992; De Palma et al., 1998; Deng et al., 2004; Elbaz et al., 2004; Kurth and Kurth, 1993; Smith et al., 1992; Tsuneoka et al., 1993)
REP1 in SNCA promoter	Polymorphisms altering expression levels	Paraquat	Shorter promoter length is typically protective; paraquat exposure increases risk in those with shorter promoters, removing a protective factor	(Gatto et al., 2009)
Dopamine transporter	Polymorphisms altering expression levels	Pesticides	Increased DAT expression may lead to increased toxicant accumulation in dopaminergic neurons; altered DAT expression may affect dopaminergic neurotransmission, increasing susceptibility to toxic insults	(Kelada et al., 2006; Ritz et al., 2009)

exposures can result in motor deficits that share features of PD (Joubert et al., 1984; Muller-Vahl et al., 1999; Senanayake and Sanmuganathan, 1995). While acute behavioral deficits may arise from imbalances between dopaminergic and cholinergic signaling, the long-term effects relevant to PD are unknown. Interestingly, it was recently found that polymorphisms in the ACHE/PON1 locus, resulting in expression variations were much higher in PD patients from agriculturally exposed areas (rural Taiwan), suggesting a gene–environment interaction (Benmoyal-Segal et al., 2005). Reduced serum AChE and PON1 activities were also found to be more prevalent in PD patients in this study, suggesting that a long-term inability to hydrolyze organophosphates (by PON1) or inability to increase AChE in response to pesticide exposure may result in gene–environment interaction that increases PD risk.

The assessment of gene–environment interactions in human populations is aided by the study of populations with high degrees of pesticide (or other relevant toxicant) exposure. In another Taiwanese population, genetic factors were not significantly associated with PD alone. However, an interaction between pesticide exposure and polymorphisms in the detoxification enzymes manganese-containing superoxide dismutase (MnSOD) and NAD(P)H: quinone reductase (NQO1) was found (Fong et al., 2007). In this study, the odds ratio was 1.69 (95% CI, 1.07–2.65) for pesticide exposure and PD, and an adjusted OR (aOR) of 2.49 (95% CI, 1.18–5.26, P = 0.0072) for MnSOD C allele and aOR of 2.42 (95% CI, 1.16–4.76, P = 0.0089) for NQO1 T and among subjects exposed to pesticide, the combined MnSOD/NQO1 variant genotype was significantly associated with a 4.09-fold increased risk of PD (95% CI, 1.34–10.64, P = 0.0052) (Fong et al., 2007). It should

Table 1B
Plausible interactions that may influence PD risk in humans. Plausible factors that may influence risk. The number of interactions that may influence risk is very large; selections are included that may bear direct relevance to the dopaminergic toxicity of environmentally relevant toxicants.

Gene/protein	Alteration	Toxicant	Potential mechanism (s)	References
MDR1/ P-glycoprotein	Haplotype differences, polymorphisms	None identified. However animal studies show altered uptake of several compounds that affect neurological function.	Increase toxicant (exogenous and endogenous) entry into the brain. Brain access for compounds typically excluded	(Drozdzik et al., 2003; Furuno et al., 2002; Kortekaas et al., 2005; Lee et al., 2004; Schinkel et al., 1994; Schinkel et al., 1996; Tan et al., 2005)
N-acetyltransferase 2	Polymorphisms resulting in slow acetylation	None yet identified	Decreased ability to metabolize toxicants, alternate metabolism producing more toxic metabolites.	(Agundez et al., 1998; Bandmann et al., 1997; Bandmann et al., 2000; Chaudhary et al., 2005)
Multiple genetic forms (notably data from parkin and PINK1 patients)	Mutations causing loss-of-function, downstream effects on mitochondrial function	No specific interacting toxicant yet identified; toxicants that target mitochondrial complex I	Potentiation of effects on mitochondrial function	(Grunewald et al., 2009; Grunewald et al., 2010; Mortiboys et al., 2008; Schapira, 2011)
LRRK2	Numerous mutations	None identified yet in humans; animal data also limited	Mechanism of interaction relevant to human health is unknown; variable penetrance suggests environmental factors may play a role	None yet strongly implicating environmentally relevant toxicants

be noted that the total sample size was 153 PD patients 155 controls. However, the polymorphisms studied were relatively common, with enough patients in each group to typically calculate and adjust odds ratio and perform statistical analysis.

Cytochrome P450s are a group of enzymes involved in Phase I biotransformation of numerous classes of toxicants (Parkinson and Ogilvie, 2008). Mutations in CYP2D6 have received the most attention of the group and have been reported as a risk factor for PD, with an increase risk of ~2–3 fold (Agundez et al., 1995; Armstrong et al., 1992; Kurth and Kurth, 1993; Smith et al., 1992; Tsuneoka et al., 1993). While many of these studies have examined widespread polymorphisms (poor metabolizer), most of the significant effects were observed in the rarer mutation Hha I RFLP, with a metanalysis not supporting a polymorphism contribution, in addition to many inconsistent follow-up studies (Rostami-Hodjegan et al., 1998). Further, age of onset may be influenced by mutations in CYP2D6, with significant effects observed in early onset cases (Agundez et al., 1995). One study did find a significant interaction between CYP2D6 mutation and solvent exposure (De Palma et al., 1998). While the sample size was very small ($n = 5$), the findings suggest that a 'real-world' gene–environment interaction may influence pathogenesis. Solvents have long been reported to reproduce certain behavioral effects, but more recent data suggest that prolonged exposure to trichloroethylene in rats and humans may increase risk and reproduce key disease features in a rat model (Gash et al., 2008; Liu et al., 2010). The substrates for CYP2D6 are diverse and including multiple drugs relevant to neurological function (desipramine and several opioids) (Parkinson and Ogilvie, 2008). The environmentally relevant dopaminergic neurotoxicant rotenone is also metabolized by several P450s, including CYP2D6 (Caboni et al., 2004). Multiple, more comprehensive studies have also found interactions between CYP2D6 mutations and pesticide exposures (Deng et al., 2004; Elbaz et al., 2004). These studies may help explain the inconsistencies in the link between poor metabolizers and PD. Expression of the poor metabolizer polymorphism itself was not a risk factor. However, risk increased when poor metabolizers were exposed to pesticides. Thus, a specific gene–environment interaction is required in this instance to quantify increased risk. Further, a gene–environment interaction may influence the severity of specific types of symptoms. One study found that patients with PD and dementia were much more likely to have metabolically deficient CYP2D6 than PD patients without dementia (Hubble et al., 1998). A potential mechanism of interaction between an environmentally relevant compound and CYP2D6 mutations remains undetermined. However, it is plausible that the poor metabolizer polymorphism results in the accumulation of the toxic parent compound or that the parent compound is metabolized through an alternate metabolic pathway to a more toxic species.

Additional lines of research found that metabolic differences in acetylation could influence risk. Slow acetylator mutated alleles for *N*-acetyltransferase 2 were more common in PD patients (OR 3.79) (Bandmann et al., 1997). N-acetylation is a major route of biotransformation for a variety of xenobiotics, particularly those containing an aromatic amine ($R\text{-}NH_2$) or hydrazine group ($R\text{-}NH\text{-}NH_2$) (Parkinson and Ogilvie, 2008). While this predisposition was not linked with a specific toxin and was also more common in Huntington patients than controls (OR 2.49), it did raise the possibility that genetic differences in neurotoxicant metabolism could influence risk. While not all of the follow-up studies support a link, several have (Agundez et al., 1998; Bandmann et al., 2000; Chan et al., 2003); including one that showed that the slow acetylator type was associated with young age of onset (Chaudhary et al., 2005). While many polymorphisms have been examined in this group of genes, the data for the slow acetylator forms is the strongest.

Solvent exposure and PD have been discussed above. It appears that differences in solvent metabolism may also have a role in PD. Interestingly, PD patients were found to exhibit poor metabolism of the hydrocarbon solvent n-hexane (Canesi et al., 2003). Again, the mechanism is unknown, but it is possible that alternate pathways result in more toxic species. This has long been postulated for TCE metabolism, where TaClo (1-trichloromethyl-1,2,3,4-tetrahydro-beta-carboline), which may be produced during TCE metabolism has been proposed as a metabolite that is toxic to dopaminergic neurons and a potential mitochondrial complex I inhibitor (Gash et al., 2008).

Many epidemiological studies with small to medium sample sizes have found statistically significant associations between PD and specific exposures. Unfortunately, many of these findings have not been replicated in more comprehensive and larger studies. There may be more variables that account for such discrepancies than simply the power of the study, such as the genetic makeup of the population, methods, and variables assessed. Examining gene–environment interactions in human populations adds another set of variables and undoubtedly a greater degree of difficulty. Thus, it is unsurprising that a newer large study (767 PD patients, and 1989 controls across 5 European centers) was unable to replicate many of the findings of previous studies (Elbaz and Tranchant, 2007). Here, only 1 out of 31 gene–environment interactions (null glutathione *S*-transferase mu 1 and solvents) was replicated in this study. These discrepancies illustrate the challenge in identifying relevant gene–environment interactions in human PD populations.

Protein degradation

A recent case–control study found that both the length of a dinucleotide repeat sequence (REP1) within the SNCA promoter in α-synuclein (a known PD risk factor, increased length was found to increase PD risk) and herbicide exposure were significant risk factors. However, they did not interact (Brighina et al., 2008). A further study utilizing the availability of detailed long-term exposure data assessed specific REP1 genotypes and found an interesting interaction. As in the previous study, increased base-pair repeat length in the REP1 promoter was a risk factor. However, paraquat exposure increased risk in those with shorter promoters (typically a protective factor) (Gatto et al., 2010). Thus, the protective effect of shorter REP1 appears to be lost upon pesticide exposure. While interactions between disease causing mutations in α-synuclein and environmental factors may occur, these mutations are very rare and highly penetrant. Therefore, while mechanistically important, these interactions would not represent the pathophysiology of a significant number of human cases.

Mitochondrial complex I function

Systemic mitochondrial complex I deficiency is evident in humans with PD (Parker et al., 1989; Schapira et al., 1989). The highly lipophilic pesticide rotenone is a potent inhibitor of mitochondrial complex I inhibitor and has been used to model PD in rats and now has been epidemiologically linked to PD (Betarbet et al., 2000; Tanner et al., 2011). While a specific interaction between a mitochondrial complex I inhibitor and genetic factor has not yet been epidemiologically identified in humans, the fact that rotenone exposure is a risk factor and that rotenone in multiple models affects several pathways genetically linked to PD (α-synuclein, DJ-1, parkin, etc.) suggests that such an interaction is plausible (Betarbet et al., 2000, 2006; Tanner et al., 2011; Wang et al., 2005). Further, mitochondrial function is affected in multiple genetic forms of PD (Schapira, 2011). Parkin positive patients exhibit system complex I activity reduction and complex I-linked ATP production (Grunewald et al., 2010; Mortiboys et al., 2008). PTEN-induced putative kinase 1 (PINK1) patients exhibit peripheral mitochondrial dysfunction (Grunewald et al., 2009). Undoubtedly, mitochondrial dysfunction will be identified in additional genetic forms. It is also expected that environmental toxicants affecting mitochondrial function, in particular, complex I activity will continue to be identified. Thus, an interaction at the level of mitochondrial function is expected to be an important

pathogenic mechanism of the interplay between genetic and environmental factors.

Transporters

Many toxicants exhibit harmful effects based upon distribution. Therefore, a relevant dopaminergic neurotoxicant, or its metabolite would need to gain access to the brain and then dopaminergic neurons. The classic dopaminergic neurotoxicant MPTP has been shown to enter dopamine neurons through the dopamine transporter (DAT) (Javitch et al., 1985). Since this finding, many compounds bearing structural similarities to dopamine or MPTP have been postulated to gain access to dopamine neurons through this route. Numerous single-nucleotide polymorphisms in DAT have been identified as risk factors for PD. The expression of two or more of these factors modestly increases PD risk [OR = 1.58; 95% CI: 1.03–2.40] (Kelada et al., 2006). Interestingly, a significant interaction between occupational pesticide exposure in men and the number of risk alleles was detected, where, among pesticide-exposed subjects, the OR for having two or more risk alleles was 5.66 (95% CI: 1.73–18.53). The functional consequences of these alleles are not understood. It is possible that risk is increased through increased toxicant uptake through DAT for these alleles. Alternatively, risk alleles in DAT may alter dopaminergic metabolism in a way that contributes to disease pathogenesis. An additional study confirmed and extended these findings, specifically showing that expression of one 'risk' allele increased the OR for PD in those exposed to paraquat and maneb to ~3 OR, with a ~4 OR in those expressing two or more of these risk alleles (Ritz et al., 2009). While the results are still from only a few studies, the data for DAT genetics and pesticide exposure are currently among the strongest human data on specific gene–environment interactions and warrant further mechanistic studies.

Mammalian models of gene–environment interactions

Rare mutations and neurotoxicants

Much of the work on gene–environment interactions in animal models of PD has focused on determining toxicant sensitivity in knockout or transgenic animals expressing rare PD-causing mutations. α-Synuclein mouse models in particular have been used extensively. α-Synuclein null mice exhibit marked resistance to the classic dopaminergic neurotoxicants MPTP and 6-OHDA (Alvarez-Fischer et al., 2008; Dauer et al., 2002; Drolet et al., 2004; Schluter et al., 2003). Transgenic mice expressing disease-causing mutations in α-synuclein have produced mixed results with respect to toxicant sensitivity. The A30P transgenic mice have shown conflicting results on alterations in sensitivity to MPTP, with some studies showing heightened sensitivity and others finding no increase (Nieto et al., 2006; Rathke-Hartlieb et al., 2001). Expression of the A53T mutation has been shown to increase toxicity (Nieto et al., 2006; Rathke-Hartlieb et al., 2001). Expression of wild-type human α-synuclein also increases MPTP sensitivity (Richfield et al., 2002; Song et al., 2004). Such expression has not been found to increase sensitivity to the dopaminergic neurotoxicant paraquat (Fernagut et al., 2007). While these mutations are fully penetrant in humans, it is clear from the studies above and others that most transgenic models do not replicate the key pathogenic features of PD on their own (for example striatal dopamine loss and nigral dopamine neuron loss). A major limitation is likely the lifespan of the rodent, which is only a few years. These mutations require many decades to produce a phenotype in humans. Thus, the above studies may actually be testing the ability of a toxicant to decrease the age-of-onset of a PD phenotype in these transgenic lines.

Inconsistencies in the results from transgenic animals expressing human mutated α-synuclein + toxicant exposure may result in differences in expression levels and expression patterns. Different promoter systems are often used, and in many cases expression is targeted specifically to catecholaminergic neurons using the tyrosine hydroxylase promoter, which does not replicate what occurs in humans. Further, in these models the magnitude of the expression relative to basal native levels is often not assessed—or is many times greater, thereby raising questions about physiological relevance. While these studies do not represent a 'real world' interaction because these mutations are extremely rare and MPTP is highly unlikely to be encountered, much can be learned from the results. First, the data support a pathogenic role for α-synuclein in the pathogenesis of both sporadic and genetic cases of PD. Second, mutations or overexpression may sensitize the nigrostriatal dopamine system to insults by environmentally relevant toxins. Thus, further studies should utilize compounds relevant to human health to test sensitivity. Further, given that REP1 expansions may be present in up to 10% of individuals in certain populations, relevant genetic animal models + environmental toxicants may represent more relevant assessment of such interactions (Shulman et al., 2011).

Other mammalian models of gene–environment interactions have also yielded mixed results. *Parkin* is an E3 ubiquitin ligase involved in protein degradation, and loss-of-function mutations cause early onset PD (Kitada et al., 1998; Lucking et al., 2000; Periquet et al., 2003). Because of early onset and a lack of relevant extranigral pathology, it has been argued that this genetic mutation induces a syndrome distinct from sporadic PD (Shulman et al., 2011). Nonetheless, mechanistic studies have shown that *parkin* may play a pathogenic role in PD, with S-nitrosylated *parkin* occurring in humans with PD and in disease models (Chung et al., 2004). In this study, S-nitrosylation inhibited *parkin* E3 ligase activity. Initial studies using parkin deficient mice found no loss of ubiquitin function or alterations in sensitivity to methamphetamine, MPTP or 6-OHDA (Perez et al., 2005; Thomas et al., 2007). Overexpression by a viral vector system has been reported to be protective in an MPTP mouse model (Yasuda et al., 2011). Interestingly, *parkin* deficient mice displayed marked sensitivity to inflammatory insult (lipopolysaccharide), exhibiting selective loss of nigral dopaminergic neurons (Frank-Cannon et al., 2008). Thus, genetic and environmental insults that affect parkin function and also induce neuroinflammation are worth investigating.

Rare mutations causing loss-of-function in DJ-1, which is thought to be involved in the oxidative stress response, cause PD (Bonifati et al., 2003). DJ-1 knockout mice do not exhibit loss of striatal dopamine, nigral dopamine neurons, or gross anatomical abnormalities. However, they exhibit heightened sensitivity to MPTP (Kim et al., 2005). This exacerbation of toxicity was ameliorated by using a viral vector system to restore DJ-1. However, a follow-up study using a different null line did not fully support such a finding; only exacerbation in dopamine depletion, but not cell loss (Manning-Bog et al., 2007). Further, it was found that DAT levels in the presynaptic fraction, MPP + uptake, and MPP + accumulation in the striatum were all increased. Thus, hypersensitivity is likely mediated by alterations in toxicant uptake, which always needs to be considered when assessing MPTP (or other toxicants that enter through DAT) data. Whether or not DAT alterations occur in humans with DJ-1 mutations is not known. It is worth noting that a number of *in vitro* reports suggest that DJ-1 serves an important role in the response to environmentally relevant toxicants, including rotenone (Liu et al., 2008; Mullett and Hinkle, 2009, 2011). Thus, the investigation of the response to rotenone and other relevant environmental compounds in animals with altered DJ-1 function may be interesting. While the rotenone model does not typically work well in the mouse for unknown reasons, it is expected that the availability of transgenic rat models will soon make such experiments possible.

Nearly 50 variants in leucine-rich-repeat kinase 2 (LRRK2) protein have been linked to PD (Shulman et al., 2011). It is currently the most common genetic cause of PD, with a single disease causing mutation (G2019S), present in 6–40% of patients in specific populations (Bras et al., 2005; Lesage et al., 2005; Ozelius et al., 2006). It should be

noted that the normal function of LRRK2 is not fully understood. It is a large protein with multiple functional domains and the studies above have identified mutations in multiple domains that cause PD. Incomplete penetrance and variable pathology have suggested that factors such as environmental exposures may contribute to emergence of PD in individuals with LRRK2 variants. While one study in humans suggests that environmental exposures may influence LRRK2-mediated PD risk, data is extremely limited (Lin et al., 2011). An initial study has shown that LRRK2 knockout mice do not exhibit increased sensitivity to MPTP (Andres-Mateos et al., 2009). Clearly, there is much more to be done to model interactions. Using animal models that express specific disease-causing or modifying mutations to test sensitivity to an environmental toxicant will provide much more information. Full gene knockout does not likely replicate the key functional consequences in human LRRK2-induced PD.

Future directions

There are several clear needs in assessing the role of gene–environment interactions in PD. Methods for human epidemiological studies have significantly improved. Much data on specific pesticide usage is now available. Future studies examining as many known genetic factors as possible in conjunction with exposure to pesticides or industrial toxicants will provide the most information on gene–environment interactions. To determine such interactions, a study must be sufficiently powered.

There is much room for advancement in modeling relevant gene–environment interactions in animal models. High doses of toxicants that bear no environmental relevance in animals expressing rare, highly penetrant mutations may produce a desired phenotype, but likely do not represent 'real-world' interactions and may not recapitulate pathogenic features of human interactions. Optimally, animals expressing highly prevalent risk factors with incomplete penetrance will be created. These animals can then be exposed to environmentally relevant compounds at doses that model human exposures. Such a regimen would bear much more relevance to a pathogenic interaction in humans. A potential drawback is that it will probably be difficult to produce an end-stage phenotype in such a model, exhibiting major loss of nigral dopamine neurons. This type of model would be expected to produce subtle behavioral, neurochemical, and pathological features characteristic of preclinical, early-stage PD. Thus, endpoints that assess the earliest known features of the pathogenesis will need to be included.

The ultimate major goals of understanding PD-causing gene–environment interactions are two-fold. First, individuals with specific genetic susceptibilities may be cautioned against exposure to certain classes of compounds, thereby reducing incidence. Second, understanding the mechanistic features of these interactions may identify new pathogenic pathways, offering new targets for therapeutic intervention that produce novel disease-modifying or curative treatments.

Summary

Many researchers believe that gene–environment interactions account for the majority of PD cases. While our understanding of these factors remains rudimentary, powerful epidemiological studies have begun to identify specific interactions. Therefore, it is expected that in the near future considerably more interactions and potential mechanisms will emerge.

Animal models have yielded mixed results, but strongly suggest that gene–environment interactions are important. While the field has been mostly limited to exposing animals expressing rare mutations to compounds that bear no environmental relevance, future modeling of relevant gene–environment interactions is expected to significantly advance the field.

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