Etiology of Parkinson's Disease

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ABSTRACT: There is growing recognition that Parkinson's disease (PD) is likely to arise from the combined effects of genetic predisposition as well as largely unidentified environmental factors. The relative contribution of each varies from one individual to another. Even in situations where more than one family member is affected, the predominant influence may be environmental. Although responsible for only a small minority of cases of PD, recently identified genetic mutations have provided tremendous insights into the basis for neurodegeneration and have led to growing recognition of the importance of abnormal protein handling in Parkinson's as well as other neurodegenerative disorders. Abnormal protein handling may increase susceptibility to oxidative stress; conversely, numerous other factors, including oxidative stress and impaired mitochondrial function can lead to impaired protein degradation. A limited number of environmental factors are known to be toxic to the substantia nigra; in contrast, some factors such as caffeine intake and cigarette smoking may protect against the development of PD, although the mechanisms are not established. We review the various genetic and environmental factors thought to be involved in PD, as well as the mechanisms that contribute to selective nigral cell death.

RÉSUMÉ: Étiologie de la maladie de Parkinson. L'opinion qui prévaut actuellement est que la maladie de Parkinson résulte de l'interaction entre une prédisposition génétique et des facteurs environnementaux qui demeurent en grande partie inconnus. La contribution relative de chacun varie d'un individu à l'autre. Même dans les familles où plus d'un membre est atteint, l'influence prédominante peut être environnementale. Bien qu'elles soient en cause dans seulement une minorité de cas de la maladie, des mutations génétiques identifiées récemment ont fourni des indices précieux sur l'étiologie de la dégénérescence neuronale et ont permis de reconnaître l'importance d'un métabolisme protéique anormal dans la maladie de Parkinson ainsi que dans d'autres maladies neurodégénératrices. Un métabolisme protéique anormal peut augmenter la susceptibilité au stress oxydatif; à l'inverse, plusieurs autres facteurs, dont le stress oxydatif et une fonction mitochondriale altérée, peuvent induire une altération de la dégradation protéique. On connaît l'effet toxique d'un certain nombre de facteurs environnementaux sur la substance noire; par contre, certains facteurs tels la consommation de caféine et le tabagisme pourraient protéger de la maladie de Parkinson, bien que les mécanismes n'en soient pas établis. Nous revoyons les différents facteurs génétiques et environnementaux qu'on pense impliqués dans la maladie de Parkinson ainsi que les mécanismes qui contribuent à la mort sélective de cellules de la substance noire.

The prevalence of Parkinson's disease (PD) is 200-300 cases per 100,000 persons, with an overall estimated annual incidence of 12 cases per 100,000.[1] The prevalence is heavily age-dependent, estimated at 1% in subjects over the age of 65, and increasing to 4.3% in those over 85 years of age.[2] In addition, there seems to be a gender effect; men have a somewhat higher risk of PD than women.[3]

Despite intense research efforts over many years, the cause(s) of PD still await elucidation. Over the past two decades, scientific opinion has varied between two extreme poles: from a position in which only environmental factors were deemed to be relevant, to a position where genetic factors were considered to be dominant. The importance of heredity in the etiology of PD has been strengthened by the discovery of some kindreds with rare genetic forms of PD.[4,5] Environmental risk factors, including exposure to pesticides and metals, well water drinking, rural living and farming, have been investigated in many recent case-control and epidemiological studies.[6-9] The common view today is that PD results from the combined effects of genetic susceptibility, environmental exposure and complex genetic-environmental interactions. Aging is also a likely contributory factor.[10] Several mechanisms have been proposed to explain cell death in PD, including oxidative stress, mitochondrial dysfunction, apoptosis, excitotoxicity and inflammatory responses.

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PARKINSON'S DISEASE IN DIFFERENT POPULATIONS

Although PD has a worldwide distribution, incidence rates may vary among populations. The results are, however, somewhat contradictory. Thus, while the prevalence of PD has been reported to be relatively low in South African and Nigerian blacks, blacks living in Mississippi are affected to a comparable degree as the white population.[11] Also, an autopsy study found that black Africans have an equivalent prevalence of incidental Lewy body disease as compared with white populations.[12] Similarly, while lower prevalence rates have also been reported in some Oriental populations,[13,14] the prevalence of PD in Taiwan is much higher and closer to that in Western countries.[15] Even if population differences in PD incidence do exist, the question still remains as to the relative contribution of genetic or environmental variations to such differences.

There is also evidence that PD patients are more likely to have a close relative with PD compared to controls.[3,16] This observation, however, does not necessarily imply genetic causation. Shared environmental exposure could also explain some of the patterns of familial aggregation observed in PD.[17] For example, disease onset among affected family members seems to cluster around the same *calendar* year, which supports a shared environmental exposure.[18]

GENETIC FACTORS AND ABNORMAL PROTEIN PROCESSING

There is increasing interest in the heritability of PD. This heightened interest was greatly promoted by the clinical observation of familial aggregation of PD cases[3,19] and by the discovery of families with genetic forms of parkinsonism.[4,5,20,21] Nevertheless, we have already noted that familial aggregation does not necessarily imply genetic causation[17,18] and that most PD cases test negative for known mutations. In fact, a recent large twin study comparing clinical concordance rates between monozygotic and dizygotic twins detected increased concordance only in monozygotic twins who developed PD symptoms before the age of 50 years; no increased concordance was found in those who manifested disease at a later age.[22] Although a small twin study using both clinical assessment and [^{18}F]fluoro-dopa positron emission tomography did report increased concordance among identical twins,[23] this important observation needs to be confirmed in further studies. The effect of maternal factors on their children's risk of PD may mask the distinction between environmental and genetic causation.[24] A recent epidemiological, statistical and mathematical study on PD patients and their parents showed that the child's risk of PD was related to the *child's* age at the time the parent developed PD rather than the *parental* age at onset of PD.[25] Thus, the younger the child at the time the parent developed PD, the higher the risk for the child. This relationship was especially apparent when the affected parent was the mother. The degree to which parents and children share their environment usually decreases with age. Furthermore, for inherited illnesses, the risk for the child is usually related to *parental* age at onset. Taken together, the observations support the notion that most PD cases, including most familial cases (at least those families in which only two members are affected), are due to shared environmental exposure.

Although genetic mutations have only been associated with rare forms of parkinsonism, the discovery of these genes has provided a tremendous insight into the pathogenesis of PD. The role of abnormal protein processing in particular has now been recognized as a major mechanism of cell death not only in genetic forms of parkinsonism[26,27] but also in sporadic PD[28] and in other neurodegenerative disorders.[28,29]

Mutations in three identified genes have been associated with parkinsonism: -synuclein, on locus 4q21-23,[4,21] *parkin* on locus 6q25.2-27[5] and ubiquitin C-terminal hydrolase L1 (*UCH-L1*), on locus 4p14.[30] Moreover, five additional gene loci with linkage to inherited parkinsonism have recently been identified: 2p13,[20] 4p14-16,[31] 1p35-35,[32] 1p36[33] and 12p11.2-q13.1[34] (Table), and there is evidence for additional loci.[3,35] Whereas only two disease causing mutations, A53T and A30P, of -synuclein have been identified,[4,21] multiple mutations in the *parkin* gene have already been described.[36,37] The phenotype associated with -synuclein and *parkin* mutations is variable. While parkinsonism arising from mutation in the -synuclein gene is usually characterized by an early age at onset compared to sporadic PD, *parkin*-associated parkinsonism has been reported with onset in the 7th decade (in addition to the originally described juvenile onset). To date, only one *UCH-L1* mutation has been described[30] and the relationship to disease has been controversial.[38,39]

All proteins currently associated with monogenic forms of parkinsonism appear to be involved in the ubiquitin-mediated

Table: Genes responsible for parkinsonism

Gene	Locus	Inheritance	Phenotype	Reference
-synuclein	4q21-23	Autosomal dominant	Early onset PD	Polymeropoulos et al., 1997[4] Kruger et al., 1998[21]
parkin	6q25.2-27	Autosomal recessive	Juvenile onset PD	Kitada et al., 1998[5]
UCH-L1	4p14	Autosomal dominant	Typical PD	Leroy et al., 1998[30]
PARK3	2p13	Autosomal dominant	Typical PD	Gasser et al., 1998[20]
PARK4	4p14-16	Autosomal dominant	PD / Essential tremor	Farrer et al., 1999[31]
PARK6	1p35-35	Autosomal recessive	Early onset PD	Valente et la., 2001[32]
PARK7	1p36	Autosomal recessive	Early onset PD	van Duijn et al., 2001[33]
PARK8	12p11.2-q13.1	Autosomal dominant	Typical PD	Funayama et al., 2002[34]

pathway of protein degradation. Proteins that are degraded through this system are tagged with polyubiquitin chains through a series of enzymatic reactions and then degraded by the proteasome, a multicatalytic complex.[40] Some ubiquitinated proteins may also be degraded by the lysosomal system.[41] - *Synuclein* is a protein localized within presynaptic terminals in the central nervous system (CNS)[42] and, together with ubiquitin, is a major component of the filaments associated with Lewy bodies.[43] Parkinsonism associated with mutations of -synuclein resembles clinically sporadic PD, and is characterized by the presence of Lewy bodies in surviving cells of the substantia nigra. Expression of mutant A53T[44] or A30P[21] -synuclein leads to the formation of small ubiquitinated aggregates, and to autophagic cellular degeneration. These effects are accompanied by, and may be consequences of, defects in the lysosomal and proteasomal degradation systems.[40,45] Transgenic expression of human – synuclein results in degeneration of dopaminergic terminals in the mouse[46] and loss of dopaminergic neurons in *Drosophila*.[47] In the latter model, degeneration is even greater when mutant human – synuclein (either A30P or A53T) is expressed, and there is formation of abnormal protein inclusions reminiscent of Lewy bodies.[47] Aberrant – synuclein appears to increase cell vulnerability to oxidative stress[48] and conversely, oxidative stress may result in increased – synuclein aggregation.[49] -Synuclein accumulation appears to result in dopamine-dependent apoptosis;[49a] this may be one explanation for the selectivity of neuronal loss seen in parkinsonism.

A juvenile autosomal recessive form of parkinsonism was initially described in Japan and was found to be characterized by selective loss of nigral dopamine neurons, without Lewy bodies.[50] This disorder, which is caused by mutations of the *parkin* gene,[5] has now been shown to have a worldwide distribution, particularly among patients younger than 50 years of age.[36,51] *Parkin* (the gene product) functions as an E3 ubiquitin-protein ligase, responsible for the attachment of ubiquitin to substrates such as synaptic vesicle-associated protein, PNUTL1 (*drosophila peanut-like gene 1* protein)/CDCrel-1,[52] *parkin*-associated endothelin receptor-like receptor (Pael receptor),[53] and a glycosylated form of -synuclein.[54] It has been suggested that mutations in the *parkin* gene could result in abnormal accumulation of its substrate proteins, which could potentially lead to inhibition of transmitter release and/or insoluble Pael-R mediated cell death.[53]

A mutation in the gene encoding for *UCH-L1* has been associated with parkinsonism in one family.[30] *UCH-L1* is an enzyme that hydrolyzes small C-terminal adducts of ubiquitin to generate ubiquitin monomers, which can then be recycled and used to clear other proteins. The mutant form of *UCH-L1* has diminished enzymatic activity resulting in impaired protein clearance through the ubiquitin-proteasome pathway.[41]

ENVIRONMENTAL FACTORS

Several epidemiological studies have given support to the environmental hypothesis of PD.[3,55] Most studies agree on the role played by pesticide exposure and smoking on the risk of PD.[3,6] While the exposure to pesticides may be associated with an increased risk of PD, smoking seems to play a protective role. Other factors often imputed to increase the risk of PD (e.g., head trauma) have not been supported by consistent evidence.[56] In addition, many of these factors may be associated with one another, which poses difficulties in teasing apart their individual contribution, if any. For example, rural living, well water drinking, and farming activity may be compound risk factors.[6] Young-onset parkinsonism in particular has been associated with exposure to well water.[57] While no toxic constituents have been identified, well water drinking may simply be a marker for rural environment, which might, in turn, point to pesticide exposure. Dietary factors have also been purported to have an effect on the risk of PD.[3] Thus, for example, consumption of products containing niacin may reduce the risk;[58] diets heavily dependent on animal fat, on the other hand, may increase the risk of PD.[59,60] No evidence has yet been provided to support a role for antioxidants (e.g., vitamin E) as potential neuroprotective agents.[3]

As noted above, a key factor in the etiology of PD may be pesticide exposure;[3,6,8,9,61] this association has recently been confirmed in the meta-analysis by Priyadarshi and colleagues.[62] There is also some evidence that exposure to pesticides may increase mortality in PD patients.[63] It should be noted that most studies grouped several agents, including pesticides, herbicides, and insecticides, as "pesticides". Hence, we do not know the risk associated with each specific substance. Interestingly, the potential relationship between pesticides and PD has received experimental support from the recent demonstration of selective nigral dopaminergic cell degeneration in rats exposed to chronic low-dose rotenone.[64] The rotenone model, if confirmed, may help identify specific factors involved in the etiology of PD. Rotenone-induced dopaminergic neuronal degeneration is thought to result from selective dysfunction of mitochondrial Complex I, as is the case for the other selective dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (see discussion below). MPTP results in parkinsonism in both humans[65] and experimental animals.[66] Associations between PD and exposure to plastic or epoxy resin and metals such as manganese[7,67] have also been reported, but the results are less consistent.[68,69] It has also been suggested that exposure to industrial toxins may explain the higher risk in urban compared to rural environments found in China.[70]

In contrast to pesticide exposure, numerous investigators have suggested an inverse relationship between smoking and the risk of PD,[3,71-74] although not all studies have found such an association.[70,75,76] Whereas a case-control study confirmed a lower prevalence of *current* smoking in parkinsonian patients, but no difference in prior exposure (suggesting that there is no protective effect, but rather that PD itself leads to reduced smoking),[75] a recent study demonstrated that the risk of PD is inversely correlated with the dose of cigarette smoking in twin pairs.[77] This effect is most pronounced in monozygotic twins. Another prospective study of more than 8,000 men enrolled in the Honolulu Heart Program did indeed support a reduced risk of PD in smokers or ex-smokers, with an apparent dose-response effect.[78] Similarly, this inverse relationship was found to be more striking among current smokers than among ex-smokers.[71] If the relationship is indeed a real one, there still exists the question of whether it reflects a 'rigid' premorbid personality trait, as has been repeatedly described in PD,[56] or a lower propensity to nicotine addiction (perhaps in relation to dysfunctional reward

mechanisms), rather than a 'protective' effect of smoking. Nevertheless, there is some evidence to suggest that nicotine may indeed play a protective role in PD,[79] possibly acting on toxin-neutralizing enzymatic pathways.[80] Cerebral MAO-B activity was reported to be significantly lower in heavy cigarette smokers than in nonsmokers.[81] A more recent study demonstrated that nicotine was capable of inducing neurotrophic factors, such as basic fibroblast growth factor, in the striatum.[82] It has been suggested that caffeine intake may also decrease the risk of PD, independently of the effect of smoking.[83] This may correspond to recent evidence for a neuroprotective effect of adenosine receptor blockade in experimental models of parkinsonism.[84,85]

There is some evidence to suggest that PD may be more prevalent in certain occupations. A recent study suggested a higher risk of PD among physicians, teachers, miners and loggers.[86] One could argue that miners and loggers may be preferentially exposed to some of the neurotoxins mentioned earlier. This explanation, however, would not apply to physicians and teachers. Given the heavy exposure of physicians and teachers to the public at large and the shared environment due to frequently cramped living arrangements for the latter two (often staying in crowded camps while working), the authors of the study proposed that PD could be due to droplet-spread infections (especially viral infections). Indeed, although viruses have been neglected as potential agents, several threads of evidence indicate that they deserve attention.

It is now generally believed that the pandemic of encephalitis lethargica, which occurred in the early 20th century, was probably related to influenza infection.[87,88] Like PD, postencephalitic parkinsonism is also associated with late progression.[89] In addition, clinically typical parkinsonism with image evidence of damage confined to the substantia nigra has been reported in patients with sporadic encephalitis[90] and there is experimental evidence that the substantia nigra is particularly vulnerable to virulent influenza A virus.[91] Naturally, other viruses could also be involved in the etiology of PD.[92] Most importantly, a recent mathematical model based on the age at onset of PD symptoms predicts that PD is caused by exposure to randomly distributed discrete events.[25] Infections in general (and viral infections in particular) may well be such discrete events.

MECHANISMS OF CELL DEATH

We have already seen that abnormal protein processing is likely to play a pivotal role in cell death in PD and, perhaps, in other neurodegenerative disorders as well. We will review now other factors – namely, oxidative stress, mitochondrial dysfunction, apoptosis, excitotoxicity, and inflammation – that may also be involved. None of these factors should, however, be seen as mutually exclusive. Abnormal protein processing, for example, may increase the susceptibility to oxidative stress (and vice versa). Impaired mitochondrial function may promote both excitotoxicity and free radical damage. Naturally, environmental toxins could act at any of these stages, with the common end result of selective nigral death (Figure).

Oxidative stress

Oxidative stress is thought to play a pathogenic role in PD. This has been evidenced by increased lipid peroxidation,[40]

reduced glutathione levels[93,94] a high concentration of iron and reactive oxygen free radical generation via autocatalytic mechanisms within neuromelanin-containing catecholaminergic neurons in the substantia nigra.[40,95] In addition, the observation that exogenous administration of cysteine, N-acetyl cysteine or glutathione decreased the neurotoxic effects of 6-hydroxy-dopamine (6-OHDA) *in vitro* and *in vivo* reinforces this hypothesis.[96] It is recognized that dopamine itself undergoes both enzymatic and nonenzymatic reactions that result in the formation of toxic radicals.[97]

One such toxic radical is the superoxide anion which, under normal circumstances, is cleared by superoxide dismutase (SOD1), resulting in the formation of hydrogen peroxide.[98,99] Hydrogen peroxide is, in turn, usually cleared by reduced glutathione (via glutathione peroxidase) or catalase but there is a deficiency of reduced gluthatione in the substantia nigra of parkinsonian subjects.[100] Gluthatione deficiency appears to result at least in part from increased activity of the degradative enzyme -glutamyltranspeptidase. Thus, in PD, there may be an excess of hydrogen peroxide, which is now free to undergo nonenzymatic (Fenton) reactions with iron, thereby resulting in the formation of highly toxic hydroxyl radicals.[97] While there is evidence for increased lipid peroxidase and abnormally oxidized DNA[98,99] in PD, these findings are not restricted to the substantia nigra and it is not clear to what extent they may reflect the effects of treatment. One obvious concern which arose from the free radical hypothesis was the possibility that levodopa itself could be toxic to substantia nigra neurons; there is, however, no *in vivo* evidence that this is the case.[101] While high concentrations of levodopa in artificial conditions do indeed result in oxidative cell death,[102,] levodopa could even be neuroprotective to neurons of the substantia nigra in rodent models[103] and in humans.[104]

Selegiline is a potent and selective monoamine oxidase B (MAO-B) inhibitor. This led to speculation that selegiline could be neuroprotective by diminishing oxidative stress. Unfortunately there is no convincing clinical evidence for a neuroprotective effect of selegiline.[105,106] More recently, a new MAO-B inhibitor (rasagiline) has shown some experimental promise[107] and is currently under investigation.[108] However, in both cases, any protective effects may be independent of MAO-B inhibition.[109,110] The mechanism of action has been related to either altering protein synthesis[109] or stablizing mitochondrial membrane potential,[111] thus protecting neuronal cells against apoptotic injury.

Mitochondrial dysfunction

Mitochondrial DNAdeletions or point mutations that cause a reduced capacity for oxidative phosphorylation (OXPHOS) result in a number of diseases and pathologies.[112,113] Mitochondria play a critical role in the health and survival of cells by providing the energy that fuels the maintenance, repair, and turnover of cellular components. Deterioration of mitochondrial function is therefore thought to play a major role in aging and neurological diseases as a result of the buildup of damage caused by reactive oxygen free radicals produced by the mitochondrion itself during oxidative phosphorylation.[114,115] Reactive oxygen free radical production is a function both of the inefficiency of transfer of electrons through the respiratory chain and the level of antioxidant defenses in the cell.
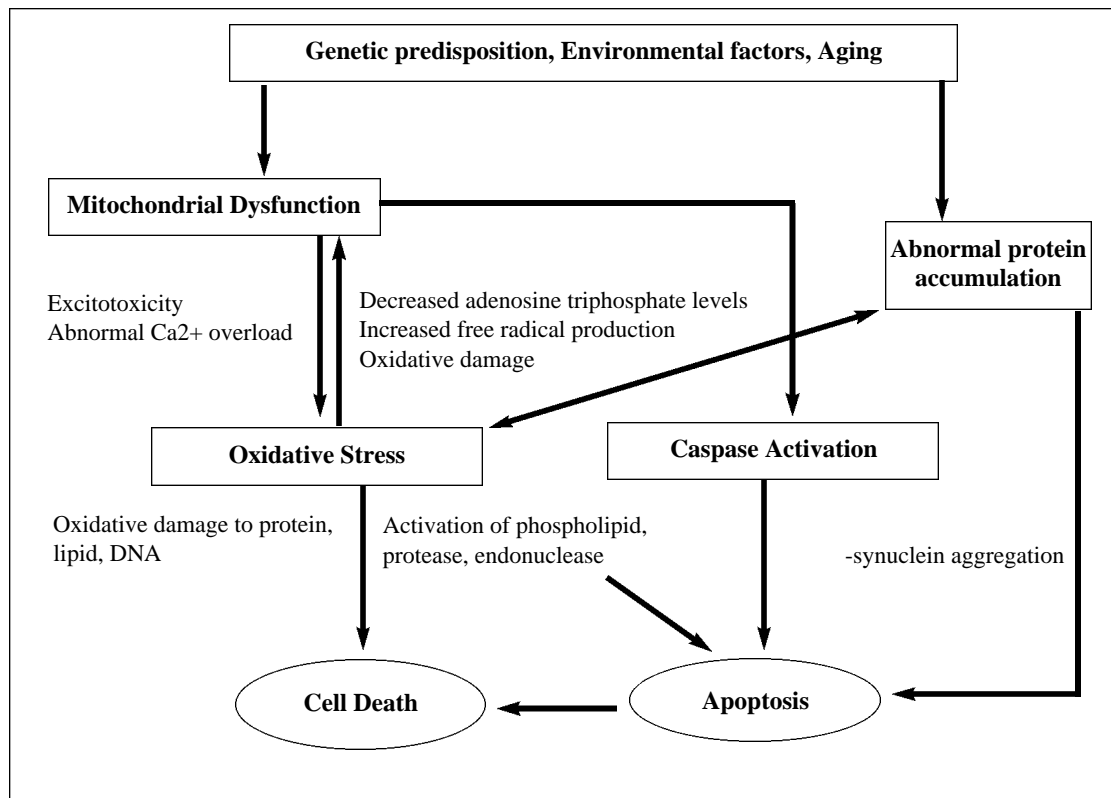
Figure: *Possible mechanisms leading to the neuronal cell death in PD. Inflammatory responses may occur at different levels of the cascade leading to cell death.*

The discovery that MPTP exposure produces CNS pathology very similar to that observed in PD strengthened the hypothesis that PD could be caused by exogenous or endogenous neurotoxins, and provided a heuristic model for investigating the pathological process of PD in animals. The first stage in the mechanism of action of MPTP is its deamination by MAO-B in glial cells, which results in the formation of the 1-methyl-4-phenylpyridinium ion (MPP+). MPP+ is then selectively accumulated in dopamine nerve terminals by the plasma membrane dopamine transporter. Once inside the dopamine nerve terminals, MPP+ acts in a manner similar to 6-OHDA by generating hydrogen peroxide and other free radicals that interfere with mitochondrial respiration.[116] MPP+ is concentrated in mitochondria, where it impairs mitochondrial respiration by inhibiting complex I of the electron transfer complex and consequently causing the death of neurons. It has also been suggested that the neuromelanin present in dopaminergic neurons may act as a storage site for MPP+ or other neurotoxins. Hence, MPTP-related dopaminergic cell death is caused by oxidative stress followed by lipid peroxidation brought about by inhibition of mitochondrial enzymes participating in the synthesis of adenosine triphosphate. In experimental models, selegiline protects substantia nigra neurons by blocking the conversion of MPTP to MPP+.[117]

There is fairly consistent evidence for impairment of mitochondrial complex I function in PD. Complex I deficiency was first identified in the substantia nigra of postmortem PD brain.[118-120] The complex I defect appears to be specific and restricted to the substantia nigra, i.e., other brain areas, including striatum, cortex, cerebellum, globus pallidus and substantia innominata were reported to have normal OXPHOS activity.[118,119] There are also reports of reduced complex I activity in muscle[121] and platelets[122] in PD patients, suggesting systemic involvement. The importance of impaired complex I function in the pathogenesis of PD received further support from the demonstration of selective nigral death following chronic exposure to rotenone, a well-known inhibitor of complex I.[64] Unlike MPP+, rotenone is not dependent upon selective uptake via the membrane dopamine transporter. However, other reports have suggested additional defects in complexes II and III, as well as abnormal immunoreactivity for -ketoglutarate, an enzyme of the citric acid cycle.[123] In multiple system atrophy, a disorder with degeneration of neurons in substantia nigra, no OXPHOS defect was found[124] and there was no complex I abnormality in Lewy body rich cingulate cortex of diffuse Lewy body brains.[118] This suggests that the complex I defect is specific to PD and selective for the substantia nigra but not related to the formation of Lewy bodies.

Apoptosis

A number of reports have demonstrated apoptotic cell death in the substantia nigra of parkinsonian patients,[125-127] but this is still somewhat controversial and some studies have reported little or no evidence of apoptotic cell death in PD tissue.[128-130]

Furthermore, the presence of apoptosis does not necessarily provide significant insight into the etiopathogenesis of selective cell death in PD, as oxidative stress, mitochondrial dysfunction and excitotoxicity (see below) can all result in apoptotic death rather than necrosis, depending, perhaps, on a dose effect.

A number of pro- and anti-apoptotic genes have been reported to be associated with PD. Activated caspase 3, considered the major downstream caspase involved in the execution phase of neuronal cell death, has been detected in the substantia nigra of PD patients.[131]. Nevertheless, it has been suggested that this caspase activation may occur in reactive astrocytes and microglial cells rather than in neurons themselves.[132] Recent studies suggest that activated forms of both caspase 8 and caspase 9, upstream caspases that are known to cleave and activate caspase 3, are present in dopaminergic neurons of the substantia nigra in MPTP-treated mice.[133] Caspase-mediated *parkin* cleavage that compromises *parkin* function was also recently demonstrated in cell lines.[134] Upregulation of the anti-apoptotic gene *bcl-2*[135] may, on the other hand, reflect an incomplete compensatory response; it is also possible that neurons expressing higher levels of *bcl-2* are those more likely to survive. A selective elevation of calpain activity in dopaminergic neurons of the substantia nigra further supports the notion of active apoptosis.[136] There is a single report of increased translocation of NF- B in the substantia nigra of parkinsonian subjects;[137] this study has not yet been replicated and it is not clear whether such increased translocation represents active apoptosis or a compensatory response.

Excitotoxicity

Although there is no direct evidence for increased levels of excitatory amino acids prior to the onset of symptomatic PD, it has been suggested that mitochondrial dysfunction might promote toxicity resulting from normal levels of excitatory amino acid transmission.[138] Interestingly, treatment with amantadine, a weak N-methyl-D-aspartate blocker, is associated with prolonged survival in PD.[139] However, there is no direct evidence for neuroprotective effects of excitatory amino acid antagonists. Clinical trials of the sodium-dependent glutamate release blocker riluzole were recently terminated due to lack of clear benefit.

Inflammatory response

Activated microglia have been demonstrated in the substantia nigra in PD and other degenerative disorders.[140] Inflammatory and glial responses have also been observed in the substantia nigra of patients exposed to MPTP[141] and in MPTP-treated primates.[66] In addition, a significant inflammatory response to progressive dopaminergic degeneration was recently also demonstrated in the nigrostriatal system of animals after 6-OHDA administration.[142]

It is not clear, however, whether inflammation plays a primary role or whether it represents a secondary phenomenon. Although there have been reports of disease-specific antineuronal antibodies in the cerebrospinal fluid and there may be complement-dependent dopaminergic toxicity in PD serum,[143] there is no direct evidence to suggest a primary immunological abnormality in PD. Interestingly, treatment with aspirin was found to attenuate MPTP toxicity in mice.[144]

Conclusion

The etiology of PD remains a mystery. Specific environmental and genetic factors, as well as complex genetic-environmental interactions are likely to be involved. Current evidence suggests that environmental exposure plays a major role in the majority of PD cases. It should be noted, however, that no specific agent has yet been identified. Experiments based on recently discovered mutations in − *synuclein* and *parkin* genes have provided evidence to suggest that abnormal protein processing leading to aberrant protein accumulation is a major pathogenetic mechanism in PD. Contributory mechanisms of cell death in PD include, excessive generation of free radicals, impaired function of mitochondrial complex I and inflammatory responses; abnormal regulation of 'pro- or anti-apoptotic'factors and excitotoxicity may also be involved. Improved understanding of these issues will allow the development of more rational treatment strategies for PD and, perhaps, for other neurodegenerative disorders as well.

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