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Role of mitochondria in the etiology and pathogenesis of Parkinson's disease

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Abstract

We discuss the etiology and pathogenesis of Parkinson's disease (PD). Our group and others have found a decrease in complex I of the mitochondrial electron transfer complex in the substantia nigra of patients with PD; in addition, we reported loss of the α-ketoglutarate dehydrogenase complex (KGDHC) in the substantia nigra. Dual loss of complex I and the KGDHC will deleteriously affect the electron transport and ATP synthesis; we believe that energy crisis is the most important mechanism of nigral cell death in PD. Oxidative stress has also been implicated as an important contributor to nigral cell death in PD, but we believe that oxidative stress is a secondary phenomenon to respiratory failure, because respiratory failure will increase oxygen free-radical formation and consume glutathione. The primary cause of mitochondrial respiratory failure has not been elucidated yet, but additive effect of environmental neurotoxins in genetically predisposed persons appears to be the most likely possibility.

Keywords: Parkinson's disease; Mitochondrion; Oxidative stress; Etiology; Pathogenesis

1. Introduction

Parkinson's disease (PD) is a disease of middle to elderly age characterized clinically by resting tremor, rigidity, akinesia, and postural disturbance; its prevalence varies from a country to another, and the disease is more frequent among Western countries than Asian and African countries [1–3]. Pathologically PD is characterized by degeneration of the substantia nigra and the locus coeruleus, and appearance of Lewy bodies in the neuronal cytoplasm. As the substantia nigra sends dopaminergic fibers to the striatum, dopamine content and the tyrosine hydroxylase activity of the striatum are drastically decreased [4–6].

As the primary cause of PD has not been elucidated yet, numbers of hypotheses have been postulated which include mitochondrial theory, iron accumulation theory, free radical theory, neurotoxin theory, and genetic predisposition theory. These theories are not mutually exclusive; more than two of these mechanisms may play a role together. Mitochondrial hypothesis was born after the discovery of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). We will briefly review the mechanism of nigral cell death in MPTP-induced Parkinsonism, and then discuss the etiology of PD.

2. Mitochondria in MPTP-induced Parkinsonism

MPTP was found as a contaminant of illicit narcotics in the United States [7,8]. People who injected narcotic drugs contaminated by MPTP developed severe Parkinsonism [7–9]. MPTP is oxidized to MPP^+ (1-methyl-4-phenylpyridinium ion) by monoamine oxidase B [10] (Fig. 1), and this MPP^+ is the actual substance which is toxic to nigral cells [11,12]. As monoamine oxidase B is mainly expressed in glia cells and serotonergic neurons [13,14], this oxidation of MPTP probably takes place mainly in glia cells. Nigrostriatal dopaminergic neurons contain monoamine oxidase A [15]. MPP^+ is taken up actively through the dopamine transporter, and is accumulated within nigrostriatal dopaminergic neurons [12,16–18].

We were interested in the mechanism of MPP^+-induced neuronal death; we noted a structural similarity between MPP^+ and NAD^+ (Fig. 1), and we thought MPP^+ might inhibit NAD-linked mitochondrial respiratory enzymes; we found dose-dependent inhibition of the complex I activity by MPP^+ using mouse brain mitochondria as an enzyme

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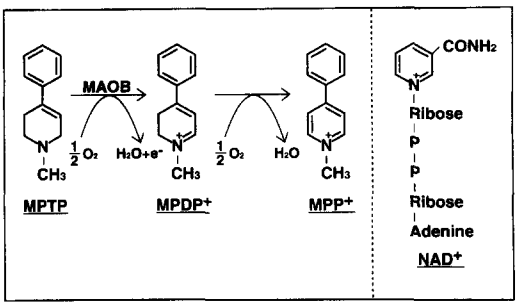

Fig. 1. Structure of MPTP, oxidation of MPTP by monoamine oxidase B, MPP^+, and similarity between MPP^+ and NAD^+.

source [19–22]. Shortly before our publication, Nicklas et al. [23] found inhibition of state 3 respiration supported by NAD^+-linked substrates, and Ramsay et al. [24] found inhibition of mitochondrial NADH dehydrogenase. The question was a fact that mM order of MPP^+ was necessary to inhibit complex I when freeze-thawed mitochondrial preparation was used, but only μM order of MPP^+ was suffice to inhibit state 3 respiration of intact mitochondria. This question was soon resolved by the discovery of active transport of MPP^+ into mitochondria [25,26] and 40-fold concentration within them [26].

To explicitly prove that complex I inhibition is the cause of mitochondrial respiratory failure in MPP^+-toxicity, we measured the complex I activity using intact mitochondria which had been incubated with μM order of MPP^+ together with NAD^+-linked substrates and ADP; as shown in Table 1, 50 μM MPP^+ was suffice to obtain 50% inhibition of complex I in this condition [20,22]. In addition, the cerebral complex I activity was decreased in mice treated with MPTP subcutaneously [28]. Furthermore, we noted that the magnitude of inhibition of state 3 respiration was far greater than that of the complex I (88% vs. 53%, Table 1). We thought there might be another enzyme that would be inhibited by MPP^+, and thus we found inhibition of the α-ketoglutarate dehydrogenase complex (KGDHC) of mitochondria by MPP^+ ([27], Table 2); the magnitude of inhibition was in the same order as that of complex I. Therefore, in this model, inhibitions of complex I as well as the KGDHC play an important role in the respiratory failure and energy crisis.

Table 1
Effect of MPP^+ on mitochondrial respiration, complex I activity, and ATP synthesis

	Control	MPP^+
State 3 [a]	180±25	21±4 *
State 4 [a]	30±5	11±3 *
Complex I [b]	57±13	27±6 *
ATP formed	637±23	210±31 *

Mean±S.E., $n=9$. *: $P<0.001$, glutamate+malate as substrates, $MPP^+ = 50$ μM.
[a] (nAtom O/min per mg prot.)
[b] (nmol NADH oxidized/min per mg prot.)
[c] (nmol ATP formed from 750 nmol ADP), cited from Ref. [22].

Table 2
Effect of MPP^+ on dehydrogenases in the TCA cycle

Dehydrogenase	Control	MPP^+
Isocitrate DH	285±37	266±35
Glutamate DH	556±50	545±52
α-Ketoglutarate DHC	34±5	19±3 *
Malate DH	4760±530	4870±690

Units: nmol NADH formed/min per mg prot.; mean±S.E., $n=8$. *: $P<0.001$, $MPP^+ = 2$ mM, cited from Ref. [22].

3. Mitochondria in PD

3.1. Electron transfer complexes in PD brains

Schapira et al. [29,30] first reported a significant reduction in the complex I activity in the substantia nigra of patients with PD; this decrease was not found in other disorders which affected the substantia nigra such as multiple system degeneration [31]. Reichmann et al. [32] also reported a slight but significant decrease in NADH-cytochrome c reductase in the substantia nigra, but in their second series of subjects, they could not detect loss of complex I activity. We also measured activity of complex I in the striatum in a small number of patients died of PD [33], however, the decrease in complex I activity did not reach the statistical significance. Therefore, we studied the amount of complex I protein by Western blotting [34] and immunohistochemistry [35]. In Western blotting, the lower

Table 3
Potential causes of mitochondrial respiratory failure

Cause
Mitochondrial DNA deletions
Mitochondrial DNA mutations or polymorphisms
Mutations or polymorphisms of nuclear DNA coding subunits of complex I
Mutations or polymorphisms of nuclear DNA coding enzymes regulating the transport and metabolism of potential nigral neurotoxins
Endogenous or exogenous nigral neurotoxins
Localized accelerated ageing
Oxidative stress
Secondary to neurodegeneration

Table 4
Complex I activity in tissues other than the brain in PD

Author	PD	(n)	Control	(n)	Reference
Muscle					
Bindoff et al.	132.4 ± 39.9 **	(5)	222.0 ± 29.5	(4)	[36]
Shoffner et al.	16–174 #	(6)	197 ± 50	(16)	[38]
Nakagawa-Hattori et al.	64.10 ± 21.30 **	(4)	125.1 ± 13.7	(6)	[40]
Mann et al.	62.4 ± 7.8	(9)	63.2 ± 1.9	(6)	[41]
Anderson et al.	14 ± 2	(4)	16 ± 2	(5)	[42]
DiDonato et al.	11.6 ± 3.4 ##	(6)	11.0 ± 2.9	(6) ##	[43]
Cardellach et al.	245.8 ± 42.8 **	(8)	331.6 ± 60.1	(10)	[44]
Platelet					
Parker et al.	8.7 ± 2.9 ***	(10)	19.1 ± 5.6	(8)	[45]
Yoshino et al.	9.14 ± 1.86 ***	(20)	12.37 ± 2.66	(17)	[46]
Mann et al.	3.51 ± 0.79	(14)	3.53 ± 0.72	(9)	[41]
Krige et al.	8.26 ± 1.34 **	(25)	9.88 ± 2.14	(15)	[47]
Lymphocyte					
Yoshino et al.	10.10 ± 2.93	(20)	11.11 ± 1.18	(17)	[46]

Units: nmol/min per mg prot.; mean ± S.E. ** $P < 0.01$, *** $P < 0.001$. #: Four out of 6 patients below the 5% confidence level for the control subjects. ##: Expressed as % nmol of substrate/min per mg prot. normalized to citrate synthase. PD: Parkinson's disease.

molecular mass subunits (20 to 30 kDa) of complex I was reduced in 4 out of 5 patients with PD in the striatum. In immunohistochemistry, the intensity of immunostaining of the substantia nigra was semiquantitatively analyzed, and we counted those neurons showing marked reduction in immunostaining [35]. In controls subjects, 13.6 ± 4.2% (mean ± S.D., $n = 6$) of nigral neurons showed marked reduction in immunostaining for complex I; interestingly, there was a positive correlation between the age of the patients and the loss of immunoreactivity to complex I. In PD patients, significantly higher proportions of neurons (35.6 ± 17.6%, $n = 8$) showed marked reduction in immunostaining ($P < 0.01$).

Thus there is no question about the loss of neuronal complex I in PD, but it is unlikely that this loss is the primary and a genetically determined defect, as the loss of complex I was rather modest both biochemically [29,30] and immunohistochemically [35]. Potential causes of complex I deficiencies in PD are listed in Table 3; all of those possibilities have to be studied extensively to elucidate the pathogenesis of PD. It seems unlikely that the loss of complex I is a mere reflection of neuronal degeneration, as other electron transfer complexes were normal [29,30,35].

3.2. Complex I in tissues other than brain

Regarding the complex I in tissues other than the brain, some controversies exist in the literature [36–47]. As shown in Table 4, most of the studies showed slight but significant decreases in complex I activity in skeletal

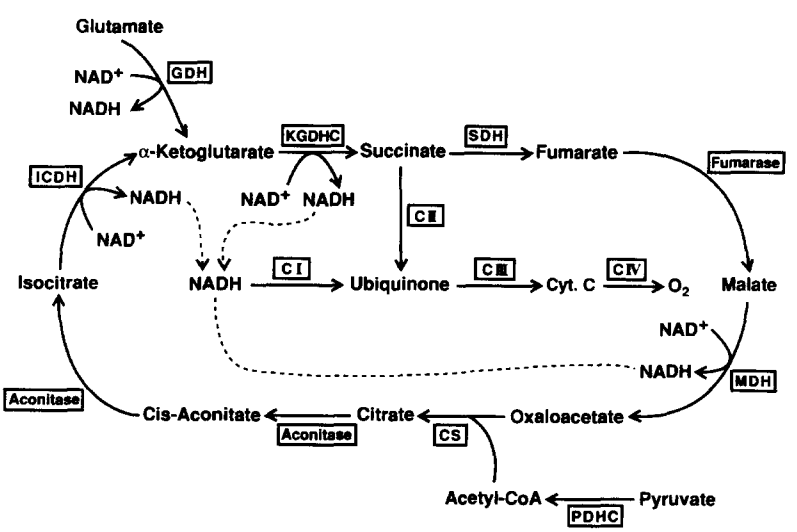

Fig. 2. Schematic representation showing the relationship between the α-ketoglutarate dehydrogenase complex in the TCA cycle and the electron transfer complex. The KGDHC provides not only NADH for complex I but also succinate for complex II. PDHC, pyruvate dehydrogenase complex; CS, citrate synthase; ICDH, isocitrate dehydrogenase; GDH, glutamate dehydrogenase; KGDHC, α-ketoglutarate dehydrogenase complex; SDH, succinate dehydrogenase; MDH, malate dehydrogenase; CI, complex I; CII, complex II; CIII, complex III; CIV, complex IV; Cyt. C, cytochrome *c*.

muscles and platelets. The question is whether they represent mere by chance observations or they reflects the underlying pathologic process of PD. Suppose environmental neurotoxins and/or genetic predisposition are involved in PD, they may present a modest abnormality in platelets and the skeletal muscle, as platelets do not have a nucleus and the skeletal muscles are largely composed of post-mitotic cells; both of them are not expected to have ample compensatory mechanisms to eliminate noxious stimuli imposed upon them. Therefore, marginal abnormalities may appear in those tissues, and we cannot dismiss those abnormalities. As the substantia nigra has a unique property to augment the effect of those noxious stimuli such as the dopamine transporter, neuromelanin, and high iron and dopamine contents, more severe damage may be induced.

3.3. α-Ketoglutarate dehydrogenase complex in PD

As we [27] found inhibition of the KGDHC by MPP^+, we thought this enzyme complex might also be impaired in PD. The KGDHC, consisting of α-ketoglutarate decarboxylase, dihydrolipoamide succinyltransferase, and dihydrolipoamide dehydrogenase, is located between α-ketoglutarate and succinate in the TCA cycle; the overall reaction oxidizes α-ketoglutarate to succinate which becomes the substrate of complex II (Fig. 2). Therefore, the KGDHC is a very important enzyme; when complex I is decreased, electron transfer will shift toward the complex II to complex III pathway; for the effective electron transfer through this pathway, supply of succinate is mandatory. In addition, it has been claimed that the KGDHC is the rate-regulating enzyme of the TCA cycle [48].

We wanted to measure the enzymatic activity of this enzyme on autopsy-obtained brain tissue [33], but we could not recover the biochemical activity in autopsy-obtained brain tissue apparently due to unstableness of this enzyme; acidosis in the agonal stage was reported to influence the enzyme activity significantly [49]. Therefore, we adopted an immunohistochemical method [50]. The specific antibody was kindly supplied by Dr. Matuda of Kanoya University of Sports and Fitness. We studied 6 control subjects and 9 Parkinsonian patients; the details were published elsewhere [50]. In the control subjects, the substantia nigra showed uniform immunostaining for the KGDHC; the lateral part of the substantia nigra showed somewhat weaker immunostaining. The lateral part is most extensively involved in PD; the reason for this vulnerability of the lateral part is not known, however, it may in part be related to this medial to lateral gradient in the amount of this enzyme complex. We counted the number of neurons showing marked reduction in immunostaining for the KGDHC in the substantia nigra. In control patients, only elderly subjects had a small number of neurons showing marked reduction in the immunostaining, however, in PD, there was a marked increase in the proportion of those

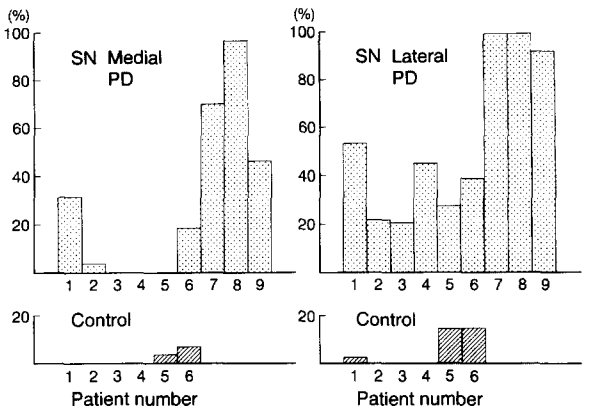

Fig. 3. Semiquantitative analysis of immunohistochemistry for the KGDHC. The upper graphs represent PD patients, and the lower graphs control subjects; each number corresponds to the case number; the ordinate represents percentages of nigral neurons showing marked reduction in the immunostaining for the KGDHC in respective regions of the substantia nigra; 'medial' denotes the medial one-third of the substantia nigra, and 'lateral' the lateral one-third of the substantia nigra.

neurons showing marked reduction in the immunostaining (Fig. 3); this increase was particularly prominent in the lateral part of the substantia nigra. There was a rough correlation between the loss of immunoreactivity and the severity of degenerative changes.

Dual loss of complex I and the KGDHC will severely impair the electron transfer. The KGDHC appear to be another vulnerable enzyme complex of mitochondria; other NAD-linked dehydrogenases (glutamate dehydrogenase, isocitrate dehydrogenase, and malate dehydrogenase) in the TCA cycle were not decreased in PD in our previous study [33]. The KGDHC was reported to be inhibited by pathological concentrations of ammonia (0.2–2 mM) and by calcium at concentrations above 100 μM [51]; therefore, decrease in the urea cycle activity and accumulation of calcium ion from any cause would have a deleterious effect on the KGDHC. Recently, Mastrogiacomo et al. [49] reported a significant decrease in the cortical KGDHC activity in Alzheimer's disease; this may be another evidence to indicate the vulnerability of this enzyme complex. Interestingly, complex I and the KGDHC are located in close proximity each other within mitochondria [52].

3.4. Mitochondrial DNA in PD

As complex I is composed of 41 subunits [53] and 7 out of those 41 subunits are encoded by mtDNA [54,55], we wanted to study mtDNA for mutations in PD. First of all, we looked at the so-called common 5 kb deletion of mtDNA by the PCR method. This 5 kb deletion occurs between the 13-base pair direct repeat sequence [56] encompassing genes for ND 5, ND 4, ND 4L, ND 3, CO 3, and ATPase 6/8. Therefore, deletion in this part would cause loss of complex I. Ikebe et al. [57] studied striatal mtDNA of 5 patients died of PD; in all the PD patients

studied, the 5 kb common deletion was found; in addition 2 elderly control subjects above 70 years of age also harbored the same deletion. However, the amount of deletion was rather small, less than 5% of striatal mitochondrial DNA [58]. This may be the reason why mtDNA deletion could not be detected by the Southern blotting method in other laboratories [59,60]. Since then, many reports appeared confirming the presence of the 5 kb common deletion in PD brains [43,61,62], but they detected the same deletion in the age-matched control subjects, and the deletion was ascribed to the ageing process. Mann et al. [62] quantitated the amount of mtDNA deletion in PD and control subjects, and found that the both groups showed same amount of the deletion ($4.1 \pm 0.6\%$); DiDonato et al. [43] also quantitated the percentage of the common deletion in brain areas, and that approx. 3% of mtDNA was deleted in the substantia nigra in both control and PD subjects.

The common 5 kb deletion was also found in tissues other than the brain; Sandy et al. [63] found the 5 kb deletion in platelets of both PD and control subjects, and we found the same deletion in the skeletal muscle; although the same deletion was found also in control subjects, the deletion appeared to be seen in earlier ages in PD, in that, a 52 year-old control subject did not have this deletion, but 61 year-old control person had the deletion; in PD patients, this deletion was seen in patients at age 53 or above in our condition (Fig. 4). However, as ageing-associated mtDNA deletions have frequently been reported not only in brains [64–67] but also in cardiac muscles [67–70], skeletal muscles [67,71,72], and the liver [73], mtDNA deletions found in PD may not have an etiologic significance. MtDNA deletion in ageing itself is an interesting observation.

Regarding mtDNA sequence, Shoffner et al. [74] reported higher incidence of PD patients carrying A to G mutation at nucleotide pair 4336 of the mitochondrial gene

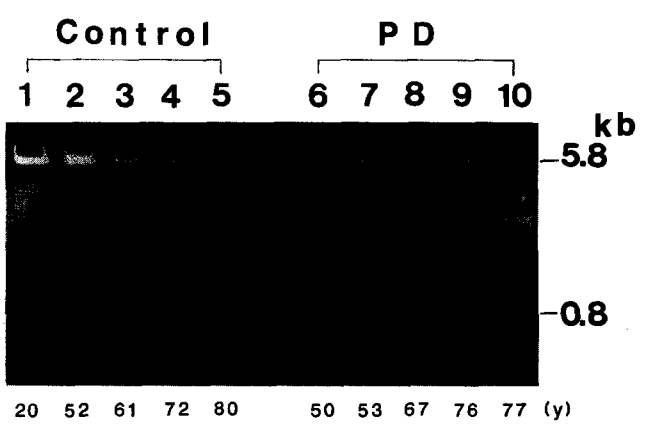

Fig. 4. PCR analysis of skeletal muscle mtDNA for the so-called common 5 kb deletion in control subjects and PD patients; the numbers in each lane represent the age of the subjects; the 52 year-old control subject does not have the deletion, but the 61 year-old control person had the deletion; in PD patients, this deletion is seen in patients at age 53 or above.

for $tRNA^{gln}$ (5.3% in PD vs. 0.7% in their controls); we are also studying mtDNA sequence in PD, however, we could not detect a point mutation common to PD patients.

4. Oxidative stress in PD

4.1. Free radicals and glutathione in PD

Marttila et al. [75] reported 55% increase in the Cu-Zn SOD activity and Saggu et al. [76] 33% increase in the Mn SOD in the PD substantia nigra. These results were interpreted as indicating increased formation of superoxide anions. Increase in the lipid peroxidation was also reported [77]. These represent earlier reports suggesting the presence of oxidative stress in PD.

Another evidence for oxidative stress came from the observation on iron in PD. There are many papers reporting increase in iron content in the substantia nigra of PD patients compared with the controls [78–84]. Ferrous iron may interact with hydrogen peroxide to produce hydroxyl radicals [85]. Thus, iron may be toxic to neurons; Tanaka et al. [86,87] reported that iron could be toxic to cultured neurons as well. We also showed toxicity of iron using nigral and striatal co-culture [88]; this co-culture simulates the in vivo state better than mesencephalic culture alone, as it includes target cells and striatal trophic factors; arborization of neural processes is much better than the mesencephalic culture alone, being suitable for the study of potential neurotoxins. Co-administration of synthetic neuromelanin and iron markedly inhibited the development of dendritic processes with neuronal degeneration and increase in the lipid peroxidation [88]. However, we believe that iron increase in PD is secondary to neuronal degeneration, as iron was also increased in the substantia nigra of MPTP-treated monkeys [89].

Another interesting observation which suggests the presence of oxidative stress in PD is reduced level of GSH (glutathione) in the substantia nigra [79,90–93]. GSH is a substrate for glutathione peroxidase which not only decomposes hydrogen peroxide and lipid peroxides but also protects cell membranes from oxidative damage together with glutathione peroxidase [94,95].

4.2. Relationship between mitochondrial respiratory failure and oxidative stress

Recently, Jenner et al. [92] postulated that complex I deficiency might be secondary to oxidative stress; this notion is based on the observation on GSH and complex I in incidental Lewy body disease where Lewy bodies are discovered incidentally in patients who died without clinical as well as biochemical evidence of PD; the condition may represent preclinical stage of PD [96]. GSH was reported to be significantly decreased whereas complex I

was marginally diminished in incidental Lewy body disease [92,93]; this appears to be the reason why they thought complex I deficiency was secondary to oxidative stress.

Although oxidative stress hypothesis is very attractive, it is difficult to consider that the oxidative stress is the primary event. First of all, GSH is synthesized in astrocytes [97–100], and only a small amount is contained in neurons if any [97,98,100,101]. Mitochondrial GSH is transported from the cytoplasm through the high affinity transporter [102]. Suppose the oxidative stress is the primary event in PD, loss of GSH would suggest that the disease starts in nigral astrocytes, but neurons are mainly involved in PD. Secondary, not only complex I but also the KGDHC is reduced in PD; therefore, impairment of mitochondrial respiration would more severe than what would be expected from complex I deficiency alone.

Furthermore, there is a good reason to believe that mitochondrial respiratory failure will induce oxidative stress. Production of hydrogen peroxide [103,104] and superoxide anions [105,106] were shown in normal mitochondria; the site of superoxide anion production was ascribed to ubiquinol and ubisemiquinone [107,108]. Furthermore, when complex I or III is inhibited, formation of superoxide anions is markedly augmented [109–112]. Hydroxyl radicals are also formed within mitochondria [113]. Hydroxyl radicals are very cytotoxic including oxidative DNA damage [85]; in fact, Hayakawa et al. [114,115] reported age associated oxidative damage in cardiac muscles and accumulation of 8-hydroxydeoxy-guanosine, an indicator of oxidative DNA damage [116], in human diaphragm. Thus mitochondrial respiratory failure will induce oxidative stress within mitochondria. In addition, normally high content of dopamine and iron [117] predisposes the substantia nigra to oxidative stress.

Oxidative stress within mitochondria will consume GSH. When reduced level of mitochondrial GSH is associated with increase in activated oxygen species, mitochondrial calcium homeostasis will be disrupted, in that pores in the inner membrane will open resulting in release of Ca^{2+} and influx of cytoplasmic components [118]. In fact, swelling of mitochondria occurs in experimentally induced GSH deficient rats [119]. ATP deficiency also causes swelling of mitochondria [120]; therefore, mitochondrial swelling in GSH deficient rats may be the result of ATP deficiency. ATP deficiency will increase cytoplasmic Ca^{2+}, and increase in Ca^{2+} will initiate protean adverse reactions in neurons including apoptosis [121]. Respiratory failure and oxidative stress will induce a vicious cycle, in that, oxidative stress in turn compromises electron transport further; hydroxyl radicals are known to attack NADH dehydrogenase, ATPase and succinate dehydrogenase, and superoxide anions inhibit the activities of NADH dehydrogenase and ATPase [122]; the reason for these vulnerability is thought to be due to the fact that cardiolipin, which is an essential cofactor for those enzymes, is rich in unsaturated fatty acid and is liable to be attacked by oxygen free radicals [123].

5. Etiology of PD

5.1. Potential nigral neurotoxins

PD may be caused by neurotoxins which accumulate selectively within nigral neurons and inhibits complex I like MPP^+. Based on this hypothesis, numbers of endogenous and exogenous compounds have been tested for nigral or mitochondrial toxicity. Thus tetrahydroisoquinolines (TIQ) were studied first. As shown in Fig. 5, tetrahy-

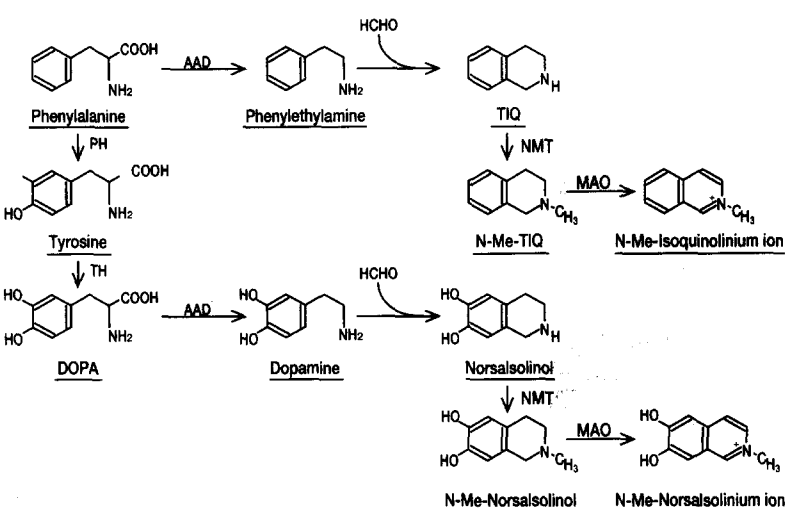

Fig. 5. Formation of tetrahydroisoquinoline and salsolinol from phenylethylamine and dopamine, respectively. Tetrahydroisoquinolines are further *N*-methylated and oxidized to quinolinium ions by monoamine oxidase or by auto-oxidation. PH, phenylalanine hydroxylase; TH, tyrosine hydroxylase; AAD, aromatic L-amino acid decarboxylase; NMT, *N*-methyltransferase; MAO, monoamine oxidase; TIQ, tetrahydroisoquinoline.

droisoquinolines have structural similarity to MPP^+, and numbers of derivatives are known. In addition, some of them are formed endogenously from phenylethylamine [124,125] or from catecholamines [126,127], and found in human brains [124–127]; furthermore they exist in some of natural plants and foods such as cheese, cocoa, banana, milk, egg and beef [128,129]. In addition, transport of TIQ from foods to the brain was shown in monkeys [130]. Another interesting observation is that 1-methyl derivative of TIQ was found decreased in the striatum of PD patients [131], and it prevented MPTP-induced Parkinsonism in mice [132]; thus less toxic substances may be neuroprotective against more toxic compounds, and this observation may have a therapeutic implication in future.

Yoshida et al. [133] treated monkeys with a large amount of tetrahydroisoquinoline, and those monkeys showed clinical manifestations similar to Parkinsonism and decrease in dopamine, tyrosine hydroxylase and biopterine in the nigrostriatal regions [134]. Mice treated with TIQ showed a marked decrease in tyrosine hydroxylase-positive neurons in the substantia nigra, however, cell death did not occur [135]. In an effort to find a more toxic substance, Naoi et al. [136,137] found *N*-methylation reaction of TIQ, and oxidation reaction of *N*-methyl-TIQ to *N*-methylisoquinolinium ion ($NMIQ^+$); this oxidized compound was found more toxic than the parent compound inhibiting tyrosine hydroxylase, aromatic L-amino acid decarboxylase and monoamine oxidase [138]. In addition, $NMIQ^+$ was found toxic to cultured mesencephalic dopaminergic neurons [139,140], and to the nigral neurons of mice treated with *N*-methyl TIQ [141]. Furthermore, TIQs inhibit mitochondrial respiration and complex I [142,143], but the potency to inhibit state 3 respiration is much weaker than that of MPP^+.

Naoi and his associates also studied dopamine derived TIQs [144–147], i.e., salsolinol and its derivatives (Fig. 4); salsolinol was found to inhibit tyrosine hydroxylase [145], to stimulate release of monoamines with inhibition of monoamine oxidase and catechol-*O*-methyltransferase [146]; melanin was found to bind *N*-methylsalsolinium ion [147].

Another interesting group of substance includes β-carbolines, derivatives of tryptamine, which have been shown to be toxic to catecholaminergic neurons [148,149]; they exist in human brains [150,151], inhibit mitochondrial respiration [152], bioactivated by monoamine oxidase [153], and inhibit dopamine uptake into the catecholaminergic neurons [154]. Thus both TIQs and β-carbolines represent candidates for the etiologic agent of PD.

5.2. Environmental factors

Connection between rural living and well water drinking and PD [155–157], and connection between pesticide and herbicide exposure [158–164] as well as industrial exposures to chemicals, heavy metals [159,165] and PD have been reported; however, some studies could not find connection between PD and well water drinking [166] or herbicides exposure [156,166]. Recently, Fleming et al. [167] reported presence of diedline (an organic mercury compound) in 6 of 20 PD brains, but none in the control subjects; but they reserved the conclusion regarding whether or not diedline is an etiologic agent for PD. Kondo and Watanabe [168] reported deficiencies in the intake of protein, carbohydrates, fruits, and dairy products prior to the secondary growth period as a possible contributor to the pathogenesis of PD. Therefore, there is no question about the role of certain environmental exposures in the development of PD, but its exact chemical nature awaits further investigations.

5.3. Genetic predisposition

Genetic difference in the activities of enzymes which regulate the transport and metabolism of potential neurotoxins may also play a role in the pathogenesis of PD.

In this respect, Armstrong et al. [169] and Smith et al. [170] found higher incidence of the genetic defects which would result in debrisoquine poor metabolizers among patients with PD; Smith et al. [171] found a higher incidence of G-to-A transition at the junction of intron 3/exon 4 and 1 bp deletion mutation at the exon 5 of CYP2D6 gene in PD; both of those mutations render the subjects poor metabolizers for debrisoquine, and the incidence of poor metabolizers was 11.8% in PD and 5.0% in the control subjects.

Kurth et al. [171] found higher frequency of allele 1 of the gene for monoamine oxidase B (62% in PD vs. 45% in their controls). Hotamisligil et al. [172] reported a significant difference in the alleles frequencies of MAO A and MAO B between PD and the controls, in that, one particular haplotype marked by the RFLPs at MAO A was three times more frequent in PD patients (14%) compared with controls (5%), and the distribution of MAO A alleles defined by the RFLPs was significantly different ($P < 0.03$); for MAO B alleles defined by the $(GT)_n$ repeat, the incidence of allele 180 was almost twice as common in PD patients (21%) as controls (12%), and the overall distribution of alleles was significantly different between patients with PD and controls.

In summary, PD may be initiated by nigral neurotoxins in the environment in genetically susceptible persons; more than two genetic predispositions may be necessary to be afflicted with PD.

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