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Brain Mitochondrial Dysfunction and Complex I Syndrome in Parkinson´s Disease

Laura B. Valdez[1], Manuel J. Bandez[2], Ana Navarro[2]† and Alberto Boveris[1]
[1]*Laboratory of Free Radical Biology, School of Pharmacy and Biochemistry, University of Buenos Aires,*
[2]*Department of Biochemistry and Molecular Biology, School of Medicine, University of Cádiz,*
[1]*Argentina*
[2]*Spain*

1. Introduction

1.1 Clinical characteristics of Parkinson's disease

Parkinson's disease (PD) is an old-age neurodegenerative disease with a small but significant genetic risk. The prevalence of PD is of 0.3% in the whole population, affecting more than 1% of the humans over 60 years of age (de Lau & Breteler, 2006). Parkinson´s disease is characterized by the progressive loss of dopamine due to degeneration of dopaminergic neurons in the *substancia nigra, striatum* body and brain cortex. In addition, α-synuclein-positive Lewy bodies in brainstem and neocortex are consistently found at autopsy (Forno, 1996; Jellinger & Mizuno, 2003). Therefore, in patients with PD, movements, sleep, autonomic functions and cognition become progressively impaired.

Complex factors contribute to the appearance of PD but with a constant mitochondrial involvement and a decreased capacity to produce energy (ATP) in the affected brain areas (Shapira, 1998; Shapira, 2008). Mitochondrial dysfunction in the human frontal cortex is to be considered a factor contributing to impaired cognition in PD.

2. Environmental aspects and experimental models

Both environmental chemicals and genetic susceptibility are thought to contribute to the etiology of sporadic PD (Nagatsu, 2002). Despite of familial PD was correlated with a series of genes mutations, the etiology of idiopathic PD, which accounts for more than 90% of PD, is still not fully understood. It is well documented that there is an epidemiological link between PD and individuals who lives and works in rural areas and who has been exposed to various herbicides and insecticides (Gorell et al. 1998; Ayala et al., 2007; Gomez et al., 2007).

Although the etiopathogenesis of PD is still elusive, *post mortem* studies support the involvement of oxidative stress in neurons with an increased production of superoxide

radical (O_2^-) and hydrogen peroxide (H_2O_2) and of mitochondrial dysfunction, especially of complex I of mitochondrial respiratory chain (Shapira et al., 1989; Shapira et al., 1990a, 1990b; Gomez et al., 2007; Navarro & Boveris, 2009; Navarro et al., 2009).

The early hints about the central role of mitochondria in the pathogenesis of PD resulted from the observation that human exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a contaminant in synthetic opiates, triggered an acute and permanent parkinsonism with death of dopamine neurons (Langston et al., 1983). It was found that the MPTP active metabolite is the 1-methyl-4-phenilpyridinium ion (MPP^+). This compound is accumulated in mitochondria and produces their toxicity by inhibiting mitochondrial complex I, the proton pumping NADH:ubiquinone oxidoreductase.

As was mentioned above, epidemiological research indicates that exposure to pesticides and welding elevates the risk of PD (Chade et al., 2006; Dhillon et al., 2008). Most of pesticides are inhibitors of mitochondrial complex I, which is the first and the most vulnerable complex in the series of membrane H^+ pumps of the mitochondrial respiratory chain (Wallace et al., 1997). The pesticide rotenone ((2R,6aS,12aS)-1,2,6,6a,12,12a-hexahydro-2-isopropenyl-8,9-dimethoxychromeno [3,4-b]furo(2,3-h)chromen-6-one) is a powerful inhibitor of mitochondrial complex I: in isolated beef heart and liver mitochondria, rotenone median inhibitory concentration (IC_{50}) is 0.05 nmol/mg protein with a Ki of 4 nM (Degli, 1998). When neuron cultures are exposed to rotenone, the cells increase the O_2^- production rate leading them to death (Ahmadi et al., 2003; Moon et al., 2005). Furthermore, dopaminergic neuronal cells exposed to rotenone reproduce many of the features of PD including α-synuclein inclusions bodies in rats (Betarber et al., 2000; Sherer et al., 2003).

The above mentioned inhibitors of complex I, rotenone and MPTP, are typically used in the experimental model of PD in laboratory animals.

3. Genetic aspects

Although most PD cases are sporadic, the discovery of genes linked to familial form of disease due to mutations in the SNCA (α-synuclein), PARK2, DJ-1, PINK1, and LRRK2 genes has provided important clues about the disease progress (Henchcliffe & Beal., 2008; Zheng et al., 2010). In the sporadic disease, α-synuclein and degenerating mitochondria are the major components of Lewy bodies, the hall mark cytoplasmic inclusions found in PD brains. Biochemical complex I deficiency is found in PD patients not only in *substancia nigra* but also in platelets (Henchcliffe & Beal, 2008).

Recently, Zheng and coworkers (2010) reported that decreases in expression of 10 gene sets are associated with PD, even in probable subclinical disease and in tissues, outside *substancia nigra*. These 10 gene sets encode proteins responsible for interconnected cellular processes: nuclear-encoded mitochondrial electron transfer, mitochondrial biogenesis, glucose oxidation, and glucose sensing (Zheng et al., 2010). The authors showed that bioenergetics genes responsive to the master regulation of PGC-1α, including genes for nuclear-encoded electron transfer carriers are under expressed in patients with PD and in incipient Lewy body diseases. Furthermore, co-activation by PGC-1α up-regulates nuclear subunits of mitochondrial respiratory chain complexes I, II, III, IV, and V and blocks dopamine neuron loss in cellular models of PD-linked α-synocleinopathy and rotenone toxicity. Moreover, genetic ablation of PGC-1α in mice markedly enhanced MPTP-induced dopamine neuron loss in the *substancia nigra* (St-Pierre et al., 2006).

4. Pathophysiological aspects

Physiological, clinical and genetic studies support the relationship between PD and energy metabolism in neurons, including mitochondrial electron transport carriers and cytosolic glucose utilization. *In vivo* and *ex vivo* experimental results have shown that PD is primarily associated to two interdependent situations of brain mitochondria: (a) mitochondrial dysfunction; and (b) mitochondrial oxidative damage. In addition, defective oxidative phosphorylation was reported in muscle, and increased level of 8-hydroxydeoxyguanosine was found in PD patients plasma (Henchcliffe & Beal, 2008).

4.1 Mitochondrial complex I and physiological production of superoxide, nitric oxide and peroxynitrite

Mitochondrial complex I (NADH-UQ reductase) catalyzes electron transfer from NADH to ubiquinone and it is the main molecular pathway to link the tricarboxylic acid cycle, the coenzyme NADH and the mitochondrial respiratory chain. Complex I is a supra-molecular protein complex composed of about 40 polypeptide subunits and contains FMN and iron-sulphur centers (Walker, 1992; Walker et al., 1992). Two complex I-linked UQ-pools have been detected (Raha & Robinson, 2000). Non-covalent hydrophobic bonds are essential in keeping together the whole structure of complex I; low concentrations of detergents, natural and synthetic steroids (Boveris & Stoppani, 1970) and hydrophobic pesticides, such as rotenone and pyridaben (Gomez et al., 2007), are effective in disrupting intra-complex I polypeptide hydrophobic bonds and in inhibiting complex I electron transfer activity.

Complex I produces significant amounts of O_2^- in physiological conditions (0.80-0.90 nmol O_2^-/min.mg protein) through the auto-oxidation reaction of flavin-semiquinone ($FMNH^\bullet$) with molecular oxygen. It is understood that the ubisemiquinone ($UQH^\bullet$) auto-oxidation contribution, in complex I, is negligible (Boveris & Cadenas, 2000; Turrens & Boveris, 1980). Superoxide anion production yields an O_2^- steady state concentration of 0.1-0.2 nM in the mitochondrial matrix (Boveris & Cadenas, 2000; Boveris et al., 2006; Valdez et al., 2006). The O_2^- production rate by complex I is increased by inhibition of electron transfer with rotenone (Boveris & Chance, 1973) or by complex I dysfunction (Hensley et al., 2000; Navarro et al., 2009; Navarro et al., 2011).

Both, nitric oxide (NO) and peroxynitrite ($ONOO^-$) have been proposed as direct inhibitors of complex I. Mitochondrial NO production is carried out by the mitochondrial nitric oxide synthase (mtNOS), an isoenzyme of the NOS family located in mitochondrial inner membrane (Tatoyan & Giulivi, 1998; Giulivi et al., 1998). Nitric oxide is produced at a rate of 1.0-1.4 nmol NO/min.mg protein and kept at a steady state level of 200-350 nM in the mitochondrial matrix (Boveris et al., 2006; Valdez et al., 2006). Peroxynitrite is generated in the mitochondrial matrix through the diffusion controlled reaction ($k = 1.9 \times 10^{10}$ M^{-1} s^{-1}) between two free radicals: O_2^- and NO. This reaction contributes with 0.38 μM $ONOO^-$/sec in the mitochondrial matrix or 0.92 nmol/min. mg protein (Valdez et al., 2000). In this approximation the contribution of cytosolic NO has not been considered. Peroxynitrite is normally reduced by the mitochondrial reductants NADH, UQH_2 and GSH and kept at intramitochondrial steady state level of 2-5 nM (Valdez et al., 2000). When the steady state concentration of $ONOO^-$ is enhanced up to 25-40 nM, tyrosine nitration, protein oxidation and damage to iron sulfur centers might takes place, leading to a sustained complex I inhibition and increased generation of O_2^- by complex I.

4.2 Brain mitochondrial dysfunction: Complex I syndrome

Several studies have shown a mitochondrial dysfunction and a reduced activity of mitochondrial complex I in *substantia nigra* (Schapira et al., 1990a; Schapira et al., 1990b; Schapira, 2008b) and in frontal cortex (Navarro et al., 2009; Navarro & Boveris, 2009) in PD patients.

Gomez et al. (2007) and Navarro et al. (2009) have shown that the *in vitro* treatment of rat brain mitochondria with rotenone (1-10 μM) inhibits complex I activity without changes in complexes II, III and IV activities. In addition, coupled mitochondria isolated from rat brain incubated with rotenone showed a dose-dependent decrease in respiratory control with malate and glutamate as substrates, without modifications in the O_2 consumption when succinate was used as substrate (Gomez et al., 2007; Navarro et al., 2009).

Rats treated with rotenone (2 mg/kg weight, i.p. and daily, during 30 to 60 days) showed a selective nigrostriatal dopaminergic degeneration similar to the one observed in PD. Respiration rates were assessed in 1 mm^3 brain cortex cubes, a thickness that allows O_2 diffusion to the center of the cube avoiding anaerobic areas. Control samples had a respiratory rate of about 0.45 μmol O_2/min. g striatum (Table 1). Rotenone treated rats during 30 and 60 days decreased 17% and 35%, respectively, the striatal O_2 uptake.

Experimental condition	O_2 consumption (ng-at O/min.g striatum)
Control	896 ± 8
30 days rotenone	744 ± 8*
60 days rotenone	582 ± 5*#

Table 1. **Striatal O_2 consumption in rotenone-treated rats during 30 and 60 days.** Respiratory rates were determined in 1 mm^3 rat striatum cubes in air-saturated Krebs suspending medium at 30ºC. The values are means ± SEM: n = 3 per group (15 rats each group in pools of 5 rats). *p<0.05, rotenone treated rats *vs.* control rats; #p<0.05, 60 days-rotenone treated rats *vs*. 30 days-rotenone treated rats.

The same phenomenon was observed in isolated striatal mitochondria. Mitochondrial state 3 respiration decreased by about 13% and 30% after 30 and 60 days of rotenone treatment, with malate-glutamate as complex I substrate. Due to the fact that no changes were observed in state 4 respiration, the respiratory control also declined (Table 2). When succinate was used as complex II substrate, a slight impairment in state 3 respiration (20%) was observed after 60 days of rotenone administration.

The respiratory deficiency was further examined by assaying the activity of mitochondrial respiratory complexes. Table 3 shows that complex I activity decreased after 30 and 60 days of rotenone administration by 17% and 57%, respectively; complex IV activity declined 23% after 60 days of treatment; and complex II activity was not modified showing, once more, the highest and selective susceptibility of complex I to the oxidative, nitrosative and/or nitrative damage associated with rotenone treatment. The pattern observed for the decline of complex I activity in striatal mitochondria was also observed in the reduction of biochemical mtNOS (27% and 62%, in 30 and 60 days rotenone-treated rats) (Table 3) and functional mtNOS activities (29% and 71%), in accordance to the reported physical and functional interaction between complex I and mtNOS (Franco et al, 2006; Valdez & Boveris, 2007; Navarro et al., 2010).

	Oxygen consumption (ng-at O/min. mg protein)		
Experimental conditions	**Control**	**Rotenone**	
		30 days	**60 days**
Substrate: malate-glutamate			
State 4	42 ± 3	40 ± 3	38 ± 3
State 3	166 ± 9	144 ± 8*	116 ± 7*#
Respiratory control	3.9 ± 0.3	3.6 ± 0.3*	3.1 ± 0.4*
Substrate: succinate			
State 4	60 ± 4	58 ± 4	52 ± 4
State 3	240 ± 14	220 ± 11	192 ± 9*#
Respiratory control	4.0 ± 0.3	3.7 ± 0.3	3.7 ± 0.3

Table 2. **Striatum mitochondrial O_2 uptake of rotenone-treated rats during 30 and 60 days.** The values are means ± SEM: n = 3 per group (15 rats each in pools of 5 rats). *p<0.05, rotenone treated rats *vs.* control rats; # p<0.05, 60 days-rotenone treated rats *vs.* 30 days-rotenone treated rats.

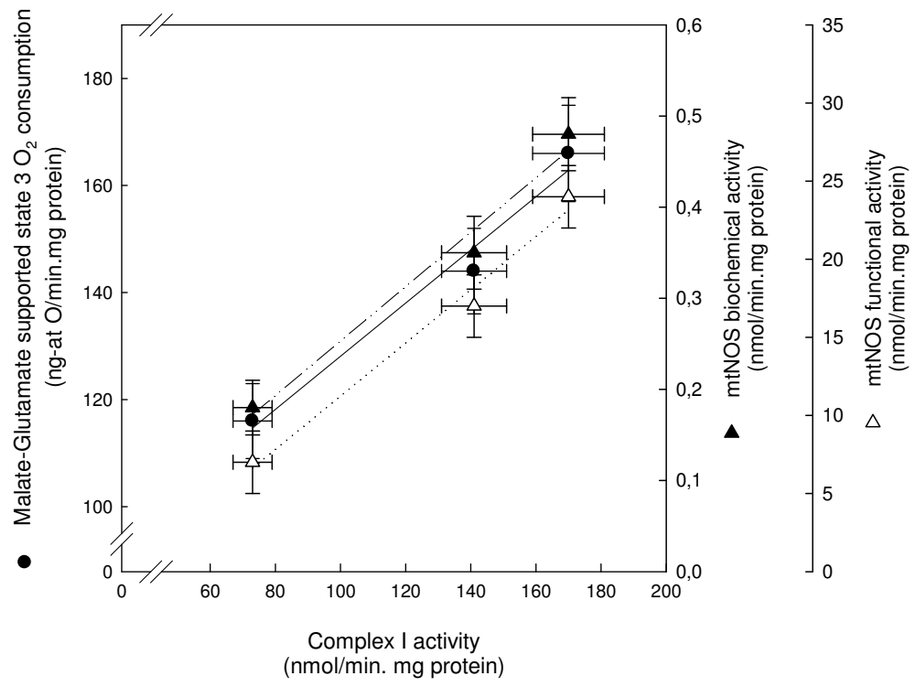

Fig. 1. Linear correlations between mitochondrial complex I activity and malate-glutamate supported state 3 respiration (•) (r^2 = 0.97) and between mitochondrial complex I activity and mtNOS biochemical (▲) (r^2 = 0.98) and functional activities (Δ) (r^2 = 0.98).

Linear correlations (Fig. 1) were obtained between mitochondrial complex I activity and either malate-glutamate supported state 3 O_2 uptake (r^2 = 0.97) or mtNOS biochemical (r^2 = 0.98) and functional activities (r^2 = 0.98), indicating that the pattern observed for the decline of complex I activity is associated to the reduction of mtNOS activity and to the impairment of striatum mitochondrial respiration.

Experimental condition	Complex I (nmol. min^{-1}. mg $protein^{-1}$)	Complex II (nmol. min^{-1}. mg $protein^{-1}$)	Complex IV (min^{-1}. mg $protein^{-1}$)	mtNOS (nmol. min^{-1}. mg $protein^{-1}$)
Control	170 ± 11	119 ± 9	75 ± 8	0.48 ± 0.04
30 days rotenone	141 ± 10*	117 ± 9	61 ± 5	0.35 ± 0.04*
60 days rotenone	73 ± 6*#	115 ± 9	58 ± 5*	0.18 ± 0.03*#

Table 3. **Striatum mitochondrial enzymatic activities of rotenone-treated rats during 30 and 60 days.** The values are means ± SEM: n = 3 per group (15 rats each in pools of 5 rats). *p<0.05, rotenone treated rats *vs.* control rats; #p<0.05, 60 days-rotenone treated rats *vs*. 30 days-rotenone treated rats.

The experimental quantitative evidence shows a range of 35% to 73% of a decline of complex I activity in brain mitochondria in aging and in neurodegenerative diseases. A value of about 50% is considered a limit of a tolerable functional impairment in terms of energy production that is compatible with the physiological function. For instance, complex I is inactivated by 36% in aged rat whole brain mitochondria (Navarro & Boveris, 2007), by 73% in aged rat hippocampal mitochondria (Navarro et al., 2008), by 57% in rat striatal mitochondria in experimental parkinsonism (Table 3 and Fig. 1), and by 43% in cortex mitochondria of human PD patients (Navarro et al., 2010). The data included in Tables 1 and 2 and in Fig. 1 allow to making some quantitative considerations respect to the basal respiration of striatal tissue under no neurological stimulus (in physiological conditions the striatal route is constantly activated). Taking into account the striatal O_2 consumption in control rats of 896 ng-at O/min. g tissue, a mitochondrial content of 12 mg protein/g striatum, and the mitochondrial respirations (in ng-at O/min. mg protein) in state 3 of 166 (malate-glutamate) and of 240 (succinate) and in state 4 of 42 and 60 (respectively), the fraction of mitochondria in state 3 and in state 4 can be calculated (Boveris & Boveris, 2007):

$$\text{Tissue } O_2 \text{ consumption (ng-at O/min x g tissue)} = \text{mg protein/g tissue x } [(a \text{ x state 3 } O_2 \text{ uptake}) + (1 - a) \text{ x (state 4 } O_2 \text{ uptake)}]$$

The state 4 and state 3 mitochondrial O_2 consumption were calculated considering the detected O_2 uptake rates (Table 2) and the substrate supply in physiological conditions: [(3 x rate with malate-glutamate) + (rate with succinate)]/4. Therefore, striatal mitochondria are in the tissue about 20% in state 3 and about 80% in state 4. Under conditions of increased ATP demand, striatum mitochondria will be able to increase ATP synthesis up to 5 times by switching mitochondria from the resting state 4 to the active state 3. At variance, in experimental parkinsonism, after 60 days of rotenone treatment, mitochondria are 8% in state 3 and 92% in state 4, showing that in parkinsonism, striatal mitochondria are severely limited in their capacity to respond to ATP demands.

Moreover, similar mitochondrial complex I dysfunctions were reported in skeletal muscle and platelets of PD patients (Mann et al., 1992). This condition of complex I impairment is likely to be of pathogenic importance because intoxication of experimental animals with inhibitors of complex I (rotenone, MPTP, MPP^+) (Bougria et al., 1995; Gomez et al., 2007) reproduces the clinical symptoms of PD in human subjects.

4.3 Brain mitochondrial oxidative damage

The mtNOS and complex I functional association in brain has been linked to the development of neurodegenerative diseases (Navarro et al., 2010). As it has been early

proposed (Hensley et al., 2000), changes in complex I proteins are certainly an explanation for the increase in O_2^- and H_2O_2 production rates. Rat treated with rotenone during 30 and 60 days increased the O_2^- production rates by about 13% and 37%, respectively (Table 4). This enhancement is in agreement with an increased generation of phospholipids oxidation and protein oxidation products in striatal mitochondria (Fig. 2 A and B).

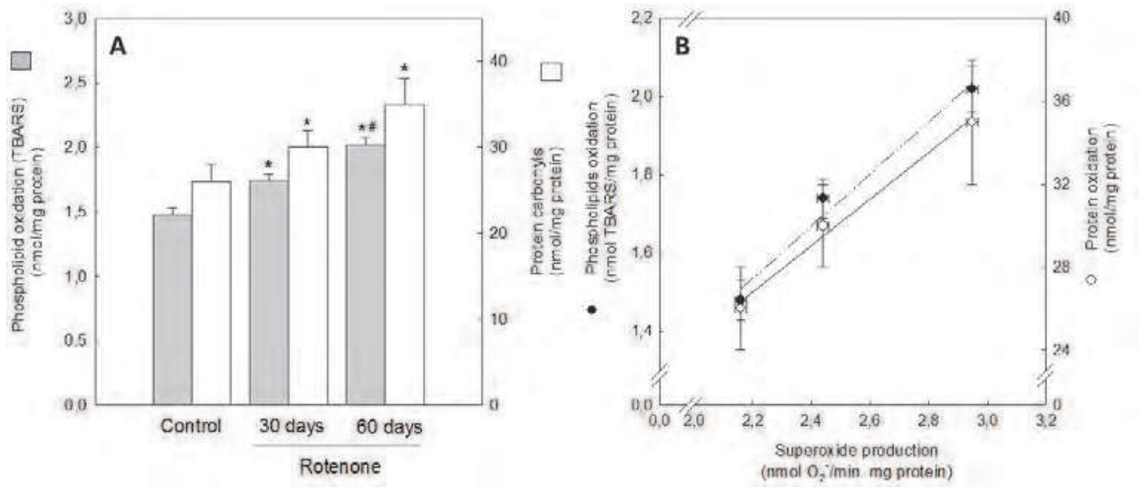

Fig. 2. **A**. Protein carbonyls and phospholipid oxidation products in striatal mitochondria of rotenone-treated rats. The values are means ± SEM: n=3 per group (15 rats each in pools of 5 rats). *p < 0.05, rotenone treated rats *vs.* control rats; #p<0.05, 60 days-rotenone treated rats *vs*. 30 days-rotenone treated rats. **B.** Linear correlations between O_2^- production rate and either phospholipid oxidation (•) ($r^2 = 0.98$) or protein oxidation (o) ($r^2 = 0.99$) products.

Navarro and co-workers (2009) have shown a marked impairments of tissue and malate-glutamate supported state 3 mitochondrial respiration and of complex I activity, associated with an oxidative damage, in frozen samples of frontal cortex (area 8) in PD patients in comparison to age-matched healthy controls (Navarro et al., 2009). Thus, human cortex mitochondrial dysfunction in PD is now added to the classical recognition of mitochondrial dysfunction in *substantia nigra*, which was early considered as specifically sensitive brain area in PD (Schapira et al., 1990a).

Experimental condition	**O_2^- production** (nmol/min. mg protein)
Control	2.16 ± 0.02
30 days rotenone	2.44 ± 0.02*
60 days rotenone	2.95 ± 0.02*#

Table 4. **Striatum mitochondrial superoxide anion production of rotenone-treated rats during 30 and 60 days.** The values are means ± SEM: n = 3 per group (15 rats each in pools of 5 rats). *p<0.05, rotenone treated rats *vs.* control rats; #p<0.05, 60 days-rotenone treated rats *vs*. 30 days-rotenone treated rats.

Mitochondrial complex I is particularly sensitive in terms of inhibition and inactivation to oxidants, oxygen free radicals and reactive nitrogen species. The mitochondrial dysfunction is currently described as "complex I syndrome", that includes decreased tissue O_2 uptake,

decreased malate/glutamate-supported mitochondrial respiration, reduced complex I (NADH-dehydrogenase) activity, increased phospholipid and protein oxidation products, increased protein nitration products, and increased O_2^- and H_2O_2 production rates (Boveris et al., 2010). Interestingly, high doses of vitamin E are able to restore to normal the age-dependent complex I syndrome in hippocampus and brain cortex (Navarro et al., 2010).This "complex I syndrome" has been observed in PD and in other neurodegenerative diseases (Schapira et al., 1990a; Schapira et al., 1990b; Cooper et al., 1992; Schapira, 2008; Carreras et al., 2004; Navarro & Boveris, 2007; Navarro et al., 2009), as well as in aging (Boveris& Navarro, 2008) and in ischemia-reperfusion (Gonzalez-Flecha et al., 1993; Valdez et al., 2011).

The molecular mechanisms responsible for complex I syndrome are likely accounted for a series of processes and reactions that lead synergistically to complex I inactivation. The involved processes and reactions are, in the first place, the lipid peroxidation process and the reactions of the reactive free radical intermediates (mainly $ROO^\bullet$) with complex I. In the second place, the reactions of the aldehydes produced in the lipid peroxidation process (4-HO-nonenal and malonaldehyde) with amino groups of the polypeptide chain of the complex I proteins. In the third place, nitration of complex I proteins following to the increased formation of $ONOO^-$, the chemical species produced by the intramitochondrial reaction of NO and O_2^-at the vicinity of NADH-dehydrogenase active center (Turrens & Boveris, 1980). The three mentioned processes provide synergistically pathways leading to complex I inactivation. Interestingly, complex I inactivation is accompanied by increased auto-oxidation and O_2^- production rate and subsequently an enlarged generation of H_2O_2 (Hensley et al., 2000; Navarro et al., 2011). It is understood that the reactions that inactivate complex I, mediated by free radicals ($ROO^\bullet$), aldehydes and $ONOO^-$, change the native non-covalent intermolecular forces bonding and synergistically promote covalent cross linking with protein inactivation (Liu et al., 2003).

5. Conclusions

Parkinson's disease is characterized by persistent, coordinated, nuclear-encoded cellular energy defects to which nigral dopamine neurons are intrinsically more susceptible than others cells. Complex I dysfunction in PD may be a biochemically detectable "tip of the iceberg" of a deeper molecular defect comprising the entire nuclear-encoded electron transfer chain. Under expression of PGC-1α-controlled genes involved in cellular energetic might represent a common link for these diverse manifestations of defects in mitochondrial biogenesis, and abnormal glucose utilization. One of the basic postulates of the mitochondrial theory of aging and neurodegenerative diseases is that there is a significant reduction in the capacity for ATP production in the brain and other organs of old mammals. The concept of a decrease in the effectiveness of the mitochondrial process of energy transduction (or oxidative phosphorylation) is expressed as an under function of "the mitochondrial redox-energy axis" (Yap et al., 2010). Although mitochondrial complexes, complex I (Valdez et al., 2004; Boveris & Navarro, 2008; Navarro et al., 2009), complex IV (Valdez et al., 2004; Boveris & Navarro, 2008), and complex V (Lam et al., 2009), are considered the main targets in neurodegeneration and aging, there are also cytosolic enzymes whose activities are simultaneously decreased, such as succinyl-CoA-transferase (Lam et al. 2009) and as 6-phosphofructo-2-kinase (Herrero-Mendez et al., 2009). The cytosolic-mitochondrial interaction is certainly affected and there is recognition of a

depressed glucose metabolism as the earliest and consistent abnormality in neurodegenerative diseases (Yap et al., 2009).

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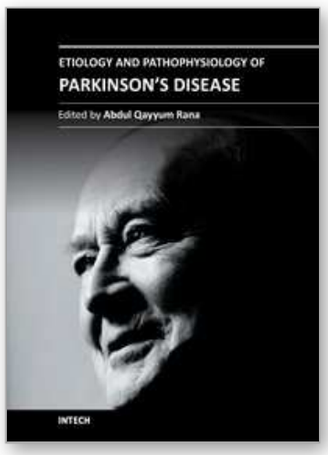

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This book about Parkinsonâ€™s disease provides a detailed account of etiology and pathophysiology of Parkinsonâ€™s disease, a complicated neurological condition. Environmental and genetic factors involved in the causation of Parkinsonâ€™s disease have been discussed in detail. This book can be used by basic scientists as well as researchers. Neuroscience fellows and life science readers can also obtain sufficient information. Beside genetic factors, other pathophysiological aspects of Parkinsonâ€™s disease have been discussed in detail. Up to date information about the changes in various neurotransmitters, inflammatory responses, oxidative pathways and biomarkers has been described at length. Each section has been written by one or more faculty members of well known academic institutions. Thus, this book brings forth both clinical and basic science aspects of Parkinsonâ€™s disease.

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InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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