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Review Article

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Role of Oxidative Stress in Parkinson's Disease

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Parkinson's disease (PD) is a progressive neurodegenerative movement disorder associated with a selective loss of the dopamine(DA) rgic neurons in the substantia nigra pars compacta and the degeneration of projecting nerve fibers in the striatum. Because there is currently no therapy that delays the neurodegenerative process, modification of the disease course by neuroprotective therapy is an important unmet clinical need. Toward this end, understanding cellular mechanisms that render the nigral neurons particularly vulnerable have been a subject of intensive research. Increasing evidence suggests that oxidative stress plays a major role. The metabolism of DA itself contributes to oxidative stress, resulting in modification of intracellular macromolecules whose functions are important for cell survival. Mitochondrial dysfunction and the consequent increase in reactive oxygen species also trigger a sequence of events that leads to cell demise. In addition, activated microglia produce nitric oxide and superoxide during neuroinflammatory responses, and this is aggravated by the molecules released by damaged DAergic neurons such as α-synuclein, neuromelanin and matrix metalloproteinase-3. Ways to reduce oxidative stress therefore can provide a therapeutic strategy. NAD(P)H:quinone reductase (NQO1) and other antioxidant enzymes, whose gene expression are commonly under the regulation of the transcription factor Nrf2, can serve as target proteins utilized toward development of disease-modifying therapy for PD.

Key words: Parkinson's disease, dopamine, oxidative stress, neuroinflammation, MMP-3, NQO1

INTRODUCTION

Parkinson's disease (PD) is associated with a selective loss of the neurons in the midbrain area called the substantia nigra pars compacta. These neurons contain the neurotransmitter dopamine (DA), and their projecting nerve fibers reside in the striatum. Because these neurons control voluntary movements, the degeneration leads to four cardinal, debilitating symptoms: resting tremor, muscular rigidity, bradykinesia, and postural imbalance. A majority of PD cases is idiopathic (90-95%). Occupational uses of herbicides or pesticides, exposure to organic solvents, carbon monoxide, and carbon disulfide, and more generally, industrialization, rural environment, well water, plant-derived toxins, and bacterial and viral infection are all thought to play roles [1]. Aging is an obvious factor associated with the onset of PD, and failure of normal cellular processes that occurs with aging is believed to cause increased vulnerability of DAergic neurons [2]. Familial forms of PD involving mutations in a number of genes have also been described. The mechanism by which mutation of these genes lead to degeneration of the nigral neurons have shed light to understanding of the pathophysiology of PD.

In both idiopathic and genetic cases of PD, oxidative stress is thought to be the common underlying mechanism that leads to cellular dysfunction and demise. As such, the substantia nigra of PD patients exhibit increased levels of oxidized lipids [3], proteins and DNA [4] and decreased levels of reduced glutathione (GSH) [5]. Oxidative stress occurs when an imbalance is formed between production of reactive oxygen species (ROS) and cellular

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antioxidant activity. Because of the presence of ROS-generating enzymes such as tyrosine hydroxylase and monoamine oxidase, the DAergic neurons are particularly prone to oxidative stress. In addition, the nigral DAergic neurons contain iron, which catalyzes the Fenton reaction, in which superoxide radicals and hydrogen peroxide can contribute to further oxidative stress [6]. Because of this intrinsic sensitivity to reactive species, a moderate oxidative stress can trigger a cascade of events that lead to cell demise. The major sources of such oxidative stress generated for the nigral DAergic neurons are thought to be the ROS produced during DA metabolism, mitochondrial dysfunction, and neuroinflammation, as discussed below in more detail.

DA METABOLISM

The neurotransmitter DA itself can be a source of oxidative stress. Lines of evidence suggest oxidation of DA and consequent quinone modification and oxidative stress as major factors contributing to the vulnerability of DAergic cells. Although DA is normally stored in vesicles, excess cytosolic DA is easily oxidized both spontaneously and enzymatically to produce DA quinone.

The DA quinone species are capable of covalently modifying cellular nucleophiles, including low molecular weight sulfhydryls such as GSH and protein cysteinyl residues, whose normal functions are important for cell survival. Notably, DA quinone has been shown to modify a number of proteins whose dysfunctions have been linked to PD pathophysiology, such as α-synuclein, parkin, DJ-1, and UCH-L1. DA quinone covalently modifies α-synuclein monomer and promotes the conversion of α-synuclein to the cytotoxic protofibril form [7]. The DA quinone-modified α-synuclein is not only poorly degraded but also inhibits the normal degradation of other proteins by chaperone-mediated autophagy [8]. Conversely, α-synuclein can bind to and permeabilize the vesicle membrane, causing leakage of DA into the cytosol [9] and this would in turn induce DA quinone generation. Parkin is also covalently modified by DA and becomes insoluble, which leads to inactivation of its E2 ubiquitin ligase activity [10]. Catechol-modified parkin has been detected in the substantia nigra but not other regions of the human brain, and parkin insolubility is observed in PD brain [10]. In addition, DA quinone modification of UCH-L1 and DJ-1 has also been observed both in brain mitochondrial preparations and DAergic cells [11]. Since both UCH-L1 and DJ-1 contain a cysteine residue that is important for their activity [12, 13] and their oxidative modification at cysteine has been observed in PD [14, 15], the DA quinone modification is likely the cause of inactivation of these enzymes.

DA quinone has also been shown to cause inactivation of the DA transporter and tyrosine hydroxyalse [16]. In addition, it leads to mitochondrial dysfunction [17] and swelling of brain mitochondria [18]. Accordingly, the subunits of Complex I and Complex III of the electron transport chain, whose dysfunction will deter mitochondrial respiration and cause ROS production, were also shown to be targets of DA quinone modification [11]. In addition, ER-60/GRP58/ERp57 and protein disulfide isomerase-5, the proteins that assist in protein folding in the endoplasmic reticulum, are also modified by DA quinine [11]. DA metabolites have also been shown to induce proteasomal inhibition, which can lead the cells to undergo apoptosis [19].

Furthermore, DA quinone can cyclize to become the highly reactive aminochrome, whose redox-cycling leads to generation of superoxide and depletion of cellular NADPH, and which ultimately polymerizes to form neuromelanin. Neuromelanin in turn can exacerbate the neurodegenerative process by triggering neuroinflammation [20]. Moreover, hydrogen peroxide is generated during DA metabolism by monoamine oxidase and is subsequently converted to the highly reactive hydroxyl radical in the presence of transition metal ions [6], contributing to oxidative stress.

Evidence of the existence of *in vivo* DA oxidation and its toxicity is also available. Neuromelanin, the final product of DA oxidation, is accumulated in the nigral region of the human brain [21]. Higher levels of cysteinyl-catechol derivatives are found in postmortem nigral tissues of PD patients compared to age-matched controls, suggesting cytotoxic nature of DA oxidation [22]. In animals, DA directly injected into the striatum caused selective toxicity to DAergic terminals that was proportional to the levels of DA oxidation and quinone-modified proteins [23]. Mice expressing a low level of ventricular monoamine transporter-2, presumably with increased cytosolic DA level, showed evidence of DA oxidation and age-dependent loss of nigral DA neurons [24].

MITOCHONDRIAL DYSFUNCTION

Mitochondrial dysfunction is another source of oxidative stress associated with the pathogenesis of PD. Neurons depend heavily on aerobic respiration for ATP, and hydrogen peroxide and superoxide radicals are normally produced during oxidative phosphorylation as byproducts in the mitochondria. Any pathological situation leading to mitochondrial dysfunction can cause a dramatic increase in ROS and overwhelm the cellular antioxidant mechanisms. Oxidative stress causes peroxidation of the mitochondria-specific lipid cardiolipin, which results in release of cytochrome c to the cytosol, triggering apoptosis.

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Because DAergic neurons are intrinsically more ROS-generating and vulnerable as described above, any event that triggers further oxidative stress can be harmful to the cell. Damage to mitochondrial Complex I in the electron transport chain causes leakage of electrons, which in turn causes ROS generation. As such, the Complex I inhibitors rotenone and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), when injected intraperitoneally, exert preferential cytotoxicity to the DAergic neurons [25]. Indeed, reduced Complex I activity has been found in tissues from subjects with PD [26]. Higher numbers of respiratory chain deficient DA neurons have been found in PD patients than in age-matched controls [27].

A line of evidence for mitochondrial dysfunction related to oxidative stress and DAergic cell damage comes from the findings that mutations in genes of mitochondrial proteins parkin, DJ-1, and PINK are linked to familial forms of PD. Cells derived from patients with *parkin* gene mutation show decreased Complex I activity [28]. Mice deficient in *parkin* gene have shown reduced striatal respiratory chain activity along with oxidative damage [29]. Mutations in *PINK1* induce mitochondrial dysfunction including excess free radical formation [30]. DJ-1 is a mitochondrially enriched, redox-sensitive protein and an atypical peroxiredoxin-like peroxidase that scavenges H_2O_2, and *DJ-1* KO mice accumulate more ROS and exhibit fragmented mitochondrial phenotype [31]. In addition, α-synuclein, although mostly cytosolic, seems to interact with mitochondrial membranes and to inhibit Complex I [32]. Mice overexpressing mutant α-synuclein exhibit abnormalities in the mitochondrial structure and function [33].

NEUROINFLAMMATION

Neuronal loss in PD is associated with chronic neuroinflammation, which is controlled primarily by microglia, the resident innate immune cells and the main immune responsive cells in the central nervous system. Microglial reaction has been found in the SN of sporadic PD patients [34] as well as familial PD patients [35] and in the SN and/or striatum of PD animal models elicited by MPTP [36].

Microglia are activated in response to injury or toxic insult as a self-defensive mechanism to remove cell debris and pathogens. When activated, they release free radicals such as nitric oxide and superoxide, which can in turn contribute to oxidative stress in the microenvironment. Overactivated and/or chronically activated state of microglia causes excessive and uncontrolled neuroinflammatory responses, leading to a self-perpetuating vicious cycle of neurodegeneration [37]. This is thought to be exacerbated by inflammatory signals generated by molecules released from damaged neurons, leading to induction of reactive microgliosis. The oxidized or ROS-induced molecules that are released from damaged nigral DAergic neurons and trigger microglial activation include neuromelanin, α-synuclein, and active form of MMP-3, as described below.

Neuromelanin is the dark insoluble polymer produced from DA oxidation and confers the dark pigmentation to the substantia nigra. Insoluble extraneuronal neuromelanin granules have been observed in patients of juvenile PD [38] and idiopathic PD, as well as those with MPTP-induced parkinsonism [39]. Addition of neuromelanin extracted from PD brain to microglia culture caused increases in and nitric oxide [40]. Intracerebral injection of neuromelanin caused strong microglia activation and a loss of DAergic neurons in the substantia nigra [20]. Neuromelanin appears to remain for a very long time in the extracellular space [39] and thus thought to be one of the molecules responsible for inducing chronic neuroinflammation in PD.

Although mostly intracellular, a fraction of α-synuclein fibril is released from neurons [41], and α-synuclein is found in the cerebrospinal fluid from PD patients and normal subjects [42], and in human plasma [43]. The addition of aggregated human α-synuclein to a primary mesencephalic neuron-glia culture causes activation of microglia and DAergic neurodegeneration, and this cytotoxicity does not occur in the absence of microglia [44]. In addition, neuron-derived α-synuclein stimulates astrocytes to produce inflammatory modulators that augment microglial chemotaxis, activation and proliferation [45]. Nitration of α-synuclein, presumably due to increased nitric oxide, facilitates the neuroinflammatory responses [46]. More recently, it has been shown that transgenic mice expressing mutant α-synuclein developed persistent neuroinflammation and chronic progressive degeneration of the nigrostriatal DA pathway when inflammation was triggered by a low level of lipopolysaccharide [47].

The active form of MMP-3 is increased in response to oxidative stress in DAergic cells, and MMP-3 causes activation of microglia, which in turn would generate reactive nitrogen species and ROS [48-51]. In MMP-3 knockout mice, the microglial activation following exposure to MPTP is abrogated, and this is accompanied by a lower level of superoxide production compared to their wild type [52]. MMP-3 causes cleavage of protease activated receptor-1 (PAR-1) [53], whose removal of N-terminal extracellular domain renders the remaining domain acting as a tethered ligand, subsequently triggering generation of intracellular signals [54] and activation of microglia [55]. Furthermore, MMP-3 participates in formation of the biologically active IL-1β from the proform [56]. In addition, MMP-3 participates in expression of inflammatory cytokines in activated microglia [57], and conversely, MMP-

3 is induced by free radicals and the cytokines in these cells [58]. Therefore, a vicious cycle may exist, where MMP-3, whose expression is induced by oxidative stress, is released from DAergic neurons and leads to production of free radicals and cytokines in the microglia. MMP-3 can also cause degradation of blood brain barrier and infiltration of neutrophils, which can further contribute to neuroinflammation [59].

THERAPEUTIC STRATEGIES

Currently, there is no therapy clinically available that delays the neurodegenerative process itself, and therefore modification of the disease course via neuroprotective therapy is an important unmet clinical need. Thus, understanding of the pathophysiology and etiology of the disease at cellular and molecular levels and finding molecular targets for neuroprotective/disease-modifying therapy is the crucial issue in the field of basic PD research.

As described above, oxidative stress originating from DA metabolism, neuroinflammation and mitochondrial dysfunction is thought to be the hallmark of PD pathogenesis, and antioxidant mechanism should prove to be an effective neuroprotective therapy for PD. However, no direct antioxidant, such as vitamin C, vitamin E, and coenzyme Q10, has provided disease modification in PD patients. Attempts have also been made to design therapies against neuroinflammation. Doxycycline, a tetracycline derivative that penetrates the blood brain barrier, suppresses the increase in MMP-3 gene expression as well as nitric oxide and inflammatory cytokines and provides protection of the nigral DAergic neurons in the MPTP-induced mouse model of PD [60]. A novel synthetic compound 7-hydroxy-6-methoxy-2-propionyl-1,2,3,4-tetrahydroisoquinoline, which downregulated expression of MMP-3 along with IL-1β, TNF-α and cyclooxygenase-2, provided neuroprotection in both cell culture and animal models of PD [61].

The enzyme NAD(P)H:quinone reductase (DT-diaphorase; NAD(P)H-(quinone acceptor) oxidoreductase; EC 1.6.99.2; NQO1) catalyzes two-electron reduction of quinone to the redox-stable hydroquinone. Since DA and its metabolites have been implicated in the pathogenesis of PD, NQO1 may exert a protective effect against such conditions. Indeed, NQO1 protected against damaging effects of cyclized quinones and oxidative stress induced during their redox cycling [19]. Induction of NQO1 by sulforaphane protected against neurocytotoxicity associated with DA quinone *in vitro* [62] and against MPTP-elicited toxicity *in vivo* [63]. In addition, NQO1 is known to maintain both α-tocopherol and coenzyme Q10 in their reduced, antioxidant state [64].

While NQO1 is abundant in the liver where it participates in the phase II detoxification, the enzyme is also expressed in the brain [65]. In addition to its predominant expression in astrocytes [66], NQO1 is also expressed, albeit to a lesser degree, in DArgic neurons in the substantia nigra [67]. Moreover, a marked increase in the neuronal expression of NQO1 was consistently observed in the Parkinsonian substantia nigra [67]. A polymorphism (C609T) of NQO1 that results in a decrease or total loss of its expression is reported to be associated with PD [68], although another group reported no such association [69].

Cellular induction of NQO1 is achieved by the transcription factor Nrf-2 binding to a cis-acting enhancer sequence termed antioxidant response element (ARE). Nrf-2 is normally present in the cytosol bound by the cytosolic protein keap1, but is released and translocated into the nucleus in response to a variety of cellular or exogenous signals. Ways to induce NQO1 expression and Nrf2 activation should therefore serve as viable approaches to develop neuroprotective therapy for PD.

CONCLUSION

PD pathogenesis seems to be closely related to oxidative stress due to ROS generated by DA metabolism, mitochondrial dysfunction and neuroiniflammation. Because there is no current therapy available that delays the neurodegenerative process, development of drugs that will modify the course of PD is crucial. Intensive studies are being carried out worldwide toward understanding the molecular mechanism of cell demise in PD, and the results are actively being utilized in attempts to design disease-modifying drugs for this devastating disease.

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REFERENCES

1. Schapira AH, Jenner P (2011) Etiology and pathogenesis of Parkinson's disease. Mov Disord 26:1049-1055.
2. Obeso JA, Rodriguez-Oroz MC, Goetz CG, Marin C, Kordower JH, Rodriguez M, Hirsch EC, Farrer M, Schapira AH, Halliday G (2010) Missing pieces in the Parkinson's disease puzzle. Nat Med 16:653-661.
3. Bosco DA, Fowler DM, Zhang Q, Nieva J, Powers ET,

 http://dx.doi.org/10.5607/en.2013.22.1.11

Wentworth P Jr, Lerner RA, Kelly JW (2006) Elevated levels of oxidized cholesterol metabolites in Lewy body disease brains accelerate alpha-synuclein fibrilization. Nat Chem Biol 2:249-253.

4. Nakabeppu Y, Tsuchimoto D, Yamaguchi H, Sakumi K (2007) Oxidative damage in nucleic acids and Parkinson's disease. J Neurosci Res 85:919-934.
5. Zeevalk GD, Razmpour R, Bernard LP (2008) Glutathione and Parkinson's disease: is this the elephant in the room? Biomed Pharmacother 62:236-249.
6. Halliwell B (1992) Reactive oxygen species and the central nervous system. J Neurochem 59:1609-1623.
7. Conway KA, Rochet JC, Bieganski RM, Lansbury PT Jr (2001) Kinetic stabilization of the alpha-synuclein protofibril by a dopamine-alpha-synuclein adduct. Science 294:1346-1349.
8. Martinez-Vicente M, Talloczy Z, Kaushik S, Massey AC, Mazzulli J, Mosharov EV, Hodara R, Fredenburg R, Wu DC, Follenzi A, Dauer W, Przedborski S, Ischiropoulos H, Lansbury PT, Sulzer D, Cuervo AM (2008) Dopamine-modified alpha-synuclein blocks chaperone-mediated autophagy. J Clin Invest 118:777-788.
9. Lotharius J, Brundin P (2002) Impaired dopamine storage resulting from alpha-synuclein mutations may contribute to the pathogenesis of Parkinson's disease. Hum Mol Genet 11:2395-2407.
10. LaVoie MJ, Ostaszewski BL, Weihofen A, Schlossmacher MG, Selkoe DJ (2005) Dopamine covalently modifies and functionally inactivates parkin. Nat Med 11:1214-1221.
11. Van Laar VS, Mishizen AJ, Cascio M, Hastings TG (2009) Proteomic identification of dopamine-conjugated proteins from isolated rat brain mitochondria and SH-SY5Y cells. Neurobiol Dis 34:487-500.
12. Nishikawa K, Li H, Kawamura R, Osaka H, Wang YL, Hara Y, Hirokawa T, Manago Y, Amano T, Noda M, Aoki S, Wada K (2003) Alterations of structure and hydrolase activity of parkinsonism-associated human ubiquitin carboxyl-terminal hydrolase L1 variants. Biochem Biophys Res Commun 304:176-183.
13. Qu W, Fan L, Kim YC, Ishikawa S, Iguchi-Ariga SM, Pu XP, Ariga H (2009) Kaempferol derivatives prevent oxidative stress-induced cell death in a DJ-1-dependent manner. J Pharmacol Sci 110:191-200.
14. Choi J, Levey AI, Weintraub ST, Rees HD, Gearing M, Chin LS, Li L (2004) Oxidative modifications and down-regulation of ubiquitin carboxyl-terminal hydrolase L1 associated with idiopathic Parkinson's and Alzheimer's diseases. J Biol Chem 279:13256-13264.
15. Choi J, Sullards MC, Olzmann JA, Rees HD, Weintraub ST, Bostwick DE, Gearing M, Levey AI, Chin LS, Li L (2006) Oxidative damage of DJ-1 is linked to sporadic Parkinson and Alzheimer diseases. J Biol Chem 281:10816-10824.
16. Kuhn DM, Arthur RE Jr, Thomas DM, Elferink LA (1999) Tyrosine hydroxylase is inactivated by catechol-quinones and converted to a redox-cycling quinoprotein: possible relevance to Parkinson's disease. J Neurochem 73:1309-1317.
17. Lee CS, Han JH, Jang YY, Song JH, Han ES (2002) Differential effect of catecholamines and MPP(+) on membrane permeability in brain mitochondria and cell viability in PC12 cells. Neurochem Int 40:361-369.
18. Berman SB, Hastings TG (1999) Dopamine oxidation alters mitochondrial respiration and induces permeability transition in brain mitochondria: implications for Parkinson's disease. J Neurochem 73:1127-1137.
19. Zafar KS, Inayat-Hussain SH, Ross D (2007) A comparative study of proteasomal inhibition and apoptosis induced in N27 mesencephalic cells by dopamine and MG132. J Neurochem 102:913-921.
20. Zecca L, Wilms H, Geick S, Claasen JH, Brandenburg LO, Holzknecht C, Panizza ML, Zucca FA, Deuschl G, Sievers J, Lucius R (2008) Human neuromelanin induces neuro-inflammation and neurodegeneration in the rat substantia nigra: implications for Parkinson's disease. Acta Neuropathol 116:47-55.
21. Zecca L, Zucca FA, Wilms H, Sulzer D (2003) Neuromelanin of the substantia nigra: a neuronal black hole with protective and toxic characteristics. Trends Neurosci 26:578-580.
22. Spencer JP, Jenner P, Daniel SE, Lees AJ, Marsden DC, Halliwell B (1998) Conjugates of catecholamines with cysteine and GSH in Parkinson's disease: possible mechanisms of formation involving reactive oxygen species. J Neurochem 71:2112-2122.
23. Rabinovic AD, Lewis DA, Hastings TG (2000) Role of oxidative changes in the degeneration of dopamine terminals after injection of neurotoxic levels of dopamine. Neuroscience 101:67-76.
24. Caudle WM, Colebrooke RE, Emson PC, Miller GW (2008) Altered vesicular dopamine storage in Parkinson's disease: a premature demise. Trends Neurosci 31:303-308.
25. Betarbet R, Sherer TB, Greenamyre JT (2002) Animal models of Parkinson's disease. Bioessays 24:308-318.
26. Parker WD Jr, Boyson SJ, Parks JK (1989) Abnormalities of the electron transport chain in idiopathic Parkinson's disease. Ann Neurol 26:719-723.
27. Bender A, Krishnan KJ, Morris CM, Taylor GA, Reeve AK,

Perry RH, Jaros E, Hersheson JS, Betts J, Klopstock T, Taylor RW, Turnbull DM (2006) High levels of mitochondrial DNA deletions in substantia nigra neurons in aging and Parkinson disease. Nat Genet 38:515-517.

28. Müftüoglu M, Elibol B, Dalmizrak O, Ercan A, Kulaksiz G, Ogüs H, Dalkara T, Ozer N (2004) Mitochondrial complex I and IV activities in leukocytes from patients with parkin mutations. Mov Disord 19:544-548.
29. Palacino JJ, Sagi D, Goldberg MS, Krauss S, Motz C, Wacker M, Klose J, Shen J (2004) Mitochondrial dysfunction and oxidative damage in parkin-deficient mice. J Biol Chem 279:18614-18622.
30. Gandhi S, Wood-Kaczmar A, Yao Z, Plun-Favreau H, Deas E, Klupsch K, Downward J, Latchman DS, Tabrizi SJ, Wood NW, Duchen MR, Abramov AY (2009) PINK1-associated Parkinson's disease is caused by neuronal vulnerability to calcium-induced cell death. Mol Cell 33:627-638.
31. Irrcher I, Aleyasin H, Seifert EL, Hewitt SJ, Chhabra S, Phillips M, Lutz AK, Rousseaux MW, Bevilacqua L, Jahani-Asl A, Callaghan S, MacLaurin JG, Winklhofer KF, Rizzu P, Rippstein P, Kim RH, Chen CX, Fon EA, Slack RS, Harper ME, McBride HM, Mak TW, Park DS (2010) Loss of the Parkinson's disease-linked gene DJ-1 perturbs mitochondrial dynamics. Hum Mol Genet 19:3734-3746.
32. Devi L, Raghavendran V, Prabhu BM, Avadhani NG, Anandatheerthavarada HK (2008) Mitochondrial import and accumulation of α-synuclein impair complex I in human dopaminergic neuronal cultures and Parkinson disease brain. J Biol Chem 283:9089-9100.
33. Martin LJ, Pan Y, Price AC, Sterling W, Copeland NG, Jenkins NA, Price DL, Lee MK (2006) Parkinson's disease α-synuclein transgenic mice develop neuronal mitochondrial degeneration and cell death. J Neurosci 26:41-50.
34. McGeer PL, Itagaki S, Boyes BE, McGeer EG (1988) Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains. Neurology 38:1285-1291.
35. Yamada T, McGeer EG, Schelper RL, Wszolek ZK, McGeer PL, Pfeiffer RF, Rodnitzky RL (1993) Histological and biochemical pathology in a family with autosomal dominant Parkinsonism and dementia. Neurol Psychiatry Brain Res 2:26-35.
36. O'Callaghan JP, Miller DB, Reinhard JF Jr (1990) Characterization of the origins of astrocyte response to injury using the dopaminergic neurotoxicant, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Brain Res 521:73-80.
37. Qian L, Flood PM, Hong JS (2010) Neuroinflammation is a key player in Parkinson's disease and a prime target for therapy. J Neural Transm 117:971-979.
38. Ishikawa A, Takahashi H (1998) Clinical and neuropathological aspects of autosomal recessive juvenile parkinsonism. J Neurol 245:P4-9.
39. Langston JW, Forno LS, Tetrud J, Reeves AG, Kaplan JA, Karluk D (1999) Evidence of active nerve cell degeneration in the substantia nigra of humans years after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine exposure. Ann Neurol 46:598-605.
40. Wilms H, Rosenstiel P, Sievers J, Deuschl G, Zecca L, Lucius R (2003) Activation of microglia by human neuromelanin is NF-kappaB dependent and involves p38 mitogen-activated protein kinase: implications for Parkinson's disease. FASEB J 17:500-502.
41. Lee HJ, Patel S, Lee SJ (2005) Intravesicular localization and exocytosis of alpha-synuclein and its aggregates. J Neurosci 25:6016-6024.
42. Borghi R, Marchese R, Negro A, Marinelli L, Forloni G, Zaccheo D, Abbruzzese G, Tabaton M (2000) Full length alpha-synuclein is present in cerebrospinal fluid from Parkinson's disease and normal subjects. Neurosci Lett 287:65-67.
43. El-Agnaf OM, Salem SA, Paleologou KE, Cooper LJ, Fullwood NJ, Gibson MJ, Curran MD, Court JA, Mann DM, Ikeda S, Cookson MR, Hardy J, Allsop D (2003) Alpha-synuclein implicated in Parkinson's disease is present in extracellular biological fluids, including human plasma. FASEB J 17:1945-1947.
44. Zhang W, Wang T, Pei Z, Miller DS, Wu X, Block ML, Wilson B, Zhang W, Zhou Y, Hong JS, Zhang J (2005) Aggregated alpha-synuclein activates microglia: a process leading to disease progression in Parkinson's disease. FASEB J 19:533-542.
45. Farina C, Aloisi F, Meinl E (2007) Astrocytes are active players in cerebral innate immunity. Trends Immunol 28:138-145.
46. Gao HM, Kotzbauer PT, Uryu K, Leight S, Trojanowski JQ, Lee VM (2008) Neuroinflammation and oxidation/nitration of alpha-synuclein linked to dopaminergic neurodegeneration. J Neurosci 28:7687-7698.
47. Gao HM, Zhang F, Zhou H, Kam W, Wilson B, Hong JS (2011) Neuroinflammation and α-synuclein dysfunction potentiate each other, driving chronic progression of neurodegeneration in a mouse model of Parkinson's disease. Environ Health Perspect 119:807-814.
48. Kim YS, Kim SS, Cho JJ, Choi DH, Hwang O, Shin DH, Chun HS, Beal MF, Joh TH (2005) Matrix metalloproteinase-3: a

 http://dx.doi.org/10.5607/en.2013.22.1.11

novel signaling proteinase from apoptotic neuronal cells that activates microglia. J Neurosci 25:3701-3711.

49. Choi DH, Kim EM, Son HJ, Joh TH, Kim YS, Kim D, Flint Beal M, Hwang O (2008) A novel intracellular role of matrix metalloproteinase-3 during apoptosis of dopaminergic cells. J Neurochem 106:405-415.
50. Kim EM, Shin EJ, Choi JH, Son HJ, Park IS, Joh TH, Hwang O (2010) Matrix metalloproteinase-3 is increased and participates in neuronal apoptotic signaling downstream of caspase-12 during endoplasmic reticulum stress. J Biol Chem 285:16444-16452.
51. Kim EM, Hwang O (2011) Role of matrix metalloproteinase-3 in neurodegeneration. J Neurochem 116:22-32.
52. Kim YS, Choi DH, Block ML, Lorenzl S, Yang L, Kim YJ, Sugama S, Cho BP, Hwang O, Browne SE, Kim SY, Hong JS, Beal MF, Joh TH (2007) A pivotal role of matrix metalloproteinase-3 activity in dopaminergic neuronal degeneration via microglial activation. FASEB J 21:179-187.
53. Lee EJ, Woo MS, Moon PG, Baek MC, Choi IY, Kim WK, Junn E, Kim HS (2010) Alpha-synuclein activates microglia by inducing the expressions of matrix metalloproteinases and the subsequent activation of protease-activated receptor-1. J Immunol 185:615-623.
54. Vu TK, Hung DT, Wheaton VI, Coughlin SR (1991) Molecular cloning of a functional thrombin receptor reveals a novel proteolytic mechanism of receptor activation. Cell 64:1057-1068.
55. Suo Z, Wu M, Ameenuddin S, Anderson HE, Zoloty JE, Citron BA, Andrade-Gordon P, Festoff BW (2002) Participation of protease-activated receptor-1 in thrombin-induced microglial activation. J Neurochem 80:655-666.
56. Schönbeck U, Mach F, Libby P (1998) Generation of biologically active IL-1 beta by matrix metalloproteinases: a novel caspase-1-independent pathway of IL-1 beta processing. J Immunol 161:3340-3346.
57. Woo MS, Park JS, Choi IY, Kim WK, Kim HS (2008) Inhibition of MMP-3 or -9 suppresses lipopolysaccharide-induced expression of proinflammatory cytokines and iNOS in microglia. J Neurochem 106:770-780.
58. Jian Liu K, Rosenberg GA (2005) Matrix metalloproteinases and free radicals in cerebral ischemia. Free Radic Biol Med 39:71-80.
59. Gurney KJ, Estrada EY, Rosenberg GA (2006) Blood-brain barrier disruption by stromelysin-1 facilitates neutrophil infiltration in neuroinflammation. Neurobiol Dis 23:87-96.
60. Cho Y, Son HJ, Kim EM, Choi JH, Kim ST, Ji IJ, Choi DH, Joh TH, Kim YS, Hwang O (2009) Doxycycline is neuroprotective against nigral dopaminergic degeneration by a dual mechanism involving MMP-3. Neurotox Res 16:361-371.
61. Son HJ, Lee JA, Shin N, Choi JH, Seo JW, Chi DY, Lee CS, Kim EM, Choe H, Hwang O (2012) A novel compound PTIQ protects the nigral dopaminergic neurones in an animal model of Parkinson's disease induced by MPTP. Br J Pharmacol 165:2213-2227.
62. Han JM, Lee YJ, Lee SY, Kim EM, Moon Y, Kim HW, Hwang O (2007) Protective effect of sulforaphane against dopaminergic cell death. J Pharmacol Exp Ther 321:249-256.
63. Jazwa A, Rojo AI, Innamorato NG, Hesse M, Fernández-Ruiz J, Cuadrado A (2011) Pharmacological targeting of the transcription factor Nrf2 at the basal ganglia provides disease modifying therapy for experimental parkinsonism. Antioxid Redox Signal 14:2347-2360.
64. Siegel D, Bolton EM, Burr JA, Liebler DC, Ross D (1997) The reduction of alpha-tocopherolquinone by human NAD(P)H: quinone oxidoreductase: the role of alpha-tocopherolhydroquinone as a cellular antioxidant. Mol Pharmacol 52:300-305.
65. Stringer JL, Gaikwad A, Gonzales BN, Long DJ Jr, Marks LM, Jaiswal AK (2004) Presence and induction of the enzyme NAD(P)H: quinone oxidoreductase 1 in the central nervous system. J Comp Neurol 471:289-297.
66. Flier J, Van Muiswinkel FL, Jongenelen CA, Drukarch B (2002) The neuroprotective antioxidant alpha-lipoic acid induces detoxication enzymes in cultured astroglial cells. Free Radic Res 36:695-699.
67. van Muiswinkel FL, de Vos RA, Bol JG, Andringa G, Jansen Steur EN, Ross D, Siegel D, Drukarch B (2004) Expression of NAD(P)H: quinone oxidoreductase in the normal and Parkinsonian substantia nigra. Neurobiol Aging 25:1253-1262.
68. Harada S, Fujii C, Hayashi A, Ohkoshi N (2001) An association between idiopathic Parkinson's disease and polymorphisms of phase II detoxification enzymes: glutathione S-transferase M1 and quinone oxidoreductase 1 and 2. Biochem Biophys Res Commun 288:887-892.
69. Okada S, Farin FM, Stapleton P, Viernes H, Quigley SD, Powers KM, Smith-Weller T, Franklin GM, Longstreth WT, Swanson PD, Checkoway H (2005) No associations between Parkinson's disease and polymorphisms of the quinone oxidoreductase (NQO1, NQO2) genes. Neurosci Lett 375:178-180.