5

# Pathology of Neurodegenerative Diseases

YoungSoo Kim[1], Yunkyung Kim[1], Onyou Hwang[2] and Dong Jin Kim[1]
[1]*Korea Institute of Science and Technology*
[2]*University of Ulsan College of Medicine, Republic of Korea*

## 1. Introduction

As the average life expectancy has been extended by the current state-of-art medical technologies, the elderly population is increasing rapidly. The world is now facing the 'ageing era', which comes with social issues like neurodegenerative diseases. Neurodegenerative diseases are progressive neurological disorders highly linked to brain injuries from which there is no recovery. Selective neuronal loss in particular regions of our brain causes different types of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), stroke, amyotrophic lateral sclerosis (ALS), and many others. Two of the most common forms are AD and PD, and currently there are no fundamental cure available.

AD is a lethal disorder associated with progressive neuronal cell death beginning in hippocampus and cortex regions. Typical indications of AD are gradual memory loss, cognitive impairment and behavior dysfunction to death. Owing to the complex pathological cascade, the cause of AD is not yet clearly understood. Among the numerous pathological causes of AD in dispute, cumulative neurotoxicity induced by misfolded β-amyloid (Aβ) and phosphorylated tau proteins is strongly supported by genetic and clinical evidences. At present, there is no cure available to treat AD patients for recovery.

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. Currently, there is no therapy clinically available that delays the neurodegenerative process, and therefore modification of the disease course via neuroprotective therapy is an important unmet clinical need. Increasing evidence suggests that oxidative stress has a major impact on the pathogenesis of PD. Studies have demonstrated both in vivo and in vitro that 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 (ROS) 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 DAergic neurons such as α-synuclein, neuromelanin and matrix metalloproteinase-3. A number of proteins whose gene mutation is linked to familial forms of PD have been found, and analyses of their normal cellular functions as well as dysfunctions as consequences of oxidative stress have shed light to understanding the pathogenesis of PD.

We will review in this chapter the current understanding of the etiology and pathogenesis of AD and PD, with an emphasis on protein abnormalities, and efforts that are being made toward development of disease-modifying therapy.

## 2. Alzheimer's disease (AD)

Alzheimer's disease (AD) is the most common and fatal neurodegenerative disorder with disastrous effects on the senior population (Maslow, 2008). About 10% of people over 65 years old and half of those over 85 suffer from AD. Prevalence of this progressive disorder increases with ageing, affecting 3% of people between 60-69-year-olds, 5% of those between 70-79 and 30-50% of those between 80-89. Typical symptoms of AD are memory loss, cognitive impairment and behavior dysfunction to death. In many cases, AD patients develop physiological dysfunctions such as swallowing, balance and bladder control. Psychological symptoms such as depression are often associated with the disorder. According to the progression of the disorder, patients are categorized into seven stages; no impairment, very mild decline, mild decline, moderate decline, moderately severe decline, severe decline and very severe decline.

At present, there are five FDA-approved medications (donepezil, galantamine, memantine, rivastigmine and tacrine) to treat symptoms of AD. However, they can only slow down the progression or temporarily increase cognitive functions by enhancing neuronal communications. These commercially available drugs target secondary symptoms such as memory loss (cholinesterase inhibitors and memantine), behavior (antidepressants, anxiolytics and antipsychotics) and sleep changes (antidepressants, benzodiazepines, sleeping pills and antipsychotics). Therefore, current AD patients lack a fundamental therapy to stop neurodegeneration. Not only is there no fundamental drug to stop or reverse AD, but also no quantitative diagnostic system has been developed yet. At this time, the only confident method to determine AD is a postmortem diagnosis. For living patients, a series of neuropsychological and medical assessment is used for primary diagnosis and dementia-like symptoms are ruled out via brain scans or blood, urine and spinal fluid test. Thus, increasing interests on early detection of the disease highlight a need for simpler and reliable diagnostic tools and robust biological markers. As a result, molecular imaging pathological hallmarks of AD, senile plaque (SP) and intracellular neurofibrillary tangles (NFT), in living brain tissues are currently on focus by many researchers and physicians. Among a wide variety of brain imaging technologies, development of radiolabeled imaging probes for single photon emission computed tomography (SPECT) and positron emission tomography (PET) are mainly studied due to several advantages; real time targeted molecular imaging with very low concentration of imaging probes and possible quantification of target molecule (Klunk et al., 1994; Skovronsky et al., 2000). Hence, development of SP and NFT binding probes for direct marking in living AD brains is urgently desired for early diagnosis and monitoring of the disease progression

### 2.1 Pathology

The etiology of AD is not clearly understood yet. However, backtracking anatomical and biochemical signs allow us to postulate etiology in the upstream of the disorder. Typical indications from autopsy are brain shrinkage, blood-brain barrier damage and synaptic loss due to neuronal cell death. A wide variety of neurotoxic candidates have been suggested

such as increased concentration of aggregated proteins, mitochondria dysfunction, reduced synthesis of neurotransmitters, inflammation and oxidative stress in AD brain. Among them, genetic and clinical evidences strongly support that the most dominant etiologic paradigm of Alzheimer's pathology is Aβ and tau hypotheses (J.A. Hardy and Higgins, 1992). Interestingly, these two proteins were already found as biomarkers of AD when a German psychiatrist, Dr. Alois Alzheimer reported the first documented case on his fifty-year-old female patient in 1907. During the brain autopsy of the patient, he discovered two pathological hallmarks in the hippocampus and neocortex regions of the postmortem brain tissue (Alzheimer, 1991; J.A. Hardy and Higgins, 1992). The former is consisted of misfolded Aβ proteins surrounded by dystrophic neurites and abnormal synapses, and the latter is made of abnormally hyperphosphorylated tau proteins of paired helical filaments. Activated microglia and neuropil threads are also known as positive findings. Significant loss of neurons and synapses has been found as highly associated with these four biomarkers.

Given the prominence of two major hallmarks, SP and NFT, there have been considerable arguments on Aβ and tau hypotheses concerning the primary element of the pathogenesis and their pathological order. According to clinical observation of temporal ordering of biomarker abnormalities based on decreased CSF Aβ(1-42) level, increased CSF tau level, decreased fluorodeoxyglucose level, increased Aβ plaque level and structural MRI measurements, deposition of Aβ leads NFT formation of tau begin simultaneously (Jack et al., 2010). Jack Jr. and colleagues also proposed SP as a target for early diagnosis and NFT for disease severity, because Aβ plaque formation almost reaches its saturation level by the time clinical symptoms appear and p-tau tangle forms in parallel to the progress of neuronal injury, dysfunction and degeneration. However, it is still debatable if abnormalities of both proteins are obligatory for AD progression.

### 2.2 Amyloidogenesis

#### 2.2.1 APP processing and the generation of Aβ

Aβ is a 39 to 43 amino acid long peptide generated through abnormal sequential proteolysis of amyloid precursor protein (APP) by β- and γ-secretases (Fig. (1)). Various Aβ isoforms (Aβ39, Aβ40, Aβ41, Aβ42 and Aβ43) are determined by cleavage within the transmembrane domain of APP by γ-secretase. Because the Aβ domain of APP, in general, is cleaved by α-secretase, Aβ is rarely produced in normal human brain (R.K. Lee et al., 1995). However, when Aβ are generated, it misfolds into β-sheet conformation in the brain and induces neurodegeneration in hippocampus and cortex. Among the several isoforms, Aβ40 and Aβ42 peptides are the most common constituents of the neurotoxic soluble oligomers (Kayed et al., 2003; Kuo et al., 1996; Roher et al., 1996) and insoluble fibrils (Blanchard et al., 1997; Shoji et al., 2000), which damage neuronal cells in AD brains. Even though Aβ40 is the most abundant isomer (90%), Aβ42 is the more fibrillogenic and toxic among all and highly related to the development of AD (Selkoe and Schenk, 2003). It was previously reported that a slight increase of Aβ42 in the brain induced symptoms of AD (Hartmann et al., 1997). In addition, Aβ42 is known to misfold into fibrils in a short period of time. Aβ40, on the other hand, is the most abundant specie with a significant role in the initiation of amyloidogenesis in AD brains (Bitan et al., 2003; Jan et al., 2008; Y. Kim et al., 2009). In addition, oxidative

stress and inflammatory damage have shown high correlation with Aβ deposition, stimulating neuronal cell death (J.A. Hardy and Higgins, 1992). Aβ40 and Aβ42 were reported to play critical roles in redox catalysis and formation of metal chelated clusters providing strong momentum to AD investigators (Balakrishnan et al., 1998; Butterfield and Kanski, 2002; S.T. Liu et al., 1999; Schoneich et al., 2003). Therefore, regulation of amyloidognesis is an excellent target for the protection of neurotoxic brain damage and holds promise in the precise understanding of the prevention or progression of AD. To this end, interpretation of the *in vivo* amyloidogenic mechanism is the key to the cure for AD.

### 2.2.2 Aβ misfolding cascade (monomer, oligomer, protofilbril, fibril)

According to previous researches on amyloidogenesis, there are three significant states of Aβ misfolding; monomers, soluble oligomers and insoluble fibrils. In addition, it was found that neurotoxic effects of Aβ are driven by misfolding (Blanchard et al., 1997; Kayed et al., 2003; Kuo et al., 1996; Roher et al., 1996; Shoji et al., 2000). Recent studies proved that soluble oligomers are commonly observed in human AD cerebrospinal fluid (Pitschke et al., 1998) and highly correlated with the severity of the disorder than insoluble fibrils (Kuo et al., 1996). In addition, APP metabolism pathway resulting in neutoxic Aβ oligomerization is observed to be related with oxidative stress and inflammatory damage in central nervous system (CNS) (Klein et al., 2004; Stine et al., 2003)Amyloidogenesis is a nucleation-dependent process and characterized by two phases; slow nucleation and fast extension phases (Jarrett and Lansbury, 1993; Lomakin et al., 1997; Naiki and Gejyo, 1999; Naiki and Nakakuki, 1996). Due to the pathological responsibility of soluble oligomers (J. Hardy and Selkoe, 2002), investigation of Aβ oligomers has become a critical target in AD research for the past three decades. However, oligomer study is challenging due to its instability and inaccessibility. Oligomers, particularly in solution, tend to quickly aggregate into larger species.

Although amyloidogenesis occurs favorably and solely within Aβ peptides, numbers of studies reported external inducers of amyloid aggregation such as metal, proteoglycan (PG) and tau. A wide variety of glycosaminoglycans (GAGs), expressed on the cell surface, are co-localized with Aβ aggregates in AD brain (Snow et al., 1994; Su et al., 1992; Wilhelmus et al., 2007). The electrostatic interactions of Aβ and GAG might result in facilitation of protein conformational changes that induce fibril formation, stabilization of the β-sheet amyloid structure, and inhibition of proteolysis (Fraser et al., 1992; McLaurin and Fraser, 2000). In addition, it was reported that the interactions between Aβ and GAGs were the result from the binding affinity of GAGs as potent accelerators or stabilizers of Aβ fibril formation (Castillo et al., 1999; McLaurin, Franklin, Kuhns, et al., 1999; McLaurin, Franklin, Zhang, et al., 1999; Verbeek et al., 1997). Particularly, highly sulfated GAGs such as heparin, heparan sulfate (HS), keratan sulfate (KS), and chondroitin sulfate (CS) are universally associated with diverse amyloidogenesis cascades, suggesting that they play a critical role in *in vivo* Aβ fibril formation (Brunden et al., 1993; Castillo et al., 1999; Kisilevsky et al., 2007; McLaurin, Franklin, Kuhns, et al., 1999; McLaurin, Franklin, Zhang, et al., 1999; Multhaup et al., 1995; Snow et al., 1995; Snow et al., 1994). Among them, HS and CS interact with the 13-16 Aβ residues (HHQK domain) that promote Aβ fibril formation and stabilize formed fibrils (Defelice and Ferreira, 2002; Motamedi-Shad et al., 2009). Thus, negatively charged sulfate moieties of GAGs are believed to bind to various forms of Aβ including preexisting fibrils

and to induce a conformational switch to β-sheet structures (Castillo et al., 1999). Therefore, GAG-induced amyloidogenesis derived from previous observations has been then confirmed by positive/negative effects to amyloidogenesis as low molecular weight (LMW) GAG derivatives and mimetics (Castillo et al., 1997; Miller et al., 1997; Santa-Maria et al., 2007; Wright, 2006).

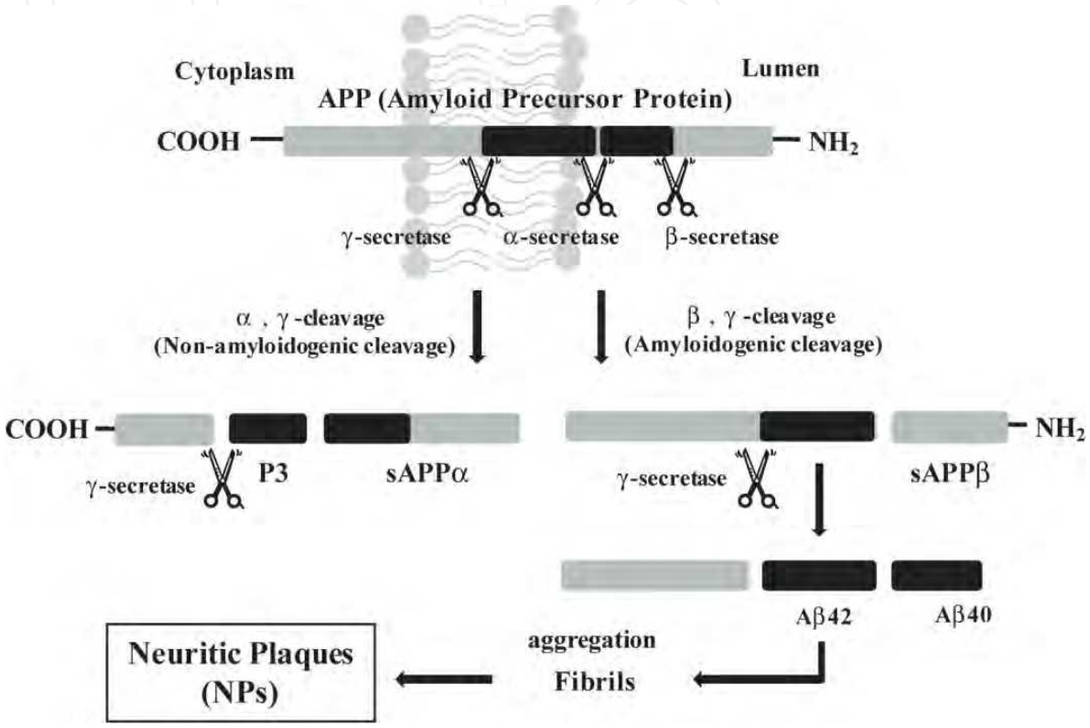



Fig. 1. APP processing and the generation of Aβ (taken from Y. Kim et al., 2009)

## 2.3 Taoupathy

### 2.3.1 Tau pathology in AD and tauopathies

Since Alois Alzheimer discovered the presence of abnormal fibrous inclusions within neurons in a patient's brain, the inclusions, called neurofibrillary tangles (NFTs) are considered one of the key requirements for making the pathological diagnosis of AD (Perl, 2010). The major component of neurofibrillary tangles is tau, which is a microtubule-associated protein that plays a important role in the development of neuronal polarity and neuronal processes (Mazanetz and Fischer, 2007). In normal adult brain, tau binds to microtubules, promoting microtubule assembly and facilitating axonal dynamics in a neuron (Brandt et al., 2005). When pathologically hyperphosphorylated, tau molecules are dissociated from microtubules and become insoluble fibrous tangles (Figure 3). NFTs are accumulated in neuronal perikarya or dystrophic neurites in axons and dendrites, causing degeneration of tangle-bearing neurons. The density of NFTs in a brain correlates fairly well with regional and global aspects of cognitive decline during the progression of AD (Binder et al., 2005).

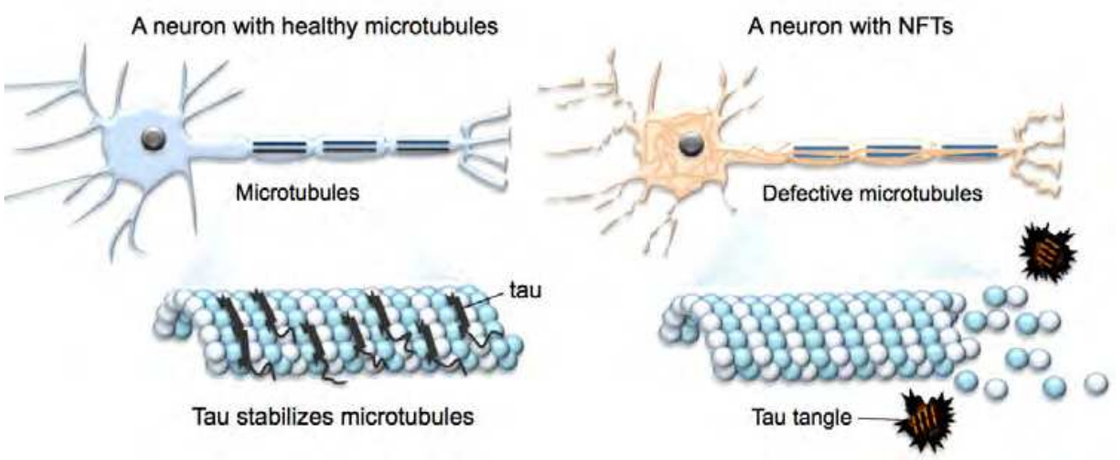



Fig. 2. The formation of NFTs and microtubule disruption (adapted from Brunden et al., 2009).

Tau and NFT pathology are not only specific for AD, but are part of the pathology in a number of neurodegenerative disorders, collectively called 'tauopahies'(Gendron and Petrucelli, 2009). In a number of tauopathies, the formation of NFTs is the primary cause of neurodegeneration (Iqbal et al., 2005). In AD pathology, however, the formation of NTFs in considered to be secondary events following Amyloidogenesis (Perl, 2010). Hence, both plaques and tangles are required to establish a definite diagnosis of AD. Regardless of whether NTFs occurs early or later in the disease pathology, it is clear that the formation of NFTs directly correlates with neurodegeneration. In this section, we will look for the genetic, biochemical and pathological mechanism of tau aggregation.

### 2.3.2 Neurofilamentary tangle (NFT) formation and neurotoxicity

NFTs are predominantly composed of paired helical filaments which appear to be made up of 10-nm filaments helically twisted each other (Perry et al., 1985). To aggregate into a paired helical filament, tau molecules undergo a series of abnormal modifications and conformational changes (Garcia-Sierra et al., 2003). Numerous studies have suggested that it is initiated by phosphorylation of tau molecules. Tau hyperphosphorylation induces a conformational shift of the molecule into a compact structure, called "Alz50 state"(Mandelkow et al., 1996). (Figure 4) In this state, a proline-rich region of a tau molecule contacts to microtubule binding region of the same molecule. In this state that tau first forms aggregates into filaments. The further filamentalization is accompanied or facilitated with proteolytic cleavages of tau (Binder et al., 2005). Many reports suggested that caspases, activated by amyloid plagues, cleave tau (Fasulo et al., 2000; Gamblin et al., 2003). The truncated tau molecule, named tau-66, assembles much faster and to a greater extent than its native form (Wischik, 1989).

The deposition of NFT is one of the most significant pathological signatures in AD and tauopathies; hence, there has been great effort to understand how the deposition of NFT cause neurodegeneration. NFT may damage neurons and glial cells in a number of ways (Gendron and Petrucelli, 2009). NFTs may be toxic to neurons by acting as physical barriers in the cytoplasm or NFT may also cause neuronal toxicity by reducing normal tau function

stabilizing microtubules. In addition, protein aggregates are not inert end-products but actively influence diverse cell metabolism, like proteasomal activity.

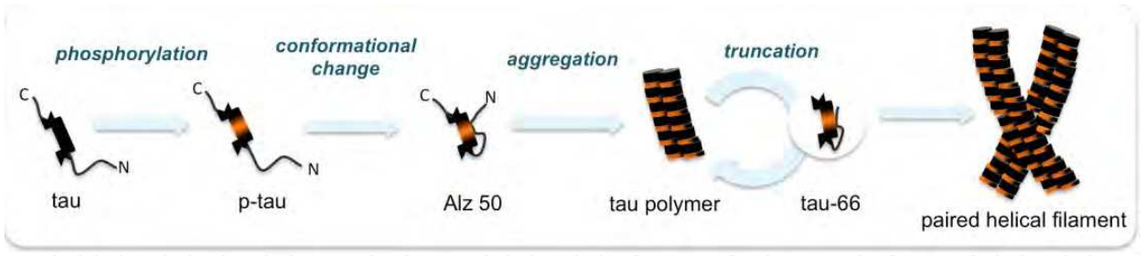



Fig. 3. Diagrammatic representation of tau conformation and NFT formation

Prior to or during NFT formation, tau undergoes numerous, and potentially harmful, modifications as shown in figure 4. The presence of these intermediates may play diverse roles in the onset and progression of disease prior to the development NFT-induced neurotoxicity. There are several mechanisms that suggest how non-fibril tau species could induce neuronal degeneration (Alonso et al., 1994). Especially hyperphosphorylated tau before NFT formation leads to microtubule disassembly, impairment of axonal transport, and organelle dysfunctions in neurons, leading to the neuronal cell apoptosis (Reddy, 2011).

### 2.3.3 Tau isoforms and mutations

The human tau gene is located on chromosome 17 and consisted of 16 exons. In an adult human brain, six isoforms of tau are produced from the single gene by alternative splicing (Iqbal et al., 2005). (Figure 5) The most striking feature of tau isoforms comes from the alternative splicing of exon 10. As the exon 9-12 encode tandem repeats that serve as microtubule binding domains, the alternative splicing of exon 10 generates tau isoforms containing three or four microtubule binding domains, respectively as Tau 3R or Tau 4R (Andreadis, 2005). In vitro studies have suggested that Tau 4R has greater affinity to microtubule and is more efficient at promoting microtubule assembly (Goedert and Jakes, 1990; Goedert et al., 1989). The splicing of tau mRNA is keenly controlled during development; tau 3R forms are predominantly expressed in a fetal brain, but the ratio of 3R and 4R tau transcripts becomes equal in adult brain. The disruption of this delicate balance is known to cause tauopathy (Kar et al., 2005). The expression levels of tau proteins in AD brains are approximately eight-fold higher than in age-matched controls, and this initiates hyperphosphorylation of tau, either polymerized into NFTs (Kopke et al., 1993).

Growing evidences also suggested that some of the missense mutations directly increase the tendency of tau to aggregate into NFTs (Nacharaju et al., 1999). There are two major types of mutations; coding mutations and intronic mutations (Hutton, 2000). Most coding mutations occur in exons 9-13 encoding microtubule binding regions, and produce tau proteins with a reduced ability in binding to microtubules (Hasegawa et al., 1998). In addition, intronic mutations that affect the splicing of exon 10, increase the proportion of 4R tau transcripts (Dayanandan et al., 1999; Hong et al., 1998; Hutton et al., 1998). As a result of the mutation, the ratio of 4R over 3R tau isoforms increases about two folds and it induces neurodegeneration (Hutton et al., 1998).

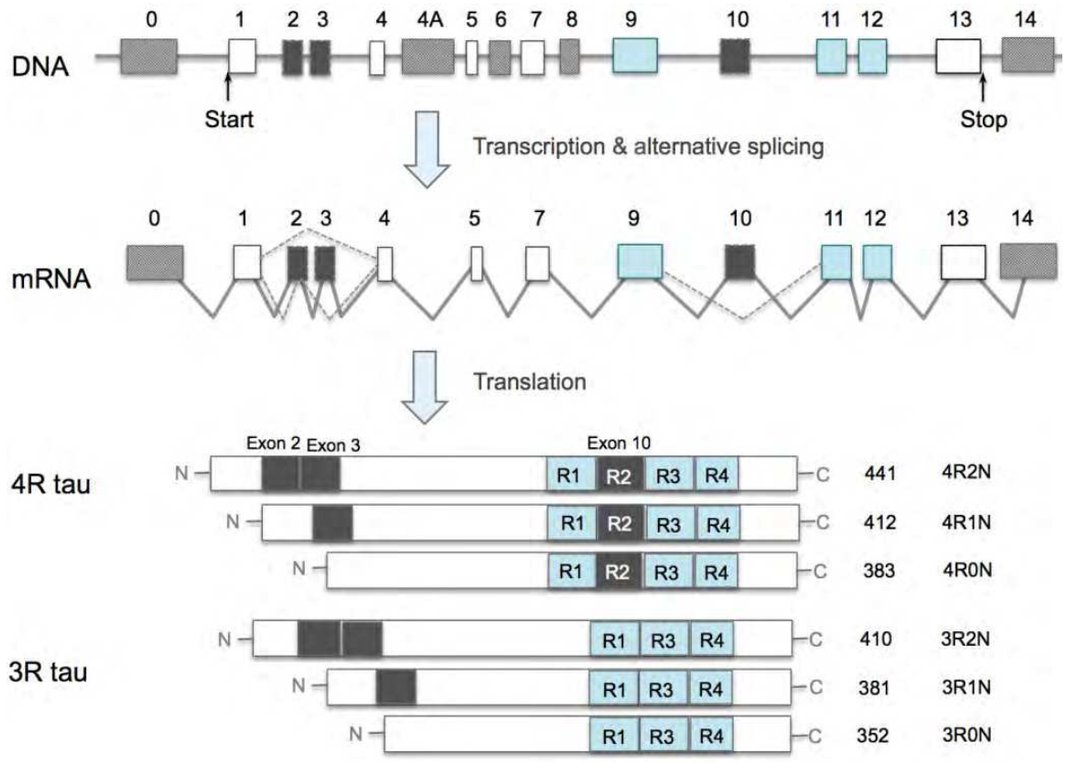



Fig. 4. Illustration represents human tau gene, mRNA, and six isoforms (adapted from Gendron and Petrucelli, 2009).

### 2.3.4 Tau hyperphosphorylation

In addition to isoform variation, phosphorylation of tau is an important factor in microtubule-binding of tau. Tau isolated from adult brain, is partially phosphorylated with an average of about 2 moles of phosphate per mole of protein, and this promotes association with tubulin, which leads to stabilization of microtubules and facilitates axonal transport (Drechsel et al., 1992; Mazanetz and Fischer, 2007). In contrast, tau isolated from the AD patient's brain (mostly NFTs) contains 6 to 8 moles of phosphate per mole of protein (Mazanetz and Fischer, 2007). The hyperphosphorylation changes tau conformation (Buee-Scherrer et al., 1995) leading to decrease in the microtubule-binding affinity (Braak and Braak, 1987).

The longest form of tau isoforms contains 79 serine or threonine residues and 5 tyrosine residues. Among these, about 30 residues are known as actual phosphorylation sites under normal physiological conditions. Of the sites that are phosphorylated in tau, 13 sites are followed by proline residues. Therefore proline-directed kinases such as GSK3β (glycogen synthase kinase 3β), CDK5 (cyclin-dependent kinase 5) and ERK2 (extracellular signal-regulated kinase 2) have received the most attention as the responsible kinases of tau (Dhavan and Tsai, 2001; Perry et al., 1999; Shelton and Johnson, 2004; Spittaels et al., 2000). In addition, non-proline-directed kinases such as microtubule affinity-regulating kinase (MARK) (Ferrer et al., 2001; Sawamura et al., 2001), and tyrosine kinases such as FYN have also been suggested to be relevant to neurodegeneration (Chin et al., 2005; G. Lee et al., 2004).

Evidences have showed that CDK5 colocalized with NFTs and its elevated activity was observed in AD brains (K.Y. Lee et al., 1999). Moreover, the association of CDK5 with pre-tangles (Augustinack et al., 2002; Tseng et al., 2002) suggested that CDK5 might be involved in the early stage of NFT formation during AD progression. GSK3β highly expressed in the brain is associated with a variety of neurodegenerative disease including AD (Bhat et al., 2004). In AD, GSK3β contributes in the generation β-amyloid and the phosphorylation of tau proteins to form NFTs. The inhibition of GSK3β efficiently reduces tau phosphorylation (Hong et al., 1997; Munoz-Montano et al., 1997). ERK2 is known to regulate microtubule-assembly of tau as tau-phosphorylation by ERK2 significantly decreases the affinity of tau to microtubules. These kinases are potential target candidates for tauopathy drug discovery.

### 2.4 Diagnosis of AD

Current clinical test of AD is mostly conducted via non-histochemical approaches like mini-mental state exam (MMSE), which are often difficult, unreliable and unfeasible as a diagnosis tool. Therefore, growing unmet needs on early detection of the disorder highlight development of simple and reliable diagnostic tools and robust biological markers. Accordingly, visualizing pathological hallmarks of AD such as SPs and NFTs in living brain is on focus. Among a wide variety of brain imaging technologies, radiolabeled imaging probes for single photon emission computed tomography (SPECT) or positron emission tomography (PET) are mainly studied for AD diagnosis due to numeral advantages; real time targeted molecular imaging with very low concentration of imaging probes and possible quantification of target molecule (Klunk et al., 1994; Skovronsky et al., 2000). Therefore, development of Aβ and phosphorylated tau binding probes for targeted molecular imaging in AD brains is urgently desired for early diagnosis and monitoring of AD progression (Fig (2)). Particularly, a probe soluble Aβ oligomer is extremely promising since oligomers are find in brains years earlier than actual AD symptoms start to occur. [$^{11}$C]PIB (Pittsburgh Compound-B, [$^{11}$C]6-OH-BTA-1) and [$^{18}$F]FDDNP (2-(1-(6-((2-[$^{18}$F]fluoroethyl)(methyl)amino)-2-naphthyl)ethylidene)malononitrile) which bind to Aβ fibrils in brain are presently available in vivo for early diagnosis of AD (Agdeppa et al., 2003; Klunk et al., 2004; Mathis et al., 2002). While [$^{11}$C]PIB is very specific to Aβ with short half life, [$^{18}$F]FDDNP can bind to both SP and NFT with approximate half life of two hours. Lately pharmaceutical companies and FDA search for molecular imaging probes which can visualize both SP and NFT, because each hallmarks is also found in other types of brain disease as described above. Amyvid™ ([$^{18}$F]AV-45), unable to bind to tau protein and recently refused by FDA, was useful in ruling out the presence of pathologically significant levels of Aβ in the brain, but insufficient to determine AD patients.

### 2.5 Therapeutic strategies of AD

At present, there is no commercially available cure for AD patients. NMDA antagonist, memantine, and acetylcholinesterase (AChE) inhibitors, Aricept, are the only available treatments in the market for AD, even though they can only decelerate the progression of the disease and provide temporal cognitive enhancement. Thus, regulation of Aβ cascade is pursued by researchers to prevent neurodegenerative progression of AD (J. Hardy and Selkoe, 2002). Among several anti-amyloidogenesis strategies, β- and γ-secretase inhibitors, Aβ protease regulators, Aβ aggregation inhibitors, metal chelators, RAGE inhibitors and

immunotherapy are promising therapeutic targets (D.S. Choi et al., 2006; Hamaguchi et al., 2006; Schenk et al., 1999). There are several drug candidates in development such as small molecule Aβ aggregation inhibitors, copper-zinc chelators and Aβ specific antibodies.

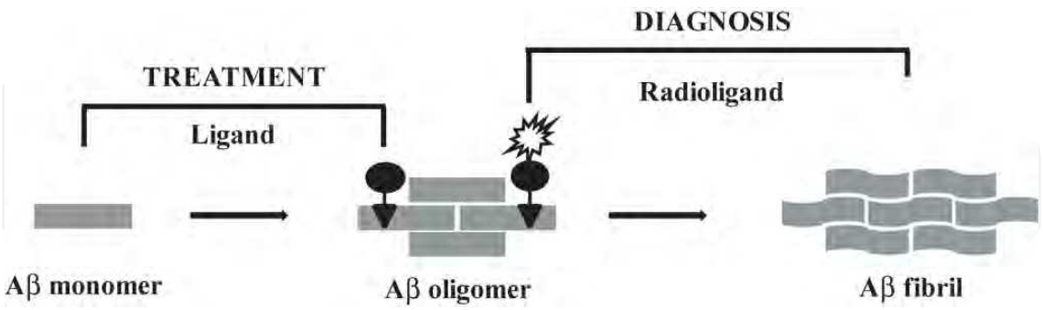



Fig. 5. Targets for amyloid treatment and diagnosis (taken from Y. Kim et al., 2009)

### 2.5.1 Anti-amyloidogenesis

For last two decades, AD drug discovery has targeted amyloidogenesis and there have been various types of drug candidates such as small molecules, peptides, natural products and antibodies. Monomeric Aβ has been considered as the precursor to neurotoxic species such as soluble oligomers and insoluble protofibrils (Barrow and Zagorski, 1991; Lazo et al., 2005; Xu et al., 2005) and induced R&D of aggregation inhibitors to prevent amyloidogenesis and to reduce neurotoxicity. Toxic oligomers and protofibrils are interesting targets for anti-inflammatory research (Finder and Glockshuber, 2007). Aβ oligomer of molecular weight 56 kDa (Aβ*56) is one of the well-known neurotoxic species (Reed et al., 2009).

Tramiprosate (Alzhemed), 3-amino-1-propanesulfonic acid, was a small molecule targeting Aβ aggregation (Gervais et al., 2007), which was unfortunately dropped in clinical trial III. It was reported to bind to soluble Aβ and to maintain the peptide in a α-helical rich conformation to inhibit Aβ deposition. It was also claimed that it might interrupt GAG from stabilizing amyloidogenesis. Tramiprosate decreased Aβ-induced neuronal cell death and crossed the BBB. An AD transgenic mouse model study resulted in significant reduction of Aβ fibrils and decrease in the levels of soluble and insoluble Aβ in the brain (Sullivan, 2007). A type of NSAIDs, Flurizan ((*R*)-flurbiprofen) (Black, 2007), by Myriad Genetics was also dropped in clinical study as an Aβ lowering drug candidate. The immunotherapeutic approach is based on the function of antibodies binding to Aβ or lowering Aβ aggregates in AD brains. Clinical trial of AN-1792 (Patton et al., 2006), a drug candidate to induce an immune response against Aβ, was stopped after severe symptoms of aseptic meningoencephalitis. Bapineuzumab (AAB-001) (Melnikova, 2007), a humanized monoclonal antibody against Aβ, is currently in final stage of clinical trial.

### 2.5.2 RAGE inhibitors

The receptor for advanced glycation end products (RAGE) is an influx transporter of Aβ monomer across the blood-brain barrier (BBB) into the brain from plasma, while the low-density lipoprotein receptor-related protein (LRP-1) regulates efflux of Aβ out of the brain. Given the critical role of RAGE in AD development, RAGE is considered as a potent target

for AD therapy. RAGE inhibitors have a significant advantage in R&D because they do not have to cross BBB even though their role is to treat a brain disease. Pfizer's PF-04494700 (TTP488) was the most advanced inhibitor of RAGE activation in clinical trial until the company discontinued its development at the end of 2011.

### 2.5.3 Secretase modulators

Preventing proteolysis of APP from Aβ release has been a promising therapeutic target. β-Secretase cleaves extracellular domain of APP to form a cell membrane-bound fragment, C99, of which transmembrane domain is then sequentially cleaved by γ-secretase to produce Aβ. The physiological function of β-secretase cleavage of APP is unknown. Numbers of secretase inhibitors have been developed and entered clinical trials by many global drug industries, but none of them received FDA approval yet.

### 2.5.4 Mitochondria dysfunction

Rediscovery of an anti-histamine drug, Dimebon (3,6-dimethyl-9-(2-methyl-pyridyl-5)-ethyl-1,2,3,4-tetrahydro-γ-carboline dihydrochloride), as an Alzheimer effective drug triggered high interests in mitochondria-mediated apoptosis in AD brain. Mitochondrial permeability transition pore (mPTP) is consisted of three major components, adenine nucleotide translocase (ANT), cyclophilin D (CypD) and the voltage-dependent anion channel (VDAC). Recent studies revealed direct interaction between Aβ and CypD and suggested mPTP opening as a promising therapeutic target for AD. Because mPTP regulates apoptosis in many cells, it is a common drug target for a wide variety of disorders.

### 2.5.5 Neurotransmitters

In AD brains, cholinergic neurons and neurotransmitters such as acetylcholine (ACh) are significantly reduced (Bartus et al., 1982; Bowen et al., 1992; Davies and Maloney, 1976). Thus, enhancement of central cholinergic neurotransmission has been a therapeutic strategy (Bartus et al., 1982; Camps and Muñoz-Torrero, 2002). Currently available major drugs to treat AD are AChE inhibitors, such as tacrine (Cognex) (Knapp et al., 1994), rivastigmine (Exelon) (Jann, 2000), donepezil (Aricept) (Rogers et al., 1998) and galantamine (Reminyl) (Wilcock et al., 2000) and used for mild to moderate AD. However, the AChEI approach is only for temporal symptomatic improvements of cognition (Ibach and Haen, 2004).

### 2.5.6 Anti-oxidants and metal chelators

Studies on neurotoxic Aβ aggregates suggested that excess generation of radical oxygen species (ROS) can be led by amyloidogenesis and induce neuronal cell death (Butterfield et al., 2001; Frank and Gupta, 2005; Tabner et al., 2001). The ROS hypothesis is supported by numbers of clinical evidences in AD brains such as increased level of neurotoxic trace elements (Fe, Al, and Hg), lipid peroxidation, protein oxidation, DNA oxidation, and decreased energy metabolism/cytochrome c oxidation (Markesbery, 1997). Thus, anti-oxidant protection strategy to reduce neuronal oxidative injuries can contribute to attenuate neurodegeneration (Behl, 1999). It was revealed that formation of oxygen free radicals needs

to be potentiated by $Fe^{II}$, $Cu^{II}$, and $Zn^{II}$ (Behl et al., 1994; Bush et al., 2003; Butterfield et al., 2001; Doraiswamy and Finefrock, 2004; Gaggelli et al., 2006; Smith et al., 1997). Studies on metal chelators showed chemical interference of ROS formation and neuronal cell protection from Aβ-induced neurotoxicity. It was found anti-oxidants inhibited amyloidogenesis both *in vitro* and *in vivo* (Ono et al., 2006).

### 2.5.7 Anti-inflammation

Neuro-inflammation has been recognized as one of the most critical factors in many neurodegenerative diseases (Halliday et al., 2000; McGeer and McGeer, 1999). Inflammatory activity is often found co-localized with Aβ fibrils in AD patients and such correlation suggested non-steroidal anti-inflammatory drugs (NSAIDs) to treat AD (Bullock, 2002; Hull et al., 1999). Significantly declined risk of AD development in rheumatoid arthritis patients administered NSAIDs brought attentions of AD researchers on anti-inflammation via inhibition of COX-1 and COX-2 pathways (McGeer et al., 1996; Pasinetti, 2001; Stewart et al., 1997)(X. Liang et al., 2005).

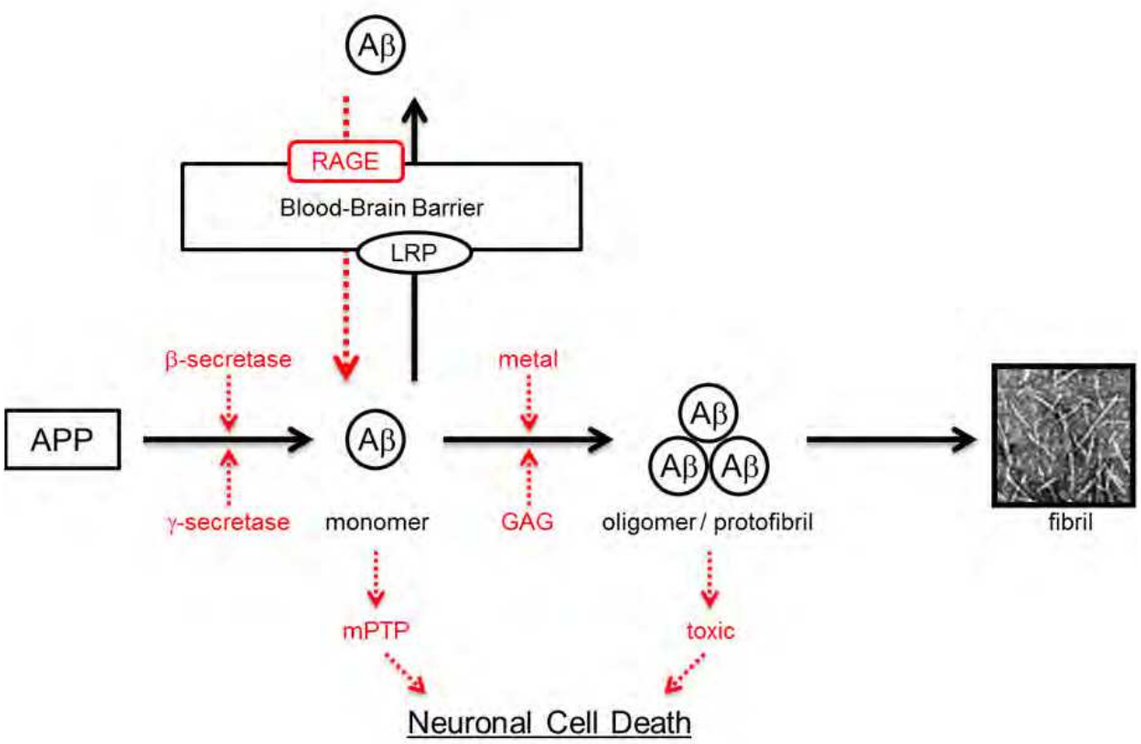



Fig. 6. Drug targets in amyloid cascade

### 2.5.8 Anti-tau phosphrylation

Prevention of tau pathology has begun to emerge as a feasible approach to prevent neurodegeneration, although efforts in this area lag behind the anti-amyloid research. The current tau-oriented therapies are focused on preventing tau phosphorylation. Recent data have implicated both GSK3β and CDK5 in aberrant tau phosphorylation and association

with microtubules (Spittaels et al., 2000), and growing evidences also suggest that ERK2 is one of the key regulators of neurofilamentary degeneration (Perry et al., 1999). Currently, these three kinases, GSK3β, CDK5, and ERK2, are the major drug targets for tau-oriented therapeutics.

## 3. Parkinson's disease (PD)

PD is the second most common neurodegenerative disease, accompanied by extrapyramidal motor dysfunction. It is a progressive disease, and the prevalence increases with age, affecting 1 % of people over 60 years of age, 3.4 % of those over 70, and 4% of those over 80 (de Lau and Breteler, 2006; Olanow et al., 2009). The primary symptoms of PD include resting tremor, bradykinesia, rigidity and postural stability, and as the disease progresses, other symptoms such as depression, dementia, sleep abnormalities and autonomic failure also become evident (Chaudhuri and Schapira, 2009).

Because the primary symptoms of PD are related to the deficiency in the neurotransmitter DA, the current treatment of PD involves administration of drugs that will facilitate DAergic neurotransmission. This includes the DA precursor L-3,4-dihydroxyphenylalanine (L-DOPA), monoamine oxidase inhibitors, and DA receptor agonists. Deep brain stimulation following surgical manipulation is also being utilized in patients with severe motor fluctuations. None of the currently available therapies, however, can delay the degeneration itself, and chronic treatment with L-DOPA often causes motor and psychiatric side effects (Fahn, 1989). Currently, ways to modify the disease course by neuroprotection are actively being sought for.

### 3.1 Pathology

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 DA, and their projecting nerve fibers reside in the striatum. Two pathological hallmarks of the postmortem brains of PD patients are the presence of proteinacious inclusion bodies called Lewy bodies and the presence of a reactive microgliosis in the affected areas.

While the majority of PD cases are sporadic (90–95%), rare familial forms involving mutations in a number of genes have been described. Although the familial forms represent only a small fraction of PD cases, the mechanism by which mutation of these genes lead to degeneration of DAergic neurons have shed light to understanding of the pathophysiology of PD. Gene multiplication or missense mutations in the α-synuclein gene have been linked to PD (Farrer, 2006). In two genome-wide association studies, the α-synuclein gene locus has been identified as a major risk factor for PD (Satake et al., 2009; Simon-Sanchez et al., 2009). Aggregated α-synuclein is a major constituent of the Lew bodies (Spillantini et al., 1998). Gene knockout of α-synuclein gene renders mice resistant to a DAergic cytotoxin (Dauer et al., 2002). Mutations of the parkin or PINK1 genes are causes of autosomal recessive PD. Their gene products are mitochondrial proteins, and mutations in the respective genes lead to mitochondrial defects, free radical formation, and consequently cell demise (Gandhi et al., 2009; Gegg et al., 2009; Grunewald et al., 2009). Mutations in the LRRK2 gene represent the most common cause among the familial cases of PD. The LRRK2 gene product is a large multidomain protein with a kinase domain (Paisan-Ruiz et al., 2004; Zimprich et al., 2004).

Mutations in the DJ- 1 gene are associated with an early onset autosomal recessive PD.(Bonifati et al., 2003) The loss of DJ-1 renders the cells vulnerable to oxidative stress, whereas overexpression of DJ-1 provides protection, suggesting the DJ-1 may be an antioxidant protein. Indeed, DJ-1 has been shown to have an atypical peroxiredoxin-peroxidase activity (Andres-Mateos et al., 2007). High temperature requirement A2 (HtrA2/Omi) is a serine protease that is present predominantly in the intermembrane space of mitochondria, where it is thought to be involved in protein quality control, and its heterozygous missense mutations have been found in sporadic cases of PD (Strauss et al., 2005).

As the majority of PD cases are sporadic, environmental factors play a critical role in the etiology of PD. Occupational uses of herbicides or pesticides increase the risk of PD (Barbeau et al., 1987; Kamel et al., 2007; Semchuk et al., 1992; Tanner et al., 2009). In animals, the pesticide rotenone and the broad-spectrum herbicide paraquat reproduce the PD phenotype in animals (Betarbet et al., 2000; Przedborski et al., 2004). In addition, exposure to organic solvents, carbon monoxide, and carbon disulfide (Corrigan et al., 1998) are thought to play roles, and more generally, industrialization, rural environment, well water, plant-derived toxins, and bacterial and viral infection (Schapira and Jenner, 2011). Interestingly, caffeine intake and cigarette smoking reduce the risk of PD, although the mechanism is not understood (Ascherio et al., 2001; Warner and Schapira, 2003). Aging is an obvious factor associated with the onset of PD, and it is generally speculated that failure of normal cellular processes that occurs with aging causes increased vulnerability of DAergic neurons (Obeso et al., 2010).

### 3.2 Oxidative stress

Oxidative stress occurs when an imbalance is formed between production of reactive oxygen species (ROS) and cellular antioxidant activity. Oxidative stress is thought to be the underlying mechanism that leads to cellular dysfunction and demise in PD (Andersen, 2004; Jenner, 2003). The substantia nigra of PD patients exhibit increased levels of oxidized lipids (Bosco et al., 2006), proteins and DNA (Nakabeppu et al., 2007) and decreased levels of reduced glutathione (GSH) (Zeevalk et al., 2008). Because of the presence of ROS-generating enzymes such as tyrosine hydroxylase, monoamine oxidase and tyrosinase, 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 create further oxidative stress (Halliwell, 1992). 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 inflammation, as discussed below in more detail.

Oxidative stress is generated from DA metabolism, mitochondrial dysfunction and microglial activation. Mitochondrial dysfunction can occur as a result of environmental factors such as dopaminergic toxins, as well as mutation of genes whose gene products are important for mitochondrial function, such as Parkin, PINK1, DJ-1, and HtrA2. Mitochondrial dysfunction leads to accumulation of ROS and release of cytochrome c and HtrA2, both of which lead to apoptosis.

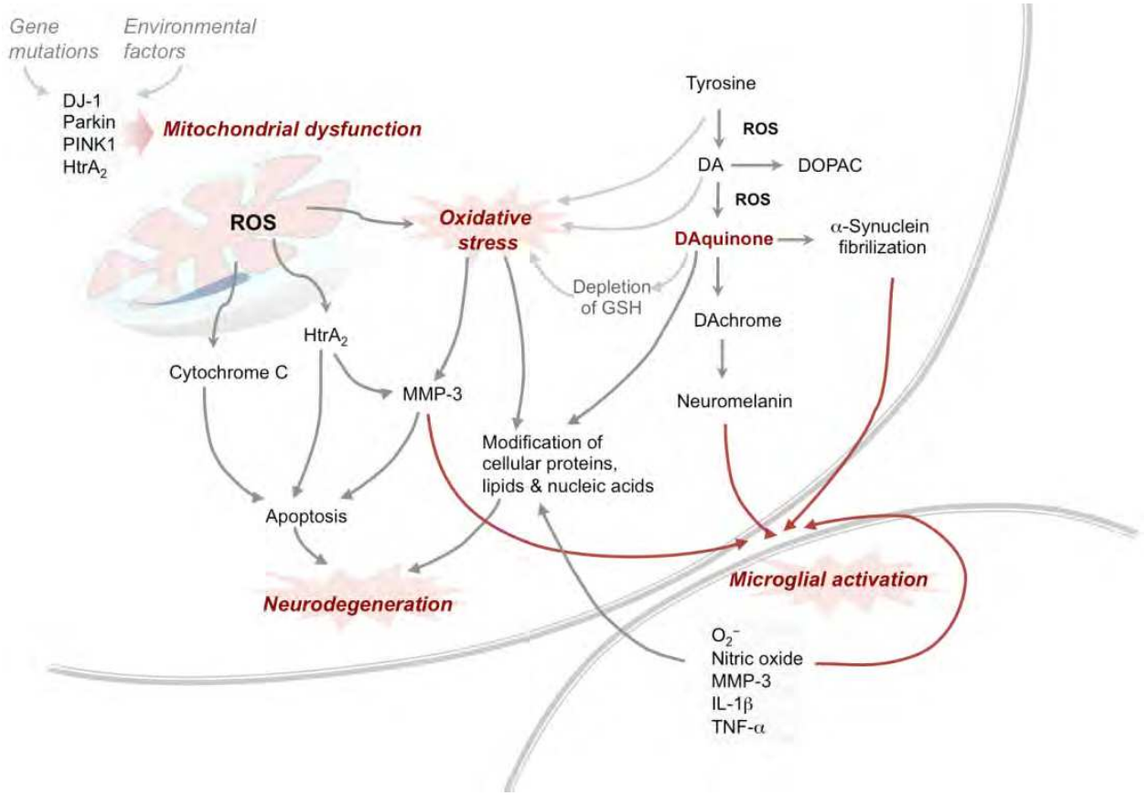



Fig. 7. Molecular cascades of DAergic neurodegeneration in the pathophysiology of PD.

### 3.3 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 a major factor contributing to the vulnerability of DAergic cells (Asanuma et al., 2003; H.J. Choi et al., 2003; Hastings and Zigmond, 1997). Although DA is normally stored in vesicles, excess cytosolic DA is easily oxidized both spontaneously (Hastings and Zigmond, 1997) and enzymatically (Maker et al., 1981) 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 (Graham, 1978), 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 ubiquitin C-terminal hydrolase L1 (UCH-L1). DA quinone covalently modifies α-synuclein monomer (Dunnett and Bjorklund, 1999) and promotes the conversion of α-synuclein to the cytotoxic protofibril form (Conway et al., 2001). The DA quinone-modified α-synuclein is not only poorly degraded but also inhibits the normal degradation of other proteins by chaperone-mediated autophagy (Martinez-Vicente et al., 2008). Conversely, α-synuclein can bind to and permeabilize the vesicle membrane, causing leakage of DA into the cytosol (Lotharius and Brundin, 2002). Parkin is also covalently modified by DA and becomes insoluble, which leads to inactivation of its E2 ubiquitin ligase activity (LaVoie et al., 2005). Catechol-mofieid

parkin has been detected in the substantia nigra but not other regions of human brain, and parkin insolubility is observed in PD brain (LaVoie et al., 2005). In addition, DA quinone modification of UCH-L1, the enzyme whose gene mutation leads to autosomal dominant PD, and DJ-1 have also been observed both in brain mitochondrial preparations and DAergic cells (Van Laar et al., 2009). Since both UCH-L1 and DJ-1 contain a cysteine residue that is important for their activity (Nishikawa et al., 2003; Qu et al., 2009) and their oxidative modification at cysteine has been observed in PD(J. Choi et al., 2004; J. Choi et al., 2006), 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 hydroxylase (Kuhn et al., 1999). In addition, it leads to mitochondrial dysfunction (C.S. Lee et al., 2002) and swelling of brain mitochondria (Berman and Hastings, 1999). Accordingly, the subunits of Complex I and Complex III of the electron transport chain in the mitochondria, whose dysfunction can affect mitochondrial respiration and ROS production, were also shown to be targets of DA quinone modification (Van Laar et al., 2009). In addition, ER-60/GRP58/ERp57 and protein disulfide isomerase-5, the proteins involved in protein folding in the endoplasmic reticulum, are also modified by DA quinone (Van Laar et al., 2009).

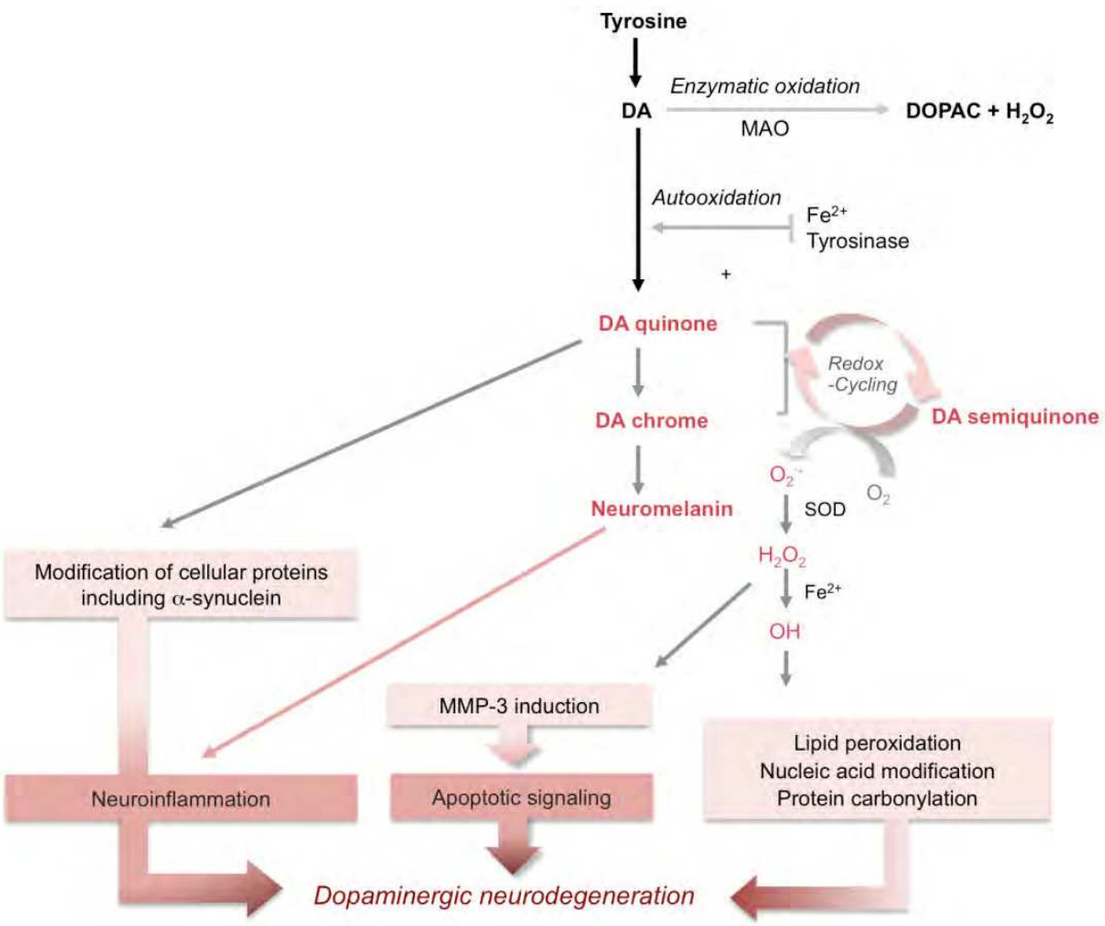



Fig. 8. Dopaminergic neurodegeneration.

In addition, when in excess, DA quinone cyclizes to become the highly reactive aminochrome, whose redox-cycling leads to generation of superoxide and depletion of cellular NADPH and ultimately polymerize to form neuromelanin (Jenner and Olanow, 1996). Neuromelanin in turn can exacerbate the neurodegenerative process by triggering neuroinflammation (Zecca et al., 2008), as described below. Furthermore, hydrogen peroxide is generated during DA metabolism by monoamine oxidase (Maker et al., 1981) and is subsequently converted to the highly reactive hydroxyl radical in the presence of transition metal ions (Halliwell, 1992), which also contributes to oxidative stress. DA metabolites have been shown to induce proteosomal inhibition, which can lead the cells to undergo apoptosis (Zafar et al., 2007; Zafar, Inayat-Hussain, et al., 2006).

A line of evidence points to the existence of in vivo DA oxidation and its toxicity in human brain. Neuromelanin, the final product of DA oxidation, is accumulated in the nigral region (Zecca et al., 2003). 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 (Spencer et al., 1998). 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 (Rabinovic et al., 2000). Mice expressing a low level of ventricular monoamine transporter-2, presumably with increased cytosolic DA level, showed evidence of DA oxidation and the age-dependent loss of nigral DA neurons (Caudle et al., 2008). In addition, accumulation of cytosolic DA induced via expression of DA transporter rendered the striatal GABA neurons vulnerable (Chen et al., 2008).

DA is either enzymatically or spontaneously converted to the highly reactive DA quinone, which depletes cellular GSH, modifies cellular proteins at their sulfhydryl groups, and induces fibrilization of α-synuclein.

### 3.4 Mitochondrial dysfunction

Mitochondrial dysfunction and the resulting oxidative stress are associated with the pathogenesis of PD (Schapira and Gegg, 2011). Oxidative stress causes peroxidation of the mitochondria-specific lipid cardiolipin, which results in release of cytochrome c to the cytosol, triggering the apoptotic pathway. Neurons heavily depend 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.

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 Complex I in the electron transport chain is thought to be especially critical. The mitochondrial 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 (Betarbet et al., 2002). Reduced Complex I activity has been found in tissues from subjects with PD (Benecke et al., 1993; Mizuno et al., 1989; Parker et al., 1989). Higher numbers of respiratory chain deficient DA neurons have been found in PD patients than in age-matched controls (Bender et al., 2006). Furthermore, mitochondrial density in the somatodendritic region of nigral neurons has been observed to be abnormally low (C.L. Liang et al., 2007).

Perhaps the strongest evidence for mitochondrial dysfunction in PD pathophysiology comes from the findings that mutations in genes of mitochondrial proteins Parkin, DJ-1, HtrA2/Omi, and PINK have all been linked to familial forms of PD. The Parkin protein is an E3 ligase (Y. Zhang et al., 2000) and is associated with the mitochondrial outer membrane (Darios et al., 2003). Cells derived from patients with Parkin gene mutation show decreased Complex I activity and ATP production (Grunewald et al., 2010; Mortiboys et al., 2008; Muftuoglu et al., 2004). Mice deficient in Parkin gene have show reduced striatal respiratory chain activity along with oxidative damage (Palacino et al., 2004). Drosophila with functional deletions of parkin has fragmented mitochondria (Greene et al., 2003).

PINK1 protein is a kinase that has been observed to be located in the mitochondria. Mutations in PINK1 induce mitochondrial dysfunction including reduced mitochondrial DNA, a deficiency of ATP, excess free radical formation and abnormal calcium handling (Gandhi et al., 2009; Gegg et al., 2009; Grunewald et al., 2009). Drosophila with functional deletions of PINK1 has fragmented mitochondria (I.E. Clark et al., 2006; Park et al., 2006).

DJ-1 is a mitochondrially enriched, redox-sensitive protein and an atypical peroxiredoxin-like peroxidase that scavenges H2O2 (Andres-Mateos et al., 2007; Canet-Aviles et al., 2004), and DJ-1 KO mice accumulate more ROS and exhibit fragmented mitochondrial phenotype (Andres-Mateos et al., 2007; Irrcher et al., 2010). Interestingly, this aberrant mitochondrial morphology could be rescued by the expression of PINK1 and parkin (Irrcher et al., 2010).

HtrA2/Omi is a mitochondrially located serine protease and has been associated with PD. HtrA2/Omi seems to promote survival under physiological conditions by maintaining homeostasis and serving as a protein quality control factor, and loss of its activity results in accumulation of unfolded mitochondrial proteins (Jones et al., 2003; Krick et al., 2008; Martins et al., 2004; Moisoi et al., 2009).

In addition, α-synuclein, although mostly cytosolic, seems to interact with mitochondrial membranes (Nakamura et al., 2008) and to inhibit complex I (Devi et al., 2008; G. Liu et al., 2009). Mice overexpressing mutant α-synuclein exhibit abnormalities in the mitochondrial structure and function (Martin et al., 2006). α-Synuclein has also been shown to inhibit mitochondrial fusion, and interestingly, this was rescued by PINK1, Parkin, and DJ-1 (Kamp et al., 2010), again suggesting the existence of a functional relationship among the products of these PD-related genes.

### 3.5 Neuroinflammation

Neuronal loss in PD is associated with chronic inflammation, 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 (Banati et al., 1998; Gerhard et al., 2006; Knott et al., 2000; McGeer et al., 1988) as well as familial PD patients (T. Yamada, 1993) and in the SN and/or striatum of PD animal models elicited by MPTP (Cicchetti et al., 2002; Francis et al., 1995; Kurkowska-Jastrzebska et al., 1999; T. Yamada, 1993).

Microglia are activated in response to injury or toxic insult as a self-defensive mechanism to remove cell debris and pathogens. When activated, microglia release free radicals such as nitric oxide and superoxide, as well as proinflammatory cytokines including IL-1β and TNF-

α, and proteases. Overactivated and/or chronically activated state of microglia causes excessive and uncontrolled neuroinflammatory responses, leading to self-perpetuating vicious cycle of neurodegeneration (Qian et al., 2010). This is thought to be exacerbated by inflammatory signals from molecules released from damaged neurons, leading to induction of reactive microgliosis (Qian et al., 2010). Molecules that are released from damaged nigral DAergic neurons and induce microglial activation include neuromelanin, α-synuclein, and active form of MMP-3, as described below.

Neuromelanin is the dark insoluble polymer made from DAchrome and confers the dark pigmentation to the substantia nigra. Insoluble extraneuronal neuromelanin granules have been observed in patients of juvenile PD (Ishikawa and Takahashi, 1998) and idiopathic PD, as well as those with MPTP-induced parkinsonism (Langston et al., 1999). Addition of neuromelanin extracted from PD brain to microglia culture caused increases in proinflammatory cytokines and nitric oxide (Wilms et al., 2003). Intracerebral injection of neuromelanin caused strong microglia activation and a loss of DAergic neurons in the substantia nigra (Zecca et al., 2008). Together with the finding that neuromelanin remains for a very long time in the extracellular space (Langston et al., 1999), neuromelanin has been proposed to be one of the molecules that are released from the nigral DAergic neurons and induce chronic neuroinflammation in PD.

Cytoplasmic accumulation of fibrillar α-synuclein in Lewy bodies (Spillantini et al., 1997) is thought to be related to pathophysiology of PD. Although mostly intracellular, a fraction of this protein is released from neurons (H.J. Lee et al., 2005), and α-synuclein is found in the cerebrospinal fluid from PD patients and normal subjects (Borghi et al., 2000), and in human plasma (El-Agnaf et al., 2003). That the released α-synuclein participates in neuroinflammation was demonstrated by the finding that the addition of aggregated human α-synuclein to a primary mesencephalic neuron-glia culture caused activation of microglia and DAergic neurodegeneration and that this cytotoxicity did not occur in the absence of microglia (W. Zhang et al., 2005). In addition, neuron-derived α-synuclein stimulates astrocytes to produce inflammatory modulators that augment microglial chemotaxis, activation and proliferation. (Farina et al., 2007) Nitration of α-synuclein, presumably due to increased nitric oxide, facilitates the neuroinflammatory responses (Benner et al., 2008; Gao et al., 2008). 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 (Gao et al., 2011).

The active form of MMP-3 is released from apoptotic DAergic cells, and the MMP-3 activity causes microglial activation as evidenced by increased production of superoxide, TNF-α, and IL-1β (Y.S. Kim et al., 2005). In addition, the MMP-3 activity is increased in DAergic neurons in response to cell stress and triggers apoptotic signaling (D.H. Choi et al., 2008; E.M. Kim and Hwang, 2011; E.M. Kim et al., 2010). 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 (Y.S. Kim et al., 2007). A recent study has demonstrated that MMP-3 causes cleavage of protease activated receptor-1 (PAR-1) (E.J. Lee et al., 2010), whose removal of N-terminal extracellular domain renders the remaining domain acting as a tethered ligand, subsequently triggering generation of intracellular signals (Vu et al., 1991) and activation of microglia (Suo et al., 2002).

Furthermore, the proform of IL-1β is cleaved by MMP-3 to yield the biologically active IL-1β (Schonbeck et al., 1998). In addition, MMP-3 expression is induced in activated microglial cells (Woo et al., 2008), and conversely, MMP-3 is induced by cytokines and free radicals in microglial cells (Jian Liu and Rosenberg, 2005). Therefore, a vicious cycle may exist, where MMP-3 released from DAergic neurons leads to production of cytokines and free radicals, and this in turn causes a further production of microglial MMP-3 and subsequent release. MMP-3 can also cause degradation of blood brain barrier and infiltration of neutrophils, which can further contribute to neuroinflammation (Gasche et al., 2001; Gurney et al., 2006).

### 3.6 Therapeutic strategies of PD

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 against which neuroprotective/disease-modifying therapy may be developed is the crucial issue in the field of PD research.

Because the clinical symptoms of PD does not manifest until more than 70% of the nigral DA neurons have degenerated (Marek K, 2009), ways to delay the degenerative progression in the presymptomatic, early stage of degeneration will prove to be highly beneficial. Early detection of PD is now available with the advances in brain imaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Biomarkers that can be used for early diagnosis of PD as well as following disease progression are being actively sought for, and some promising biomarker candidates have been discussed (Gerlach et al., 2011). Once the presymptomatic PD patients have been identified, disease-modifying, neuroprotective therapy should be able to delay development of motor disabilities and prolong time to L-DOPA initiation, allowing the pre-symptomatic patients to lead a normal life for a longer period of time. In addition, the disease-modifying drugs administered in combination with the current therapy in patients with moderate-to-advanced stages of PD may also be beneficial in improving the quality of life.

As described above, oxidative stress derived from DA metabolism, inflammation and mitochondrial dysfunction is thought to be the hallmark of PD pathogenesis, and antioxidant mechanism should prove to an effective neuroprotective therapy for PD. However, no direct antioxidant, either administered alone or in combination, has been observed to completely halt the progression of PD. The direct antioxidants vitamin C and β-carotene have shown no neuroprotective effect on PD patients (Etminan et al., 2005). Supplemental vitamin E also did not delay the need to start levodopa therapy in patients with early untreated PD in the DATATOP study (Parker et al., 1989). Coenzyme Q10, which is both an antioxidant and an enhancer of mitochondrial function, did not show benefit (Investigators, 2007), and a 16-month phase III clinical trial in a large population (600 patients with early PD (The QE3 study) was dropped in May 2011, because an interim analysis revealed no futility to complete the study (Clinicaltrials.gov).

Attempts have been made to design disease-modifying neuroprotective therapies against neuroinflammation. The steroid dexamethasone has been reported to attenuate the degeneration of DA-containing neurons induced by MPTP (Kurkowska-Jastrzebska et al.,

1999) or lipopolysaccharide (Castano et al., 2002). However, steroids have limitations for long-term use in clinical situations due to side effects. Although non-steroidal anti-inflammatory drugs, such as salicylic acid, are able to attenuate the MPTP-induced striatal DA depletion (Sairam et al., 2003), there is no clinical evidence supporting their neuroprotective effect. In addition, the tetracycline derivatives minocycline (Du et al., 2001; Tikka et al., 2001; Wu et al., 2002) has shown to inhibit neuroinflammation both in vitro and in animal models. A pilot clinical study using minocycline as a potential disease-modifying drug for PD, however, has generated disappointing results. The drug, mainly due to the large dose required, led to unwanted side effects and a high drop-out rates among patients (Investigators., 2008).

We have shown that doxycycline, another tetracycline derivative that penetrates the blood brain barrier, downregulates the cell stress-induced MMP-3 expression and release and attenuates apoptosis in the DAergic CATH.a cells (Cho et al., 2009). It also suppresses the increase in MMP-3 gene expression as well as nitric oxide and inflammatory cytokines in microglial cells in culture, and provides protection of the nigral DAergic neurons and suppresses micorglial activation and astrogliosis in the MPTP-induced mouse PD model.

We have also synthesized a novel compound 7-hydroxy-6-methoxy-2-propionyl-1,2,3,4-tetrahydroisoquinoline (PTIQ) which effectively suppressed induction of MMP-3 in DAergic cells and prevented the resulting cell death. PTIQ was able to downregulate expression of MMP-3 along with IL-1β, TNF-α and cyclooxygenase-2 and blocked nuclear translocation of NF-κB in activated microglia (Son et al., 2011). In MPTP-elicited mouse model of PD, PTIQ attenuated the associated motor deficits, prevented neurodegeneration, and suppressed microglial activation in the substantia nigra. It has a good potential as a drug for central nervous system, because it entered the brain rather rapidly, and it was relatively stable against liver microsomal enzymes, showed no apparent inhibitory effect on the cytochrome p450 subtypes or hERG channel, exhibited little cytotoxicity on liver cells or lethality.

Other molecules that downregulate MMP-3 and neuroinflammation and provide DAergic neuroprotection have been reported. It has been observed that ghrelin, an endogenous ligand for growth hormone secretagogue receptor 1a (GHS-R1a), attenuates MMP-3 expression, nigrostriatal DAergic neuron loss, microglial activation, and subsequent release of TNF-α, IL-1β, and nitrite in mesencephalic neurons in MPTP mouse model of PD (Moon et al., 2009). Another group of investigators has reported that exendin-4, a naturally occurring and more potent and stable analog of glucagons-like peptide-1 (GLP-1) that selectively binds at the GLP-1 receptor, also downregulates MMP-3 expression along with attenuation of DAergic neuron loss and microglial activation (S. Kim et al., 2009).

### 3.6.1 NQO1 and its inducers as protective agents

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 (Cavelier and Amzel, 2001; Joseph et al., 2000). Since DA and its metabolites have been implicated in the pathogenesis of PD, NQO1 may exert a protective effect against such conditions. Indeed, the toxic accumulation of the DA quinone (as well as L-DOPA quinone) can be prevented by the action of NQO1. NQO1 protected against damaging effects of cyclized quinones and oxidative stress induced during their redox

cycling (Zafar, Inayat-Hussain, et al., 2006), and against DA (Zafar, Siegel, et al., 2006) and 6-hydroxyDA (Jia et al., 2008). Induction of NQO1 by sulforaphane, dimethyl fumarate, 3H-1,2-dithiole-3-thione, tert-butylhydroquinone (tBHQ), and butylated hydroxyanisole protected against neurocytotoxicity associated with DA quinone in vitro (H.J. Choi et al., 2003; Duffy et al., 1998; Han et al., 2007; Hara et al., 2003; Jia et al., 2009; Jia et al., 2008; Miyazaki et al., 2006; Siebert et al., 2009);; and against MPTP-elicited toxicity in vivo (Jazwa et al., 2011). In addition, NQO1 is known to maintain both α-tocopherol and coenzyme Q10 in their reduced, antioxidant state (Siegel et al., 1997).

While NQO1 is abundant in the liver where it participates in the phase II detoxification, the enzyme is also expressed in the brain (Stringer et al., 2004). In addition to its predominant expression in astrocytes (Flier et al., 2002), NQO1 is also expressed, albeit to a less degree, in DArgic neurons in the substantia nigra (van Muiswinkel et al., 2004). Moreover, a marked increase in the neuronal expression of NQO1 was consistently observed in the Parkinsonian substantia nigra (van Muiswinkel et al., 2004). Studies have shown that a polymorphism (C609T) of NQO1 that results in a decrease or total loss of its expression is associated with PD (Harada et al., 2001; Jiang et al., 2004), although another group reported no such association (Okada et al., 2005).

Pharmacological induction of NQO1 is achieved by the transcription factor Nrf-2 binding to a cis-acting enhancer sequence termed antioxidant response element (ARE). Therefore, Nrf-2 activation in DAergic neurons may be accompanied by coordinate elevation of expression of many other genes that also contain the ARE sequence. These include the enzymes that are known as cytoprotective proteins, such as glutathione S-transferase, epoxide hydrolase, heme oxygenase-1, catalase, and superoxide dismutase and glucuronosyltransferase, thioredoxin, glutathione peroxidase, the catalytic and modulatory subunits of gamma-glutamyl synthase (GCLM, GCLC), and thioredoxin reductase (J. Clark and Simon, 2009). Which of these proteins are actually expressed and induced in the nigral DArgic neurons needs to be experimentally sorted out. It is likely that the protective effect of the known NQO1 inducers is contributed by the other cytoprotective enzymes coordinately induced along with NQO. It should be noted, however, that the direct ability of NQO1 to catalyze the detoxification of DA quinone metabolites seems most important in cellular defense of DAergic cells (Dinkova-Kostova and Talalay, 2010). It has been shown that catalase, superoxide dismutase, and heme oxygenase-1 are not effective in providing neuroprotection against DA quinone (Innamorato et al., 2010; Zafar, Inayat-Hussain, et al., 2006; Zafar, Siegel, et al., 2006). Therefore, NQO1 and Nrf2 should serve as viable cellular targets for neuroprotective therapy for PD.

## 4. References

Aisen, P.S. (2003). Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial. *JAMA,* Vol. 289, pp. 2819-2826, ISSN 0098-7484

Alonso, A.C. (1994). Role of abnormally phosphorylated tau in the breakdown of microtubules in Alzheimer disease. *Proceedings of the National Academy of Sciences of the United States of America,* Vol. 91, pp. 5562-5566, ISSN 0027-8424

Alvarez, A. (1997). Acetylcholinesterase promotes the aggregation of amyloid-beta-peptide fragments by forming a complex with the growing fibrils. *J Mol Biol,* Vol. 272, pp. 348-361, ISSN 0022-2836

Alzheimer, A. (1991). A contribution concerning the pathological anatomy of mental disturbances in old age, 1899. *Alzheimer Dis Assoc Disord,* Vol. 5, pp. 69-70, ISSN 0893-0341

Andersen, J.K. (2004). Oxidative stress in neurodegeneration: cause or consequence? *Nat Med,* Vol. 10 Suppl, pp. S18-25, ISSN 1078-8956

Andreadis, A. (2005). Tau gene alternative splicing: expression patterns, regulation and modulation of function in normal brain and neurodegenerative diseases. *Biochimica et biophysica acta,* Vol. 1739, pp. 91-103, ISSN 0006-3002

Andres-Mateos, E. (2007). DJ-1 gene deletion reveals that DJ-1 is an atypical peroxiredoxin-like peroxidase. *Proc Natl Acad Sci U S A,* Vol. 104, pp. 14807-14812, ISSN 0027-8424

Asanuma, M. (2003). Dopamine- or L-DOPA-induced neurotoxicity: the role of dopamine quinone formation and tyrosinase in a model of Parkinson's disease. *Neurotox Res,* Vol. 5, pp. 165-176, ISSN 1029-8428

Ascherio, A. (2001). Prospective study of caffeine consumption and risk of Parkinson's disease in men and women. *Ann Neurol,* Vol. 50, pp. 56-63, ISSN 0364-5134

Augustinack, J.C. (2002). Colocalization and fluorescence resonance energy transfer between cdk5 and AT8 suggests a close association in pre-neurofibrillary tangles and neurofibrillary tangles. *Journal of neuropathology and experimental neurology,* Vol. 61, pp. 557-564, ISSN 0022-

Balakrishnan, R. (1998). Alzheimer's beta-amyloid peptide: affinity for metal chelates. *Journal of Peptide Research,* Vol. 51, pp. 91-95.

Banati, R.B. (1998). Glial pathology but absence of apoptotic nigral neurons in long-standing Parkinson's disease. *Mov Disord,* Vol. 13, pp. 221-227, ISSN 0885-3185

Barbeau, A. (1987). Ecogenetics of Parkinson's disease: prevalence and environmental aspects in rural areas. *Can J Neurol Sci,* Vol. 14, pp. 36-41, ISSN 0317-1671

Barrow, C.J., and Zagorski, M.G. (1991). Solution structures of beta peptide and its constituent fragments: relation to amyloid deposition. *Science,* Vol. 253, pp. 179-182, ISSN

Bartolini, M. (2003). beta-Amyloid aggregation induced by human acetylcholinesterase: inhibition studies. *Biochem Pharmacol,* Vol. 65, pp. 407-416, ISSN 0006-2952

Bartus, R.T. (1982). The cholinergic hypothesis of geriatric memory dysfunction. *Science,* Vol. 217, pp. 408-414, ISSN 0036-8075

Behl, C. (1999). Alzheimer's disease and oxidative stress: implications for novel therapeutic approaches. *Prog Neurobiol,* Vol. 57, pp. 301-323, ISSN 0301-0082

Behl, C. (1994). Hydrogen peroxide mediates amyloid beta protein toxicity. *Cell,* Vol. 77, pp. 817-827, ISSN 0092-8674

Bender, A. (2006). High levels of mitochondrial DNA deletions in substantia nigra neurons in aging and Parkinson disease. *Nat Genet,* Vol. 38, pp. 515-517, ISSN 1061-4036

Benecke, R. (1993). Electron transfer complexes I and IV of platelets are abnormal in Parkinson's disease but normal in Parkinson-plus syndromes. *Brain,* Vol. 116 (Pt 6), pp. 1451-1463, ISSN 0006-8950

Benner, E.J. (2008). Nitrated alpha-synuclein immunity accelerates degeneration of nigral dopaminergic neurons. *PLoS One,* Vol. 3, pp. e1376, ISSN 1932-6203

Berman, S.B., and Hastings, T.G. (1999). Dopamine oxidation alters mitochondrial respiration and induces permeability transition in brain mitochondria: implications for Parkinson's disease. *J Neurochem,* Vol. 73, pp. 1127-1137, ISSN 0022-3042

Betarbet, R. (2002). Animal models of Parkinson's disease. *Bioessays,* Vol. 24, pp. 308-318, ISSN 0265-9247

Betarbet, R. (2000). Chronic systemic pesticide exposure reproduces features of Parkinson's disease. *Nat Neurosci,* Vol. 3, pp. 1301-1306, ISSN 1097-6256

Bhat, R.V. (2004). Glycogen synthase kinase 3: a drug target for CNS therapies. *Journal of neurochemistry,* Vol. 89, pp. 1313-1317, ISSN 0022-3042

Binder, L.I. (2005). Tau, tangles, and Alzheimer's disease. *Biochimica et biophysica acta,* Vol. 1739, pp. 216-223, ISSN 0006-3002

Bitan, G. (2003). Amyloid beta -protein (Abeta) assembly: Abeta 40 and Abeta 42 oligomerize through distinct pathways. *Proc Natl Acad Sci U S A,* Vol. 100, pp. 330-335, ISSN

Black, S.E. (2007). S3-02-02: Flurizan. *Alzheimer's Dementia,* Vol. 3, pp. S199.

Blanchard, B.J. (1997). Mechanism and prevention of neurotoxicity caused by beta-amyloid peptides: relation to Alzheimer's disease. *Brain Research,* Vol. 776, pp. 40-50.

Bonifati, V. (2003). DJ-1( PARK7), a novel gene for autosomal recessive, early onset parkinsonism. *Neurol Sci,* Vol. 24, pp. 159-160, ISSN 1590-1874

Borghi, R. (2000). Full length alpha-synuclein is present in cerebrospinal fluid from Parkinson's disease and normal subjects. *Neurosci Lett,* Vol. 287, pp. 65-67, ISSN 0304-3940

Bosco, D.A. (2006). Elevated levels of oxidized cholesterol metabolites in Lewy body disease brains accelerate alpha-synuclein fibrilization. *Nat Chem Biol,* Vol. 2, pp. 249-253, ISSN 1552-4450

Bowen, D.M. (1992). Treatment strategies for Alzheimer's disease. *Lancet,* Vol. 339, pp. 132-133, ISSN 0140-6736

Braak, H., and Braak, E. (1987). Argyrophilic grains: characteristic pathology of cerebral cortex in cases of adult onset dementia without Alzheimer changes. *Neuroscience letters,* Vol. 76, pp. 124-127, ISSN 0304-3940

Brandt, R. (2005). Tau alteration and neuronal degeneration in tauopathies: mechanisms and models. *Biochimica et biophysica acta,* Vol. 1739, pp. 331-354, ISSN 0006-3002

Brunden, K.R. (1993). pH-dependent binding of synthetic beta-amyloid peptides to glycosaminoglycans. *J Neurochem,* Vol. 61, pp. 2147-2154, ISSN 0022-3042

Brunden, K.R. (2009). Advances in tau-focused drug discovery for Alzheimer's disease and related tauopathies. *Nature reviews. Drug discovery,* Vol. 8, pp. 783-793, ISSN 1474-1784

Buee-Scherrer, V. (1995). Neurofibrillary degeneration in amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam. Immunochemical characterization of tau proteins. *The American journal of pathology,* Vol. 146, pp. 924-932, ISSN 0002-9440

Bullock, R. (2002). New drugs for Alzheimer's disease and other dementias. *Br J Psychiatry,* Vol. 180, pp. 135-139, ISSN 0007-1250

Bush, A.I. (2003). Copper, beta-amyloid, and Alzheimer's disease: tapping a sensitive connection. *Proc Natl Acad Sci U S A,* Vol. 100, pp. 11193-11194, ISSN 0027-8424

Butterfield, D.A. (2001). Evidence of oxidative damage in Alzheimer's disease brain: central role for amyloid beta-peptide. *Trends Mol Med,* Vol. 7, pp. 548-554, ISSN 1471-4914

Butterfield, D.A., and Kanski, J. (2002). Methionine residue 35 is critical for the oxidative stress and neurotoxic properties of Alzheimer's amyloid beta-peptide 1-42. *Peptides,* Vol. 23, pp. 1299-1309.

Camps, P., and Muñoz-Torrero, D. (2002). Cholinergic drugs in pharmacotherapy of Alzheimer's disease. *Mini Rev Med Chem,* Vol. 2, pp. 11-25, ISSN 1389-5575

Canet-Aviles, R.M. (2004). The Parkinson's disease protein DJ-1 is neuroprotective due to cysteine-sulfinic acid-driven mitochondrial localization. *Proc Natl Acad Sci U S A,* Vol. 101, pp. 9103-9108, ISSN 0027-8424

Castano, A. (2002). The degenerative effect of a single intranigral injection of LPS on the dopaminergic system is prevented by dexamethasone, and not mimicked by rh-TNF-alpha, IL-1beta and IFN-gamma. *J Neurochem,* Vol. 81, pp. 150-157, ISSN 0022-3042

Castillo, G.M. (1999). The sulfate moieties of glycosaminoglycans are critical for the enhancement of beta-amyloid protein fibril formation. *J Neurochem,* Vol. 72, pp. 1681-1687, ISSN 0022-3042

Castillo, G.M. (1997). Perlecan binds to the beta-amyloid proteins (A beta) of Alzheimer's disease, accelerates A beta fibril formation, and maintains A beta fibril stability. *J Neurochem,* Vol. 69, pp. 2452-2465, ISSN 0022-3042

Caudle, W.M. (2008). Altered vesicular dopamine storage in Parkinson's disease: a premature demise. *Trends Neurosci,* Vol. 31, pp. 303-308, ISSN 0166-2236

Cavelier, G., and Amzel, L.M. (2001). Mechanism of NAD(P)H:quinone reductase: Ab initio studies of reduced flavin. *Proteins,* Vol. 43, pp. 420-432, ISSN 0887-3585

Chaudhuri, K.R., and Schapira, A.H. (2009). Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. *Lancet Neurology,* Vol. 8, pp. 464-474, ISSN 1474-4422

Chen, L. (2008). Unregulated cytosolic dopamine causes neurodegeneration associated with oxidative stress in mice. *J Neurosci,* Vol. 28, pp. 425-433, ISSN 1529-2401

Cherny, R.A. (2001). Treatment with a copper-zinc chelator markedly and rapidly inhibits beta-amyloid accumulation in Alzheimer's disease transgenic mice. *Neuron,* Vol. 30, pp. 665-676, ISSN 0896-6273

Chin, J. (2005). Fyn kinase induces synaptic and cognitive impairments in a transgenic mouse model of Alzheimer's disease. *The Journal of neuroscience : the official journal of the Society for Neuroscience,* Vol. 25, pp. 9694-9703, ISSN 1529-2401

Cho, Y. (2009). Doxycycline is neuroprotective against nigral dopaminergic degeneration by a dual mechanism involving MMP-3. *Neurotox Res,* Vol. 16, pp. 361-371, ISSN 1476-3524

Choi, D.H. (2008). A novel intracellular role of matrix metalloproteinase-3 during apoptosis of dopaminergic cells. *J Neurochem,* Vol. 106, pp. 405-415, ISSN 1471-4159

Choi, D.S. (2006). PKCepsilon increases endothelin converting enzyme activity and reduces amyloid plaque pathology in transgenic mice. *Proc Natl Acad Sci U S A,* Vol. 103, pp. 8215-8220, ISSN 0027-8424

Choi, H.J. (2003). Dopamine-dependent cytotoxicity of tetrahydrobiopterin: a possible mechanism for selective neurodegeneration in Parkinson's disease. *J Neurochem,* Vol. 86, pp. 143-152, ISSN 0022-3042

Choi, J. (2004). Oxidative modifications and down-regulation of ubiquitin carboxyl-terminal hydrolase L1 associated with idiopathic Parkinson's and Alzheimer's diseases. *J Biol Chem,* Vol. 279, pp. 13256-13264, ISSN 0021-9258

Choi, J. (2006). Oxidative damage of DJ-1 is linked to sporadic Parkinson and Alzheimer diseases. *J Biol Chem,* Vol. 281, pp. 10816-10824, ISSN 0021-9258

Cicchetti, F. (2002). Neuroinflammation of the nigrostriatal pathway during progressive 6-OHDA dopamine degeneration in rats monitored by immunohistochemistry and PET imaging. *Eur J Neurosci,* Vol. 15, pp. 991-998, ISSN 0953-816X

Clark, I.E. (2006). Drosophila pink1 is required for mitochondrial function and interacts genetically with parkin. *Nature,* Vol. 441, pp. 1162-1166, ISSN 1476-4687

Clark, J., and Simon, D.K. (2009). Transcribe to survive: transcriptional control of antioxidant defense programs for neuroprotection in Parkinson's disease. *Antioxid Redox Signal,* Vol. 11, pp. 509-528, ISSN 1557-7716

Conway, K.A. (2001). Kinetic stabilization of the alpha-synuclein protofibril by a dopamine-alpha-synuclein adduct. *Science,* Vol. 294, pp. 1346-1349, ISSN 0036-8075

Corrigan, F.M. (1998). Diorthosubstituted polychlorinated biphenyls in caudate nucleus in Parkinson's disease. *Exp Neurol,* Vol. 150, pp. 339-342, ISSN 0014-4886

Darios, F. (2003). Parkin prevents mitochondrial swelling and cytochrome c release in mitochondria-dependent cell death. *Hum Mol Genet,* Vol. 12, pp. 517-526, ISSN 0964-6906

Darvesh, S. (2003). Neurobiology of butyrylcholinesterase. *Nat Rev Neurosci,* Vol. 4, pp. 131-138, ISSN 1471-003X

Dauer, W. (2002). Resistance of alpha -synuclein null mice to the parkinsonian neurotoxin MPTP. *Proc Natl Acad Sci U S A,* Vol. 99, pp. 14524-14529, ISSN 0027-8424

Davies, P., and Maloney, A.J. (1976). Selective loss of central cholinergic neurons in Alzheimer's disease. *Lancet,* Vol. 2, pp. 1403, ISSN 0140-6736

Dayanandan, R. (1999). Mutations in tau reduce its microtubule binding properties in intact cells and affect its phosphorylation. *FEBS letters,* Vol. 446, pp. 228-232, ISSN 0014-5793

De Ferrari, G.V. (2001). A structural motif of acetylcholinesterase that promotes amyloid beta-peptide fibril formation. *Biochemistry,* Vol. 40, pp. 10447-10457, ISSN 0006-2960

de Lau, L.M., and Breteler, M.M. (2006). Epidemiology of Parkinson's disease. *Lancet Neurology,* Vol. 5, pp. 525-535, ISSN 1474-4422

Defelice, F.G., and Ferreira, S.T. (2002). Physiopathological modulators of amyloid aggregation and novel pharmacological approaches in Alzheimer's disease. *An Acad Bras Cienc,* Vol. 74, pp. 265-284, ISSN 0001-3765

Devi, L. (2008). Mitochondrial import and accumulation of alpha-synuclein impair complex I in human dopaminergic neuronal cultures and Parkinson disease brain. *J Biol Chem,* Vol. 283, pp. 9089-9100, ISSN 0021-9258

Dhavan, R., and Tsai, L.H. (2001). A decade of CDK5. *Nature reviews. Molecular cell biology,* Vol. 2, pp. 749-759, ISSN 1471-0072

Diamant, S. (2006). Butyrylcholinesterase attenuates amyloid fibril formation in vitro. *Proc Natl Acad Sci U S A,* Vol. 103, pp. 8628-8633, ISSN 0027-8424

Dinkova-Kostova, A.T., and Talalay, P. (2010). NAD(P)H:quinone acceptor oxidoreductase 1 (NQO1), a multifunctional antioxidant enzyme and exceptionally versatile cytoprotector. *Arch Biochem Biophys,* Vol. 501, pp. 116-123, ISSN 1096-0384

Doraiswamy, P.M., and Finefrock, A.E. (2004). Metals in our minds: therapeutic implications for neurodegenerative disorders. *Lancet Neurol,* Vol. 3, pp. 431-434, ISSN 1474-4422

Drechsel, D.N. (1992). Modulation of the dynamic instability of tubulin assembly by the microtubule-associated protein tau. *Molecular biology of the cell,* Vol. 3, pp. 1141-1154, ISSN 1059-1524

Du, Y. (2001). Minocycline prevents nigrostriatal dopaminergic neurodegeneration in the MPTP model of Parkinson's disease. *Proc Natl Acad Sci U S A,* Vol. 98, pp. 14669-14674, ISSN 0027-8424

Duffy, S. (1998). Activation of endogenous antioxidant defenses in neuronal cells prevents free radical-mediated damage. *J Neurochem,* Vol. 71, pp. 69-77, ISSN 0022-3042

Dunnett, S.B., and Bjorklund, A. (1999). Prospects for new restorative and neuroprotective treatments in Parkinson's disease. *Nature,* Vol. 399, pp. A32-39, ISSN 0028-0836

El-Agnaf, O.M. (2003). Alpha-synuclein implicated in Parkinson's disease is present in extracellular biological fluids, including human plasma. *FASEB J,* Vol. 17, pp. 1945-1947, ISSN 1530-6860

Etminan, M. (2005). Intake of vitamin E, vitamin C, and carotenoids and the risk of Parkinson's disease: a meta-analysis. *Lancet Neurology,* Vol. 4, pp. 362-365, ISSN 1474-4422

Fahn, S. (1989). Adverse effects of levodopa in Parkinson's disease. In Handb Exp Pharmacol, Calne, D.B.,(Ed.) pp. 386-409, Berlin

Farina, C. (2007). Astrocytes are active players in cerebral innate immunity. *Trends Immunol,* Vol. 28, pp. 138-145, ISSN 1471-4906

Farrer, M.J. (2006). Genetics of Parkinson disease: paradigm shifts and future prospects. *Nat Rev Genet,* Vol. 7, pp. 306-318, ISSN 1471-0056

Fasulo, L. (2000). The neuronal microtubule-associated protein tau is a substrate for caspase-3 and an effector of apoptosis. *Journal of neurochemistry,* Vol. 75, pp. 624-633, ISSN 0022-3042

Ferrer, I. (2001). Phosphorylated map kinase (ERK1, ERK2) expression is associated with early tau deposition in neurones and glial cells, but not with increased nuclear DNA vulnerability and cell death, in Alzheimer disease, Pick's disease, progressive supranuclear palsy and corticobasal degeneration. *Brain pathology,* Vol. 11, pp. 144-158, ISSN 1015-6305

Finder, V.H., and Glockshuber, R. (2007). Amyloid-beta aggregation. *Neurodegener Dis,* Vol. 4, pp. 13-27, ISSN 1660-2854

Flier, J. (2002). The neuroprotective antioxidant alpha-lipoic acid induces detoxication enzymes in cultured astroglial cells. *Free Radic Res,* Vol. 36, pp. 695-699, ISSN 1071-5762

Francis, J.W. (1995). Neuroglial responses to the dopaminergic neurotoxicant 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in mouse striatum. *Neurotoxicol Teratol,* Vol. 17, pp. 7-12, ISSN 0892-0362

Frank, B., and Gupta, S. (2005). A review of antioxidants and Alzheimer's disease. *Ann Clin Psychiatry,* Vol. 17, pp. 269-286, ISSN 1040-1237

Fraser, P.E. (1992). Effects of sulfate ions on Alzheimer beta/A4 peptide assemblies: implications for amyloid fibril-proteoglycan interactions. *J Neurochem,* Vol. 59, pp. 1531-1540, ISSN 0022-3042

Gaggelli, E. (2006). Copper homeostasis and neurodegenerative disorders (Alzheimer's, prion, and Parkinson's diseases and amyotrophic lateral sclerosis). *Chem Rev,* Vol. 106, pp. 1995-2044, ISSN 0009-2665

Gamblin, T.C. (2003). Caspase cleavage of tau: linking amyloid and neurofibrillary tangles in Alzheimer's disease. *Proceedings of the National Academy of Sciences of the United States of America,* Vol. 100, pp. 10032-10037, ISSN 0027-8424

Gandhi, S. (2009). PINK1-associated Parkinson's disease is caused by neuronal vulnerability to calcium-induced cell death. *Mol Cell,* Vol. 33, pp. 627-638, ISSN 1097-4164

Gao, H.M. (2008). Neuroinflammation and oxidation/nitration of alpha-synuclein linked to dopaminergic neurodegeneration. *J Neurosci,* Vol. 28, pp. 7687-7698, ISSN 1529-2401

Gao, H.M. (2011). Neuroinflammation and alpha-synuclein dysfunction potentiate each other, driving chronic progression of neurodegeneration in a mouse model of Parkinson's disease. *Environ Health Perspect,* Vol. 119, pp. 807-814, ISSN 1552-9924

Garcia-Sierra, F. (2003). Conformational changes and truncation of tau protein during tangle evolution in Alzheimer's disease. *Journal of Alzheimer's disease : JAD,* Vol. 5, pp. 65-77, ISSN 1387-2877

Gasche, Y. (2001). Matrix metalloproteinase inhibition prevents oxidative stress-associated blood-brain barrier disruption after transient focal cerebral ischemia. *J Cereb Blood Flow Metab,* Vol. 21, pp. 1393-1400, ISSN 0271-678X

Gegg, M.E. (2009). Silencing of PINK1 expression affects mitochondrial DNA and oxidative phosphorylation in dopaminergic cells. *PLoS One,* Vol. 4, pp. e4756, ISSN 1932-6203

Gendron, T.F., and Petrucelli, L. (2009). The role of tau in neurodegeneration. *Molecular neurodegeneration,* Vol. 4, pp. 13, ISSN 1750-1326

Gerhard, A. (2006). In vivo imaging of microglial activation with [11C](R)-PK11195 PET in idiopathic Parkinson's disease. *Neurobiol Dis,* Vol. 21, pp. 404-412, ISSN 0969-9961

Gerlach, M. (2011). Biomarker candidates of neurodegeneration in Parkinson's disease for the evaluation of disease-modifying therapeutics. *J Neural Transm,* Vol. 1435-1463

Gervais, F. (2007). Targeting soluble Abeta peptide with Tramiprosate for the treatment of brain amyloidosis. *Neurobiol Aging,* Vol. 28, pp. 537-547, ISSN 1558-1497

Giacobini, E. (2002). Inhibition of acetyl- and butyryl-cholinesterase in the cerebrospinal fluid of patients with Alzheimer's disease by rivastigmine: correlation with cognitive benefit. *J Neural Transm,* Vol. 109, pp. 1053-1065, ISSN 0300-9564

Goedert, M., and Jakes, R. (1990). Expression of separate isoforms of human tau protein: correlation with the tau pattern in brain and effects on tubulin polymerization. *The EMBO journal,* Vol. 9, pp. 4225-4230, ISSN 0261-4189

Goedert, M. (1989). Multiple isoforms of human microtubule-associated protein tau: sequences and localization in neurofibrillary tangles of Alzheimer's disease. *Neuron,* Vol. 3, pp. 519-526, ISSN 0896-6273

Graham, D.G. (1978). Oxidative pathways for catecholamines in the genesis of neuromelanin and cytotoxic quinones. *Mol Pharmacol,* Vol. 14, pp. 633-643, ISSN 0026-895X

Greene, J.C. (2003). Mitochondrial pathology and apoptotic muscle degeneration in Drosophila parkin mutants. *Proc Natl Acad Sci U S A,* Vol. 100, pp. 4078-4083, ISSN 0027-8424

Greig, N.H. (2001). A new therapeutic target in Alzheimer's disease treatment: attention to butyrylcholinesterase. *Curr Med Res Opin,* Vol. 17, pp. 159-165, ISSN 0300-7995

Grunewald, A. (2009). Differential effects of PINK1 nonsense and missense mutations on mitochondrial function and morphology. *Exp Neurol,* Vol. 219, pp. 266-273, ISSN 1090-2430

Grunewald, A. (2010). Mutant Parkin impairs mitochondrial function and morphology in human fibroblasts. *PLoS One,* Vol. 5, pp. e12962, ISSN 1932-6203

Gurney, K.J. (2006). Blood-brain barrier disruption by stromelysin-1 facilitates neutrophil infiltration in neuroinflammation. *Neurobiol Dis,* Vol. 23, pp. 87-96, ISSN 0969-9961

Halliday, G. (2000). Alzheimer's disease and inflammation: a review of cellular and therapeutic mechanisms. *Clin Exp Pharmacol Physiol,* Vol. 27, pp. 1-8, ISSN 0305-1870

Halliwell, B. (1992). Reactive oxygen species and the central nervous system. *J Neurochem,* Vol. 59, pp. 1609-1623, ISSN 0022-3042

Hamaguchi, T. (2006). Anti-amyloidogenic therapies: strategies for prevention and treatment of Alzheimer's disease. *Cell Mol Life Sci,* Vol. 63, pp. 1538-1552, ISSN 1420-682X

Han, J.M. (2007). Protective effect of sulforaphane against dopaminergic cell death. *J Pharmacol Exp Ther,* Vol. 321, pp. 249-256, ISSN 0022-3565

Hara, H. (2003). Increase of antioxidative potential by tert-butylhydroquinone protects against cell death associated with 6-hydroxydopamine-induced oxidative stress in neuroblastoma SH-SY5Y cells. *Brain Res Mol Brain Res,* Vol. 119, pp. 125-131, ISSN 0169-328X

Harada, S. (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,* Vol. 288, pp. 887-892, ISSN 0006-291X

Hardy, J., and Selkoe, D.J. (2002). The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science,* Vol. 297, pp. 353-356, ISSN 1095-9203

Hardy, J.A., and Higgins, G.A. (1992). Alzheimer's disease: the amyloid cascade hypothesis. *Science,* Vol. 256, pp. 184-185, ISSN 0036-8075

Hartmann, T. (1997). Distinct sites of intracellular production for Alzheimer's disease A beta40/42 amyloid peptides. *Nat Med,* Vol. 3, pp. 1016-1020, ISSN 1078-8956

Hasegawa, M. (1998). Tau proteins with FTDP-17 mutations have a reduced ability to promote microtubule assembly. *FEBS letters,* Vol. 437, pp. 207-210, ISSN 0014-5793

Hastings, T.G., and Zigmond, M.J. (1997). Loss of dopaminergic neurons in parkinsonism: possible role of reactive dopamine metabolites. *J Neural Transm Suppl,* Vol. 49, pp. 103-110, ISSN 0303-6995

Hong, M. (1997). Lithium reduces tau phosphorylation by inhibition of glycogen synthase kinase-3. *The Journal of biological chemistry,* Vol. 272, pp. 25326-25332, ISSN 0021-9258

Hong, M. (1998). Mutation-specific functional impairments in distinct tau isoforms of hereditary FTDP-17. *Science,* Vol. 282, pp. 1914-1917, ISSN 0036-8075

Hull, M. (1999). Anti-inflammatory substances - a new therapeutic option in Alzheimer's disease. *Drug Discovery Today,* Vol. 4, pp. 275-282, ISSN 1359-6446

Hutton, M. (2000). Molecular genetics of chromosome 17 tauopathies. *Annals of the New York Academy of Sciences,* Vol. 920, pp. 63-73, ISSN 0077-8923

Hutton, M. (1998). Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature,* Vol. 393, pp. 702-705, ISSN 0028-0836

Ibach, B., and Haen, E. (2004). Acetylcholinesterase inhibition in Alzheimer's Disease. *Curr Pharm Des,* Vol. 10, pp. 231-251, ISSN 1381-6128

Inestrosa, N.C. (1996). Acetylcholinesterase accelerates assembly of amyloid-beta-peptides into Alzheimer's fibrils: possible role of the peripheral site of the enzyme. *Neuron,* Vol. 16, pp. 881-891, ISSN 0896-6273

Innamorato, N.G. (2010). Different susceptibility to the Parkinson's toxin MPTP in mice lacking the redox master regulator Nrf2 or its target gene heme oxygenase-1. *PLoS One,* Vol. 5, pp. e11838, ISSN 1932-6203

Investigators, T.N.N.-P. (2007). A randomized clinical trial of coenzyme Q10 and GPI-1485 in early Parkinson disease. *Neurology,* Vol. 68, pp. 20-28, ISSN 1526-632X

Investigators., N.N.-P. (2008). A pilot clinical trial of creatine and minocycline in early Parkinson disease: 18-month results. *Clin Neuropharmacol,* Vol. 31, pp. 141-150, ISSN 1537-162X

Iqbal, K. (2005). Tau pathology in Alzheimer disease and other tauopathies. *Biochimica et biophysica acta,* Vol. 1739, pp. 198-210, ISSN 0006-3002

Irrcher, I. (2010). Loss of the Parkinson's disease-linked gene DJ-1 perturbs mitochondrial dynamics. *Hum Mol Genet,* Vol. 19, pp. 3734-3746, ISSN 1460-2083

Ishikawa, A., and Takahashi, H. (1998). Clinical and neuropathological aspects of autosomal recessive juvenile parkinsonism. *J Neurol,* Vol. 245, pp. P4-9, ISSN 0340-5354

Jack, C.R. (2010). Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurology,* Vol. 9, pp. 119-128, ISSN 1474-4422

Jan, A. (2008). The ratio of monomeric to aggregated forms of Abeta40 and Abeta42 is an important determinant of amyloid-beta aggregation, fibrillogenesis, and toxicity. *J Biol Chem,* Vol. 283, pp. 28176-28189, ISSN 0021-9258

Jann, M.W. (2000). Rivastigmine, a new-generation cholinesterase inhibitor for the treatment of Alzheimer's disease. *Pharmacotherapy,* Vol. 20, pp. 1-12, ISSN 0277-0008

Jarrett, J.T., and Lansbury, P.T., Jr. (1993). Seeding "one-dimensional crystallization" of amyloid: a pathogenic mechanism in Alzheimer's disease and scrapie? *Cell,* Vol. 73, pp. 1055-1058, ISSN 0092-8674

Jazwa, A. (2011). Pharmacological targeting of the transcription factor Nrf2 at the basal ganglia provides disease modifying therapy for experimental parkinsonism. *Antioxid Redox Signal,* Vol. 14, pp. 2347-2360, ISSN 1557-7716 (Electronic)

Jenner, P. (2003). Oxidative stress in Parkinson's disease. *Ann Neurol,* Vol. 53 Suppl 3, pp. S26-36; discussion S36-28, ISSN 0364-5134

Jenner, P., and Olanow, C.W. (1996). Oxidative stress and the pathogenesis of Parkinson's disease. *Neurology,* Vol. 47, pp. S161-170, ISSN 0028-3878

Jia, Z. (2009). Cruciferous nutraceutical 3H-1,2-dithiole-3-thione protects human primary astrocytes against neurocytotoxicity elicited by MPTP, MPP(+), 6-OHDA, HNE and acrolein. *Neurochem Res,* Vol. 34, pp. 1924-1934, ISSN 1573-6903 (Electronic)

Jia, Z. (2008). Potent induction of total cellular GSH and NQO1 as well as mitochondrial GSH by 3H-1,2-dithiole-3-thione in SH-SY5Y neuroblastoma cells and primary human neurons: protection against neurocytotoxicity elicited by dopamine, 6-hydroxydopamine, 4-hydroxy-2-nonenal, or hydrogen peroxide. *Brain Res,* Vol. 1197, pp. 159-169, ISSN 0006-8993

Jian Liu, K., and Rosenberg, G.A. (2005). Matrix metalloproteinases and free radicals in cerebral ischemia. *Free Radic Biol Med,* Vol. 39, pp. 71-80, ISSN 0891-5849

Jiang, X.H. (2004). [A study on the relationship between polymorphism of human NAD(P)H: quinone oxidoreductase and Parkinson's disease in Chinese]. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi,* Vol. 21, pp. 120-123, ISSN 1003-9406

Jones, J.M. (2003). Loss of Omi mitochondrial protease activity causes the neuromuscular disorder of mnd2 mutant mice. *Nature,* Vol. 425, pp. 721-727, ISSN 1476-4687 (Electronic)

Joseph, P. (2000). Role of NAD(P)H:quinone oxidoreductase 1 (DT diaphorase) in protection against quinone toxicity. *Biochem Pharmacol,* Vol. 60, pp. 207-214, ISSN 0006-2952

Kamel, F. (2007). Pesticide exposure and self-reported Parkinson's disease in the agricultural health study. *Am J Epidemiol,* Vol. 165, pp. 364-374, ISSN 0002-9262

Kamp, F. (2010). Inhibition of mitochondrial fusion by alpha-synuclein is rescued by PINK1, Parkin and DJ-1. *EMBO J,* Vol. 29, pp. 3571-3589, ISSN 1460-2075 (Electronic)

Kar, A. (2005). Tau alternative splicing and frontotemporal dementia. *Alzheimer disease and associated disorders,* Vol. 19 Suppl 1, pp. S29-36, ISSN 0893-0341

Kayed, R. (2003). Common structure of soluble amyloid oligomers implies common mechanism of pathogenesis. *Science,* Vol. 300, pp. 486-489, ISSN

Kim, E.M., and Hwang, O. (2011). Role of matrix metalloproteinase-3 in neurodegeneration. *J Neurochem,* Vol. 116, pp. 22-32, ISSN 1471-4159

Kim, E.M. (2010). Matrix metalloproteinase-3 is increased and participates in neuronal apoptotic signaling downstream of caspase-12 during endoplasmic reticulum stress. *J Biol Chem,* Vol. 285, pp. 16444-16452, ISSN 1083-351X

Kim, S. (2009). Exendin-4 protects dopaminergic neurons by inhibition of microglial activation and matrix metalloproteinase-3 expression in an animal model of Parkinson's disease. *J Endocrinol,* Vol. 202, pp. 431-439, ISSN 1479-6805

Kim, Y. (2009). Multivalent & multifunctional ligands to beta-amyloid. *Curr Pharm Des,* Vol. 15, pp. 637-658, ISSN 1873-4286

Kim, Y.S. (2007). A pivotal role of matrix metalloproteinase-3 activity in dopaminergic neuronal degeneration via microglial activation. *FASEB J,* Vol. 21, pp. 179-187, ISSN 1530-6860

Kim, Y.S. (2005). Matrix metalloproteinase-3: a novel signaling proteinase from apoptotic neuronal cells that activates microglia. *J Neurosci,* Vol. 25, pp. 3701-3711, ISSN 1529-2401

Kisilevsky, R. (2007). Heparan sulfate as a therapeutic target in amyloidogenesis: prospects and possible complications. *Amyloid,* Vol. 14, pp. 21-32, ISSN 1350-6129

Klein, W.L. (2004). Small assemblies of unmodified amyloid beta-protein are the proximate neurotoxin in Alzheimer's disease. *Neurobiol Aging,* Vol. 25, pp. 569-580, ISSN 0197-4580

Klunk, W.E. (1994). Development of small molecule probes for the beta-amyloid protein of Alzheimer's disease. *Neurobiol Aging,* Vol. 15, pp. 691-698, ISSN 0197-4580

Knapp, M.J. (1994). A 30-week randomized controlled trial of high-dose tacrine in patients with Alzheimer's disease. The Tacrine Study Group. *JAMA,* Vol. 271, pp. 985-991, ISSN 0098-7484

Knott, C. (2000). Inflammatory regulators in Parkinson's disease: iNOS, lipocortin-1, and cyclooxygenases-1 and -2. *Mol Cell Neurosci,* Vol. 16, pp. 724-739, ISSN 1044-7431

Kopke, E. (1993). Microtubule-associated protein tau. Abnormal phosphorylation of a non-paired helical filament pool in Alzheimer disease. *The Journal of biological chemistry,* Vol. 268, pp. 24374-24384, ISSN 0021-9258

Krick, S. (2008). Mpv17l protects against mitochondrial oxidative stress and apoptosis by activation of Omi/HtrA2 protease. *Proc Natl Acad Sci U S A,* Vol. 105, pp. 14106-14111, ISSN 1091-6490

Kuhn, D.M. (1999). Tyrosine hydroxylase is inactivated by catechol-quinones and converted to a redox-cycling quinoprotein: possible relevance to Parkinson's disease. *J Neurochem,* Vol. 73, pp. 1309-1317, ISSN 0022-3042

Kuo, Y.M. (1996). Water-soluble Abeta (N-40, N-42) oligomers in normal and Alzheimer disease brains. *J Biol Chem,* Vol. 271, pp. 4077-4081, ISSN 0021-9258

Kurkowska-Jastrzebska, I. (1999). The inflammatory reaction following 1-methyl-4-phenyl-1,2,3, 6-tetrahydropyridine intoxication in mouse. *Exp Neurol,* Vol. 156, pp. 50-61, ISSN 0014-4886

Langston, J.W. (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,* Vol. 46, pp. 598-605, ISSN 0364-5134 0364-5134

LaVoie, M.J. (2005). Dopamine covalently modifies and functionally inactivates parkin. *Nat Med,* Vol. 11, pp. 1214-1221, ISSN 1078-8956

Lazo, N.D. (2005). On the nucleation of amyloid beta-protein monomer folding. *Protein Sci,* Vol. 14, pp. 1581-1596, ISSN 0961-8368

Lee, C.S. (2002). Differential effect of catecholamines and MPP(+) on membrane permeability in brain mitochondria and cell viability in PC12 cells. *Neurochem Int,* Vol. 40, pp. 361-369, ISSN 0197-0186

Lee, E.J. (2010). Alpha-synuclein activates microglia by inducing the expressions of matrix metalloproteinases and the subsequent activation of protease-activated receptor-1. *J Immunol,* Vol. 185, pp. 615-623, ISSN 1550-6606 (Electronic)

Lee, G. (2004). Phosphorylation of tau by fyn: implications for Alzheimer's disease. *The Journal of neuroscience : the official journal of the Society for Neuroscience,* Vol. 24, pp. 2304-2312, ISSN 1529-2401

Lee, H.J. (2005). Intravesicular localization and exocytosis of alpha-synuclein and its aggregates. *J Neurosci,* Vol. 25, pp. 6016-6024, ISSN 1529-2401

Lee, K.Y. (1999). Elevated neuronal Cdc2-like kinase activity in the Alzheimer disease brain. *Neuroscience research,* Vol. 34, pp. 21-29, ISSN 0168-0102

Lee, R.K. (1995). Amyloid precursor protein processing is stimulated by metabotropic glutamate receptors. *Proc Natl Acad Sci U S A,* Vol. 92, pp. 8083-8087, ISSN 0027-8424

Liang, C.L. (2007). Mitochondria mass is low in mouse substantia nigra dopamine neurons: implications for Parkinson's disease. *Exp Neurol,* Vol. 203, pp. 370-380, ISSN 0014-4886

Liang, X. (2005). Deletion of the prostaglandin E2 EP2 receptor reduces oxidative damage and amyloid burden in a model of Alzheimer's disease. *J Neurosci,* Vol. 25, pp. 10180-10187, ISSN 1529-2401 (Electronic)

Lim, G.P. (2000). Ibuprofen suppresses plaque pathology and inflammation in a mouse model for Alzheimer's disease. *J Neurosci,* Vol. 20, pp. 5709-5714, ISSN 0270-6474

Liu, G. (2009). alpha-Synuclein is differentially expressed in mitochondria from different rat brain regions and dose-dependently down-regulates complex I activity. *Neurosci Lett,* Vol. 454, pp. 187-192, ISSN 1872-7972 (Electronic)

Liu, S.T. (1999). Histidine-13 is a crucial residue in the zinc ion-induced aggregation of the A beta peptide of Alzheimer's disease. *Biochemistry,* Vol. 38, pp. 9373-9378, ISSN

Lomakin, A. (1997). Kinetic theory of fibrillogenesis of amyloid beta-protein. *Proc Natl Acad Sci U S A,* Vol. 94, pp. 7942-7947, ISSN 0027-8424

Lotharius, J., and Brundin, P. (2002). Pathogenesis of Parkinson's disease: dopamine, vesicles and alpha-synuclein. *Nat Rev Neurosci,* Vol. 3, pp. 932-942, ISSN 1471-003X

Maker, H.S. (1981). Coupling of dopamine oxidation (monoamine oxidase activity) to glutathione oxidation via the generation of hydrogen peroxide in rat brain homogenates. *J Neurochem,* Vol. 36, pp. 589-593, ISSN 0022-3042

Mandelkow, E.M. (1996). Structure, microtubule interactions, and phosphorylation of tau protein. *Annals of the New York Academy of Sciences,* Vol. 777, pp. 96-106, ISSN 0077-8923

Marek K, J.D. (2009). Can we image premotor Parkinson disease? *Neurology,* Vol. S21-26,

Markesbery, W.R. (1997). Oxidative Stress Hypothesis in Alzheimer's Disease. *Free Radical Biol Med,* Vol. 23, pp. 134-147,

Martin, L.J. (2006). Parkinson's disease alpha-synuclein transgenic mice develop neuronal mitochondrial degeneration and cell death. *J Neurosci,* Vol. 26, pp. 41-50, ISSN 1529-2401

Martinez-Vicente, M. (2008). Dopamine-modified alpha-synuclein blocks chaperone-mediated autophagy. *J Clin Invest,* Vol. 118, pp. 777-788, ISSN 0021-9738

Martins, L.M. (2004). Neuroprotective role of the Reaper-related serine protease HtrA2/Omi revealed by targeted deletion in mice. *Mol Cell Biol,* Vol. 24, pp. 9848-9862, ISSN 0270-7306

Maslow, K. (2008). 2008 Alzheimer's disease facts and figures. *Alzheimer's Dementia,* Vol. 4, pp. 110-133, ISSN 1552-5260

Mazanetz, M.P., and Fischer, P.M. (2007). Untangling tau hyperphosphorylation in drug design for neurodegenerative diseases. *Nature Reviews Drug Discovery,* Vol. 6, pp. 464-479, ISSN 1474-1776

McGeer, P.L. (1988). Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains. *Neurology,* Vol. 38, pp. 1285-1291, ISSN 0028-3878

McGeer, P.L., and McGeer, E.G. (1999). Inflammation of the brain in Alzheimer's disease: implications for therapy. *J Leukoc Biol,* Vol. 65, pp. 409-415, ISSN 0741-5400

McGeer, P.L. (1996). Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: a review of 17 epidemiologic studies. *Neurology,* Vol. 47, pp. 425-432, ISSN 0028-3878

McLaurin, J. (1999). A sulfated proteoglycan aggregation factor mediates amyloid-beta peptide fibril formation and neurotoxicity. *Amyloid,* Vol. 6, pp. 233-243, ISSN 1350-6129

McLaurin, J. (1999). Interactions of Alzheimer amyloid-beta peptides with glycosaminoglycans effects on fibril nucleation and growth. *Eur J Biochem,* Vol. 266, pp. 1101-1110, ISSN 0014-2956

McLaurin, J., and Fraser, P.E. (2000). Effect of amino-acid substitutions on Alzheimer's amyloid-beta peptide-glycosaminoglycan interactions. *Eur J Biochem,* Vol. 267, pp. 6353-6361, ISSN 0014-2956

Melnikova, I. (2007). Therapies for Alzheimer's disease. *Nat Rev Drug Discovery,* Vol. 6, pp. 341-342, ISSN 1474-1776

Miller, J.D. (1997). Localization of perlecan (or a perlecan-related macromolecule) to isolated microglia in vitro and to microglia/macrophages following infusion of beta-amyloid protein into rodent hippocampus. *Glia,* Vol. 21, pp. 228-243, ISSN 0894-1491

Miyazaki, I. (2006). Methamphetamine-induced dopaminergic neurotoxicity is regulated by quinone-formation-related molecules. *FASEB J,* Vol. 20, pp. 571-573, ISSN 1530-6860

Mizuno, Y. (1989). Deficiencies in complex I subunits of the respiratory chain in Parkinson's disease. *Biochem Biophys Res Commun,* Vol. 163, pp. 1450-1455, ISSN 0006-291X

Moisoi, N. (2009). Mitochondrial dysfunction triggered by loss of HtrA2 results in the activation of a brain-specific transcriptional stress response. *Cell Death Differ,* Vol. 16, pp. 449-464, ISSN 1476-5403

Moon, M. (2009). Neuroprotective effect of ghrelin in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson's disease by blocking microglial activation. *Neurotox Res,* Vol. 15, pp. 332-347, ISSN 1476-3524

Mortiboys, H. (2008). Mitochondrial function and morphology are impaired in parkin-mutant fibroblasts. *Ann Neurol,* Vol. 64, pp. 555-565, ISSN 1531-8249

Motamedi-Shad, N. (2009). Kinetic analysis of amyloid formation in the presence of heparan sulfate: faster unfolding and change of pathway. *J Biol Chem,* Vol. 284, pp. 29921-29934, ISSN 1083-351X

Muftuoglu, M. (2004). Mitochondrial complex I and IV activities in leukocytes from patients with parkin mutations. *Mov Disord,* Vol. 19, pp. 544-548, ISSN 0885-3185

Multhaup, G. (1995). Characterization of the high affinity heparin binding site of the Alzheimer's disease beta A4 amyloid precursor protein (APP) and its enhancement by zinc(II). *J Mol Recognit,* Vol. 8, pp. 247-257, ISSN 0952-3499

Muñoz, F.J., and Inestrosa, N.C. (1999). Neurotoxicity of acetylcholinesterase amyloid beta-peptide aggregates is dependent on the type of Abeta peptide and the AChE concentration present in the complexes. *FEBS Lett,* Vol. 450, pp. 205-209, ISSN 0014-5793

Munoz-Montano, J.R. (1997). Lithium inhibits Alzheimer's disease-like tau protein phosphorylation in neurons. *FEBS letters,* Vol. 411, pp. 183-188, ISSN 0014-5793

Nacharaju, P. (1999). Accelerated filament formation from tau protein with specific FTDP-17 missense mutations. *FEBS letters,* Vol. 447, pp. 195-199, ISSN 0014-5793

Naiki, H., and Gejyo, F. (1999). Kinetic analysis of amyloid fibril formation. *Methods Enzymol,* Vol. 309, pp. 305-318, ISSN 0076-6879

Naiki, H., and Nakakuki, K. (1996). First-order kinetic model of Alzheimer's beta-amyloid fibril extension in vitro. *Lab Invest,* Vol. 74, pp. 374-383, ISSN 0023-6837

Nakabeppu, Y. (2007). Oxidative damage in nucleic acids and Parkinson's disease. *J Neurosci Res,* Vol. 85, pp. 919-934, ISSN 0360-4012

Nakamura, K. (2008). Optical reporters for the conformation of alpha-synuclein reveal a specific interaction with mitochondria. *J Neurosci,* Vol. 28, pp. 12305-12317, ISSN 1529-2401

Nikoulina, S.E. (2002). Inhibition of glycogen synthase kinase 3 improves insulin action and glucose metabolism in human skeletal muscle. *Diabetes,* Vol. 51, pp. 2190-2198, ISSN 0012-1797

Nishikawa, K. (2003). Alterations of structure and hydrolase activity of parkinsonism-associated human ubiquitin carboxyl-terminal hydrolase L1 variants. *Biochem Biophys Res Commun,* Vol. 304, pp. 176-183, ISSN 0006-291X

Obeso, J.A. (2010). Missing pieces in the Parkinson's disease puzzle. *Nat Med,* Vol. 16, pp. 653-661, ISSN 1546-170X (Electronic)

Okada, S. (2005). No associations between Parkinson's disease and polymorphisms of the quinone oxidoreductase (NQO1, NQO2) genes. *Neurosci Lett,* Vol. 375, pp. 178-180, ISSN 0304-3940

Olanow, C.W. (2009). The scientific and clinical basis for the treatment of Parkinson disease (2009). *Neurology,* Vol. 72, pp. S1-136, ISSN 1526-632X (Electronic)

Ono, K. (2006). Anti-amyloidogenic effects of antioxidants: implications for the prevention and therapeutics of Alzheimer's disease. *Biochim Biophys Acta,* Vol. 1762, pp. 575-586, ISSN 0006-3002

Paisan-Ruiz, C. (2004). Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. *Neuron,* Vol. 44, pp. 595-600, ISSN 0896-6273

Palacino, J.J. (2004). Mitochondrial dysfunction and oxidative damage in parkin-deficient mice. *J Biol Chem,* Vol. 279, pp. 18614-18622, ISSN 0021-9258

Park, J. (2006). Mitochondrial dysfunction in Drosophila PINK1 mutants is complemented by parkin. *Nature,* Vol. 441, pp. 1157-1161, ISSN 1476-4687 (Electronic)

Parker, W.D., Jr. (1989). Abnormalities of the electron transport chain in idiopathic Parkinson's disease. *Ann Neurol,* Vol. 26, pp. 719-723, ISSN 0364-5134

Pasinetti, G.M. (2001). Cyclooxygenase and Alzheimer's disease: implications for preventive initiatives to slow the progression of clinical dementia. *Arch Gerontol Geriatr,* Vol. 33, pp. 13-28

Patton, R.L. (2006). Amyloid-{beta} peptide remnants in AN-1792-immunized Alzheimer's disease patients: a biochemical analysis. *Am J Pathol,* Vol. 169, pp. 1048-1063, ISSN

Perl, D.P. (2010). Neuropathology of Alzheimer's disease. *The Mount Sinai journal of medicine, New York,* Vol. 77, pp. 32-42, ISSN 1931-7581 (Electronic)

Perry, G. (1985). Paired helical filaments from Alzheimer disease patients contain cytoskeletal components. *Proceedings of the National Academy of Sciences of the United States of America,* Vol. 82, pp. 3916-3920, ISSN 0027-8424

Perry, G. (1999). Activation of neuronal extracellular receptor kinase (ERK) in Alzheimer disease links oxidative stress to abnormal phosphorylation. *Neuroreport,* Vol. 10, pp. 2411-2415, ISSN 0959-4965

Pitschke, M. (1998). Detection of single amyloid beta-protein aggregates in the cerebrospinal fluid of Alzheimer's patients by fluorescence correlation spectroscopy. *Nat Med,* Vol. 4, pp. 832-834, ISSN 1078-8956

Poorkaj, P. (1998). Tau is a candidate gene for chromosome 17 frontotemporal dementia. *Annals of neurology,* Vol. 43, pp. 815-825, ISSN 0364-5134

Przedborski, S. (2004). MPTP as a mitochondrial neurotoxic model of Parkinson's disease. *J Bioenerg Biomembr,* Vol. 36, pp. 375-379, ISSN 0145-479X

Qian, L. (2010). Neuroinflammation is a key player in Parkinson's disease and a prime target for therapy. *J Neural Transm,* Vol. 117, pp. 971-979, ISSN 1435-1463 (Electronic)

Qu, W. (2009). Kaempferol derivatives prevent oxidative stress-induced cell death in a DJ-1-dependent manner. *J Pharmacol Sci,* Vol. 110, pp. 191-200, ISSN 1347-8613

Rabinovic, A.D. (2000). Role of oxidative changes in the degeneration of dopamine terminals after injection of neurotoxic levels of dopamine. *Neuroscience,* Vol. 101, pp. 67-76, ISSN 0306-4522

Reddy, P.H. (2011). Abnormal tau, mitochondrial dysfunction, impaired axonal transport of mitochondria, and synaptic deprivation in Alzheimer's disease. *Brain research,* Vol. 1415, pp. 136-148, ISSN 1872-6240 (Electronic)

Reed, M.N. (2009). Cognitive effects of cell-derived and synthetically derived Abeta oligomers. *Neurobiol Aging,* Vol. 1558-1497 (Electronic)

Rogers, S.L. (1998). Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebo-controlled study. Donepezil Study Group. *Arch Intern Med,* Vol. 158, pp. 1021-1031, ISSN 0003-9926

Roher, A.E. (1996). Morphology and toxicity of A beta-(1-42) dimer derived from neuritic and vascular amyloid deposits of Alzheimer's disease. *J Biol Chem,* Vol. 271, pp. 20631-20635,

Sairam, K. (2003). Non-steroidal anti-inflammatory drug sodium salicylate, but not diclofenac or celecoxib, protects against 1-methyl-4-phenyl pyridinium-induced dopaminergic neurotoxicity in rats. *Brain Res,* Vol. 966, pp. 245-252, ISSN 0006-8993

Santa-Maria, I. (2007). Tramiprosate, a drug of potential interest for the treatment of Alzheimer's disease, promotes an abnormal aggregation of tau. *Mol Neurodegener,* Vol. 2, pp. 17, ISSN 1750-1326

Satake, W. (2009). Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease. *Nat Genet,* Vol. 41, pp. 1303-1307, ISSN 1546-1718

Sawamura, N. (2001). Site-specific phosphorylation of tau accompanied by activation of mitogen-activated protein kinase (MAPK) in brains of Niemann-Pick type C mice. *The Journal of biological chemistry,* Vol. 276, pp. 10314-10319, ISSN 0021-9258

Schapira, A.H., and Gegg, M. (2011). Mitochondrial contribution to Parkinson's disease pathogenesis. *Parkinsons Dis,* Vol. 2011, pp. 159160, ISSN 2042-0080 (Electronic)

Schapira, A.H., and Jenner, P. (2011). Etiology and pathogenesis of Parkinson's disease. *Mov Disord,* Vol. 26, pp. 1049-1055, ISSN 1531-8257 (Electronic)

Schenk, D. (1999). Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse. *Nature,* Vol. 400, pp. 173-177, ISSN 0028-0836

Schmechel, A. (2003). Alzheimer beta-amyloid homodimers facilitate A beta fibrillization and the generation of conformational antibodies. *J Biol Chem,* Vol. 278, pp. 35317-35324, ISSN 0021-9258

Schonbeck, U. (1998). Generation of biologically active IL-1 beta by matrix metalloproteinases: a novel caspase-1-independent pathway of IL-1 beta processing. *J Immunol,* Vol. 161, pp. 3340-3346, ISSN 0022-1767

Schoneich, C. (2003). Free radical reactions of methionine in peptides: Mechanisms relevant to beta-amyloid oxidation and Alzheimer's disease. *Journal of the American Chemical Society,* Vol. 125, pp. 13700-13713, ISSN

Selkoe, D.J., and Schenk, D. (2003). Alzheimer's disease: molecular understanding predicts amyloid-based therapeutics. *Annu Rev Pharmacol Toxicol,* Vol. 43, pp. 545-584, ISSN 0362-1642

Semchuk, K.M. (1992). Parkinson's disease and exposure to agricultural work and pesticide chemicals. *Neurology,* Vol. 42, pp. 1328-1335, ISSN 0028-3878

Shelton, S.B., and Johnson, G.V. (2004). Cyclin-dependent kinase-5 in neurodegeneration. *Journal of neurochemistry,* Vol. 88, pp. 1313-1326, ISSN 0022-3042

Shoji, M. (2000). Age-related amyloid beta protein accumulation induces cellular death and macrophage activation in transgenic mice. *J Pathol,* Vol. 191, pp. 93-101, ISSN

Siebert, A. (2009). Nrf2 activators provide neuroprotection against 6-hydroxydopamine toxicity in rat organotypic nigrostriatal cocultures. *J Neurosci Res,* Vol. 87, pp. 1659-1669, ISSN 1097-4547 (Electronic)

Siegel, 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,* Vol. 52, pp. 300-305, ISSN 0026-895X

Simon-Sanchez, J. (2009). Genome-wide association study reveals genetic risk underlying Parkinson's disease. *Nat Genet,* Vol. 41, pp. 1308-1312, ISSN 1546-1718

Skovronsky, D.M. (2000). In vivo detection of amyloid plaques in a mouse model of Alzheimer's disease. *Proc Natl Acad Sci U S A,* Vol. 97, pp. 7609-7614, ISSN 0027-8424

Smith, M.A. (1997). Iron accumulation in Alzheimer disease is a source of redox-generated free radicals. *Proc Natl Acad Sci U S A,* Vol. 94, pp. 9866-9868, ISSN 0027-8424

Snow, A.D. (1995). Differential binding of vascular cell-derived proteoglycans (perlecan, biglycan, decorin, and versican) to the beta-amyloid protein of Alzheimer's disease. *Arch Biochem Biophys,* Vol. 320, pp. 84-95, ISSN 0003-9861

Snow, A.D. (1994). Heparan sulfate proteoglycan in diffuse plaques of hippocampus but not of cerebellum in Alzheimer's disease brain. *Am J Pathol,* Vol. 144, pp. 337-347, ISSN 0002-9440

Son, H.J. (2011). A novel compound PTIQ protects the nigral dopaminergic neurons in MPTP-induced animal model of Parkinson's disease. *Br J Pharmacol,* Vol. 1476-5381

Spencer, J.P. (1998). Conjugates of catecholamines with cysteine and GSH in Parkinson's disease: possible mechanisms of formation involving reactive oxygen species. *J Neurochem,* Vol. 71, pp. 2112-2122, ISSN 0022-3042

Spillantini, M.G. (1998). Mutation in the tau gene in familial multiple system tauopathy with presenile dementia. *Proceedings of the National Academy of Sciences of the United States of America,* Vol. 95, pp. 7737-7741, ISSN 0027-8424

Spillantini, M.G. (1997). Alpha-synuclein in Lewy bodies. *Nature,* Vol. 388, pp. 839-840, ISSN 0028-0836

Spittaels, K. (2000). Glycogen synthase kinase-3beta phosphorylates protein tau and rescues the axonopathy in the central nervous system of human four-repeat tau transgenic mice. *The Journal of biological chemistry,* Vol. 275, pp. 41340-41349, ISSN 0021-9258

Stewart, W.F. (1997). Risk of Alzheimer's disease and duration of NSAID use. *Neurology,* Vol. 48, pp. 626-632, ISSN 0028-3878

Stine, W.B., Jr. (2003). In vitro characterization of conditions for amyloid-beta peptide oligomerization and fibrillogenesis. *J Biol Chem,* Vol. 278, pp. 11612-11622, ISSN 0021-9258

Strauss, K.M. (2005). Loss of function mutations in the gene encoding Omi/HtrA2 in Parkinson's disease. *Hum Mol Genet,* Vol. 14, pp. 2099-2111, ISSN 0964-6906

Stringer, J.L. (2004). Presence and induction of the enzyme NAD(P)H: quinone oxidoreductase 1 in the central nervous system. *J Comp Neurol,* Vol. 471, pp. 289-297, ISSN 0021-9967

Su, J.H. (1992). Localization of heparan sulfate glycosaminoglycan and proteoglycan core protein in aged brain and Alzheimer's disease. *Neuroscience,* Vol. 51, pp. 801-813, ISSN 0306-4522

Sullivan, M. (2007). Tramiprosate falls short in phase III Alzheimer's trial. *Clin Psychiatry News,* Vol. 35, pp. 27, ISSN

Suo, Z. (2002). Participation of protease-activated receptor-1 in thrombin-induced microglial activation. *J Neurochem,* Vol. 80, pp. 655-666, ISSN 0022-3042

T. Yamada, E.G.M., R.L. Schelper (1993). Histological and biochemical pathology in a family with autosomal dominant Parkinsonism and dementia. *Neurol Psychiatry Brain Res,* Vol. 26–35

Tabner, B.J. (2001). Production of reactive oxygen species from aggregating proteins implicated in Alzheimer's disease, Parkinson's disease and other neurodegenerative diseases. *Curr Top Med Chem,* Vol. 1, pp. 507-517, ISSN 1568-0266

Tanner, C.M. (2009). Occupation and risk of parkinsonism: a multicenter case-control study. *Arch Neurol,* Vol. 66, pp. 1106-1113, ISSN 1538-3687 (Electronic)

Tikka, T. (2001). Minocycline, a tetracycline derivative, is neuroprotective against excitotoxicity by inhibiting activation and proliferation of microglia. *J Neurosci,* Vol. 21, pp. 2580-2588, ISSN 1529-2401 (Electronic)

Tseng, H.C. (2002). A survey of Cdk5 activator p35 and p25 levels in Alzheimer's disease brains. *FEBS letters,* Vol. 523, pp. 58-62, ISSN 0014-5793

Van Laar, V.S. (2009). Proteomic identification of dopamine-conjugated proteins from isolated rat brain mitochondria and SH-SY5Y cells. *Neurobiol Dis,* Vol. 34, pp. 487-500, ISSN 1095-953X (Electronic)

van Muiswinkel, F.L. (2004). Expression of NAD(P)H:quinone oxidoreductase in the normal and Parkinsonian substantia nigra. *Neurobiol Aging,* Vol. 25, pp. 1253-1262, ISSN 0197-4580

Verbeek, M.M. (1997). Differences between the pathogenesis of senile plaques and congophilic angiopathy in Alzheimer disease. *J Neuropathol Exp Neurol,* Vol. 56, pp. 751-761, ISSN 0022-3069

Vu, T.K. (1991). Molecular cloning of a functional thrombin receptor reveals a novel proteolytic mechanism of receptor activation. *Cell,* Vol. 64, pp. 1057-1068, ISSN 0092-8674

Warner, T.T., and Schapira, A.H. (2003). Genetic and environmental factors in the cause of Parkinson's disease. *Ann Neurol,* Vol. 53 Suppl 3, pp. S16-23; discussion S23-15, ISSN 0364-5134

Wilcock, G.K. (2000). Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. Galantamine International-1 Study Group. *Br Med J,* Vol. 321, pp. 1445-1449, ISSN 0959-8138

Wilhelmus, M.M. (2007). Heat shock proteins and amateur chaperones in amyloid-Beta accumulation and clearance in Alzheimer's disease. *Mol Neurobiol,* Vol. 35, pp. 203-216, ISSN 0893-7648

Wilms, H. (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,* Vol. 17, pp. 500-502, ISSN 1530-6860 (Electronic)

Wischik, C.M. (1989). Cell biology of the Alzheimer tangle. *Current opinion in cell biology,* Vol. 1, pp. 115-122, ISSN 0955-0674

Woo, M.S. (2008). Inhibition of MMP-3 or -9 suppresses lipopolysaccharide-induced expression of proinflammatory cytokines and iNOS in microglia. *J Neurochem,* Vol. 106, pp. 770-780, ISSN 1471-4159 (Electronic)

Wright, T.M. (2006). Tramiprosate. *Drugs Today (Barc),* Vol. 42, pp. 291-298, ISSN 1699-3993

Wu, D.C. (2002). Blockade of microglial activation is neuroprotective in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson disease. *J Neurosci,* Vol. 22, pp. 1763-1771, ISSN 1529-2401 (Electronic)

Xu, Y. (2005). Conformational transition of amyloid beta-peptide. *Proc Natl Acad Sci U S A,* Vol. 102, pp. 5403-5407, ISSN 0027-8424

Zafar, K.S. (2007). A comparative study of proteasomal inhibition and apoptosis induced in N27 mesencephalic cells by dopamine and MG132. *J Neurochem,* Vol. 102, pp. 913-921, ISSN 0022-3042

Zafar, K.S. (2006). Overexpression of NQO1 protects human SK-N-MC neuroblastoma cells against dopamine-induced cell death. *Toxicol Lett,* Vol. 166, pp. 261-267, ISSN 0378-4274

Zafar, K.S. (2006). A potential role for cyclized quinones derived from dopamine, DOPA, and 3,4-dihydroxyphenylacetic acid in proteasomal inhibition. *Mol Pharmacol,* Vol. 70, pp. 1079-1086, ISSN 0026-895X

Zecca, L. (2008). Human neuromelanin induces neuroinflammation and neurodegeneration in the rat substantia nigra: implications for Parkinson's disease. *Acta Neuropathol,* Vol. 116, pp. 47-55, ISSN 0001-6322

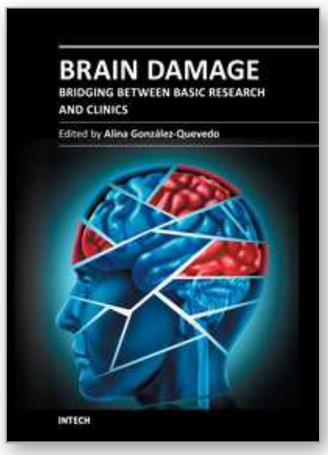
Zecca, L. (2003). The neuromelanin of human substantia nigra: structure, synthesis and molecular behaviour. *J Neural Transm Suppl,* Vol. 145-155, ISSN 0303-6995

Zeevalk, G.D. (2008). Glutathione and Parkinson's disease: is this the elephant in the room? *Biomed Pharmacother,* Vol. 62, pp. 236-249, ISSN 0753-3322

Zhang, W. (2005). Aggregated alpha-synuclein activates microglia: a process leading to disease progression in Parkinson's disease. *FASEB J,* Vol. 19, pp. 533-542, ISSN 1530-6860

Zhang, Y. (2000). Parkin functions as an E2-dependent ubiquitin- protein ligase and promotes the degradation of the synaptic vesicle-associated protein, CDCrel-1. *Proc Natl Acad Sci U S A,* Vol. 97, pp. 13354-13359, ISSN 0027-8424

Zimprich, A. (2004). Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. *Neuron,* Vol. 44, pp. 601-607, ISSN 0896-6273




**Brain Damage - Bridging Between Basic Research and Clinics**
Edited by Dr. Alina Gonzalez-Quevedo

ISBN 978-953-51-0375-2
Hard cover, 282 pages
**Publisher** InTech
**Published online** 16, March, 2012
**Published in print edition** March, 2012

"Brain Damage - Bridging Between Basic Research and Clinics" represents a collection of papers in an attempt to provide an up-to-date approach to the fascinating topic of brain damage in different pathological situations, combining the authors' personal experiences with current knowledge in this field. In general, the necessary link between basic and clinical neurosciences is highlighted, as it is through this interaction that the theoretical understanding of the pathophysiological mechanisms can be successfully translated into better ways to diagnose, treat and prevent the catastrophic events that occur when the brain suffers from external or internal noxious events. The book spans different aspects of brain injury, starting from damage occurring in the fetal and child brain, followed by different neurodegenerative processes. Attention is also focused on the negative effects of drug addictions and sleep deprivation on the brain, as well as on the early assessment of brain injury for preventive strategies employing sensitive biomarkers.

**How to reference**
In order to correctly reference this scholarly work, feel free to copy and paste the following:

YoungSoo Kim, Yunkyung Kim, Onyou Hwang and Dong Jin Kim (2012). Pathology of Neurodegenerative Diseases, Brain Damage - Bridging Between Basic Research and Clinics, Dr. Alina Gonzalez-Quevedo (Ed.), ISBN: 978-953-51-0375-2, InTech, Available from: http://www.intechopen.com/books/brain-damage-bridging-between-basic-research-and-clinics/pathology-of-neurodegenerative-disease

INTECH
open science | open minds

**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

IntechOpen