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Pathology of Neurodegenerative Diseases

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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).

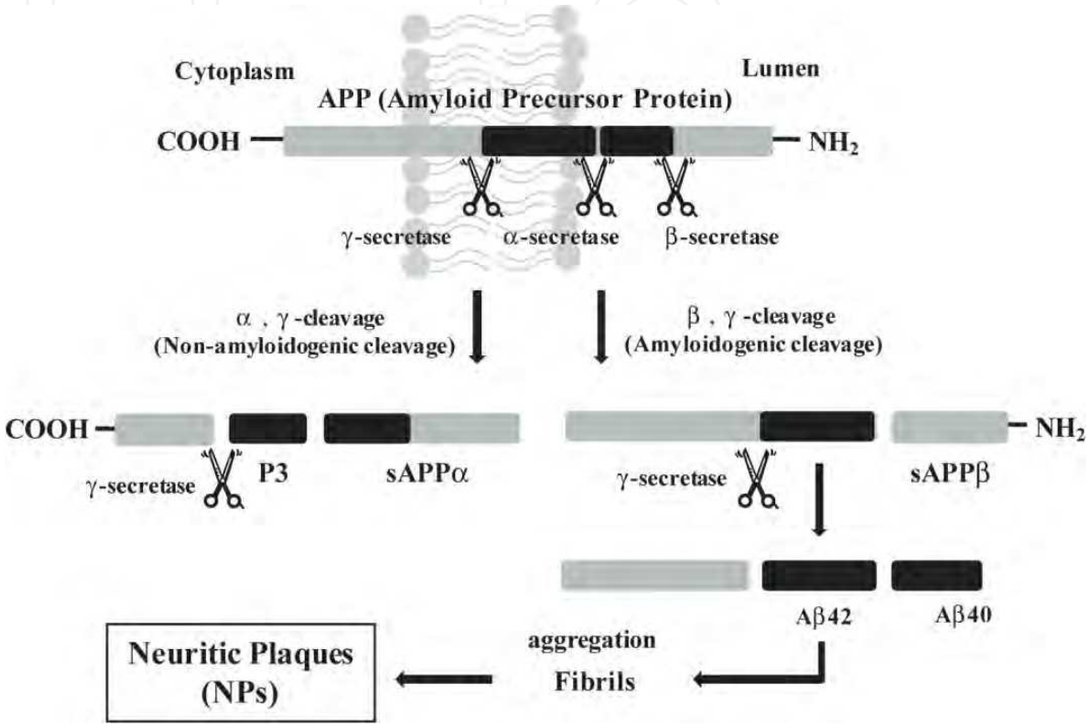

Fig. 1. APP processing and the generation of Aβ (taken from Y. Kim et al., 2009)

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).

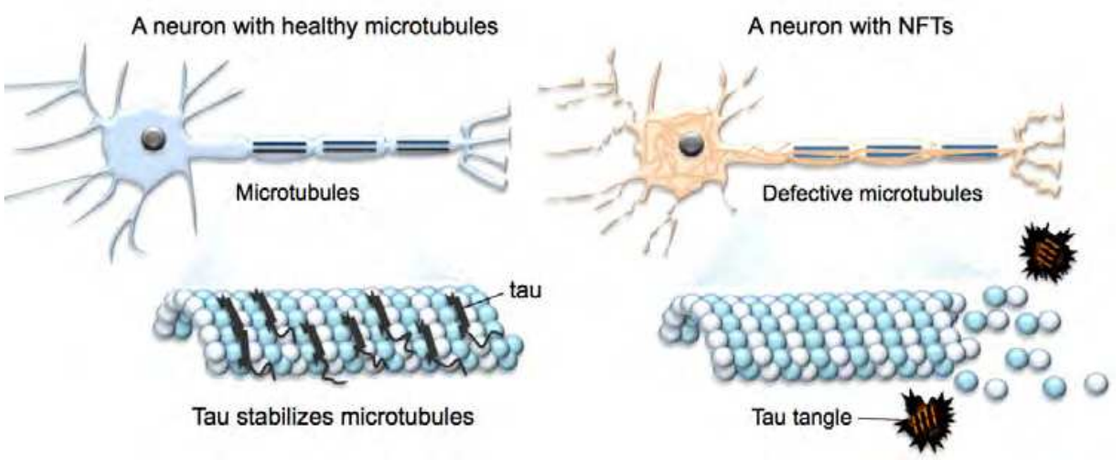

Fig. 2. The formation of NFTs and microtubule disruption (adapted from Brunden et al., 2009).

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.

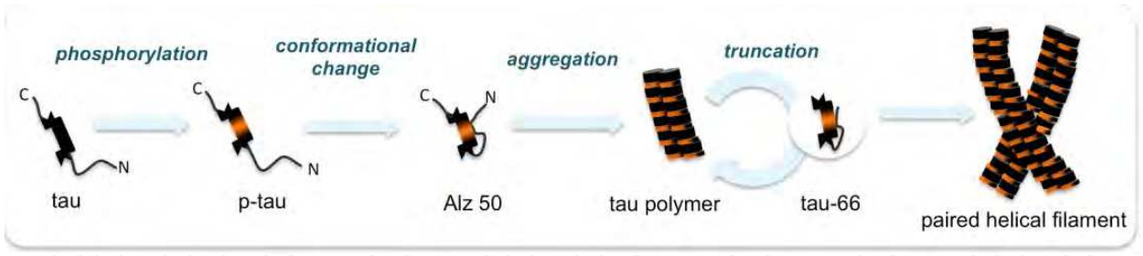

Fig. 3. Diagrammatic representation of tau conformation and NFT formation

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).

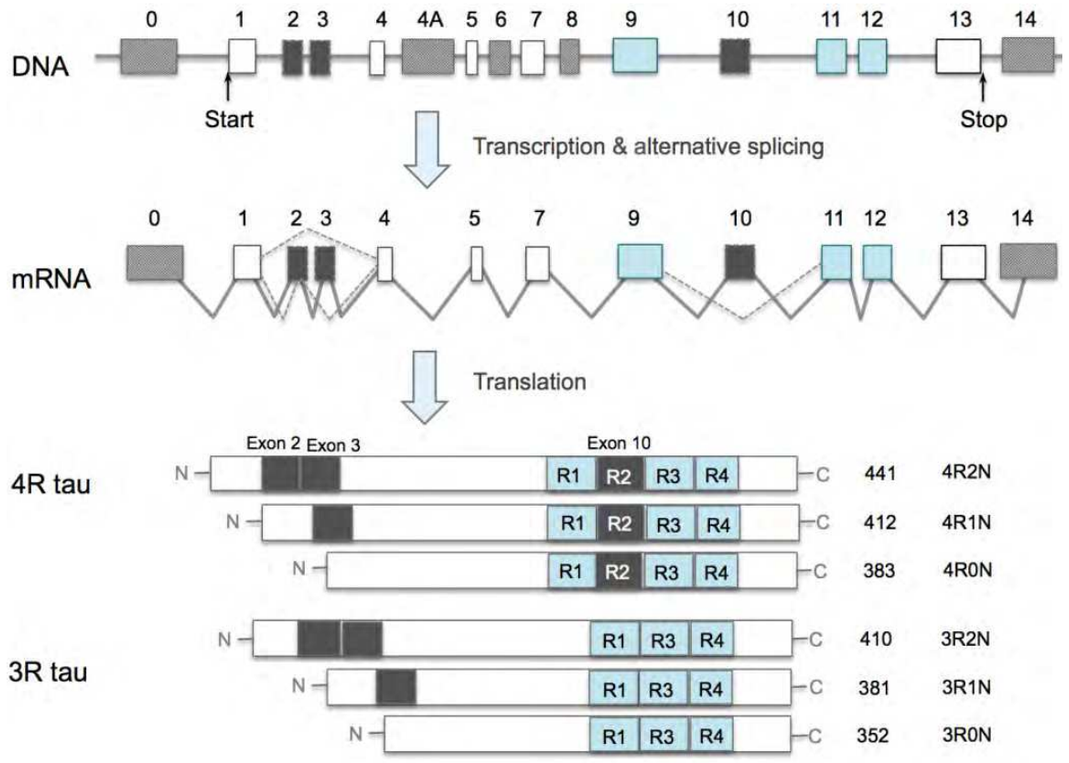

Fig. 4. Illustration represents human tau gene, mRNA, and six isoforms (adapted from Gendron and Petrucelli, 2009).

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.

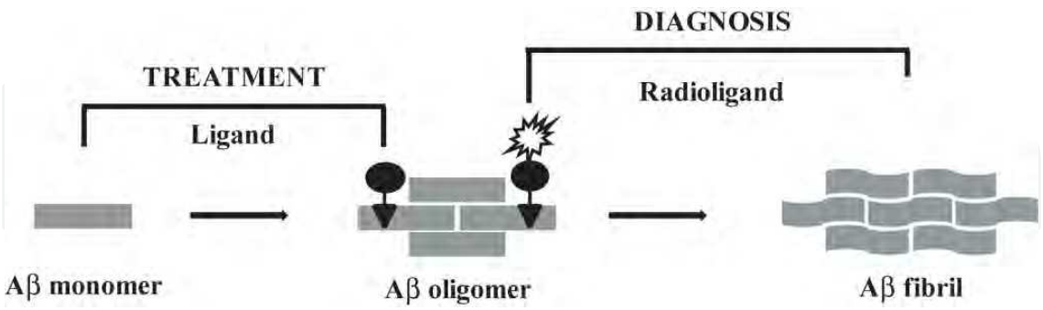

Fig. 5. Targets for amyloid treatment and diagnosis (taken from Y. Kim et al., 2009)

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).

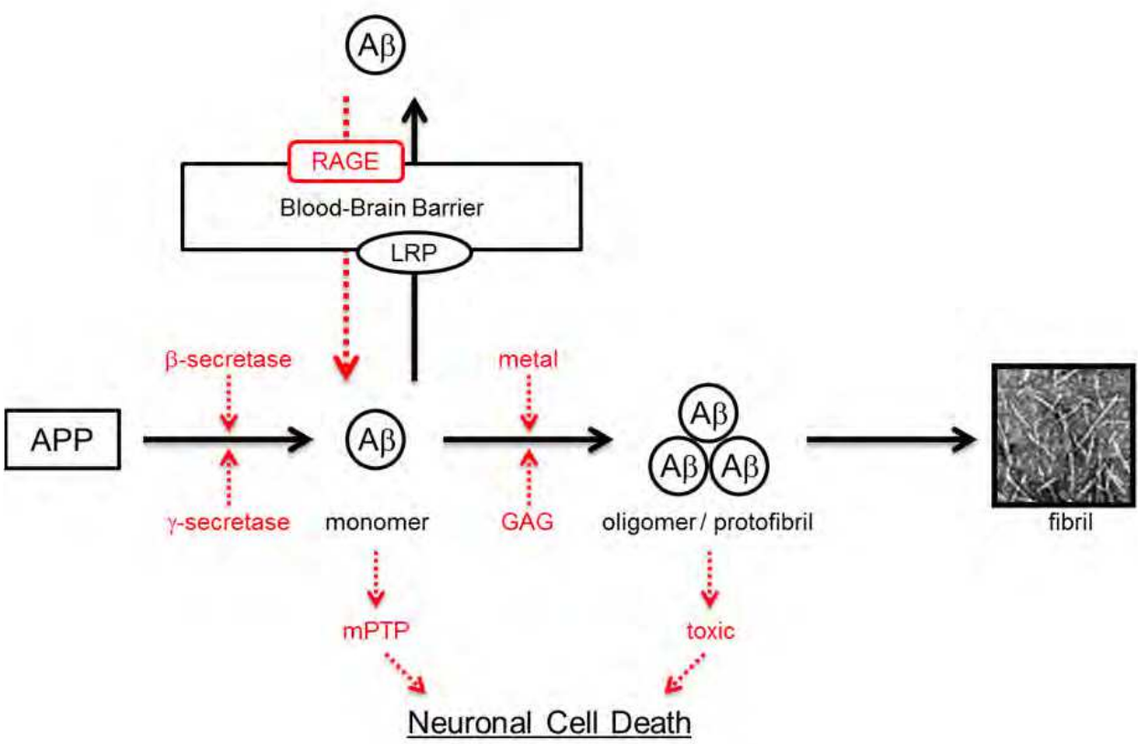

Fig. 6. Drug targets in amyloid cascade

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.

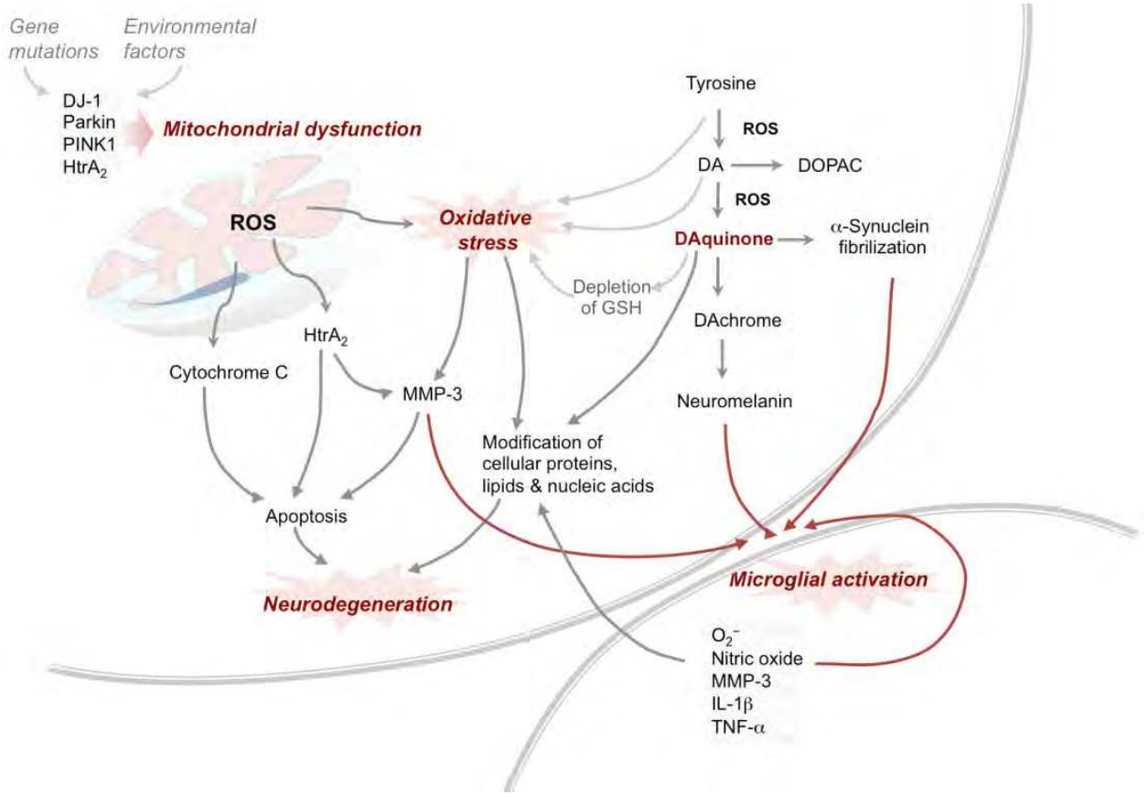

Fig. 7. Molecular cascades of DAergic neurodegeneration in the pathophysiology of PD.

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).

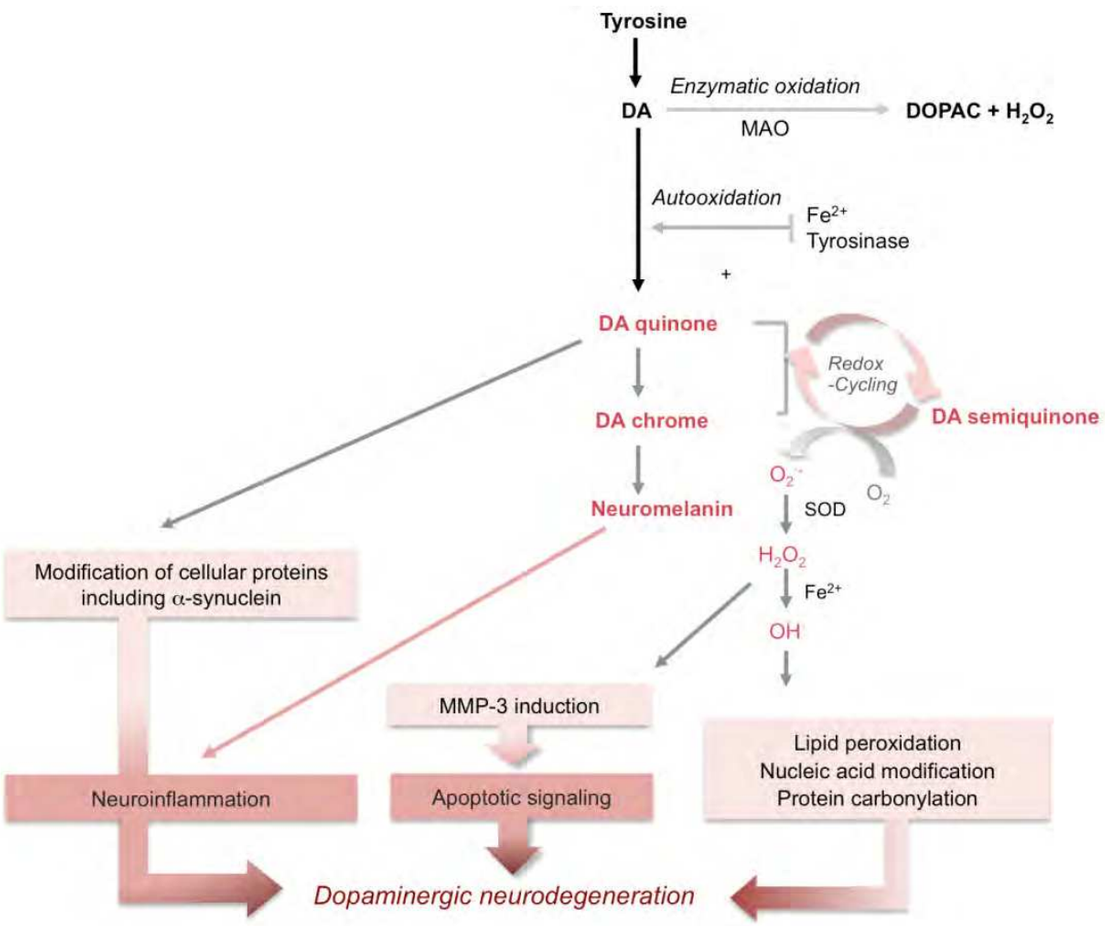

Fig. 8. Dopaminergic neurodegeneration.

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.

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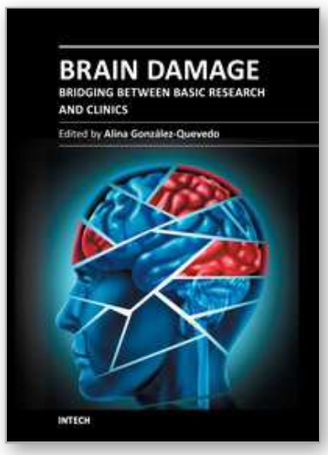

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"Brain Damage - Bridging Between Basic Research and Clinics" represents a collection of papers in an attempt to provide an up-to-date approach to the fascinating topic of brain damage in different pathological situations, combining the authors' personal 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.

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