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An Overview of Target Specific Neuro-Protective and Neuro-Restorative Strategies

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1. Introduction

The cellular mechanisms underlying neuronal loss and neurodegeneration have been an area of great interest for neuroscientists throughout the world. The development of animal models that simulate critical components of clinical neurodegenerative diseases have provided tremendous insight into the pathophysiological pathways and have facilitated the application of targeted pharmacotherapy. Although neurodegenerative diseases (ND), such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), and multiple sclerosis (MS) each have distinct clinical symptoms and pathologies, they also share common mechanisms such as intra- and/or extracellular accumulation of misfolded proteins; apoptosis; neuroinflammation; mitochondrial injury, oxidative stress and excitotoxic insult (Tarawneh and Galvin, 2010). No one mechanism appears to be primary in all cases of a particular ND, and these pathogenic most mechanisms most likely act synergistically through complex interactions to promote neurodegeneration. Discussion of these mechanisms is briefly reviewed here in reference to their implications for the development of novel neuroprotective /neuro-restorative agents targeting one or more of these pathways.

2. Misfolding of protein: An important target of treatment for neurodegenerative diseases

Protein misfolding is the physical process by which a polypeptide folds into its characteristic and functional three dimensional structures. Failure to fold into native structure results in inactive protein which is referred to as misfolded protein (Soto, 2003). Neuronal tissues are exquisitely sensitive to defective protein folding, and the accumulation of misfolded proteins is proteotoxic due to dominant effects of insolubility, inappropriate intermolecular interactions, and long half-lives (Neef et al., 2010). Protein misfolding and improper processing by the cellular quality-control system causes many highly debilitating disorders, ranging from heritable diseases, such as cystic fibrosis (CF) and α 1-antitrypsin deficiency as well as several other several neurodegenerative disorders (Soto, 2003; Singh, 2010). Hereditary protein

conformational disorders are characterized by coding region trinucleotide expansions resulting in the insertion of poly-glutamine (polyQ) tracts that adopt β -sheet structures and that are prone to incorrect folding and aggregation (Neef et al., 2010; Soto, 2003). Expansion of poly Q tracts has been associated with at least nine neurodegenerative diseases (Khare et al., 2005). There are currently no cure for any of the polyQ diseases, but researchers hypothesize that if the abnormal polyQ proteins could be stabilized into their correct conformation, the neurotoxicity associated with protein misfolding in neuronal tissues might be prevented, leading to arrest of the disease process (Heller, 2010).

2.1 Alzheimer's disease (AD)

Alzheimer's disease is characterized by the aggregation and accumulation of two proteins: amyloid beta-peptide (A β) which is deposited in extracellular senile plaques and the microtubule-associated protein tau which accumulates in a highly phosphorylated form as paired helical filaments that comprise the intraneuronal neurofibrillary tangles (NFTs) and neuropil threads (Hanger et al., 2009). In AD, tau appears to become hyperphosphorylated, which may contribute to destabilization of microtubules and may be incorporated into neuro-fibrillary tangles. One approach used with transgenic mice has involved NAP (Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln; NAPVSIPQ), an octapeptide that prevents disruption of microtubules by binding to tubulin. Administration of this compound decreased hyperphosphorylation of tau and improved cognitive function in mice (Matsuoka et al., 2008), recently this drug has entered a clinical trial (Potter, 2010). Another approach focuses on enzymes involved in phosphorylating tau. Glycogen synthase kinase-3 (GSK-3), has been shown to cause hyperphosphorylation of tau when over expressed in transgenic mice, and inhibition of this enzyme decreases levels of β -amyloid (Phiel et al., 2003). Lithium chloride by inhibiting GSK-3, decreases hyperphosphorylation of tau and improves cognition (Noble et al., 2005).

One of the approaches to decrease the levels of β -amyloid is passive immunization with antibodies targeting portions of the β -amyloid molecule. Bapineuzumab (AAB-001) is a humanized monoclonal antibody to the N-terminus of β -amyloid. Two phase 2 trials have been conducted with this drug. In one trial, cortical β -amyloid load was significantly decreased (Rinne et al., 2010). In the other trial, no statistically significant difference in cognitive function was found (Salloway et al., 2009). Interestingly, bapineuzumab appeared to produce some beneficial cognitive effects in individuals who did not have the $\epsilon 4$ allele of the apolipoprotein E (ApoE) gene, but those results were not statistically significant (Rinne et al., 2010). Treatment with bapineuzumab has also been found to reduce tau levels in patients with AD in two clinical trials (Kerchner & Boxer, 2010). A phase 3 clinical trial is currently being conducted with bapineuzumab. Ponezumab (PF-04360365), an antibody targeted to the free carboxy terminus of β -amyloid 1-40, has undergone preliminary human trials and has been shown to increase CSF β -amyloid (Zhao et al., 2010). It seems likely that drugs targeting β -amyloid would need to be given to patients early in the course of disease—before neurodegeneration becomes severe enough to impair cognitive function (Potter, 2010).

The most common pathogenesis of familial AD involves misprocessing of amyloid precursor protein (APP) by enzyme gamma secretase. Targeting of gamma-secretase is another area of drug development for AD (Tomita, 2009). One of these gamma-secretase

inhibitors, begacestat (GSI- 953), decreased plasma levels, but not CSF levels, of β -amyloid in humans (Jacobsen et al., 2009; Martone et al., 2009). Another gamma-secretase inhibitor, BMS- 708163, decreased CSF levels of β -amyloid in humans (Ereshfksy et al., 2009). A third gamma- secretase inhibitor, PF-3084014 ([(S) -2-[((S) -5,7- difluoro-1,2,3,4-tetrahydronaphthalen-3-ylamino)- N -(1-(2-methyl-1-(neopentylamino) propan-2-yl)-1H-imidazol-4-yl), pentanamide]], decreased plasma and CSF levels of β -amyloid in animals, but only plasma levels in humans (Soares et al., 2009). Stimulation of α -secretase leads to non-amyloidogenic processing of amyloid processing protein (APP). Some of the muscarinic agonists have been shown to increase α -secretase activity, and a number of other drugs are being investigated for their ability to inhibit gamma secretase (Mangliasche et al., 2010).

Inhibition of tau aggregation is yet another approach. Immunotherapy with antibodies directed at tau decreased tangles in the Tg P301L mouse model (Asuni et al., 2007). Another avenue that has currently passed a phase 2 trial is blocking tau aggregation with methylene blue (Staff et al., 2008). Methylene blue has also been shown to enhance mitochondrial function (Pandey et al., 2008), and decrease the levels of β -amyloid, and cognitive deficits in 3xTg-AD transgenic mice (Medina et al., 2011). A larger phase 3 trial has been planned. Other such inhibitors which are being studied as potential therapeutic agents for AD include phenothiazines, porphyrins and polyphenols (Brunden et al., 2009).

Heat shock protein 90 (Hsp90) is a member of a large family of molecules that help in regulating pathogenic transformation, and the stability of abnormally folded neuronal proteins, allowing the accumulation of toxic aggregates (Lu et al., 2009; Luo et al., 2010). Inhibition of Hsp 90 activates heat shock factor I (HSF- I) to induce production of Hsp 70 and Hsp40 as well as other chaperones may be promising treatment for AD and other neurodegenerative diseases (Luo et al., 2010). A new Hsp90 inhibitor novobiocin provided excellent neuroprotection, with little or no toxicity in a cell culture model of beta-amyloid (Lu et al., 2009).

2.2 Parkinson's disease (PD)

PD is characterized mainly by progressive and selective loss of dopaminergic neurons in the substantia nigra pars compacta, with subsequent dopamine (DA) decline in the nigrostriatal pathway, and by the presence of intracytoplasmic fibrillar α -Synuclein (α -Syn) protein aggregates (Lewy Bodies, LB) in the remaining nigral neurons (Turturici et al., 2011). α -Syn is a 140- amino acid neuronal protein probably involved in regulating cell differentiation, synaptic plasticity, and dopaminergic neurotransmission. The presence of large amounts of α -syn aggregates in the presynaptic nerve terminals has been reported. It is plausible that either misfolded α -Syn, or increased amounts of normal α -syn, contribute to neurotoxicity in PD (Kramer & Schaeffer, 2007). The formation of an N-methylated derivative of α -Syn, by the replacement of the Gly73 with sarcosine, resulted in reduced fibril formation and markedly reduces toxicity (Paleologou et al., 2005). α -Syn peptide fragments that bind to full length α -syn have also been studied as potential targets for inhibiting α -syn aggregation. Peptides derived from the N-terminal of the non-amyloidogenic component (NAC) region of α -syn can bind to the full length α -syn and block the assembly of α -syn into both early oligomers and mature amyloid-like fibrils. Furthermore, the addition of a polyarginine-peptide delivery system has allowed the development of a cell permeable inhibitor of aggregation, the peptide RGGAVVTGRRRRR-amide, that inhibits iron-induced DNA

damage in cells transfected with α -synuclein (A53T) (Paleologou et al., 2005). The other compounds which have been shown to inhibit α -synuclein aggregation include melatonin (Sae-Ung et al., 2011), and statins (Bar-On et al., 2008).

2.3 Huntington's disease (HD)

Inclusion bodies of aggregated mutant huntingtin protein (htt) fragments are a neuropathological hallmark of HD. The disease is caused by expansion of a CAG repeat in the Huntington's gene coding for polyQ which leads to the formation of fibrillar protein aggregates and neuronal cell death. Preventing misfolding steps and thereby aggregation of the polyQ containing protein htt may represent an attractive therapeutic strategy to postpone the onset and progression of HD (Wytenbach et al., 2002). Moreover expression of several molecular chaperones such as Hsp70, Hsp40, Hsp27, Hsp84, and Hsp105 have been shown to increase the solubility of polyQ proteins in *Drosophila* and mouse models of HD (Tarawneh & Galvin, 2010).

Intracellular antibodies (intrabodies) which target polyQ protein and prevent its aggregation have been identified. Clumps of htt have also been seen in neuronal nucleus and cytoplasm in mice and monkey model of HD. Intrabodies created by injecting the virus into mice brain have been shown to mop up mutant proteins that drive neurodegeneration in HD (Wang et al., 2008). One of the first detectable signs of cellular dysfunction in striatal medium spiny neurons in HD is the loss of cannabinoid G protein coupled receptors (GPCRs) (Glass et al., 2000). Activation of cannabinoid receptor 1 (CB1), in an invitro model of HD has been recently observed to confer significant level of protection against mutant htt induced cell death, (Scotter et al., 2010). Endocannabinoids act as neuromodulatory and neuroprotective cues by engaging type 1 cannabinoid receptors (CB1). Drugs that can activate CB1 receptor are expected to attenuate disease progression (Blazquez et al., 2011). It has been suggested that the htt aggregates may be cleared by autophagy (Rubinshtein et al., 2005). In addition, administration of small molecules that promote autophagy has improved phenotypes in cell and animal models of HD (Ravikumar et al., 2004).

Enhancing autophagy with rapamycin accelerated mutant htt clearance and improved cell viability. The levels of wild-type htt were not affected by these compounds, suggesting that autophagy plays a specific role in the clearance of aggregate-prone htt (Krainc, 2010). Recent studies have identified microtubule-associated protein light chain 3 proteins (LC3), interacting proteins, such as p62, that play a role in the autophagic clearance of protein aggregates (Komatsu et al., 2007). A multifunctional protein, p62 has been shown to bind ubiquitin and LC3; possibly providing a molecular shuttle for misfolded aggregated proteins to promote their clearance by autophagy (Bjorkoy et al., 2005). This data supports the idea that P62 induced autophagy may have significant potential for treating HD. Studies have also demonstrated that mutant htt interacts directly with the histone acetyltransferase (HAT) domain of the cyclic AMP response element binding protein (CBP) (Steffan et al., 2001). Depletion of CBP enhances toxicity whereas over expression of CBP suppresses toxicity by mutant htt. Jeong et al. (2009) showed that acetylation of mutant htt by CBP leads to neuroprotection by improving clearance of the mutant protein.

The green tea polyphenol (-) - epigallocatechin-3-gallate (EGCG), can potently inhibit htt aggregation in vitro and in a *Drosophila* model of HD (Ehrnhoefer et al., 2006). The agents

that can stabilize native conformation such as dimethyl sulfoxide (DMSO), glycerol, trimethylamine N-oxide (TMAO), and trehalose offer utility in preventing aggregation (Nagai and Popiel, 2008).

2.4 Amyotrophic lateral sclerosis (ALS)

Abnormal protein aggregates are seen in brain and spinal cord samples from patients with sporadic ALS, which suggests that protein misfolding and aggregation contribute to the pathogenesis of ALS, although a causative role remains controversial (Bosco et al., 2010; Kerman et al., 2010; Liu et al., 2009). The development of a vaccine or immunoglobulins to remove misfolded protein in ALS is a novel therapeutic strategy. There is emerging evidence for the existence of secretory pathways for superoxide dismutase (SOD1) mutant linked to ALS. Vaccination with SOD1 mutant protein in the ALS SOD1 transgenic mouse model delayed disease onset and significantly extended survival suggesting that immunization strategies should be considered as potential for treatment of familial ALS (Takeuchi et al., 2010).

Arimoclomol an amplifier of heat shock protein expression is involved in cellular stress response, and has emerged as a potential therapeutic candidate in ALS in recent years. Treatment with arimoclomol was reported to improve survival and muscle function in a mouse model of motor neuron disease. Several single and multiple dose safety studies have been completed in healthy control subjects. A 3 month Phase IIa study in people with ALS demonstrated safety at dosages up to 300mg/day and another study is currently recruiting participants with familial ALS (Lanka et al., 2009). Up-regulation of endoplasmic reticulum chaperones and eukaryotic initiation factor 2 (eIF2) (Ilieva et al., 2007), activation of unfolded protein response cascades (Atkin et al., 2006) and ribosomal detachment resulting in endoplasmic reticulum distention and motor neuron shrinkage have all been demonstrated in pathological studies of sporadic ALS (Oyanagi et al., 2008). Increased levels of protein disulfide isomerase (PDI), an endoplasmic reticulum-localized chaperone molecule that promotes protein folding, have been found in cerebrospinal fluid of ALS (Atkin et al., 2006).

These findings indicate an important role for endoplasmic reticulum stress and unfolded protein response dysregulation in the pathogenesis of ALS. Interestingly, lithium and valproic acid induce BiP and other endoplasmic reticulum chaperone proteins and reduce endoplasmic reticulum stress. Both of these drugs have been investigated in human studies without benefit (Aggarwal et al., 2010).

3. Mitochondrial dysfunction

Mitochondrial dysfunction has long been associated with neurodegenerative diseases (Burchell et al., 2010). Several lines of research suggest that mitochondrial abnormalities, including defects in oxidative phosphorylation, increased accumulation of mitochondrial DNA defects, impaired calcium influx, and accumulation of mutant proteins in mitochondria, are important cellular changes in both early and late-onset neurodegenerative diseases (Burchell et al., 2010). Therefore, one would predict that agents that alleviate mitochondrial dysfunction could be beneficial and exert neuroprotective effects (Burchell et al., 2010).

3.1 Alzheimer's disease (AD)

There is accumulating evidence suggesting that mitochondrial dysfunction occurs prior to the onset of symptoms in AD (Su et al., 2009). Mitochondria are exceptionally poised to play a crucial role in neuronal cell survival or neurodegeneration because they are regulators of both energy metabolism and apoptotic pathways (Su et al., 2009). In a recent study the mitochondria-targeted antioxidants (MTAs) MitoQ and SS31 and the anti-aging agent resveratrol were found to have a protective effect on neurons in a mouse model of AD (Manczak et al., 2010). In primary neurons from A β PP transgenic mice, which were treated with MitoQ and SS31, neurite outgrowth significantly increased and cyclophilin D expression significantly decreased indicating potential of these drugs to treat AD (Manczak et al., 2010).

Mitochondrial antioxidants acetyl-L-carnitine (ALCAR) and R- α -lipoic acid (LA) reduced oxidative stress and mitochondrial abnormalities in cellular mouse models of AD and restored cognitive functions in aged rats (Aliev et al., 2009). A meta analysis of 21 double blind randomized, placebo controlled studies showed that ALCAR either improved cognitive deficits or delayed the progression of cognitive decline in AD (Montgomery et al., 2003).

Coenzyme Q10 (CoQ10) is essential for mitochondrial energy production. CoQ10 was observed to reduce oxidative stress and tau pathology in mice (Dumont et al., 2011), and inhibited β -amyloid (β A) formation (Ono et al., 2005). CoQ10 treatment has also been shown to decrease brain oxidative stress, reduce β A plaque load, and improve cognitive performance in a transgenic mouse model of Alzheimer's disease (Dumont et al., 2011). In a recent study dietary supplementation of carnosine an endogenous peptide with metal chelating and free radical scavenging properties was observed to completely rescue AD and aging related mitochondrial dysfunction and was suggested as a potential candidate for a combined therapeutic approach for the treatment of AD (Corona et al., 2011).

3.2 Parkinson's disease (PD)

The most convincing evidence for the role of mitochondrial damage in PD comes from studies of rare familial forms of PD, in which genetic mutations linked to PD result in mitochondrial impairments and increased susceptibility to oxidative stress (Martin et al., 2011). Parkin knockout mouse model demonstrate impaired mitochondrial activity and altered oxidative stress proteins in PD (Palacino et al., 2004). Further studies in this direction are likely to provide elaborate knowledge about mitochondrial dysfunction pathways in PD and help in developing new therapeutic strategies.

A significant reduction in CoQ10 levels in mitochondria has been reported in the platelets of patients with PD, which directly correlates with a decrease in complex-I activity. CoQ10 provides significant protection against MPTP-induced dopaminergic neuronal degeneration (Faust et al., 2009). The oral administration of CoQ10 in PD patients resulted in reduction of Unified Parkinson's Disease Rating Scale (UPDRS) scores (Shults et al., 2004). The mitochondrial targeted antioxidant MitoQ has been shown to help in preservation of mitochondrial function after glutathione depletion, this drug is currently in a phase II clinical trial for Parkinson's disease (<http://www.parkinsons.org.nz/news/protectstudy.asp>). The other compounds which have shown promise in ameliorating the mitochondrial

dysfunction in experimental PD studies include creatine, lanosterol, melatonin, edaravone and trolox (Shim et al., 2011). However further studies are warranted before the clinical use of these drugs.

3.3 Huntington's disease (HD)

Abnormal mitochondrial function, decreased respiratory enzyme complex activities, increased electron leakage, and increased Ca^{2+} entry have all been shown to play a significant role in the pathophysiology of many neurodegenerative disorders including HD. Current evidence from genetic models of HD including mutation of the Huntington gene (mhtt), supports the mitochondrial dysfunction as major cause of the disease, with respiratory chain impairment relegated to a late secondary event. HD is associated with significant defects in mitochondrial respiratory enzymes, including mitochondrial succinate dehydrogenase (SDH, complex II) and aconitase a transglutaminase substrate. Protein aggregates interfere with mitochondrial function, mitochondrial trafficking in axons, and result in mitochondrial fragmentation and inhibition of mitochondrial fusion. SDH inhibitors including 3-nitropropionic acid and malonate cause medium spiny neuronal loss and clinical and pathological features reminiscent of HD in rodents and non-human primates (Chaturvedi and Beal, 2008).

High dose of CoQ10 significantly extends survival, improves motor performance and grip strength, and reduces brain atrophy in R6/2 HD mice. The combination of CoQ10 and minocycline in R6/2 mouse model of HD resulted in significantly improved behavioral measures, reduced neuropathological deficits, extended survival, and attenuated striatal neuron atrophy, as compared to either agent alone. Similarly, the combination of CoQ10 and remacemide resulted in significantly improved motor performance and increased survival in the R6/2 and the N-171-82Q transgenic mouse models of HD (Ferrante, 2002). These two compounds have been clinically tested separately and in combination in 340 patients with HD. Administration of CoQ10 resulted in a 14% decrease in disease progression while remacemide demonstrated no efficacy (Huntington Study Group, 2001). Creatine significantly improves survival, improves motor performance, increases brain ATP levels, and delays atrophy of striatal neurons and the formation of htt-positive aggregates in transgenic mice (Andreassen, 2001). Sirtuins (silent information regulators SIRT) are members of the NAD⁺-dependent histone deacetylase family of proteins in yeast, and play an important role in regulating mitochondrial function. Inhibition of sirtuins has been shown to suppress disease pathogenesis in *Drosophila* models of HD (Pallos, 2008).

Reduced levels of peroxisome proliferator activated receptor gamma co activator alpha (PGC-1 α), a transcriptional regulator of several enzymes has been shown in the striatum of R6/2 HD mice. The PGC-1 α pathway plays an important role in regulating cellular energy metabolism. PGC-1 α induces mitochondrial biogenesis and respiration in muscle cells and regulates several aspects of adaptive thermogenesis by increasing expression of nuclear-encoded electron transport chain components, metabolic enzymes, and uncoupling proteins. Increasing PGC-1 α levels dramatically protect neural cells in culture from oxidative stress-mediated death (St -Pierre et al., 2006). Thus activity of PGC-1 α pathways promises to be an effective therapeutic approach for mitochondrial disorders. Metformin can enhance the PGC-1 α expression and mitochondrial biogenesis possibly at least in part via AMPK phosphorylation in the skeletal muscle (Suwa et al., 2006). The therapeutic effects of

metformin on HD warrants further studies. A recent study demonstrated that transcription factor peroxisome proliferator activated receptor γ (PPAR γ) plays a major role in energy homeostasis of HD. Rosiglitazone a potent agonist of PPAR γ has been shown to prevent mitochondrial dysfunction in mutant htt expressing cells and in R6/2 HD mice (Chiang et al., 2010; Quintanilla et al., 2008). These findings support the view that upregulation of PPAR γ plays a major role in HD.

3.4 Amyotrophic lateral sclerosis (ALS)

Mitochondrial and bioenergetic defects have been claimed to play a vital role in ALS pathogenesis. Altered respiratory chain enzyme activities and CNS energy hypometabolism in spinal cord and motor cortex are the hallmark of ALS (Sasaki et al. 2005). Swelling and vacuolar degeneration of mitochondria is a prominent finding prior to the onset of clinical deficits in experimental HD mice. Mutant SOD1 is found in the mitochondrial inter-membrane space and binds to the inner mitochondrial membrane in the SOD1G93A mouse (Ahtoniemi et al., 2008) causing peroxidation of cardiolipin and alteration of anchor cytochrome c to the inner mitochondrial membrane which activates programmed cell death (Kirkinezos et al., 2004).

Pramipexole a lipophilic cation that concentrates into brain and mitochondria significantly lowers oxidative stress, maintains mitochondrial function, and has neuroprotective effects independent of dopamine-receptor agonism. R+ pramipexole, prolonged survival of ALS SOD1 transgenic mice, and in a phase 2 study of 102 patients with ALS it was found to be safe and well tolerated (Cudkowicz et al., 2010). Motor decline seemed to lessen with increasing doses (Cudkowicz et al., 2010). These encouraging results in Phase II studies warrant further studies. Olesoxime (previously TRO19622) is a mitochondrial pore modulator that was discovered after screening about 40,000 compounds in an in-vitro motor neuron cell death assay (Bordet et al., 2007). In SOD1 transgenic mouse model, olesoxime showed a delayed onset and prolonged survival (Bordet et al., 2007). A phase 2/3 study of olesoxime is underway in Europe (NCT00868166).

3.5 Multiple sclerosis (MS)

There is increasing evidence implicating mitochondria in the pathogenesis of multiple sclerosis. Mitochondrial respiratory chain complex I and complex III activity is reduced in non-lesional motor cortex, where a number of nuclear DNA-encoded transcripts of mitochondrial proteins are decreased (Dutta et al., 2006). Interestingly, complex IV activity and mitochondrial DNA copy number are increased in chronic active lesion homogenates and within normal appearing grey matter neurons, respectively, possibly as a compensatory mechanism (Blokchin et al., 2008). Defects of mitochondrial respiratory chain complexes and depletion of mitochondria not only cause an energy deficit but may increase the susceptibility of axons to excitotoxic injury through impaired calcium handling capacity (Blokchin et al., 2008). The detoxification of mitochondrial superoxide by transfecting adeno associated virus containing manganese super oxide dismutase (SOD), led to a reduction in degeneration of mitochondrial structure (Qi et al., 2007). The Carboxyfullerene a fullerene compound that increased survival of mice lacking mitochondrial MnSOD (SOD-1) localized to mitochondria and reduced superoxide production. When combined with N-methyl D-aspartate (NMDA) receptor antagonist a fullerene derivative (ABS75) reduced axonal

degeneration and disease progression. The mitochondrial permeability transition pore which allows calcium efflux from mitochondria, when opened and is modulated during hypoxic preconditioning has been identified as a potential therapeutic target in MS (Forte et al., 2007)

Polyunsaturated fatty acid (PUFA) and antioxidant deficiencies along with decreased cellular antioxidant defense mechanisms have been observed in MS patients. Both dietary antioxidants and PUFAs have the potential to diminish disease symptoms by targeting specific pathomechanisms and supporting recovery in MS (van Meeteren et al., 2005). Supplementation with long chain omega-3 PUFAs in MS patients and healthy controls decreased the secretion of the pro-inflammatory cytokines, IL-1b, TNF- α , IL-2, and IFN- γ by stimulated peripheral blood mononuclear cells as well as reduced secretion of the inflammatory eicosanoids such as, prostaglandin E2, and leukotriene B4 (LTB4), which are known to be increased in MS patients (Weinstock-Guttman et al., 2005). Thus dietary supplements which can modulate these eicosanoids help to reduce the severity of the disease and prevent recurrence, and in particular fish oil supplementation given together with vitamins C and E. can improve clinical outcome in patients with newly diagnosed MS. Although a few antioxidants showed some efficacy in animal models, there is limited and conflicting evidence of potential therapeutic effects of antioxidants such as vitamins C and E in treating MS.

4. Inflammation

Brain inflammation is a typical feature of neurodegenerative diseases and acute forms of brain injury. A large number of neurodegenerative diseases are associated with chronic inflammation, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis and all of the tauopathies, and age-related macular degeneration (Tansey and Goldberg, 2010). Considering the involvement of inflammatory processes in mechanism of neurodegeneration, and keeping in mind that activated microglia and astrocytes are a rich source of oxygen radicals, nitric oxide and neurotoxic and proinflammatory cytokines; anti-inflammatory drugs acting on these targets have the potential to exert beneficial effects in experimental and clinical neurodegenerative disorders.

4.1 Alzheimer's disease (AD)

The brains of AD patients have increased concentrations of acute phase reactants, cytokines, and complement protein as compared to age-matched controls (Heng et al., 2007). In a prospective cohort study of subjects with AD, high baseline levels of tumor necrosis factor (TNF) alpha were also found to be associated with a 4-fold increase in the rate of cognitive decline (Holmes et al., 2009).

Earlier studies have suggested a beneficial effect from non steroidal anti-inflammatory drugs (NSAIDs) in decreasing the risk of AD. Treatment with NSAIDs has been shown to decrease β -amyloid and tau levels in animal models of AD (Yoshiyama et al., 2007). These effects of NSAID's have been attributed to the inhibition of APP-associated γ -secretase (Sastre and Gentleman, 2010). It has been proposed that NSAIDs cause a delay in the onset or slow down progression of AD, through the inhibition of cyclooxygenase (COX) and lipooxygenases, leading to a decrease in prostaglandin synthesis and reactive oxygen

species formation (Leoutsakos et al., 2011). On the other hand, some other studies have suggested a possible deleterious effect of NSAIDs on cognition and an increase in neuronal damage (Breitner et al., 2011). The neurohormone melatonin was observed to exert inhibitory effects on β -amyloid aggregation, oxidation, and inflammation *in vitro*, and showed behavioral improvement in animal model of AD. Although melatonin can improve mild cognition impairment, it is not a cure for AD (Olcese, 2009). Combination of ibuprofen with glutathione and lipoic acid has proven to be useful in controlling AD induced cerebral amyloid deposits and behavioral deterioration (Pinnen et al., 2011).

4.2 Parkinson's disease (PD)

Systemic inflammation has been shown to promote microglial activation in PD, on the other hand genes implicated in PD may also influence inflammatory mediators. Over expression of wild-type α -synuclein in neurons is associated with the activation of microglia, and the release of TNF, IL-1 β , IL-6, COX-2, and iNOS (Tarawneh & Galvin, 2010). Minocycline, a tetracycline derivative, has been shown to possess anti-inflammatory and anti-apoptotic properties, which reduces microglial activation and inhibit the release of potentially toxic cytokines in the striatal region of MPTP mice. Pretreatment with minocycline improved survival of dopaminergic neurons in animal models of PD (Peng et al., 2006). Based on the efficacy, safety and tolerability of minocycline in a randomized, double-blind, Phase II clinical trial (The NINDS NET -PD 2006), it has been recommended for long-term treatment of PD.

NSAIDs have been associated with a 45% reduction in the risk of developing PD in one prospective study with 14 years of follow up (Wahner et al., 2007). On the other hand a case control study of 22,007 patients did not find evidence that NSAIDs use reduces PD (Driver et al., 2011). Triptolide, an active component of Tripterygium extracts, which possesses potent anti-inflammatory and immunosuppressive properties, exerts neuroprotective and neurotrophic activities in animal models of PD (Chen et al., 2010). Currently, the application of triptolide for PD is in preclinical stages. Similarly, the synthetic triterpenoid CDDO-Me, an inhibitor of NF κ B attenuates production of TNF and other glial-derived inflammatory mediators has been shown to protect dopaminergic neurons (Trans et al., 2008). Glatiramer acetate (GA) is an artificial copolymer of a pool of peptides (45 ~ 100 amino acids, MW 4.7 ~ 11 kDa) (Kipnis and Schwartz, 2002) which exerts anti-inflammatory effects through adaptive immunomodulation. Tsai (2007) suggested that it enhances the production of brain derived neuroprotective factor (BDNF) and has therapeutic potential for the treatment of familial PD. On the other hand immunomodulatory drugs including pargyline, selegiline (Deprenyl) and pentoxifylline, have all shown neuroprotective activity in both MPTP- (Liu and Hong, 2007) and the 6-OHDA rodent models of PD (Sanchez-Pernaute et al., 2004). Similarly, the glucocorticoid dexamethasone was shown to be protective against MPTP (Kurkowska-Jastrzebska et al., 2004). Other anti-inflammatory regimens such as steroids, which have been shown to be effective at arresting DA neuron loss in rodents, need further studies. At this time use of anti inflammatory drugs as a potential preventive therapeutic measure in PD remains but a promising possibility.

4.3 Huntington's disease (HD)

Neuroinflammation is a prominent feature associated with HD and may constitute a novel target for neuroprotection. Increased expression of several key inflammatory mediators,

including IL-6, IL-8, and MMP9, in the striatum, cortex and cerebellum in experimental and clinical HD has been reported (Silvestroni, 2009). Treatment of quinolic acid induced HD rats with minocycline resulted in the attenuation of inflammation, and reduction of striatal lesions (Ryu et al., 2006). In a first open-label safety and efficacy trial, 10 out of 14 HD patients treated with minocycline (100mgday⁻¹) showed an improvement in their Unified HD Rating (Bonelli et al., 2004). In striking disagreement with this study, subsequent studies using higher doses of minocycline (200mgday⁻¹) showed good tolerance and apparent safety, but failed to exhibit any improvement in HD features (Reynolds, 2007). Besides these conflicting results, the safety of minocycline has recently been questioned when two-thirds of subjects who were administered minocycline discontinued the drug after developing serious hyperpigmentation only 1 year into the 5-year treatment regime (Reynolds, 2007).

Treatment with acetylsalicylate or rofecoxib in transgenic mice model of HD failed to show any beneficial effects (Norfus et al., 2004). Dexamethasone treatment (4mg daily for 20 days followed by 8mg daily for an additional 20 days) in HD patients has demonstrated improvement of abnormal involuntary movements, and manual dexterity, with no observable side-effects (Bonnucci et al., 1992). Accumulating evidence suggests that changes in the immune system may critically contribute to the pathology of HD. However, the nature of this contribution remains unclear, to the extent that it is not even known whether the immune activation has a beneficial or detrimental role in HD patients (Soulet and Cicchetti, 2011).

4.4 Amyotrophic lateral sclerosis (ALS)

Inflammation has been shown to play a critical role in the pathogenesis of ALS. Markers of inflammation, including microglial stimulating factors and pro-inflammatory cytokines, such as TNF alpha and FasL are increased in ALS (Kiaei et al., 2006). Several places in the inflammatory events that appear to accompany ALS might be amenable to drug action. Animal experiments have suggested that Cox 2 inhibitors might be of use in ALS, but a clinical trial of a direct inhibitor of Cox2 has failed to give a definite answer.

Lenalidomide a potent immunomodulatory agent with ability to down regulate pro-inflammatory cytokines prolong survival in the transgenic mouse model of ALS (G93A mice) by destabilizing DNA coding for TNF α and other cytokines (Kiaei, 2006). Lenalidomide significantly attenuated neuronal loss, improved motor performance, and survival. These data encourage clinical evaluation of lenalidomide to slow or block progression of ALS (Neymotin et al 2009). Pioglitazone, a peroxisome proliferator-activated receptor-gamma (PPAR γ) agonist with anti-inflammatory properties, has been shown to improve motor performance, delay weight loss, attenuate motor neuron loss, and extend survival of transgenic mouse models of ALS (Kiaei, 2005). A clinical trial for safety and efficacy of pioglitazone in ALS patients - models is expected to be completed by the end of 2011. Although immune modulators/anti inflammatory drugs including minocycline, celecoxib, rofecoxib, and sulindac showed protection in mouse models of ALS, but these drugs failed in human ALS trials (Gordon et al., 2007).

4.5 Multiple sclerosis (MS)

Multiple Sclerosis is an idiopathic disease in which the body's immune response attacks the central nervous system resulting in demyelination. Although its exact etiology and

pathogenesis are still unclear, there is much evidence to suggest the involvement of T cell triggered inflammation. In MS, peripheral T cells gain entry into the brain via the BBB, recognize myelin as foreign body and attack it as if it were an invading virus. This triggers inflammatory processes and stimulates other immune cells and soluble factors such as cytokines and antibodies (Leary and Thompson, 2005).

In a large clinical trial, immunomodulatory drug, glatiramer acetate was found to be efficient in the treatment of relapsing remitting multiple sclerosis, however the trial had to be terminated prematurely because the drug failed to stop disease progression after two years (Wolinsky et al., 2007). The results of trials with the immunomodulatory drug, interferon beta (IFN beta), in patients with MS were also disappointing (Montalban, 2004). Recently, a single-center, phase two pilot study with interferon beta-1b on primary progressive MS disease showed no effect on sustained disability assessed by expanded disability status scale (EDSS), but surprisingly revealed statistically significant differences for the multiple sclerosis functional composite score and for T1 and T2 lesion volume (Montalban et al., 2009). Studies on humanized monoclonal antibody, alemtuzumab (Campath-1H), which induces the cytolysis of CD52 positive cells leading to a T cell depletion is highly effective in reducing relapse rate, MRI lesion load and disease progression in relapsing remitting multiple sclerosis (The CAMMS223 Trial 2008). However, it does not seem to protect from disease progression once patients have progressed to secondary progressive stage (SPMS) (Coles et al., 2006). Laquinimod (ABR-215062) is another orally administered investigational agent that, in animal models of MS, has been shown to decrease leukocyte infiltration into the central nervous system and to induce a shift from T-helper type 1 (Th1; proinflammatory) cells to Th2/3 (anti-inflammatory) cells (Miron et al., 2008). Phase III clinical trials suggested a significant activity of laquinimod (as shown on MRI measures) against the relapsing form of MS (Miron et al., 2008). The agent also appears to exhibit synergistic immune modulating effects when given with interferon therapy (Miron et al., 2008).

5. Oxidative stress

Neuronal cells in the brain are highly sensitive to oxidative stress due to their large dependence on oxidative phosphorylation for energy, normal functioning and survival. In brain the demand for oxygen consumption is extremely high with 1-2% of the oxygen being converted into superoxide anion radicals ($O_2^{\cdot -}$) and hydrogen peroxide, leading to oxidative stress (Moura et al., 2010). Oxidative stress results when there is an imbalance of reactive oxygen species (ROS) production and availability of endogenous antioxidants to scavenge the ROS. Generation of high levels of ROS, and down regulation of anti-oxidant mechanisms, results in neuronal cell death in neurodegenerative diseases (Farooqui and Farooqui, 2009). The role of oxidative stress and use of antioxidants as neuroprotective agents in some of the common neurodegenerative disorders is discussed below:

5.1 Alzheimer's disease (AD)

Oxidative stress has been associated in beta amyloid ($A\beta$) toxicity; It is clearly evident from in vitro studies that oxidation of soluble $A\beta$ promotes its transformation into the aggregated form creating a vicious cycle of aggregation and oxidative damage (Lee, 2010). There is ample evidence to suggest that amyloid aggregation can be inhibited by antioxidants, and

free radical scavengers, such as vitamin E and propyl gallate, have been shown to protect neuronal cells against A β toxicity (Behl, 1999). The most common antioxidant vitamin E has been found to delay clinical progression in AD patients from moderate to severe impairment, although no cognitive benefit was found (Wytttenbach et al., 2000). On the other hand Masaki et al. (2000), reported that vitamin E improves cognitive performance in AD. According to some recent reports antioxidant supplementation has not been effective for the treatment of AD (Mecocci and Polidori, 2011). In spite of these conflicting reports there remains considerable interest in vitamin E, and an important ongoing study (Dysken, 2010), is expected to clarify these doubts.

Recent studies have shown that melatonin levels are lower in AD patients compared to age-matched control subjects (Mahlberg et al., 2008). Treatment with melatonin provides protection against AD by inhibiting A β -induced toxicity (Zhou et al., 2008; Wang, 2009). However there is insufficient evidence to support the effectiveness of melatonin for managing cognitive impairment in AD (Jansen et al., 2006). Further clinical phase II trial to determine the effect of melatonin on cognitive function in mild cognitive impaired (MCI) patients is presently undergoing (ClinicalTrials.gov Identifier: NCT00544791).

Statins by virtue of their hypocholesteremic, antioxidant and anti inflammatory properties have been shown to lower A β production and to reduce A β -mediated neurotoxicity. On the contrary no significant clinical benefit on cognition or global functioning was shown by atorvastatin in a phase 3 clinical trial in patients with mild-to-moderate AD already taking donepezil (Feldman et al., 2010). Another clinical trial, to test the effectiveness of statins in prevention and therapy of Alzheimer's disease, is ongoing (Mangialasche et al., 2010).

Recent experimental studies using a wide range of antioxidants including P- P methoxy - diphenyl diselenide (Pinton et al., 2011), S allyl cysteine (Javed et al., 2011), conjugates of ibuprofen and glutathione (Pinnen et al., 2011), tirilazad (Youdim et al., 2004), Ibuprofen and lipoic acid (Distefano et al., 2010), and chlorogenic acid (Kwon et al., 2010), have shown neuroprotective effects in animal models of AD. On the other hand mitochondria specific antioxidants such as acetyl-L-carnitine and R-alpha lipoic acid have been suggested to be beneficial for treatments for AD (Palacios et al., 2011). Further clinical studies are warranted to establish the therapeutic efficacy of these drugs in AD.

5.2 Parkinson's disease (PD)

Oxidative damage to proteins, lipids, and nucleic acids has been found in the substantia nigra of patients with PD (Fasano, 2006). The metabolism of dopamine (DA) itself creates a favorable environment for oxidative damage through intermediates such as DA-quinone and 3, 4- dihydroxy phenylacetaldehyde (Jackson and Smeyne , 2005). On the other hand reduced plasma levels of anti-oxidants such as glutathione and uric acid have been reported in PD patients (Elokda et al., 2010).

An open label study of Vitamin E and Vitamin C, suggested that these antioxidants delay the need to initiate levodopa therapy for the treatment of PD by 2.5 years (Fahn et al., 1992), while other randomized placebo controlled trials showed no disease-modifying effect for Vitamin E, (Shoulson, 1998), but a modest protective effect and slowing of disease progression was observed when vitamin E was given with with Deprenyl, (Olanow, 1995). The use of glutathione (600 mg twice daily) in patients with PD resulted in significant

decrease in their disability scores (Sechi, 1996). Selegiline and rasagiline the inhibitors of monoamine oxidase B (MAOB) also significantly delayed the onset of L dopa in PD patients. Oral Coenzyme Q10 (CoQ10), a cofactor in electron transport chain in mitochondria, was shown to slow motor deterioration, and improve activities of daily living in patients with mild PD (Shults, 2002). Studies on beneficial effect of lycopene supplementation suggest its therapeutic potential in PD (Kaur et al., 2011). A small number of controlled trials indicate that melatonin is useful to treat disturbed sleep in PD (Medeiros et al., 2007), particularly rapid eye movement-associated sleep behavior disorder (Aurora et al., 2010). Melatonin and the recently introduced melatonergic agents (ramelteon, agomelatine) merit further investigations (Srinivasan et al., 2011).

5.3 Huntington's disease (HD)

Oxidative stress has been shown to play an important role in the pathogenesis of HD. Elevated levels of oxidative damage products such as malondialdehyde, 8 hydroxyguanosine, 3 nitrotyrosine and heme oxygenase in the brain of HD patients and increased free radical production in animal models indicates the involvement of oxidative stress either as a causative event, or as a secondary constituent of the cell death cascade. Recently Lee et al (2011), observed an increase in the level of 4 hydroxynonenal (4 HNE) a useful marker for the oxidative stress in both human and animal models of HD, suggesting that the lipid peroxidation pathway may be a novel therapeutic target for preventing oxidative damage in HD.

Treatment with CoQ10 was associated with reduced levels of 8-hydroxyguanosine (a marker of oxidative damage) and improved survival in experimental model of HD mice. In a multicenter, blinded, randomized study on HD patients administered 300 mg CoQ10 slowed the decline of total functional capacity (Huntington Study Group 2001). A higher dose of coenzyme Q10 (2400 mg) for HD, is now in phase III of clinical trial (NCT00608881). Results of a recent study using antioxidant dimebon (the old Russian cold medicine), showed that 60 mg per day was safe and well tolerated and improved cognition in individuals with HD (Kieburtz, 2010). However in a clinical trial on late stage HD patients dimebon failed to show a significant improvement in cognition or global functioning.

The antioxidant response element (ARE) signaling pathway is an important pathway involved in antioxidant and anti-inflammatory responses (Johnson et al., 2008). The ARE is activated through the binding of its transcription factor, Nrf2 (NF-E2-related factor 2). In addition to the typical induction of detoxification enzymes, Nrf2-ARE activation results in increased cellular energy and redox potential, inhibitory neurotransmitter signaling, and metabolic processes (Nguyen et al., 2004). Synthetic triterpenoids, which are derived from 2-Cyano-3,12-Dioxooleana1,9-Dien-28-Oic acid (CDDO) have been shown to up-regulate Nrf2/ARE induced genes in the brain and peripheral tissues, reduce oxidative stress, improve motor impairment and increase longevity in HD mice (Stack 2010). This compound showed a great potential for treatment of HD. Eriodictyol, a flavonoid found in citrus fruits, induces the nuclear translocation of Nrf2, enhances the expression of heme-oxygenase-1 (HO-1) and quinone oxidoreductase 1 (NQO-1), and increases the levels of endogenous antioxidant glutathione (Johnson et al., 2009), these findings suggest its potential use for the treatment for HD and other neurodegenerative disorders.

5.4 Amyotrophic lateral sclerosis (ALS)

Oxidative damage mediated by toxic free radicals has been implicated in the pathogenesis of ALS (Graf et al 2005). Abundant evidence of oxidative stress has been found in autopsy specimens of ALS, including elevated protein carbonyl levels, increased 3-nitrotyrosine levels, 8-hydroxy-2-deoxyguanosine (a marker for oxidative DNA damage) and 4 HNE levels (an indicator of lipid peroxidation) (Barber et al., 2006).

About 20% of familial ALS is caused by a genetic defect in an antioxidant enzyme called super oxide dismutase -1 (SOD-1). A study on AEOL 10150, a manganoporphyrin antioxidant that catalytically neutralizes superoxide, hydrogen peroxide, and peroxynitrite, and inhibits lipid peroxidation showed that administration of this drug to SOD1G93A transgenic mice at symptom onset improved the survival period by 196% (Crow et al., 2005). In 2005 a phase I single dose escalating study of AEOL 10150 showed that the drug was well tolerated with no serious adverse events [www.rideforlife.com]. Clinical trials with promising second-generation antioxidant, edavarone which was shown to slow motor decline and neuron degeneration in a - a mice model of ALS are underway (Kuzma-Kozakiewicz and Kwiecinski, 2011). A recent study utilizing dietary supplementation with S adenosyl methionine (SAM) altered the course of motor neuron pathology in G93A mutant SOD1 mice by preventing loss of motor neurons and reducing gliosis, SOD-1 aggregation, protein carbonylation, and induction of antioxidant activity (Suchy et al., 2010).

5.5 Multiple sclerosis (MS)

It has been suggested that mitochondrial injury and subsequent energy failure is a major factor driving axonal injury in MS patients (Witte et al., 2010). As the mitochondrial proteins and DNA are highly vulnerable to oxidative damage (Higgins et al., 2010), it has been proposed that free radical-mediated mechanisms may lead to mitochondrial injury in MS (van Horssen et al., 2011). Oxidized lipids and oxidized DNA have been detected in the brain tissues from patients with MS (Quin et al., 2007). Results from a recent study (Haider et al., 2011), on autopsy material from HD patients provide extensive evidence for an important role of oxidative damage in the pathogenesis of demyelination and neurodegeneration in MS.

Treatment with lipoic acid and anti-acrolein compound hydrazine both potent antioxidants, were observed to reduce axonal injury in experimental models of MS (Chaudhary et al., 2011). Recently C-Phycocyanin and saffron naturally occurring antioxidants improved experimental Autoimmune Encephalitis (EAE) and peripheral blood mononuclear cells from MS patients (Penton -Rol et al., 2011; Ghazavi et al., 2009). Viral mediated delivery of antioxidant genes of superoxide dismutase and catalase in EAE mice has also been observed to suppress neuronal and axonal loss (Qi et al., 2007). Inosine is a widely distributed nucleoside in the body and is a potent scavenger of free radicals. Administration of inosine in MS patients resulted in a significant decrease in the number of lesions and improved disability status (Markowitz et al., 2009). Erythropoietin (Epo), a hematopoietic growth factor and an antioxidant, showed clinical and electrophysiological improvement of motor function as well as improved cognitive performance in MS patients (Ehrenreich et al., 2007).

6. Targeting glutamate excitotoxicity

Excessive activation of glutamate receptors by excitatory amino acids leads to a number of deleterious consequences, including impairment of calcium buffering, generation of free radicals, activation of the mitochondrial permeability transition and secondary excitotoxicity (Berliocchi et al., 2005). A pivotal role for excitotoxicity in neurodegenerative diseases is gaining increasingly more acceptance (Kim et al., 2011). Progress in the use of anti-excitotoxic drugs for the treatment of neurodegenerative disorders is discussed below.

6.1 Alzheimer's disease (AD)

Several studies have linked tau and amyloid aggregation to glutamate mediated toxicity and clearly suggest the involvement of N-methyl-D-Aspartate (NMDA) receptor subunits (NR1 and NR2) in the pathogenesis of AD (Koutsilieri and Riederer, 2007). Alzheimer's disease is associated with reduced levels of two mRNA isoform subsets of the NR1 receptor and changes in the expression of NR2A and NR2B in the superior temporal cortex, cingulate cortex and hippocampus (Hynd et al., 2004). The presence of presenilin-1 in a macromolecular complex with NR1 and NR2A further supports a role for excitotoxicity in AD (Saura et al., 2004).

Memantine is an uncompetitive NMDA receptor antagonist that can decrease pathological activation of NMDA receptors without affecting physiological NMDA receptor activity (Farlow, 2008). Memantine is associated with functional improvement in AD patients and has been approved by FDA for the treatment of AD (Farlow, 2008). Latrepirdine (Dimebon), a nonselective antihistamine and weak NMDA receptor blocker was found to have beneficial effects in animal models of AD (Santamaría et al., 2001). It has also been shown to enhance mitochondrial function (Wytenbach et al., 2002). In a clinical trial (Goswami et al., 2006), on 183 patients with mild to moderate AD, latrepirdine, improved performance on the primary cognitive outcome, behavioral activities of daily living, and global function. The most common side effects were dry mouth and depressed mood, in some patients. However, a recent phase III AD trial of Dimebon in 598 patients did not show any significant improvement in primary or secondary outcomes (Bezprozvanny, 2010).

6.2 Parkinson's disease (PD)

Brain glutamate over activity is well documented in Parkinson's disease (Morin et al., 2010). Studies on dopamine denervated rats and MPTP-treated Parkinsonian monkeys have clearly provided insight into the relative abundance of different NMDA subunits in the striatum. Dopamine depletion in the 6-OHDA rat models, and MPTP primate models results in relative decrease in the abundance of NMDA receptor subtype 1 (NR1) and subtype 2B (NR2B) subunits in the synaptosomal membranes, which is restored by chronic levodopa therapy (Dunah, 2000; Hallett et al., 2005). Since stimulation of NR2B-containing NMDA receptors contributes to the generation of Parkinsonian symptoms (Hallett and Standaert, 2004), NR2B-selective NMDA receptor antagonists may be therapeutically beneficial for Parkinsonian patients. Prior administration of NMDA receptor antagonist dizocilpine suppresses the dopa-induced increase in glutamate in 6-hydroxydopamine-lesioned rats and may therefore offer neuroprotection (Jonkers, 2002).

Several NMDA antagonists have been studied in PD (Tarawneh and Galvin, 2010). Both amantidine and dextromethorphan have antidyskinetic effects. Amantidine has been associated with increased lifespan (Uitti, 1996; Verhagen, 1998). Selective NMDA receptor antagonists, such as ifenprodil and CP-101,606, have been developed in an attempt to avoid the side effects of non-selective blockers. Ifenprodil, has anti-Parkinsonian actions in rat and, and nonhuman primates (Nash and Brotchie, 2002). CP-101,606 reduced Parkinsonian symptoms, in both haloperidol-treated rats, and MPTP-lesioned nonhuman primates (Steece, 2000). Pretreatment of 6-OHDA lesioned rats with 4-trifluoromethoxy-N-(2-trifluoromethyl-benzyl)-benzamidine (BZAD-01), a novel selective inhibitor of the NMDA NR1A/2B receptor, significantly reduced the amount of dopaminergic cell loss and significantly improved all behavioral measures (Leaver et al., 2008). When given in combination with levodopa-carbidopa, the NMDA-antagonist remacemide, has been shown to reduce parkinsonism in rodent and monkey models of Parkinson's disease (Greenamyre, 1994). A clinical study confirmed that remacemide is safe and well tolerated in PD patients who are treated with L-DOPA (Clarke, 2001).

The simultaneous blockade of AMPA (α -amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid) and NMDA receptor offers substantially greater reduction in the response alterations induced by levodopa than inhibition of either of these receptors alone in both rat and primate models of PD. Simultaneous blockade of the AMPA receptors with GYKI-47261 and NMDA receptor with amantadine or MK-801 resulted in significant reductions in levodopa-induced dyskinesias in a primate model, while the wearing-off dyskinesias were completely ameliorated in rat models of PD (Bibbiani, 2005). Treatment with NMDA glutamate receptor antagonist memantine for 52 weeks resulted in the improvements in cognitive functions and stabilization of motor impairments in PD patients (Litvinenko et al., 2010).

6.3 Huntington's disease (HD)

The major hypothesis driving HD synaptic research is the excitability of medium spiny projection neurons (MSNs). Injections of excitatory amino acids into the striatum of rodents, and primates results in neuronal death and a neurologic phenotype similar to that of Huntington's disease. Intra-striatal injections of NMDA glutamate agonists, such as quinolinic acid, have been used to create animal models of HD. Animal models and human studies show evidence of decreased glutamate receptors, in particular the mGluR2 subtypes, down-regulation of the GLT-1 glial glutamate transporter, and increased sensitization of NMDA receptors (Leegwater and Cha, 2004). Since excitotoxicity is known to be involved in the development of HD, approaches to reduce extra synaptic glutamate signaling have been explored and include modulation of NR2 B signaling (Heng et al., 2009), lowering glutamate receptor activation with NMDA receptor antagonists (Ketamine and memantine), and modulating the interplay of glutamate and dopamine on MSNs (Andre et al., 2010). The efficacy of memantine in slowing down the rate of progression of HD was studied in a two year, open and multicenter trial with promising results (Beister et al., 2004).

Cannabinoid-derived drugs also hold great promise in protecting neurons from glutamate mediated toxicity. Activation of neuronal CB (1) or CB (2) cannabinoid receptors attenuates excitotoxic glutamatergic neurotransmission and triggers prosurvival signaling pathways. The administration of CB (2) receptor-selective agonists reduced neuroinflammation, brain edema, striatal neuronal loss and motor symptoms in wild-type mouse models subjected to

excitotoxicity (Palazuelos, 2009). Treatment with the analogue of the ant glutamatergic agent and the tryptophan metabolite kynurenic acid (KYNA), in transgenic mouse model of HD resulted in prolonged survival, reduction in hypo-locomotion, and prevention of atrophy of the striatal neurons (Zadori et al., 2011).

6.4 Amyotrophic lateral sclerosis (ALS)

Glutamate-mediated excitotoxicity arising from repetitive firing or elevation of intracellular calcium by calcium permeable glutamate receptors has long been postulated to have an important role in motor neuron degeneration in ALS (Rowland and Schneider, 2001). Glutamate levels are increased in cerebrospinal fluid of patients with sporadic ALS (Rothstein et al 1990) and clearance of glutamate from neuromuscular synapses is diminished in patients with ALS due to loss of the astroglial glutamate transporter EAAT2 (excitatory amino acid transporter 2), that is of major importance for synaptic glutamate reuptake (Rothstein et al., 1995).

Cephalosporins increase EAAT2 promoter activity and protect motor neurons from glutamate toxicity in organotypic spinal cord slice cultures of rats (Rothstein et al., 1993). Controversial but mainly negative data on the efficacy of cephalosporins in ALS have been published (Norris, 1994). However, gabapentin, lamotrigine, and topiramate, and other agents known to alter glutamate synthesis and release, appeared promising in pre-clinical studies (Maragakis et al., 2003) but showed no benefit in ALS patients (Cudkowicz et al., 2003). Beta-lactam antibiotics exert neuroprotective effects by up-regulating GLT-1 receptors in vitro and in vivo in normal rats (Rothstein et al., 1995) and in transgenic ALS mice treated with ceftriaxone (Rothstein et al., 2005). Harvey and Martz (2007) have reported prolonged treatment with atovaquone, an antimalaric drug, showed a persistent disease remission. This observation confirms the previous reports of a possible therapeutic effect of beta-lactam antibiotics in ALS. A double blind placebo controlled clinical trial on about 600 patients using a β lactam antibiotic ceftriaxone which is a safe EAAT2 expression enhancer, is being carried out in the United States of America (NCT00349622) since July 2006. Final data collection for the primary outcome measure (survival and rate of change in ALSFRS-r - stage 3) will be available in March 2012. Talampanel (8-methyl-7H-1,3-dioxolo(2,3)benzodiazepine), is a noncompetitive modulator of AMPA glutamate receptors which is under development as an antiepileptic agent, has been shown to prolong survival of SOD1G93A ALS mouse (Traynor et al., 2006). The ALS Functional Rating Scale-revised (ALSFRS-r) scores declined at a slower rate in a 9-month phase II study of talampanel in 60 patients (Traynor et al., 2006). The inhibitor of presynaptic glutamate release, riluzole, is currently the only drug that has shown efficacy in a phase 3 study in ALS patients (Zinman and Cudkowicz, 2011). On the other hand memantine was well tolerated in combination with riluzole in patients with ALS resulting in some improvement in function rating of disease (Levine et al., 2010).

6.5 Multiple sclerosis (MS)

Glutamate excitotoxicity mediated by the AMPA /kainate type of glutamate receptors not only damage neurons but also the myelin producing of oligodendrocytes of the CNS. In MS, oligodendrocytes and some axons are lost as a result of excessive release of glutamate by activated immune cells. It has been suggested that glutamate activates immune cells and

inflammation and contributes to lesion formation in MS (Gonsette, 2008). The hypothesis that the excitatory neurotransmitter glutamate contributes to axonal damage has been strengthened by several studies demonstrating the neuroprotective effects of AMPA receptor antagonists such as NBQX (2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(F)quinoxaline) in animals (Pitt et al., 2003). In addition, memantine, a NMDA antagonist currently available for the management of Alzheimer's disease, ameliorates disability in experimental autoimmune encephalomyelitis-affected rats, raising the possibility of its neuroprotective effect in MS (Wallström et al., 1996). The protective effects of glutamate antagonists are important, especially as it has been hypothesized that AMPA/kainate receptors become the primary mediators of axonal injury during prolonged and intensified injury exposure in the chronic phase (Ouardouz et al., 2006) suggesting the possibility of a potential benefit in targeting these receptors. Riluzole inhibits the release of glutamate from nerve terminals and modulates the activities of both kainate and NMDA receptors is presently undergoing a clinical trial alone and in combination with interferon β (NCT 00501943) at University of California, USA.

Another promising compound for treating MS is minocycline, which has been found to be protective in many neurodegenerative diseases (Fong et al., 2008). Experimental studies using both invitro (Defaux et al., 2011) and invivo (Chen et al., 2010) models of MS showed protective effects of minocycline. Combination of minocycline with methylprednisolone and atorvastatin was observed to synergistically suppress EAE severity in mice (Chen et al 2010). At the same time results of a clinical trial, involving minocycline alone and in combination with glatiramer acetate in patients with MS, showed minocycline to be safe and well tolerated with a reduction in the relapse rate (Zhang et al., 2008). The encouraging results from the animal models and clinical experiments on minocycline make it a promising candidate for MS treatment whether used alone or combined with other drugs (Chen, 2011).

7. Apoptosis

Apoptosis is a form of cell death in which programmed sequence of events lead to elimination of cells without releasing harmful substances in surrounding area. It plays a crucial role in developing and maintaining health by eliminating old cells, unnecessary cells and unhealthy cells. However premature apoptosis and/or an aberration in apoptosis regulation may lead to degenerative disorders. Neuronal apoptosis can be induced both in vivo and in vitro by different stimuli including oxidative stress, calcium toxicity, excitotoxicity, inhibition of the mitochondrial respiratory chain, and deficiency of survival factors which may contribute to disorders including Alzheimer's disease, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis and multiple sclerosis. Inhibition of apoptosis could constitute a suitable therapeutic strategy for delaying the progression of neurodegenerative disease (Sureda et al., 2011).

7.1 Alzheimer's disease (AD)

Extensive evidence showed that apoptosis is involved in neuronal loss in AD. Postmortem analysis of AD brain showed DNA fragmentation in neurons and glia of hippocampus and cortex as detected by TdT-mediated dUTP nick end labeling (TUNEL) (Vila and Przedborski, 2003). Rohn, et al. (2002) demonstrated the activation of mitochondrial and receptor-mediated apoptotic pathways in AD hippocampal brain sections wherein active

caspase-9 was co-localized with active caspase-8. Recently, a marked co-localization of pathological hyperphosphorylated tau, cleaved caspase-3 and caspase-6 has been reported in TUNEL-positive neurons in the brain stem of AD patients (Wai et al., 2009). Furthermore, in vitro studies have shown that amyloid beta protein ($A\beta$) provokes a significant down regulation of antiapoptotic proteins such as Bcl-2, Bcl-xl and Bcl-w and a significant up-regulation of pro-apoptotic proteins such as bax (Yao et al., 2005).

The activation of Poly ADP-ribose polymerase (PARP) plays a critical role in caspase-independent apoptosis. Therefore, PARP inhibitors represent one possible therapeutic strategy in AD. Insulin like growth factor-binding protein-3 (IGFBP-3) modulates cell growth and survival. Humanin (HN) a peptide and IGFBP3 coactivator significantly inhibited neuronal cell death induced by familial Alzheimer's disease mutant gene and amyloid β ($A\beta$) (Ikonen et al., 2003). Thus HN acts as AD related survival factor by interacting with IGFBP-3. Recently, it has been suggested that a potent humanin derivative may be a promising alternative strategy for AD therapy (Matsuoka & Hashimoto, 2009). Pycnogenol (PYC), a potent antioxidant suppressed caspase-3 activation, DNA fragmentation, PARP cleavage, and eventually protected against $A\beta$ -induced apoptosis in animal model of AD. PYC is a promising candidate for clinical trials in AD (Ishrat et al., 2009).

In vitro studies demonstrated antiapoptotic activity of the endogenous antioxidants geniposide and estrogen (Liu et al., 2009). Recently Puerarin, a phytoestrogen was observed to prevent $A\beta$ -induced neurotoxicity through inhibiting neuronal apoptosis. Further studies are warranted to study these antiapoptotic drugs for their, preventive or therapeutic efficacy in AD (Xing et al., 2011).

Melatonin is a natural hormone secreted by the pineal gland. In vitro experiments showed that $A\beta$ -treated cultures exhibited characteristic features of apoptosis, and melatonin attenuated $A\beta$ -induced apoptosis and activated the survival signal pathways stabilizing mitochondrial function by acting as anti-apoptotic Bcl-2 family modulator (Jang et al., 2005). Melatonin significantly delays the development of the signs of AD, prevents cognitive impairment, and ameliorates sundowning in AD patients (Gehrman et al., 2009).

7.2 Parkinson's disease (PD)

Accumulating evidence suggests that the molecular and biochemical pathways of apoptosis are involved in dopaminergic cell death in PD. This evidence includes the activation of the mitogen activated protein (MAP) kinase pathway, the induction of Bax, prostate apoptosis response-4 (Pa 4) and glyceraldehyde 3 phosphate dehydrogenase, as well as the activation of caspases. In cell culture and animal models therapeutic interference with the signaling phase of apoptosis, e.g. inhibition of the MAP kinase pathway, provides morphological and function protection. In contrast, inhibition of the propagation and execution phase of apoptosis (e.g. by inhibition of the caspases), blocks cell death but may result in survival of dysfunctional neuron. For full functional recovery, the combination of an antiapoptotic together with a neuro-restorative therapy may be necessary (Tatton et al., 2003).

Dopaminergic cells from animal models of PD exhibit increased expression of the pro-apoptotic protein Bax effector protease caspase-3 and caspase-8 (Tatton et al., 2003). Treatment with L-Dopa and dopamine agonists is associated with lower levels of anti-

apoptotic Bcl-2 in the blood (Blandini, 2004). The peptidyl inhibitor carbobenzoxy-Val-Ala-Asp-fluoromethylketone (zVADfmk) can protect neurons from apoptosis induced by mitochondrial toxins. However, its therapeutic efficacy is limited by its poor penetrability into the brain (Yang et al., 2004). The more potent broad-spectrum caspase inhibitor, Q-VD-OPH, may be more promising. Specific caspase inhibitor such as acetyl-tyrosinyl-valyl-alanyl-aspartyl-chloro-methylketone (Ac-YVAD-cmk), has also demonstrated efficacy in several experimental paradigms of Parkinson's disease (Yang et al., 2004).

Propargylamines including selegiline and rasagiline besides their MAO -B activity have proven to be potent anti-apoptotic agents in both in vitro and in vivo studies (Olanow, 2006). These drugs inhibit apoptosis through caspase inhibition (Bonuccelli & Del Dotto, 2006). Moreover, rasagiline appears to induce anti-apoptotic pro-survival proteins, Bcl-2 and glial cell-line derived neurotrophic factor (Maruyama, 2004). Selegiline has also been shown to delay the need for symptomatic therapy in untreated Parkinson's disease patients (Shoulson, 1998). Further studies to determine utility of these propargylamines in the treatment of PD and their mechanism of neuroprotective activity are in progress.

In an experimental study, melatonin showed neuroprotective effects against MPP⁺- induced apoptosis by inhibiting the calpain/cdk5 signaling cascade in cerebellar granule neurons (CGNs) (Alvira et al., 2006). Mounting evidence indicates that melatonin blocks the MPT dependent apoptotic fragmentation of nuclear DNA in rat astrocytes (Jou et al., 2004). On the other hand, human trials of melatonin showed significantly improved effect on sleep disturbances in PD (Medeiros et al., 2007; Dowling et al., 2005), but there were undetected differences in motor dysfunction (Medeiros et al., 2007).

Oral administration of Co Q10 resulted in amelioration of mitochondria induced apoptosis by dose-dependent restoration of striatal complex I activity, increase in expression of Bcl-2 as well as decrease in catalepsy score in an animal model of PD (Abdin & Hamouda, 2008). Treatment with CoQ10 also resulted in restoration of striatal dopamine levels (Abdin & Hamouda, 2008). In a multicenter clinical trial Co Q10 appears to slow progressive deterioration of function in PD through increased expression of Bcl-2 (Shults et al., 2002). However these findings were questioned in a later trial (Storch et al., 2007).

7.3 Huntington's disease (HD)

Several lines of evidence point to a role for apoptosis in HD in animal models and in postmortem tissues. Caspase 3 has been shown to cleave mutant huntingtin and the activation of caspase 1 in HD brain. The expression of expanded polyglutamine residues has been associated with apoptotic mechanisms via caspase activation, cleavage of the death substrates lamin B and inhibition of caspase-activated DNase. Bax expression in peripheral B and T lymphocytes and monocytes is increased in HD, and lymphoblasts derived from HD patients show increased stress-induced apoptotic cell death associated with caspase-3 activation (Vis, 2005).

Recent findings suggest a possible role for the hypoxia-inducible factor 1 (HIF-1) in HD. HIF-1 regulates the expression of several genes, including mediators of apoptosis, making it a potential target for future therapies (Correia and Moreira, 2010). Extracellular ATP stimulates apoptosis through stimulation of purinergic P2X7 receptors, and subsequent alterations in calcium permeability, both of which have been described in HD. The

administration of the P2X7-antagonist Brilliant Blue-G (BBG) to HD mice prevented neuronal apoptosis, and attenuated motor-coordination deficits (Diaz-Hernandez et al., 2009), suggesting the role of P2X7 in pathogenesis of HD and highlighting the therapeutic potential of a P2X7 antagonist for its treatment.

Melatonin has been shown to defer the signs of HD in a 3-nitropropionic acid-induced rat animal model of HD (Tunéz et al., 2004). In a human study administration of tryptophan, resulted in melatonin levels rising significantly in both of control and HD groups (Christofides et al., 2006). Moreover, the delayed onset of the diurnal melatonin rise in patients with HD has been currently reported (Aziz et al., 2009). Larger scale studies in detecting the level of melatonin in HD patients and further human trials on the impact of melatonin on HD are needed.

7.4 Amyotrophic lateral sclerosis (ALS)

Apoptosis is a potential mechanism of motor neuron death in ALS. Morphological studies are difficult as dying motor neurons may exhibit features of apoptotic as well as cytoplasmic and autophagic neuronal death and distinctly apoptotic cells are found only rarely in spinal cord specimens. Caspases, members of the cysteine protease family, are known effectors or executioners of apoptosis. The activity of caspase-1 (Li, et al., 2000) and caspase-9 were found higher in the spinal cords of patients with ALS (Inoue et al 2003). Activation of caspase 1 has been shown to be an early event in SOD1G37R and SOD1G85R transgenic ALS mice, occurring months before neuronal death, whereas activation of caspase 3 is coincident with the onset of motor axon loss in three different mSOD1 lines (G93A, G37R and G85R) (Pasinelli et al., 2000). Intraventricular injection of zVADfmk, a broad caspase inhibitor, suppresses caspase upregulation and delays disease onset and mortality in mouse models of ALS (Li et al., 2000).

Members of the Bcl-2 family of proteins are important regulators of apoptosis, including both suppressors (Bcl-2, Bcl-XL) and promoters (Bax, Bad, Bak and Bcl-xS) of programmed cell death. Decreased expression of the anti-apoptotic proteins and increased expression of the proapoptotic proteins has been found in human ALS as well as transgenic mouse models (Guegan and Przedborski, 2003). Over-expression of Bcl-2 (Kostic et al., 1997) and deletion of Bax (Gould et al., 2006) independently result in delayed onset of motor decline and prolonged survival without reducing disease duration.

Minocycline prolonged survival by 10-22% in transgenic mouse models of ALS (van den Bosch et al., 2002). In these SOD1 G37R mice, minocycline reduces the activity of caspase 1, caspase 3, inducible nitric oxide synthase, and p38 mitogen-activated protein kinase, and diminishes loss of motor neurons. Minocycline has been tested in two preliminary human trials and has been shown to be safe in patients with ALS (Pontieri et al., 2005). However, in a multicentre, phase III trial (NCT00047723) minocycline failed to show any protective effect.

Lithium is a neuroprotective and antiapoptotic agent that promotes autophagy. It prolonged survival in SOD1-transgenic mice and increased the number of autophagic vacuoles in motor neurons (Fornai et al., 2008). Preliminary results of a small open-label study suggested longer survival and slower disease progression in ALS patients treated with lithium (Fornai et al., 2008). At least two other Phase II trials with lithium carbonate are under way (Clinical Trials.gov NCT00790582, NCT00925847).

7.5 Multiple sclerosis (MS)

Apoptosis is important for the homeostasis of the immune system and presumably plays a two sided role in the pathogenesis of MS. On the other hand evidence has been provided that impaired apoptosis might result in increased numbers or persistence of activated myelin – specific T cells, thus inducing the pathophysiologic processes in MS. On the other hand, local tissue damage might involve apoptosis of glial and neuronal cells and lead to the clinical symptoms (Todaro et al., 2004). It has been hypothesized that a failure of auto-reactive T- and B-lymphocytes, as well as activated macrophages, to undergo apoptosis contributes to the pathogenesis of MS (Pender and Rist, 2001). Inhibitor of apoptosis (IAP), a family of anti-apoptotic genes were shown to be elevated in peripheral blood immune cells (monocytes T cells), in MS patients (Hebb et al., 2008). Moreover antisense mediated knock down of inhibitor of apoptosis (IAP) family member known as X linked IAP (XIAP) reverses paralysis in an animal model of MS (Zehutner et al., 2007) suggesting that treatments targeting XIAP and perhaps other IAPs may have utility in the treatment of MS.

Histone deacetylase 3 (HDAC 3) belongs to a family of proteins which plays an important role in protein acetylation, chromatin remodeling and transcription of genes, including those that are involved in cell proliferation and cell death. An increased expression of HDAC3 and relative resistance to Trichostatin A (TSA) induced apoptosis in T cells in MS patients has been reported (Zhang et al., 2011). A number of selective and non selective HDAC inhibitors have been developed that could also become part of the therapeutic strategy in the treatment of immune disorders including MS (Zhang et al., 2011).

8. Conclusion

Neuroprotection in neurodegenerative diseases remains an important but elusive goal. A successful neuroprotective treatment could transform neurodegenerative diseases from a relentless progressive and disabling disease to a problem that can be managed with only a modest effect on quality of life. Current barriers include a lack of knowledge of the basic mechanism of neurodegenerative diseases and deficiencies in the methodology used to study disease progression. Overall, however the activity aimed at understanding and treating neurodegenerative diseases has grown exponentially and should ultimately result in better therapy for these diseases.

The authors would like to make clear that this review cannot cover all drugs under investigation for the therapy of neurodegenerative diseases. For a more accurate list of these molecules the reader has to refer to reviews on each single neurodegenerative disorder.

9. References

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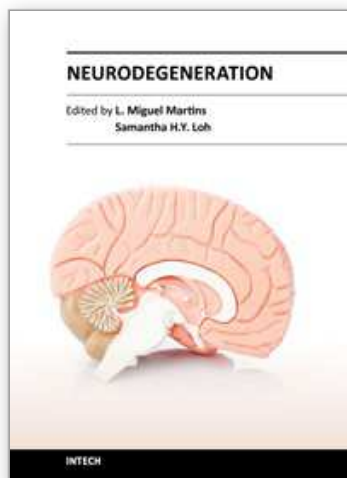
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Currently, the human population is on a collision course for a social and economic burden. As a consequence of changing demographics and an increase in human individuals over the age of 60, age-related neurodegenerative disorders are likely to become more prevalent. It is therefore essential to increase our understanding of such neurodegenerative disorders in order to be more pro-active in managing these diseases processes. The focus of this book is to provide a snapshot of recent advancements in the understanding of basic biological processes that modulate the onset and progression of neurodegenerative processes. This is tackled at the molecular, cellular and whole organism level. We hope that some of the recent discoveries outlined in this book will help to better define the basic biological mechanisms behind neurodegenerative processes and, in the long term, help in the development of novel therapeutic approaches.

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