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POTENTIAL FUTURE NEUROPROTECTIVE THERAPIES FOR NEURODEGENERATIVE DISORDERS AND STROKE

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Abstract

The cellular mechanisms underlying neuronal loss and neurodegeneration have been an area of interest in the last decade. Although neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD) each have distinct clinical symptoms and pathologies, they all share common mechanisms such as protein aggregation, oxidative injury, inflammation, apoptosis and mitochondrial injury that contribute to neuronal loss. Although cerebrovascular disease is due to etiologies quite different from the neurodegenerative disorders, many of the same common disease mechanisms come into play following a stroke. Novel therapies that target each of these mechanisms may be effective in decreasing the risk of disease, abating symptoms or slowing down their progression. While most of these therapies are experimental, and require further investigation, a few seem to offer promise in the near future.

Keywords

Parkinson's disease; Alzheimer's disease; ischemic stroke; amyotrophic lateral sclerosis; Huntington's disease

Introduction

The cellular mechanisms underlying neuronal loss and neurodegeneration have been an area of interest in the last decade. Although neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) each have specific pathologies, they all share common mechanisms such as protein aggregation, oxidative injury, neuroinflammation, apoptosis and mitochondrial injury that contribute to neuronal loss. Current research in these areas has focused on developing

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neuroprotective therapies that target each of these mechanisms. Studies from animal and cell models have greatly expanded our knowledge in this field and form the basis of clinical trials of neuroprotective therapies. Results have been variable; it is very likely that no single therapy will be satisfactory, and that multiple agents working through different mechanisms or novel agents that target more than disease mechanism may offer the best hope for a future neuroprotective therapy. In this review, we address several disease mechanisms of pathogenesis in neurodegenerative disease and stroke, along with some examples of therapies targeting each of these mechanisms. While we attempted to provide a comprehensive review of the available literature, we realize that inclusion of all studies and hypotheses in this area is beyond the scope of this review.

Targeting specific mechanisms of disease pathogenesis

1. Oxidative stress

Parkinson's disease—The substantia nigra (SN) of PD contains high levels of reactive oxygen species (ROS) such as superoxide and peroxynitrites in conjunction with a high iron content associated with neuromelanin⁴⁹, and reduced levels of anti-oxidant mechanisms such as glutathione and uric acid^{71,135}. The mitochondrial toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) blocks the mitochondrial electron transport chain by inhibiting complex I¹⁰⁷, and several abnormalities in complex I and IV have been implicated in PD⁹⁹. Oxidative stress and mitochondrial dysfunction may be inter-related in a self propagating circle³⁸. Inhibition of complex I, leads to excess production of the ROS which target the electron transport chain resulting in the formation of further increased amounts of toxic radicals³⁸. Furthermore, The metabolism of dopamine itself creates a favorable environment for oxidative damage through intermediates such as DA-quinone and 3,4-dihydroxyphenylacetaldehyde (DOPAL)⁷³.

Several compounds with anti-oxidant properties such have been studied as potential neuroprotective agents in PD. One open label study of Vitamin E 3200 IU/day and Vitamin C 3000 mg/day suggested that the time to levodopa was delayed by 2.5 years⁴⁷, while another randomized placebo controlled trial showed no disease-modifying effect for Vitamin E^{47,129}. The Deprenyl and Tocopherol Anti-Oxidative Therapy of Parkinsonism (DATATOP) trial of Vitamin E Deprenyl (selegiline)¹²⁹ also showed no benefit for Vitamin E, but a modest protective effect and slowing of disease progression with Deprenyl.¹¹⁰ In one clinical trial (TEMPO)¹, patients initiated on the MAO-B inhibitor, rasagiline at baseline were improved at one year in comparison to patients initiated on placebo and switched to rasagiline at 6 months. Results from a larger randomized trial of rasagiline monotherapy (1 or 2 mg/day) in mild PD (ADAGIO - Attenuation of Disease Progression with Rasagiline Once-Daily) trial was recently reported¹¹¹. Early treatment with rasagiline at a dose of 1 mg, but not 2 mg, per day provided benefits that were consistent with a possible disease-modifying effect¹¹¹.

Oral CoQ10 1200 mg/day was shown to slow motor deterioration, and improve activities of daily living in a 16-month randomized trial of patients with mild PD¹³⁴. Experimental animal models of PD utilizing a toxic hydroxylated analogue of dopamine 6-hydroxydopamine (6-OHDA), suggest that the detrimental effects of this compound can be blocked by the use of iron chelating compounds, monoamine oxidase B inhibitors (MAO-B), and antioxidants such as vitamin E¹²⁷. In a small open pilot study, the use of glutathione 600 mg IV twice daily in patients with PD resulted in significant decrease in their disability scores¹²⁸.

Alzheimer's disease—Increased peroxidation of membrane lipids, DNA, RNA, and protein, have all been described in AD. Oxidative stress is involved in A β toxicity; *In vitro* oxidation of soluble A β promotes its transformation into the aggregated form creating a vicious cycle of aggregation and oxidative damage. There is *in vivo* evidence that amyloid aggregation

can be inhibited by antioxidants, and *in vitro* studies suggest that the free radical scavengers, vitamin E and propyl gallate, protect neuronal cells against A β toxicity¹³.

Results of clinical trials regarding the benefit of Vitamin E and C on the risk of AD have been conflicting. Supplementary intake of vitamin E or C was associated with better cognitive performance in one study⁹³. A large 6-year follow up study suggests that dietary intake of vitamin E is associated with a lower risk for developing AD, particularly in smokers, and irrespective of the apolipoprotein E genotype⁴⁶. On the other hand, other studies failed to show such a benefit, although Vitamin E may be associated with delayed the time to death, institutionalization, loss of ability to perform basic activities, and severe dementia.

In addition to vitamins, numerous free radical scavengers have been used in experimental paradigms of neuronal cell death *in vitro* and *in vivo*, such as the pineal hormone melatonin, the potent lipid peroxidation inhibitors known as the 21-aminosteroids or lazaroids, mifepristone (RU486), and the female sex hormone estrogen. Early melatonin administration reduces anti-oxidant stress and inhibits apoptosis in animal models of AD³². Lazaroids such as the U-74006F or tirilazad mesylate, can attenuate the increased lipid peroxidation observed in AD¹⁵⁸. Another series of antioxidants, the 2-methylaminochromans such as the compound U-78517F, may have be more potent and effective inhibitors of lipid peroxidation than the 21-aminosteroids⁶¹.

Stroke—Radical scavengers (such as vitamin E, sulfhydryl compounds and nitron spin traps), agents that promote detoxification of ROS (superoxide dismutase, catalase or peroxidase conjugates), and agents that prevent radical generation (e.g., the xanthine oxidase inhibitor allopurinol, nitric oxide synthase inhibitors, or nonsteroidal anti-inflammatory agents and cyclooxygenase-inhibitors) have been studied in stroke. The use of NXY-059 has been associated with clinical benefits in animal models of stroke, and was associated with a significant improvement in the modified Rankin functional scale in the Stroke-Acute Ischemic NXY Treatment-I (SAINT-I)⁸⁵. However, these results were not reproduced in the expanded SAINT-II trial^{53,131}. Ebselen and the radical scavenger edaravone (MCI- 186, Radicut) were associated with clinical improvement in a small trials⁵⁶.

HD—Anti-oxidants which have shown potential benefit in animal models of Huntington's disease include thiol, the mitochondrial enzyme cofactor lipoic acid, and the combination of vitamin E and Q10⁷⁶. Treatment with Q10 was associated with reduced levels of 8-hydroxyguanosine (a marker of oxidative damage) and improved survival in R6/2 mice. There was a trend towards slowing decline in total functional capacity although these did not reach clinical significance in a large clinical trial of Q10³. A randomized trial of Vitamin E in HD showed no benefit although post-hoc analyses suggest a possible benefit in early disease¹²⁰.

2. Excitotoxicity and NMDA glutamate receptors

Excessive NMDA (N-methyl D-aspartate) receptor activation has been implicated in the pathophysiology of several neurodegenerative diseases and in stroke.

PD—Following the loss of dopamine, enhanced N-methyl-D-aspartate (NMDA) receptor-mediated transmission in the striatum may be part of the cascade of events leading to the generation of parkinsonian symptoms. The dopaminergic deficit results in enhanced activity of the subthalamic nucleus STN and increased glutaminergic output to the basal ganglia²⁰. Studies on dopamine denervated rats and MPTP-treated parkinsonian monkeys have 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 decreases 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^{44,62}. Since stimulation of NR2B-containing NMDA receptors contributes to the generation of parkinsonian symptoms⁶³, NR2B-selective NMDA receptor antagonists may be therapeutically beneficial for parkinsonian patients. Prior administration of NMDA receptor antagonist dizocilpine MK801 suppresses the dopa-induced increase in glutamate in 6-hydroxydopamine-lesioned rats and may therefore offer neuroprotection⁷⁵.

Several NMDA antagonists have been studied in PD. Both Amantidine and dextromethorphan have antidyskinetic effects, and amantidine is associated with increased lifespan^{147,149}. On the other hand, memantine did not show any benefit in one trial⁹⁷. 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 antiparkinsonian actions in rat and, and nonhuman primates¹⁰⁴⁻¹⁰⁶. CP-101,606, reduced parkinsonian symptoms in both haloperidol-treated rats and MPTP-lesioned nonhuman primates¹⁴⁰. Pretreatment of 6-OHDA-lesioned rats with BZAD-0, 4-trifluoromethoxy-N-(2-trifluoromethyl-benzyl)-benzamidinium (BZAD-01), a novel selective inhibitor of the NMDA NR1A/2B receptor, significantly reduced the amount of dopamine cell loss and significantly improved all behavioral measures⁸². When given in combination with levodopa-carbidopa, the NMDA-antagonist remacemide, has been shown to reduce parkinsonism in rodent and monkey models of PD⁵⁷. However, it failed to demonstrate a clear benefit in clinical trials¹³⁰. The utility of riluzole, a presynaptic inhibitor of glutamate release, as neuroprotective agent in PD was addressed in a large multicenter randomized clinical trial, which was halted after preliminary results showed no evidence of a neuroprotective effect¹²³.

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 PD¹⁷.

Alzheimer's disease—Several studies have linked tau and amyloid aggregation to glutamate mediated toxicity and suggest the involvement of NMDA subunits in the pathogenesis of AD⁸⁰. *In situ* hybridization studies revealed lower NR1m RNA levels in the layer III of the entorhinal cortex and dentate gyrus in AD brains⁹⁸. AD 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 hippocampus⁷⁰. Moreover, the levels of NR1 and NR2B expression decrease with disease progression. The presence of presenilin-1 in a macromolecular complex with NR1 and NR2A further supports a role for excitotoxicity in AD¹²⁵.

Therapeutic intervention with high-affinity NMDA receptor antagonists, such as phencyclidine (PCP) and MK-801, is not practical due to adverse side effects. Memantine is an uncompetitive NMDA receptor antagonist and can decrease pathological activation of NMDA receptors without affecting physiological NMDA receptor activity⁴⁸. Memantine is associated with functional improvement in AD patients and has been FDA-approved for the treatment of AD^{10,48}.

Stroke—Excitotoxicity has been a widely investigated area in stroke. Ischemic neuronal injury *in vitro* is dependent on synaptic release of excitatory amino acids and resultant elevation of intracellular free calcium. Even transient exposure to excess excitatory amino acids (EAAs) is toxic to cultured neurons, and alterations in neuronal energy balance increases the

vulnerability of neurons to excitotoxic damage even in the presence of physiological concentrations of EAAs¹⁰⁰. Evidence that this process progresses over several hours after the ischemic insult highlights a potential role for neuroprotective strategies administered during the critical window prior to irreversible loss, although the exact duration of this window in humans remains unknown. The action of glutamate on NMDA receptors seems to play an important role in glutamate-mediated toxicity. Compounds that decrease glutamate levels or interfere with its binding to this receptor have been the focus of many studies in this area¹⁰³.

NMDA antagonists which have been investigated in stroke include Aptiganel hydrochloride (CNS 1102, Cerestat), dextrorphan and dextromethorphan. Their use was associated with side effects and no clear clinical benefit in clinical trials¹⁰⁰. Phase 2 trials of both oral and IV forms of remacemide hydrochloride in stroke are currently underway. Magnesium ion, which electrophysiologically behaves as a noncompetitive NMDA antagonist, has demonstrated efficacy as a neuroprotective agent in focal and global models of cerebral ischemia. Two preliminary trials of IV magnesium show no evidence of adverse effects^{101,151}, and phase 3 trials are currently underway. A phase 2 trial of Selfotel (CGS 19755) in acute stroke patients, reported evidence of a dose-dependent toxicity³³. Selective NMDA antagonists such as ifenprodil and eliprodil (SL82.0715) have demonstrated preclinical neuroprotective efficacy, and eliprodil is currently being investigated in early phase 3 trials in stroke patients. Other compounds under investigation are 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP), its derivative *d*-CPPene, and CGS 19755¹⁴⁴. Neuroprotection is evident for the presynaptic glutamate release inhibitors 619C89 and ubeluzole when administered within 6 hours of induced ischemia. Both drugs are currently in phase 2 trials in stroke.

Partial glycine agonists, such as HA 966, L687414, and 1-aminocyclopropanecarboxylic acid (ACPC), or full antagonists, such as 7-chlorokynurenic acid and its derivatives or ACEA 1021, are effective in stroke models. Glutamate antagonists at other receptor subtypes, such as the AMPA receptors, are under evaluation¹⁰⁰.

HD—Injections of excitatory amino acids into the striatum of rodents and primates results in neuronal death and a neurologic phenotype similar to that of HD. Intrastriatal 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 receptors⁸⁴.

The efficacy of memantine in slowing down the rate of progression was studied in a two year, open and multicenter trial with promising results¹⁴. Cannabinoid-derived drugs also offer 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 excitotoxicity¹¹⁵.

3. Inflammation

PD—There is evidence that systemic inflammation may promote microglial activation in PD, and genes implicated in PD may also influence inflammatory mediators⁸³. Overexpression 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 iNOS¹⁴². Animal models of PD utilizing MPTP also show evidence of recruitment of CD4 T cells to the SN²⁸.

Minocycline, a tetracycline derivative, has been shown to reduce microglial activation and inhibit the release of potentially toxic cytokines in the striatal region of MPTP mice.

Pretreatment with minocycline improved survival of dopaminergic SN neurons in animal models of PD⁴³. The use of nonaspirin nonsteroidal anti-inflammatory agents (NSAIDs) has been associated with a 45% reduction in the risk of developing PD in one prospective study with 14 years of follow up³¹. Cytokines (particularly TNF- α) activate COX-1 and COX-2, which catalyze the conversion of arachidonic acid to prostaglandins and thromboxanes. Mixed COX-1/COX-2 inhibitors and selective COX-2 inhibitors were shown to partially protect against MPTP-induced striatal depletion in rodents¹⁴⁵. Further preclinical studies are needed in this area.

AD—Several inflammatory mediators may have a role in the pathogenesis of AD. In a prospective cohort study of subjects with AD, acute systemic inflammatory events were associated with an increase in the serum levels of proinflammatory cytokine⁶⁷ and a 2-fold increase in the rate of cognitive decline over a 6-month period. High baseline levels of TNF- α were also found to be associated with a 4-fold increase in the rate of cognitive decline.

Clinical studies suggest that non-steroidal anti-inflammatory drugs (NSAIDs) cause a delay in the onset or slow down progression of AD, through the inhibition of COX and lipoxygenases, and resultant decrease in prostaglandin synthesis and ROS formation⁷⁸. In vitro studies of neuronal cell lines have shown that GSH depletion induces the activation of neuronal 12-lipoxygenase (12-LOX), which leads to the production of peroxides, the influx of Ca²⁺, and ultimately to cell death.⁸⁷ Exposure to glutamate is associated with induction of the enzyme COX-2, suggesting a possible role for COX inhibitors in neuroprotection¹⁴⁶. Compounds with anti-inflammatory activity such as glucocorticoids, anti-malaria drugs, and colchicines are potential areas of interest. Treatment with a moderate dose of prednisone has been shown to suppress serum levels of acute phase proteins in AD patients⁶. The neurohormone melatonin exert inhibitory effects on β -amyloid aggregation, oxidation, and inflammation in vitro, and results in behavioral improvement animal models¹¹³.

The peroxisome proliferator-activated receptor (PPAR) plays an important role in regulating the expression of enzymes involved in lipid metabolism. Specific PPAR isoforms have been shown to suppress the expression of the proinflammatory cytokines IL-1, TNF, and IL-6 and decrease the activity of the transcription factors of NF κ B, AP-1, and STAT proteins. Activation of PPAR γ results in decreased differentiation of monocytes into activated macrophages, decreased β -amyloid-stimulated expression of IL-6 and TNF- α , and decreased expression of COX-2³⁵.

Stroke—Several inflammatory mediators such as leukocytes, adhesion molecules, acute phase reactants, cytokines and proteases are increased in the plasma of patients with cerebral ischemia. The early central inflammatory events include the production of reactive oxygen species (nitric oxide, superoxide) expression of proteolytic enzymes (MMP-9, MMP-2), vasoactive substances (prostaglandins and cyclooxygenases) and vascular adhesion molecules (ICAM-1, P-selectin, L-selectin). Neutrophils and macrophages are considered early contributors to the production of ROS and cytokines, while activation of microglia and proliferation of astrocytes in the ischemic area further promote the inflammatory response in later stages⁴⁰.

Inflammatory mediators, [such as IL-1 β , IL-6, TNF α , IL-10, transforming growth factor beta (TGF β) and chemokines including MCP-1, macrophage inflammatory protein-1 (MIP-1), keratinocyte-derived chemokine/chemokine (CXC motif) ligand 1/(KC/CXCL1) and fractalkine (CX3CL1)], are also found in increased levels in brain tissue in animal models of stroke. The expression of IL-1 β mRNA is increased in the ischemic rat brain within hours after the induction of stroke⁸⁸, elevated levels of IL-6 are seen in the plasma and cerebrospinal fluid

(CSF) 3–6 h after experimental stroke in mice³⁴, and levels of pro-inflammatory cytokines such as IL-6, IFN γ , MCP-1 become elevated in the plasma within 6 hours in rodents¹⁰⁸.

The intercellular adhesion molecule-1 (ICAM-1) antibody, Enlimomab, can reduce the size of stroke when given within 1 hr reperfusion after transient, but not permanent ischemia, in a rat stroke model. However, its use was associated with significant worsening in the modified Rankin scale and higher mortality at 90 days compared to placebo in a large clinical trial⁴. Blocking neutrophil activation by a recombinant protein inhibitor of the CD11b/CD18 receptor, UK 279,276 (*Rovelizumab*), within 6 hrs of stroke also failed to show any benefits in one clinical trial which was stopped prematurely. Despite promising results for interleukin (IL)-1 receptor antagonist (RA) in several animal studies, this drug has not been investigated in humans¹². FK506 also demonstrates benefits, particularly after transient ischemia, in animal studies and remains a potential target for studies in humans⁹⁰. Systemic administration of minocycline is protective in experimental models of focal¹⁶¹ or global¹⁶⁰ cerebral ischemia. Inhibition of IL-1 β converting enzyme⁶⁴ or deletion of IL-1 β and IL-1 α results in markedly reduced ischemic damage and neuronal death in animal studies²⁵. Deficiency of inflammatory chemokines such as MCP-1⁶⁹ or fractalkine¹³⁸ is associated with less vulnerability to ischemic injury.

HD—Neuroinflammation is a prominent feature associated with Huntington's disease and may constitute a novel target for neuroprotection. Increased expression of several key inflammatory mediators, including CCL2 and IL-10, has been reported in the striatum of patients with Huntington's disease. There is also evidence of upregulation of IL-6, IL-8, and MMP9, in the cortex and notably the cerebellum¹³⁶. Minocycline can reduce calpain-mediated inflammation and caspase-dependent neurodegeneration, and was found to be neuroprotective in HD rat models. However, it cannot effectively prevent calpain-dependent neuronal death in cell culture models¹¹.

4. Mitochondrial dysfunction

PD—Perhaps, 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. For example, *Parkin* knockouts demonstrate impaired mitochondrial activity and altered oxidative stress proteins in mouse and *Drosophila* models^{58,114}. Disruption of DJ-1, a mitochondrial protein with anti-oxidant chaperone activity, and mutations in PTEN-induced kinase (PINK1),¹⁴⁸ are associated with impaired mitochondrial and proteosomal functions⁴¹.

Creatine is a precursor of the energy intermediate phosphocreatine, and transfers phosphoryl groups for ATP synthesis in mitochondria. Dietary supplementation of carnitine resulted in decreased loss of dopaminergic cells in an MPTP mouse model of PD^{15,72}, possibly through the modulation of the Ras/NF-kappaB signaling pathway. CoQ10 provides significant protection against MPTP-induced dopamine depletion^{50,133,159}. A significant reduction in CoQ10 levels in mitochondria has been reported in the platelets of patients with PD, and directly correlates with a decrease in complex-I activity. The oral administration of CoQ10 in PD patients resulted in significant dose-dependent increases in plasma CoQ10 levels, and a statistically significant dose-dependent reduction in UPDRS scores compared to placebo. MitoQ contains coenzyme Q10 (CoQ10) covalently linked to the lipophilic cation triphenylphosphonium. MitoQ helps preserve mitochondrial function after glutathione depletion³⁰, and is currently in a phase II clinical trial for PD (<http://www.parkinsons.org.nz/news/protectstudy.asp>). Preliminary data also suggest that both SS-31 and SS-20 (members of anti-apoptotic mitochondrial proteins referred to as Szeto-Schiller [SS] proteins) produce complete protection against MPTP neurotoxicity¹⁵⁶. Others

such as carnitine, β -hydroxybutyrate, and nicotinamide have been shown to protect against MPTP MPTP-induced neurodegeneration in mice.

AD—Alterations in mitochondrial size, structure, and function have been extensively reported in AD. These include deficiency in enzymes involved in oxidative metabolism (such as α -ketoglutarate dehydrogenase complex, and pyruvate dehydrogenase complex), altered calcium homeostasis, and sporadic mtDNA rearrangements. APP accumulates in mitochondria and levels of mitochondrial APP seem to directly correlate with mitochondrial dysfunction and severity of the disease. AD is also associated with abnormal distribution of mitochondria as they accumulate in the soma and are reduced in the neuronal processes of AD pyramidal neurons. Furthermore, synaptic dysfunction is one of the early and most robust correlates of AD-associated cognitive deficits, suggesting a role for A β -induced mitochondrial dysfunction in the pathogenesis of early AD¹⁴¹.

Anti-oxidants that specifically target mitochondria are currently being studied in AD²³. A phase II clinical trial of the orally active anti-oxidant MitoQ is under way in AD. CoQ10 treatment has been shown to decrease brain oxidative stress, reduce β -amyloid plaque load, and improve cognitive performance in a transgenic mouse model of AD (Kipiani et al., unpublished findings). Creatine administration protects against glutamate and β -amyloid toxicity in rat hippocampal neurons²⁷. Idebenone prevents β -amyloid-induced toxicity and, in combination with α -tocopherol, can improve β -amyloid-induced learning and memory deficits in rats^{27,154}. The administration of Idebenone 45 mg twice/day orally in AD patients was associated with statistically significant improvement of memory, attention, and behavior in a multicenter trial¹⁵². Another randomized multicenter study trial of idebenone reported a statistically significant and dose-dependent improvement in the Alzheimer's Disease Assessment Scale (ADAS) score after 6 months⁶⁰.

Stroke—The release of multiple apoptogenic proteins from mitochondria has been identified in ischemic and post-ischemic neurons. Results from animal models strongly implicate caspase-dependent and caspase-independent apoptosis and the mitochondrial permeability transition as important contributors to tissue damage, particularly when induced by short periods of temporary focal ischemia¹³⁷. Prophylactic administration of oral creatine reduces the size of ischemic brain infarctions in mice. The anti-oxidant Szeto-Schiller peptide (SS-31) plays an important role in modulating ROS-induced mitochondrial permeability transition and cell death, and has been found to be protective in several in vitro and in vivo models of ischemia and reperfusion injury. Synthetic triterpenoids (TP) are analogues of oleanolic acid, which exert anti-oxidative effects through stimulation of the antioxidant response element (ARE)–Nrf2–Keap1 signaling pathway, and have been shown to be protective in a rat model of cerebral ischemia³⁰.

HD—HD is associated with significant defects in mitochondrial respiratory enzymes, including mitochondrial succinate dehydrogenase (SDH, complex II) and aconitase. Protein aggregates interfere with mitochondrial function, mitochondrial trafficking in axon, 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 primates³⁰.

Results from studies on HD transgenic mice suggest that high dose CoQ10 significantly extends survival, improves motor performance and grip strength, and reduces brain atrophy in R6/2 HD mice in a dose-dependent manner. The combination of CoQ10 and minocycline in R6/2 mouse model of HD resulted in a significantly improved behavioral measures, reduced neuropathological deficits, extended survival, and attenuated striatal neuron atrophy, as compared to either agent alone¹³⁹. Similarly, the combination of CoQ10 and remacemide

(NMDA antagonist) resulted in significantly improved motor performance and increased survival in the R6/2 and the N-171–82Q transgenic mouse models of HD⁵¹. These two compounds were studied separately and in combination in 340 patients with HD. Administration of CoQ10 resulted in a 14% decrease in disease progression while remacemide demonstrated no efficacy³.

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 the R6/2 and N-171–82Q transgenic mouse models of HD⁸. Idebenone was not associated with significant improvement in a small trial in HD¹²². A phase III trial of 2400 mg of CoQ10 daily has recently started in HD, and phase II trial of CoQ10 in presymptomatic gene-positive HD patients (PREQUEL) will begin soon¹³².

PGC-1 α is a transcriptional regulator of several enzymes such as the nuclear respiratory factors-1 and 2, Tfam, and estrogen related receptor- α involved in mitochondrial biogenesis. Potential utility of this factor in neuroprotection has been suggested by reports of impaired expression in HD transgenic mice and HD patients. PGC-1 α induced the expression of anti-oxidant enzymes and its overexpression is associated with protection of neural cells from the oxidation by mitochondrial toxins⁹⁵. Sirtuins (silent information regulators) 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 HD¹¹⁷. SIRT1 activation by resveratrol has been associated with increased survival of motor neurons from transgenic ALS mice⁷⁷. In AD, SIRT1 activation by resveratrol significantly protects against microglia-dependent amyloid- β toxicity by inhibiting NF- κ B signaling and is associated with cognitive improvement in AD mouse models⁷⁷.

5. Apoptosis

In general, anti-apoptotic mechanisms being evaluated in neuroprotection include strategies to prevent caspase-dependent apoptosis (e.g., caspase inhibitors) or strategies to prevent caspase-independent apoptosis (e.g., PARP inhibitors).

PD—Dopaminergic cells exhibit increased expression of the pro-apoptotic protein Bax and effector protease caspase-3 compared to controls¹⁴³. Significantly higher levels of caspase -8 activation have been demonstrated in the dopaminergic (DA) neurons of substantia nigra pars compacta of patients with PD compared with controls⁶⁵, and caspase-8 activation occurs early after exposure to cellular toxins such as 1,2,3,6-tetrahydropyridine in *in vivo* experimental animal models of PD. Patients with untreated PD have high peripheral levels of caspase-3 activity in lymphocytes and upregulation of anti-apoptotic Bcl-2, which correlate with disease duration and severity. Treatment with L-Dopa and dopamine agonists is associated with lower levels of anti-apoptotic Bcl-2 in the blood, and higher densities of the peripheral benzodiazepine receptor PBRs¹⁹.

CEP-1347 is an inhibitor of mixed lineage kinases (MLK), which in turn regulate the c-jun N-terminal kinase pathway (JUNK) pathway. CEP-1347 has been shown to enhance neuronal survival in cell models of PD. However, it failed to show efficacy in the early treatment of PD in one clinical study². Minocycline has been shown to block MPTP-induced dopamine depletion in the striatum, decreases inducible NO synthase (iNOS) and caspase 1 expression, and inhibits NO-induced phosphorylation of p38 mitogen-activated protein kinase (MAPK). TCH 346 (N-methyl-N-propargyl-10-aminomethyl-dibenzo[b,f]oxepin—also referred to as CGP3466) is a potent anti-apoptotic drug that has been shown to prevent the loss of dopaminergic neurons *in vitro*, and protect against behavioral abnormalities and neurodegeneration in animal models of Parkinson's disease⁹. This novel drug is thought to

block the transcriptional upregulation of protective molecules such as Bcl-2 and superoxide dismutase⁹. However, it failed to demonstrate efficacy as a neuroprotective agent in one randomized placebo controlled trial¹¹².

Studies of caspase inhibitors in animal models of PD have led to mixed results. 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 brain¹⁵⁵. The more potent broad-spectrum caspase inhibitor, Q-VD-OPH, may be more promising. Specific caspase inhibitors such, such as acetyl-tyrosinyl- valyl- alanyl- aspartyl- chloro- methylketone (Ac-YVAD-cmk), have also demonstrated efficacy in several experimental paradigms of PD¹²⁶. On the other hand, other studies have found no benefit with caspase inhibitors. The treatment of 1-methyl-4-phenylpyridinium-intoxicated primary DA cultures with broad-spectrum and specific caspase-8 inhibitors triggered a switch from apoptosis to necrosis, with no overall neuroprotective benefits in one study⁶⁵. Further studies are needed in this area.

Propargylamines have proven to be potent anti-apoptotic agents in both in vitro and in vivo studies, as these peptides can prevent mitochondrial permeabilization, cytochrome c release, caspase activation and nuclear translocation of glyceraldehyde 3-phosphate dehydrogenase¹⁰⁹. In fact, inhibition of apoptosis through caspase inhibition may underly the action of the propargylamine-derived monamine oxidase type B (MAO-B) inhibitors such as rasagiline and deprenyl (selegiline)²⁴. Moreover, rasagiline appears to induce anti-apoptotic pro-survival proteins, Bcl-2 and glial cell-line derived neurotrophic factor⁹². In addition to its symptomatic benefits as a dopaminergic agent, selegiline has been shown to delay the need for symptomatic therapy in untreated PD patients in the DATATOP study¹²⁹. Lazabemide is a reversible inhibitor of MAO-B that is not a propargylamine. Results from a randomized double blinded study suggested a delay in the need for levodopa treatment and a possible neuroprotective benefit. However, studies on this compound have been discontinued by the sponsor.

AD—The activation of PARP (Poly(ADP-ribose) polymerase (PARP)) plays a critical role in caspase-independent apoptosis. Therefore, PARP inhibitors represent one possible therapeutic strategy in AD. PARP-1 has been implicated in DNA repair and maintenance of genomic integrity. The generation of reactive oxygen species causes overactivation of PARP resulting in the depletion of NAD(+) and ATP, and consequently in necrotic cell death and organ dysfunction³⁹.

There is evidence to suggest that apoptosis is associated with senile plaques containing amyloid- β peptide (A β) in AD brains, and this effect may be mediated through ROS. The effect of Pycnogenol (PYC), a potent antioxidant and ROS scavenger, on A β (25-35)-induced apoptosis was investigated in an animal model of AD. PYC suppressed the generation of ROS, caspase-3 activation, DNA fragmentation, PARP cleavage, and eventually protected against A β -induced apoptosis. A significant increase in ROS formation preceded apoptotic events after the cells were exposed to A β (25-35)¹¹⁸

HD—Several lines of evidence point to a role for apoptosis in HD in animal models and in postmortem tissue. Caspase 3 has been shown to cleave mutant huntingtin and the activation of caspase 1 has been reported in the HD brain. The expression of expanded polyglutamine residues has been associated with apoptotic mechanisms via caspase activation and cleavage of the death substrates lamin B and inhibitor of caspase-activated DNase (ICAD)⁵⁹. 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 activation¹⁵⁰.

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 therapies³⁶. Extracellular ATP stimulates apoptosis through stimulation of P2X7 receptors, and subsequent alterations in calcium permeability, both of which have been described in HD. The in vivo administration of the P2X7-antagonist Brilliant Blue-G (BBG) to HD mice prevented neuronal apoptosis and attenuated motor-coordination deficits⁴².

Apoptosis in stroke—Both caspase-dependent and caspase-independent mechanisms of cell death are implicated in focal cerebral ischemia. Increased expression of Fas and of mediators of the extrinsic caspase-dependent pathway have been shown following focal ischemia. Increased expression of caspase-1, -3, -8, and -9, and of cleaved caspase-8, has been observed in the penumbra. The role for apoptosis in ischemia is further supported by reports that the inhibition of caspase-3 reduces infarct size after transient focal ischemia⁵².

Intranuclear MMP activity facilitates oxidative injury in neurons during early ischemia through the cleavage of PARP-1 and XRCC1, and resultant disturbance of DNA repair mechanisms. Inhibition of MMP with the broad-spectrum inhibitor, BB1101, significantly attenuated ischemia-induced PARP-1 cleavage, and resultant cell death in rat model of focal cerebral ischemia.¹⁵⁷ The p53-dependent receptor pathway also seems to be involved in stroke induced apoptosis. Injection of netrin-1, a ligand of the receptor uncoordinated gene 5H2 (UNC5H2), was associated with significantly reduced infarct volume at 3 days after focal ischemia in an animal model of stroke, through its inhibition of p53-mediated apoptosis¹⁵³. Estrogen has also been shown to prevent Fas-mediated apoptosis in experimental models of stroke⁷⁴.

6. Misfolding of protein and protein aggregation

PD—Several animal studies or studies of familial PD have shown that the overexpression of the wild type and the mutant forms of α -synuclein can lead to loss of dopaminergic terminals, the aggregation of α -synuclein and subsequently to motor impairment. On the other hand, alpha- α -synuclein knockouts do not display any characteristic phenotype other than minor deficits in dopamine transmission⁵. Lentiviral mediated expression of wild type rat α -synuclein in rats resulted in the formation of aggregates but no cell loss⁸⁹. Based on these results, it is plausible that either misfolded α -synuclein, or increased amounts of normal α -synuclein, contribute to neurotoxicity in PD. Other studies have demonstrated the presence of large amounts of α -synuclein aggregates in the presynaptic region terminals. These occur in parallel with significant synaptic pathology and may, at least partially, account for the discrepancy between the number of neocortical LB and the degree of neuronal loss or cognitive impairment⁸¹.

Much of our current understanding of possible ways to target the accumulation of α -synuclein in α -synucleinopathies have been based on studies of amyloid aggregation in patients with Alzheimer's Disease (AD). Both animal and in vitro cell models suggest that the conversion of some amyloidogenic proteins from random structure to a beta sheet rich aggregated form can be inhibited by the addition of peptides derived from the respective amyloidogenic protein¹⁸. Previous studies on the use of peptide inhibitors in AD by the insertion of an N-methylated amino acid to provide a β sheet breaking peptide provided the basis for the development of methylated α -synuclein as a potential target in PD and LBD⁶⁸. The formation of an N-methylated derivative of synculein, by the replacement of the Gly73 with sarcosine, resulted in reduced fibril formation and markedly reduce toxicity^{22,116}.

α -synuclein peptide fragments that bind to full length α -synuclein have also been studied as potential targets for inhibiting α -synuclein aggregation. Peptides derived from the N-terminal of the non-amyloidogenic component region (NAC) of α -synuclein can bind to the full length

α -synuclein and block the assembly of α -synuclein 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)^{45,116}. A novel and potentially disease modifying approach to α -synuclein related disorders includes the inhibition of α -synuclein filament assembly with molecular compounds such as β α -synuclein -derived small peptides⁹⁴. The fibrillization of the murine α -synuclein can be inhibited by human α -synuclein, with possible role for at least one of the six mismatched residues between the two proteins; most of which were located in the C terminal region¹²⁴. Along this line, β -synuclein is a nonamyloidogenic homologue of a α -synuclein and has been characterized as inhibitor of alpha α -synuclein aggregation either by direct interactions or indirect inhibitory effects on the accumulation of toxic α -synuclein oligomers⁹⁴. A number of catecholamines, including dopamine, have been shown to exhibit inhibitory effects on α -synuclein fibrillization depending on their state of oxidation and leads to the accumulation of α -synuclein protofibrils⁵⁴.

AD—Potential inhibitors of A β aggregation include rifampicin, 5,8-dihydroxy-3*R*-methyl-2*R*-(dipropylamino)-1,2,3,4-tetrahydronaphthalene, type IV collagen, melatonin, danuomycin, glycosaminoglycans, fullerene, apomorphine derivatives, 3-indole propionic acid, nordihydroguaiaretic acid, tannic acid, 3-amino-1-propanesulfonic acid (Alzhemed or Tramiposate), Salvianolic acid B, and Δ^9 -tetrahydrocannabinol among others.

Several reports have shown that peptides or peptidomimetics can inhibit A β aggregation. Peptides which incorporate N-methylated amino acids in critical positions exert such an effect. N-methyl derivatives of the aggregation-prone fragment of A β , A β -(25–35), have been shown to prevent A β -(25–35) aggregation and inhibit toxicity in PC12 cells. N-methylated peptides of other regions of the peptides, such as A β -(36–40) may also be effectively inhibit aggregation. PPI-1019 D-(His-[(mLeu)-Val-Phe-Phe-Leu]-NH₂) is another effective N-methylated peptide inhibitor of A β aggregation and toxicity, which utilizes the methylation of an amine, rather than amide, in the unacetylated N-terminus⁷. The efficacy of these agents in inhibiting aggregation is sensitive to minor changes in testing conditions. However, the translation of these findings into development of disease modifying therapies is less than straightforward. Drug development of compounds such as Alzhemed and iA β 5p has been discontinued.

Similarly, there has been a search for inhibitors of tau aggregation. Methylene blue was the first such substance identified, followed by a number of anthraquinones such as daunorubicin and adriamycin. Anthraquinone analogue can reduce the formation of tau inclusions in neuroblastoma cells that overexpress a 4R human tau fragment. Other inhibitors include phenothiazines, porphyrins and polyphenols among others²⁹. A number of *N*-phenylamine, phenylthiazolyhydrazide, and rhodanine compounds have been added to the list of the tau aggregation inhibitors of interest.

Protein aggregation HD—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 disease models. *In vitro* studies showing that Hsp70 and Hsp40 promote the formation of soluble unstructured aggregates. The Hsp90 inhibitor geldanamycin, and its less toxic derivative 17-demethoxygeldanamycin (17-AAG), increase the expression of molecular chaperones thereby preventing the aggregation of the polyQ protein in cell culture and animal models.

Intracellular antibodies (intrabodies) which target polyQ protein and prevent its aggregation have been identified. These include the intrabody C4 which recognizes the N-terminal region of huntingtin protein (htt), and intrabodies MW7 and VL 12.3, which recognize regions

adjacent to the polyQ stretch of htt. These antibodies can inhibit inclusion body formation in cell cultures and prevent neurodegeneration in *Drosophila* and yeast models of HD. Other peptides, such as Polyglutamine Binding Peptide 1-6 (QBP1-6) and QBP1 (SNWKWWPGIFD), can interfere with the conformational changes associated with aggregation. Peptides consisting of two normal-length polyQ stretches connected by a spacer, have been developed that can break β -pleated sheets and inhibit their aggregation, although they may be less effective than QB1¹⁰².

Orally administered molecules that can mimic the therapeutic effects of biomolecules offer another potential area for development of poly Q aggregation inhibitors. Benzothiazole derivatives, including PGL-135, offered promise *in vitro* and in cell culture; however, these results were not reproduced in mouse models. The green tea polyphenol (–)-epigallocatechin-3-gallate (EGCG), can potently inhibit htt aggregation *in vitro* and in a *Drosophila* model of HD. Along the same line, compounds that can stabilize the native conformation may offer utility in preventing aggregation. Examples of these include dimethyl sulfoxide (DMSO), glycerol, trimethylamine *N*-oxide (TMAO), and trehalose. Using a yeast model-based high-throughput screening assay, thousands of similar compounds have been identified and will need to be evaluated in larger studies¹⁰².

7. Growth factors and gene therapies

Several trophic factors have been shown to protect dopaminergic neurons when given prior to exposure to toxins, *in vivo* and *in vitro* models of PD. Only a few, such as Glial-derived neurotrophic factor (GDNF) and its relative, neurturin (NRTN; also known as NTN), have been shown to promote restoration of neurons in the aftermath of a toxic exposure; therefore, making them potential therapeutic candidates for Parkinson's disease^{55,119}. However, their use has been limited by lack of effective means of delivery into the selected cell population; GDNF delivered by intracerebroventricular injection in patients had limited penetration into the putamen, and intraputamenal infusions were ineffective, probably due to limited distribution within the putamen¹¹⁹. Gene therapies utilize a viral vector to deliver a protein of interest to specific brain regions and may offer utility as a mean for delivery of trophic factors¹⁶. Preliminary results from a phase 2 randomized clinical trial with gene therapy for NRTN, using adeno-associated virus to deliver the trophic factor to the striatum, has recently been completed. (www.ceregene.com).

GPI-1485 and NIL-A belong to the group of neuroimmunophilins; compounds which are derived from the immunosuppressant FK 506 (tacrolimus), but have no immunosuppressant function. Neuroimmunophilins exhibit neurotrophic effects in animal models of PD, and can easily cross the blood brain barrier. Their exact mechanism of action is unknown, but may involve indirect stimulation of neurotrophic factor production. The results of clinical trials with these compounds have been insignificant. GPI-1046 is another neuroimmunophilin which is under development^{91,121}. GM-1 ganglioside, a constituent of cell membranes, has been shown to facilitate the neurotrophic action of GDNF and BDNF and inhibit apoptosis *in vivo* and *in vitro* models of PD. Phase I studies of this compound seem to be promising²⁴.

Stem cells are pluripotent cells that offer the potential of generating unlimited numbers of optimized dopamine cells for transplantation. Stem cells can be grown and expanded in tissue culture and then induced to differentiate into dopamine neuronal phenotypes. Transplantation of these cells into the striatum has been associated with behavioral improvement in 6-OHDA rodents and MPTP monkeys³⁷. Results of fetal cell transplant have been inconclusive, with conflicting results regarding the survival of the grafts^{79,86,96}, and questions remain regarding the optimization of selective dopaminergic cell transplantation²⁶.

AD—Hippocampal neural stem cell transplantation has been shown to improve the spatial learning and memory deficits in aged transgenic mice without altering A β or tau pathology. This beneficial effect seems to be mediated through brain-derived neurotrophic factor (BDNF) and resultant enhancement of hippocampal synaptic density²¹.

Estrogen modulates the expression of neurotrophic factors, such as NGF, enhances a non-amyloidogenic processing of amyloid precursor protein (APP), and prevention of apoptosis. Observational evidence implies that use of hormone therapy at a younger age close to the time of menopause may reduce risk of Alzheimer's disease later in life, while initiation of estrogen therapy during late post menopause has been associated with increased risk for dementia. Trials to address this issue are currently under way (Early versus Late Intervention Trial with Estrogen; Kronos Early Estrogen Prevention Study)⁶⁶. Neurosteroid allopregnanolones (APalpha) are potent proliferative agents which can promote neurogenesis in vitro and in vivo of both rodent and human neural stem cells, and are being studied in AD.

HD—Trophic factors such as TrkB, the receptor for BDNF have been investigated as potential neuroprotective agents in HD. The Ciliary neurotrophic factor (CNTF) and BDNF have benefit *in vivo* in mouse models of HD. However, their use in clinical trials will depend on the development of delivery methods to the brain such as the use of encapsulated cells or viral-mediated expression. Cysteamine, one candidate drug for HD, has been shown to increase BDNF levels in brain and to induce neuroprotection in HD mouse models¹⁰².

Concluding Remarks

After reading this review, it should be apparent of the depth and breadth of possible targets for the therapeutic intervention of diverse diseases such as PD, AD and Stroke. It should also be noted that although each of these disorders have quite different etiologies, clinical and cognitive symptoms, disease course, duration and progression and pathologies, the underlying pathways subserving these diverse disorders share common targets. Lastly, it should also be obvious that most of these approaches will never make it to Phase III clinical trials. What is important however is that in a relatively short period of roughly 40 years from the introduction of L-Dopa for the symptomatic treatment of PD, 20 years of thrombolytic therapies for stroke and 15 years of symptomatic treatment of AD with cholinesterase inhibitors, rapid advances in molecular biology and genetics have opened new avenues of research including the hundred some odd targets discussed in this review as well as the hundreds more that we were unable to address.

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Table 1

Potential Targets for Novel Therapies

Oxidative Stress
Excitotoxicity
Inflammation
Mitochondrial dysfunction
Apoptosis
Protein misfolding/aggregation
Neurotrophic factors
Gene therapy