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Review article

NEURODEGENRATIVE DISORDERS: PAST, PRESENT AND FUTURE

Bijaya Choudhury[1]*, Prem Saytode[1], Viral Shah[1]

[1]Dept. of Pharmaceutics, National Institute of Pharmaceutical Education and Research, Ahmedabad, Gujarat, India.

ABSTRACT: In neuroscientific research the field of neurodegeneration is most active in respect to both medical and associated social issues. Neurodegenration is a broad term used for the progressive loss of structure or function of neurons, including neural death. Neurodegenration can be found in many different levels of neuronal circuitry ranging from molecular to systemic. Many neurodegenerative disorders (NDD) occurs as a result of neurodegenerative process. According to National Institute of Neurological disorders and stroke there are more than 600 neurological disorders. Over last few decades there has been great progress with respect to understanding the triggers of most neurodegenerative diseases. Recent advancements in the basic knowledge of such diseases have led to speculation of new therapeutical approaches, to illustrate one, if we look at NDD as proteinopathy, it can be extrapolated that curing one of the disease could probably contribute to a cure of entire group of diseases related to given proteinopathy. The purpose of this article is to overview the history, epidemiology, etiology, leading pathways and possible treatment of neurodegenerative disorders which would possibly reinvigorate efforts to conduct researches in neuroscientific area for the ultimate benefit of the human community.

INTRODUCTION

A neurodegenerative disease (NDD) is defined as a deterioration (often irreversible) in the intellectual and cognitive faculties. Degenerative diseases of the central nervous system are significant causes of mortality among elderly people in industrialized countries. Neurodegenerative diseases are one of the greatest challenges society and medicine is facing at present. Due to an ageing population, it is expected to increase in prevalence and are predicted to become the second most common cause of morbidity in the developed world by 2040.The consequences are very significant both in terms of pathology and the cost of caring for patients. In general, the elderly are most at risk. The majority of neurodegenerative diseases are difficult to diagnose accurately, a clinical diagnosis is usually made through a process of elimination. The causes of most neurodegenerative diseases remain unknown. A lot of research has been directed at deciphering the molecular and biochemical mechanisms that lead to neurodegeneration. Despite having distinct clinical, pathological and biochemical signatures, neurodegenerative diseases are classified as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), Lewy body dementia (LBD), Vascular dementia(VD), Progressive supranuclear palsy(PSP),Corticobasal degeneration (CBD), Amyotrophic lateral sclerosis (ALS), Multiple system atrophy (MSA), Front temporal dementia (FTD), Multiple sclerosis (MS).

HISTORY

Several early sources, including an Egyptian papyrus, an ayurvedic medical treatise, the Bible, ancient Greek, Roman philosophers and Galen's writings, describe symptoms resembling those of NDD(García Ruiz, 2004). In the17th and 18th centuries, several authors wrote about elements of the disease,including Sylvius, Gaubius, Hunter and Chomel (Koehler & Keyser, 1997). At first In 1817 an English doctor, James Parkinson, published an essay on the Shaking Palsy describing the characteristic resting tremor, abnormal posture and gait, paralysis and diminished muscle strength, and the way that the disease progresses overtime(Lees, 2007).Jean-Martin Charcot, studies between 1868 and 1881 were a landmark in the understanding of the Parkinson's disease making the distinction between rigidity, weakness and bradykinesia(Lees, 2007). In 1912 Rederic Lewy described microscopic particles in affected brains, later named "Lewy bodies.In 1997, alpha-Synuclein was found to be the main component of Lewy bodies(Schulz-Schaeffer, 2010).Anticholinergics and surgery (lesioning of the corticospinal pathway or some of the basal ganglia structures) were the only treatments until the arrival of levodopa, which reduced their use dramatically.In 1901 German psychiatrist Alois Alzheimer identified the first case of Alzheimer's disease in a fifty-year-old woman.Huntington's was given different names in history like "simply chorea"hereditary chorea" and "chronic progressive chorea"(Morrison, 2002).

In 1963 Canadian physicians described Progressive supranuclear palsy as adegenerative disease involving the gradual deterioration and death of specific volumes of the brain(Steele, Richardson, & Olszewski, 1964).Corticobasal degeneration disease was first identified by Rebeiz and his associates in 1968. The French neurologist Jean-Martin Charcot was thefirst person to recognize multiple sclerosis as a distinct disease in1868(Steele et al., 1964).

EPIDEMIOLOGY

Degenerative diseases of the central nervous system are significant causes of mortality among elderly people in industrialized countries. The annual rate of 2.9 cases per 100,000 among subjects of European and American origin compared with a rate of 1.4 per 100,000 among subjects of African and Asian origin was observed.In the United States Alzheimer prevalence was estimated to be 1.6% in 2000 in the 65–74 age group, with the rate increasing to 19% in the 75–84 group and to 42% in greater than 84 group(Hebert, Scherr, Bienias, Bennett, & Evans, 2003).The World Health Organization estimated that in 2005, 0.379% of people worldwide had dementia, and that the prevalence would increase to 0.441% in 2015 and to 0.556% in 2030(Evidence, Team, & Project, 2006).Another study estimated that in 2006, 0.40% of the world population (range 0.17–0.89%, absolute number 26.6 million, range 11.4–59.4 million) were afflicted by AD, and that the prevalence rate would triple and the absolute number would quadruple by 2050(Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007).PD is the second most common neurodegenerative disorder after Alzheimer's disease, and affects approximately seven million people globally and one million people in the United States(De Lau & Breteler, 2006).PD is more common in the elderly and prevalence rises from 1% in those over 60 years of age to 4% of the population over 80(De Lau & Breteler, 2006). A 2013 epidemiological study of the prevalence of Huntington's Disease in the UK between 1990 and 2010 found that the average prevalence for the UK was 12.3 per 100,000(Walker, 2007).Currently, an estimated 60 to 75% of diagnosed dementias are of the Alzheimer's and mixed (Alzheimer's and vascular dementia) type, 10 to 15% are Lewy body type. It is slightly more prevalent in men than women(Crystal, 2008).The number of people with MS(Multiple sclerosis), as of 2010, is 2-2.5 million (approximately 30 per 100,000) globally.

TYPES AND ETIOLOGY OF NEURODEGENERATIVE DISORDER

When classifying neurodegenerative diseases, an initial question is “how much is enough?” When a patient first presents with abnormal neurological findings, symptoms may be mild and nonspecific and the course that the condition will take is often unclear: will the symptoms grow progressively worse, will they subside or will they not change at all? The associated neuropathology is also unknown initially and, depending on the condition, may remain unknown or unrevealed until much later, perhaps at post-mortem examination. In some neurodegenerative disorders, health and disease may be separated by shades of gray. Neurological changes build up gradually over time and clinicians frequently ask how severe symptoms must be or how much pathology is necessary to apply a disease label. A second problem relates to categorizing or naming the disease. When more than one possible diagnosis exists for a given set of symptoms or tissue pathologies, which one is appropriate? Neurodegenerative disorders sometimes defy rigid classification and subjective judgment is often unavoidable in the diagnosis of this condition. Despite the limitations of the current framework of neurodegenerative diseases, it at least offers a starting point for understanding this wide range of conditions. Table 1 is a brief overview of some of the currently recognized forms of neurodegeneration, following the one disease–one pathology framework.

MECHANISM OF NEURODEGENERATIVE DISORDERS

Neurodegenerative diseases are characterized by progressive dysfunction of specific population of neurons, determining clinical presentation. Neuronal loss is associated with extra and intracellular accumulation of misfolded proteins, the hallmark of many neurodegenerative proteinopathies. Major basic processes include abnormal protein dynamics due to deficiency of the ubiquitin–proteosome–autophagy system, oxidative stress and free radical formation, mitochondrial dysfunction, impaired bioenergetics, dysfunction of neurotrophins, neuroinflammatory processes and secondary disruptions of neuronal Golgi apparatus and axonal transport. These interrelated mechanisms lead to programmed cell death in a long run over many years. Neurodegenerative disorders are classified according to known genetic mechanisms or to major components of protein deposits.

Common pathogenic mechanisms underlying many NDDs includes:

1. Abnormal protein dynamics with misfolding, defective degradation, proteasomal dysfunction and aggregation, often with actions and mutations of molecular chaperones;
2. Oxidative stress (OS) and formation of free radicals/reactiveoxygen species (ROS);
3. Impaired bioenergetics, mitochondrial dysfunctions and DNAdamage;
4. Fragmentation of neuronal Golgi apparatus(secondary effect);

5. Disruption of cellular/axonal transport (secondary effect);
6. Dysfunction of neurotrophins (NTFs);
7. Neuroinflammatory processes;
8. Multifaceted neuronal death;
9. Cell death cascades;
10. Excitotoxicity.

Table 1:Types and etiology of neurodegenerative disorders(Esiri et al., 2001; Langa, Foster, & Larson, 2004; Prohovnik et al., 2006; Riley, Snowdon, & Markesbery, 2002; Schneider, Arvanitakis, Bang, & Bennett, 2007).

Condition	Pathological markers	Affected areas	Symptoms
Alzheimer's disease	Amyloid plaques, neurofibrillary tangle, gene: UBB+1	Cerebral cortex, hippocampus, basal nucleus of meynert	Cognitive impairments, motor difficulties, delusions, hallucinations
Parkinson's disease	Lewy bodies, gene: PARK2, PARK5 ,UCHL-1	Substantia nigra dorsal motor nucleus of the vagus, basal nucleus of meynert.	Muscle rigidity, resting tremor, difficulty in speaking and swallowing, postural disturbances
Lewy body dementia	Lewy bodies gene: PARK11, DLB	Cerebral cortex, substantia nigra, basal nucleus of meynert	Cognitive impairments, syncope, delusion, hallucinations, depression, anxiety
Vascular dementia	Vascular infarctions, atherosclerosis	Cerebral cortex hippocampus	Cognitive deficits with strokes, symptoms of alzheimer's disease
Progressive supranuclear palsy	Neurofibrillary tangles, variant gene: tau protein	Cerebral cortex, basal ganglia, spinal cord, midbrain	Loss of balance , difficulty moving eyes, slowing of movement , slurred speech
Corticobasal degeneration	Ballooned neurons with tau inclusions	Cerebral cortex, basal ganglia	Abnormal posture, muscle twitches, alien hand syndrome
Amyotrophic lateral sclerosis	Gene: SOD1,ALS2, SETX,FUS ,VAPB, ANG, TARDBP, FIG4,OPTN,ATXN2,	Motor cortex, brain stem, spinal cord	Motor impairment, impaired speech, muscle twitching & cramping.
Multiple system atrophy	Alpha-synuclein inclusions	Hindbrain involved in balance and autonomic functions	Postural hypotension, abnormal breathing , difficulty urinating, dry mouth and skin,
Frontotemporal dementia	Gene:FTLD-tau, FTLD-TDP43.	Temporal-limbics	Progressive nonfluent aphasia, behavioural variant
Multiple sclerosis	Environmental factors, infectious agents, genetics(HLA)	Many body parts	Motor abnormality, impaired bladder function, depression, memory impairment
Huntington's disease	BDNF by damaging microtubules.	Striatum, frontal and temporal cortices	Astrogliosis, loss of medium spiny neurons

ABNORMAL PROTEIN DYNAMICS

Protein aggregation

Abnormal interactions between proteins that result in aberrant intra and extracellular deposition of self-aggregating misfolded proteins with formation of high-ordered insoluble fibrils are pathological hallmark of diverse NDDs(Jellinger, 2009; Ovádi & Orosz, 2009). In general, the identity of the underlying protein determines the affected neurons and hence the clinical manifestation of NDDs(Dickson, 2009).

However, the same neuronal populations can be affected by different disorders, same neurodegenerative process and the same mutation in the genes encoding protein constituents may be associated with a variety of clinico-pathological phenotypes, whereas similar or identical phenotypes may be related to different genetic defects, resulting from complex gene–gene and gene-environmental interplay(Migliore & Coppedè, 2009). Abnormal protein–protein interactions and/or the lesions that result from them, trigger vicious circles leading to dysfunction and death of neuronal and glial cells with ensuing disintegration of neuronal networks(Palop, Chin, & Mucke, 2006). Abnormal interaction between normal, highly soluble brain proteins alters their conformation, and misfolding gradually converts them into insoluble polymers with the aggregates adopting either highly ordered (cross-pleated -sheet structures) or disordered (amorphous) forms(Ecroyd & Carver, 2008). Since deposits of natively unfolded proteins aggregated into defined fibrillar structures often display the properties of amyloid (i.e. ~10-nm-wide fibrils with crossed -pleated sheet structures), these disorders are grouped together as brain amyloidosis (Morris, Watzky, & Finke, 2009).

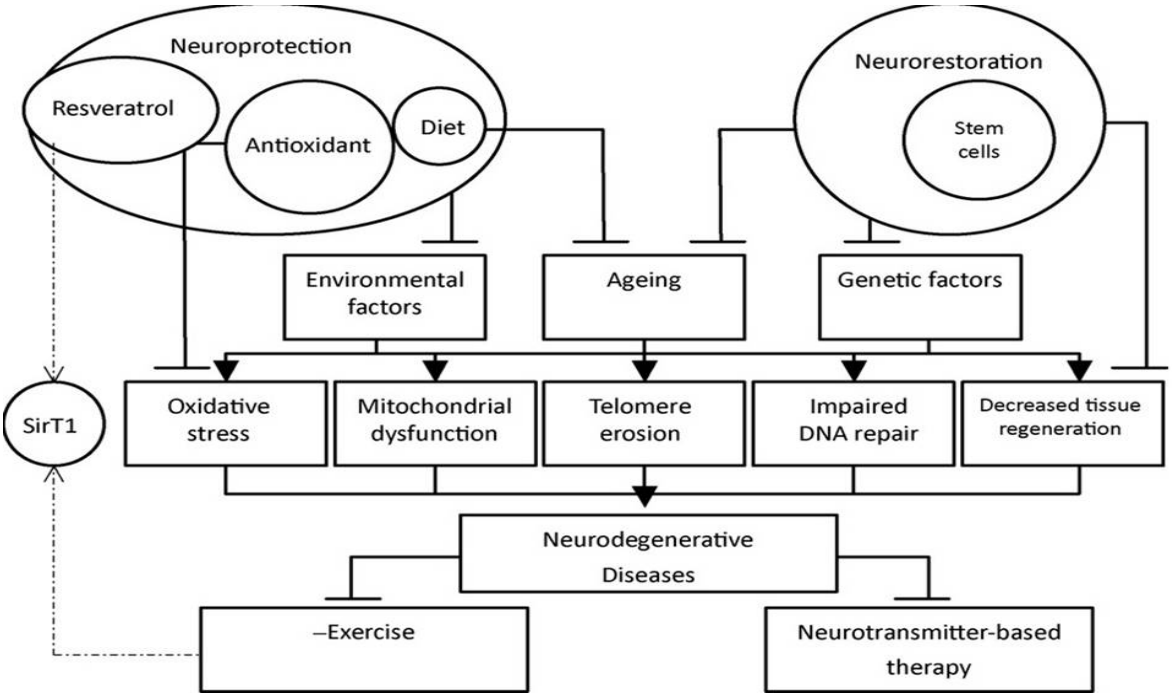

Figure 1: Etiology of neurodegenerative diseases

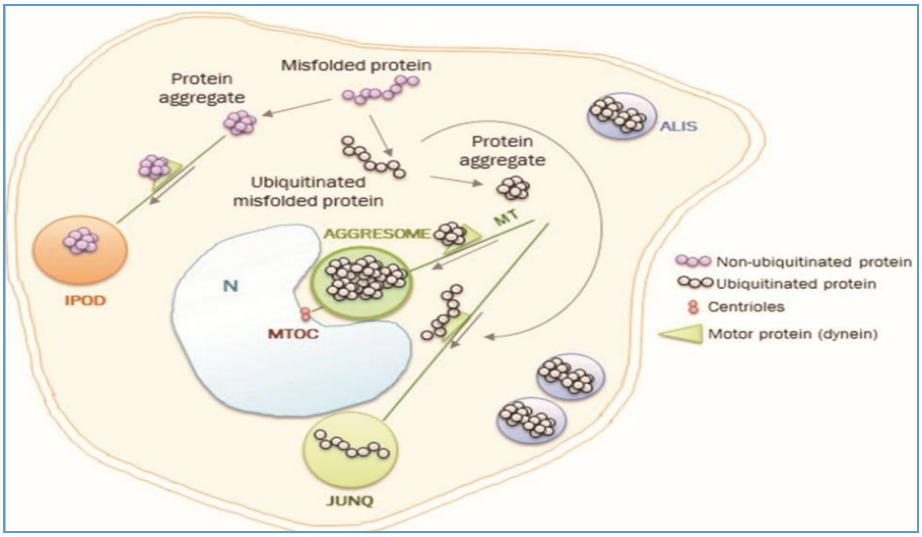

Figure 2: Mechanism of protein aggregation

Protein misfolding and endoplasmic reticulum stress

In neurons, the ER is important for the synthesis, folding and post-translational modification of transmembrane and secreted proteins. The ER response is characterized by changes in specific proteins, causing translational attenuation, induction of ER chaperones and degradation of misfolded proteins. In prolonged or aggravated ER stress, cellular signals leading to cell death are activated. ER stress may be involved in some human neuronal diseases such as AD, PD, prion diseases, etc.(Malhotra & Kaufman, 2007).

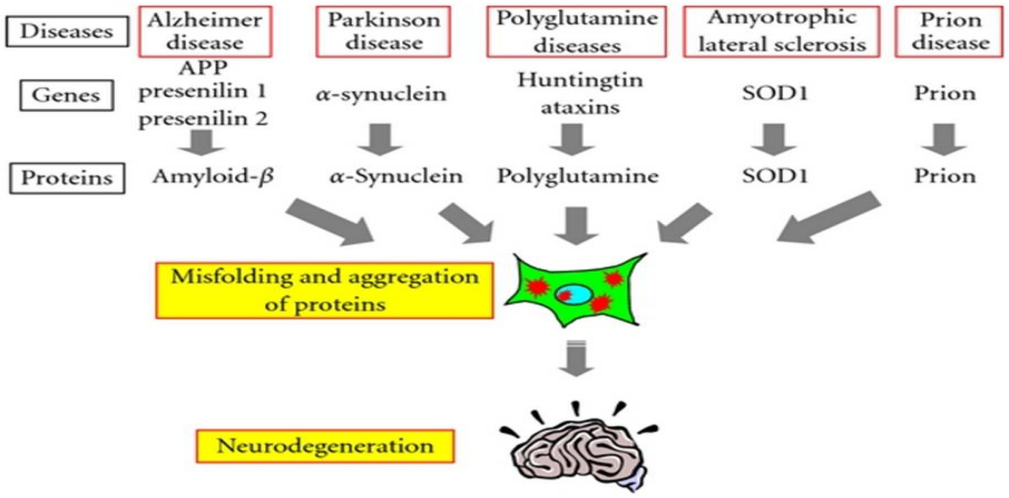

Figure 3: Different type of protein misfolding causing neurodegenration

Autophagy and neurodegeneration

Autophagy is a major protein degradation pathway for the clearance of intra-cytosolic aggregate-prone proteins associated with neurodegenerative diseases. Chemical inducers of autophagy acting via the mTOR-dependent and mTOR- independent pathways lead to the formation of double membrane structures called phagophores whose membrane origin has been suggested to be from plasma membrane, endoplasmic reticulum or mitochondria. The expanding phagophores sequester portions of cytoplasm along with misfolded proteins or damaged cell organelles to form the double- membrane vesicles called autophagosomes. Autophagy substrates also include neurodegeneration-associated aggregate-prone proteins (such as mutant hunting tin) and p 62.

UPS in neurodegenerative disorders

Ubiquitin proteasome system (UPS), the major non-lysosomal system for regulating protein turnover, and the autophagylysosome pathway (ALP) are the two most important mechanisms for regulating protein handling. Deregulation in the UPS appears to be both a cause and a result of ND processes. Its dysfunction has already been implicated in the pathogenesis of PD(Lim, 2007), and the demonstration that Syn is degraded by both proteasome and autophagy indicates a possible linkage between the UPS and ALP(Martinez-Vicente et al., 2008). Mutated Syn inhibits ALP by binding to the receptor on the lysosomal membrane for autophagy (Greek: self-digestion) pathway supporting the assumption that the ALP may be related to the development of PD(Pan, Kondo, Le, & Jankovic, 2008).

Aggresomes

When the capacity of the proteasome system to degrade misfolded proteins is overwhelmed, aggregation occurs and proteins are moved to an Ub-rich structure termed asaggresomes. It forms part of the cellular response to aggregated proteins and appears as inclusions in a number of proteinopathies. Aggresomes have been reported for superoxide dismutase (SOD), parkin, Syn and prion proteins, the formation of which has been associated with activation of caspases and apoptosis(Eliezer, 2009). Ubiquitination and sequestration of protein (e.g.Syn, synphilin-1) in aggresomes and cytoplasmic inclusions may represent a mechanism of cell protection. On the other hand, Syn aggregation is associated with decline in proteasome and lysosome, which may be involved in the pathogenesis of cell degeneration in PD(Chu, Dodiya, Aebischer, Olanow, & Kordower, 2009).

OXIDATIVE INJURY

Oxidative stressoccurs when the production of free radicals or their products are in excess of antioxidant defence mechanisms. It can damage biological molecules and initiate a cascade of events, including dysfunction of mitochondrial respiration, excitotoxicity, and a fatal rise in cytosolic calcium leading to cellular dysfunction together with nitric oxide and reactive nitrogen species. Thus, it is a major factor of the cytopathology of many diseases including NDDs and their models(Gardiner, Barton, Overall, & Marc, 2009).

A major source of ROS in neurons may result from escaping electrons from the respiratory chain reacting with oxygen. Other contributors are metal-iron associated Fenton reactions, lipid peroxidation and nitric oxide induced protein nitrosylation. Generation of excessive nitric oxide and ROS can mediate protein misfolding in the absence of genetic predisposition(Jaeger et al., 2009). Increased levels of oxidative damage to DNA, lipids and proteins have been detected in post-mortem tissues from patients with PD, AD, ALS, progressive supranuclear pals (PSP) and aging, some of which are environment-induced(Migliore & Coppedè, 2009). Oxidative damage to nuclear and mitochondrial DNA (mt-DNA) occurs in the earliest detectable phase of AD, PD and HD(Praticò & Sung, 2004).

Oxidative stress in Parkinson disease

In PD,many biochemical changes indicate compromised antioxidant systems to underlie cellular vulnerability to progressive OS which generates excessive ROS or free radicals in substantia nigra (SN) with subsequent cell damage(Miller, James-Kracke, Sun, & Sun, 2009; Olivares, Huang, Branden, Greig, & Rogers, 2009). Protein misfolding in PD has been associated with ROS as products of O_2 reduction(Arreguin, Nelson, Padway, Shirazi, & Pierpont, 2009).

Oxidative stress in Alzheimer disease

OS induces macroautophagy of a protein ensuing apoptosis(Zheng et al., 2009). Mutant APP and its derivates are involved in the generation of free radicals in mitochondria and cause mitochondrial oxidative damage, generation of free radicals and oxidative damage in the pathogenesis of AD(Reddy & Beal, 2008). OS or neurotoxic by-products of lipid peroxidation may damage DNA and lead to programmed cell death (PCD) in AD.

Oxidative stress in other neurodegenerative disorders

OS is also recognized as a major pathogenic factor in other NDDs(Jellinger, 2009). In PSP, increased lipid peroxidation in cerebral cortex is proportional to the extent of pathology, increased activity of antioxidant systems, e.g.SOD and glutathione, is seen in multiple brain areas, and oxidative damage affects regions vulnerable to PSP and argyrophilic grain disease(Santpere & Ferrer, 2009).

IMPAIREDBIOENERGETICS AND MITOCHONDRIAL DYSFUNCTION

Mitochondria the energy powerhouse of the cell, are key cytoplasmic organelles vital for the function and survival of neurons. They provide energy from aerobic metabolism viathe oxidative phosphorylation system (OXPHOS), the principal source of high-energy(Yang, Weissman, Bohr, & Mattson, 2008). In a variety of tissues, cumulative OS, disrupted mitochondrial respiration and oxidative mitochondrial damage are associated with, and may promote cell death(Reddy, 2008; J.-L. Yang et al., 2008). Dysfunctions of mitochondria disturb cell function, cause DNA damage, sensitize cells to neurotoxic insults and may initiate cell death, all significant phenomena in the pathogenesis of NDDs(Reddy, 2008). OS and damage to DNA during aging impair mitochondrial energy metabolism and ion homeostasis in neurons, thereby rendering them vulnerable to degeneration.

FRAGMENTATION OF NEURONAL GOLGI APPARATUS

Fragmentation of the neuronal Golgi apparatus–probably a secondary effect of the above mentioned basic mechanisms – was reported in ALS, CBD, AD, PD, and in spinocerebellar ataxia type 2 (SCA2)(Fan et al., 2008). Mechanisms involved in Golgi fragmentation include: (i) deregulation by mutant SOD1 of the microtubule-destabilizing protein Stathmin, (ii) disruption by mutant SOD1 of the neuronal cytoplasmic dynein, (iii) co-precipitation of mutant SOD1 with heat shock proteins HSP25 and HSP27, (iv) reduction of detyrosinated microtubules by aggregated which resulted in non-apoptotic cell death and (v) disruption by mutant growth hormone of the trafficking from the rough ER to the Golgi apparatus(Gonatas, Stieber, & Gonatas, 2006). Syn has been shown to block ER Golgi traffic causing Golgi fragmentation and neuronal Golgi fragmentation is an early and probably irreversible lesion in NDDs.

DISRUPTION OF CELLULAR/AXONAL TRANSPORT

There is growing evidence that defective neuronal and axonal transport due to early axonal dysfunction play a mechanistic role in most NDDs(Morfini et al., 2009). Three mechanisms highlight the significance of disrupted cellular/axonal transport in human NDDs: (i) human motor protein mutations in these disorders, (ii) axonal transport defects in animal and in vitrocellular models harbouring human mutations and (iii) roles for pathogenic proteins like APP, presenilin and synuclein, in the regulation of axonal transport (Roy, Zhang, Lee, & Trojanowski, 2005). Initial perturbation of the axon and its cytoskeleton, which then results in slow neuronal degeneration and loss of connectivity.

Axonal transport in tauopathies

Axonal transport is impaired in AD and other tauopathies, probably early in their pathogenesis(Schindowski, Belarbi, & Buee, 2008). Proteolytic cleavage of amyloid precursor protein (APP) occurs before its sorting into axonal transport vesicles(Muresan, Varvel, Lamb, & Muresan, 2009). It travels via fast axonal transport in vesicular complexes containing presenilin and site APP cleaving enzyme 1 (BACE1) and acts as a receptor for the anterograde motor kinesin.

Decreased retrograde transport of nerve growth factor (NGF) in human brain, leads to loss of neuronal markers and shrinkage of neurons in the cholinergic basal forebrain. Mis-regulation of APP can transduce into mis-regulation of fast axonal transport, which is a pathogenic mechanism for intraneuronal A(Pigino et al., 2009). Interfering with axonal transport may activate stress kinase pathways initiating a biochemical cascade that drives normal proteins into a pathogenic state.

Axonal transport in synucleinopathies

Syn is a highly conserved protein, strongly expressed in neurons and enriched in presynaptic terminals. Significant age-related transport retardation may lead to accumulation of Syn over time and produces pathology suggesting axonal transport abnormalities in synucleinopathies(Li, Hoffman, Stirling, Price, & Lee, 2004). Accumulations of small Syn aggregates in presynaptic terminals in the cortex suggest a pathological impact on synaptic functions leading to NDD.(Kramer & Schulz-Schaeffer, 2007).

DYSFUNCTION OF NEUROTROPHINS

There is growing evidence that reduced neurotropic support is a significant factor in the pathogenesis of NDDs(Bossers et al., 2009). NTFs affect neuronal survival; influence synaptic function and plasticity. NTFs bind to different receptors, to a common receptor, and each of them also binds to one of the family of Trk receptors. Since NTFs in neurons are subject to retrograde and to anterograde transport from and to targeting neurons, their effects may be related to synthesis in local or remote sites or to changes in axonal transport. In CNS disorders, such as AD, PD and HD. OS appears linked to the loss of neurotropic support(Gardiner et al., 2009); Amay induce the TrkA pathway activation and promote NGF secretion(Tapia-Arancibia, Aliaga, Silhol, & Arancibia, 2008). Inhibition of soluble NTF signalling in a mouse model of AD prevents/slows pre-plaque Amyloid-associated neuropathology, and potentially the progressive neuron loss in AD(Fombonne, Rabizadeh, Banwait, Mehlen, & Bredesen, 2009). In PD, decreased neuronal content and their receptors in SN indicate a reduction of neurotropic support and alterations in axon guidance in early stages of cellular stress, leading to dopaminergic cell death(Bossers et al., 2009).

NEUROINFLAMMATORY PROCESSES

Chronic inflammatory reactions and signs of immune activation in the CNS, with major histocompatibility complex (MHC) class II expression, glial reaction, T-cell infiltration, and blood-brain barrier dysfunction are prominent pathological features in the pathogenesis and progression of NDDs(Stolp & Dziegielewska, 2009). A central question is whether immune and inflammatory pathways become hyper activated with age and promote ND or whether insufficient immune responses, which fail to cope with age-related stress, may contribute to NDDs. Age-related neuroinflammatory changes negatively impact neuronal function(Lynch, 2009). Breakdown of the normal blood-brain barrier with influx of blood-born molecules (plasma proteins) have been suggested to cause local damage as starting mechanisms of some NDDs(Stolp & Dziegielewska, 2009). A leaky BBB, fibrinogen infiltration and microglial activity may cause neuronal damage in inflamed AD brain. Inflammation potentially increases brain levels of Aβ three mechanisms: increased influx, decreased efflux, and increased neuronal production(Jaeger et al., 2009). In PD, SN cell degeneration is accompanied by astroglial reaction and proliferation of MHC class II positive microglia releasing pro-inflammatory cytokines, nitric oxide, complements, and OS that may be either inducing factors or squeal of neuronal death(Hirsch & Hunot, 2009).

MULTIFACETED NEURONAL DEATH

Neurons undergo diverse forms of cell death depending on the nature and severity of the stress. The nature, time course and molecular causes of cell death in NDDs and their relations to basic processes are still a matter of discussion(Jellinger, 2009). Based on distinct morphologic criteria and biochemical features, PCD is classified into three major types: apoptosis (PCD type I), autophagy (PCD type II) and oncotic necrosis, a passive killing of the cell (PCD type III) (Bredesen, 2008; Kroemer et al., 2008).

CELL DEATH CASCADES

Despite demonstration of DNA fragmentation and up-regulation of pro-apoptotic and cell death regulator proteins, it is still unclear, whether apoptotic or necrotic modes are responsible for cell death in NDDs. It is preceded by the activation of caspases and altered expression of pro-apoptotic members of the Bcl-2 family and other actin-related proteins (ARPs). Multiple caspases and elevated caspases mRNAs have been detected in post-mortem tissue from AD brains, while others observed no apoptotic morphology in AD(Woodhouse, Dickson, West, McLean, & Vickers, 2006). Pro-apoptotic ligands cause a selective vulnerability of neurons in the cholinergic forebrain in APP(Fombonne et al., 2009). Caspase-3 has been found to be enriched in post-synaptic densities and increased in AD(Louneva et al., 2008)and activation of caspases by PSEN1 gene and its inhibition by secretase inhibition were reported(Miyoshi et al., 2009). Associations between tangle bearing neurons with caspases activation suggests that tangles are at least markers of neuronal disease.

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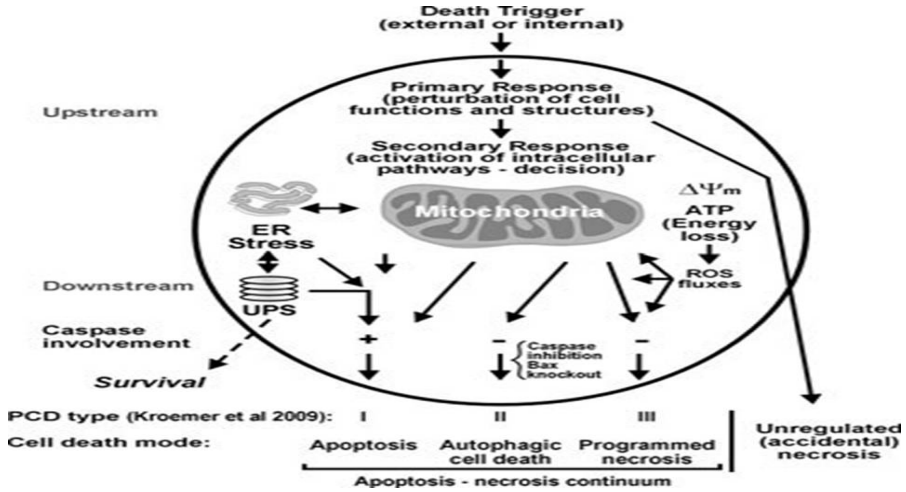

Figure 4: Diverse pathways leading to cell death, illustrated by the concept of the apoptosis-necrosis continuum that integrates the various death pathways andsubsequent intracellular signalling pathways.

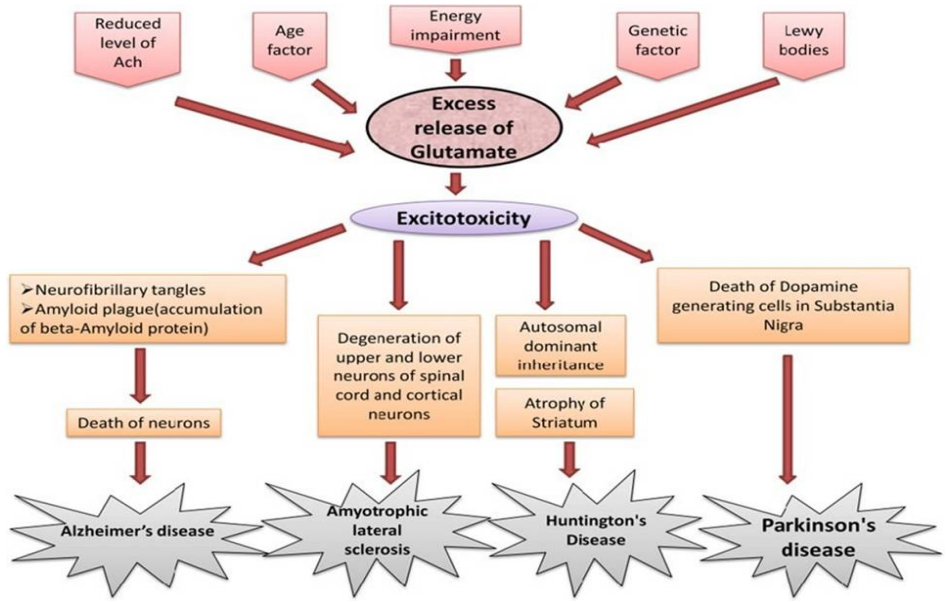

Figure 5: Factors for the genesis of neurodegenerative disorders

Table 2: Mitochondria-targeted therapeutics for neurodegenerative diseases(Bacman, Williams, Hernandez, & Moraes, 2007; Chinnery et al., 1999; Naderi et al., 2006; Nanjo et al., 1996; Y. Yang et al., 2008)

Class of drug	Drug	Mechanism
Redox therapy	Vitamin C (ascorbate)	Strong intracellular reducing molecule
Redox therapy	Vitamin E.	Scavenger of lipid oxidation in brain.
Redox therapy	Coenzyme Q10 and MitoQ (ubiquinone, coenzyme Q and ubidecarenone)	Strong lipid oxidant scavenger, inhibit mitochondrial permeability transition pore; and block Bax translocation to mitochondria.
Mitochondrial targeted small peptide	SS peptides	Free radical scavenging effect.
Natural antioxidants	Polyphenol, isoflavone, ginsenosides,alavonoids	Proven to effectively attenuate oxidative stress and apoptosis in cells
Mitochondrial permeability transition inhibition	Cyclosporine A (CsA), Sanglifehrin A (SfA)	Inhibit mitochondrial permeability transition pore (mPTP) formation
Mitochondrial gene therapy	COX-PstI, COX8-ApaLI and ScaI	Selective inhibition of mutant mt-DNA, recombinant mt-DNA substitution

EXCITOTOXICITY

Glutamate plays an important role in neuronal excitation. Multiple abnormal triggers such as energy deficiency, oxidative stress, mitochondrial dysfunction, calcium overload etc. can lead to aberration in neuronal excitation process. Such an aberration, serves as a common pool or bridge between abnormal triggers and deleterious signalling processes with which central neurons cannot cope up, leading to death. Excitotoxicity is the pathological process by which nerve cells are damaged and killed by excessive stimulation by neurotransmitters such as glutamate and similar substances, Such excitotoxic neuronal death has been implicated in spinal cord injury, stroke, traumatic brain injury, hearing loss and in neurodegenerative diseases of the central nervous system such as stroke, epilepsy, multiple sclerosis, Alzheimer disease, Amyotrophic lateral sclerosis, Parkinson's disease, Huntington disease.(Mehta, Prabhakar, Kumar, Deshmukh, & Sharma, 2012).

Table 3:Treatment of Alzheimer's disease(Hong-Qi, Zhi-Kun, & Sheng-Di, 2012)

Class of drug	Drug	Mechanism
Cholinesterase inhibitors	Tacrine,donepezil, rivastigmine,galantamine	Increase acetylcholine by inhibiting itsdegradation
Aβ-targeting strategies	Kmi-429,Gsk188909,Pms777	Inhibit β-secretase (BAC E1)
Aβ-targeting strategies	Bms-299897,Mrk-560, Ly450139 dihydrate	γ-secretase inhibitors decrease Aβ levels in plasma &cerebrospinal fluid
Aβ-targeting strategies	Adamalysin family of proteins	α-secretase activators decrease Aβ secretion&activate protein kinase C
M1 muscarinic agonists	Talsaclidine	Decrease tau-phosphorylation
Aβ-aggregation inhibitors	Tramiprosate	Binds to soluble Aβ and inhibits the formation of neurotoxic aggregates
Immunotherapy Monoclonal antibodies	An1792/qs-21,An1792/qs-21, Ly2062430, Bapineuzumab	Active immunization against Aβ42, thereby clearance of amyloid plaques
Aβ-degrading enzymes	Neprilysin, Insulin-degrading enzyme,Plasmin Endothelin Converting enzyme, ACE inhibitor	Proteinases(side enzyme), degrading Aβ peptide
Apolipoprotein E	Bexarotene	ApoE activator resulting activation of microglia &astrocyte to degrade Aβ
HMG-CoA reductase inhibitors	Statins atorvastatin	Cholesterol lowering resulted in decreased Aβ production.
Monoamine oxidase inhibitors	Deprenyl rasagiline	Inhibition of cell death markers and up regulation of neurotrophic factors
Treatments based on tau pathology Prevention of phosphorylation of tau	Protein phosphatase, Cyclin-dependent kinase-5, glycogen synthase kinase	Tau kinase inhibitors resulting increase dephosphorylation of tau.
B.Prevention of the aggregation of tau	Phenothiazines,Anthraquinones, polyphenols, thiacarbocyanine dye,N-phenylamines	Inhibits tau aggregation
C. Prevent the misfolding of tau	Heat shock proteins	Increases the activation of molecular chaperones thereby preventing the misfolding of tau
Tau immunotherapy	P301L-tau	Reduction in soluble and insoluble tau phosphorylation.
N-methyl-D-aspartate receptor (NMDA) antagonist	Memantine	Block abnormal transmission of glutamate and allow normal transmission for cell functioning
NSAIDS	Indomethacin,celecoxib, naproxen, dapsone,prednisone	Decrease size of Microglial cells.
Estrogens	Estrogen , progestin	Antiapoptotic,antiamyloidogenic activities.
Cell transplantation and gene therapy	Nerve growth factor	Rescues neurons from injury-induced cell damage
Other pharmacological therapies	DHA, clioquinol, resveratrol	Antiamyloid, antioxidant, and neuroprotective, neuroprotectiveinhibition of Aβ aggregation

TREATMENT OF NEURODEGENERATIVE DISORDERS

Mitochondria-targeted therapeutics for neurodegenerative diseases

Mitochondrial dysfunction, including oxidative stress, low ATP generation, mt-DNA mutation, calcium perturbation, MPTP, and mitochondrial dynamic malfunction are commonly seen in neurodegenerative diseases, such as AD, PD, HD, ALS and PSP. Since damaged mitochondria exacerbate and participate in the pathogenesis of these diseases.

Table 4:Treatment of parkinson's disease (Aarsland, Zaccai, & Brayne, 2005; De Lau & Breteler, 2006; Guttmacher, Collins, Nussbaum, & Ellis, 2003; Hughes, Daniel, & Lees, 2001; Priyadarshi, Khuder, Schaub, & Shrivastava, 2000)

Class of drug	Drug	Mechanism
Monoamine oxidase inhibitors	Selegiline,Rasagiline	Inhibit MAO-B in neuronesand glial cells, Increases availabledopamine in synaptic cleft.
COMT inhibitors	Entacapone, tolcapone	Inhibit catechol-O-methyl transferase, increase half-life of levodopa
Anticholinergics	Trihexyphenidyl, orphenadrine	Muscarinic receptorantagonists
Dopamine facilitator	Amantadine	Unclear action.

Table 5: Treatment of huntington's disease (Bonelli, Wenning, & Kapfhammer, 2004; Quinn & Busse, 2012; Walker, 2007)

Class of drug	Drug	Mechanism
Dopamine-depleting agents	Tetrabenazine	Reduce the involuntary movements by modifying DA input to the striatum
Benzodiazepines	Clonazepam	Decrease excitatory activity by acting on BZD receptor
Anticonvulsant	Sodium valproate, levetiracetam	Decrease excitatory activity
Amino acid precursor of dopamine	Levodopa	Act on dopaminergic receptor
Skeletal muscle relaxants	Baclofen, tizanidine, botulinum toxin	Inhibits acetycholine release at neuromuscular junction.
Atypical neuroleptics	Olanzapine,quetiapine, risperidone,sulpiride haloperidol,aripiprazole	work on the dopamine system
SSRI,α2-antagonist , NA reuptake inhibitor	Citalopram, fluoxetine, paroxetine, sertraline, mirtazapine, venlafaxine	Inhibiting the reuptake of serotonin after being released in synapses
Hypnotics	Zopiclone, zolpidem	Exert their effects through the benzodiazepine binding site on GABAreceptors
Anticonvulsants	Sodium valproate, carbamazepine	Act on voltage-dependent Na^+ channels.
Mood stabiliser	Lithium	Inhibit inositol phosphatises, blocks the triphosphate (IP3) formation by receptorphosphatidyl inositol (PI) pathway.

Table 6:Treatment of Multiple sclerosis(Cohen, 2009)

Class of drug	Drug	Mechanism
Anti-CD52 Mab Depletes T-cells, B cells	Alumtuzumab (CAMPATH-1h)	Work via the activation of antibody-dependent cell mediatedcytotoxicity (ADCC).
Anti- D25 Mab IL-2R antagonist	Daclizumab (zenapax)	Works by binding to CD25, the alpha subunit of the IL-2 receptor of T cells.
Anti-CD20 Mab Depletes B-cells	Rituximab (rituxan)	Binds to CD20, play a role in Ca2+ influx across plasma membranes which activate B cells and induce apoptosis of CD20+.
Soluble MBP-derived peptide	MBP 8298(Dirucotide)	T cells producing receptors recognizing MBP fragments presented by the MHC molecules of antigen, represses immunological response against MBP.
Purine analogue	Cladribine	Mimics the nucleoside adenosine &thus inhibits the enzyme adenosine deaminase.
Myriocin derivative S1PR agonist/antagonist	Fingolimod	Can sequester lymphocytes in lymph nodes, preventing them from moving to the central nervous system for autoimmune responses
Roquinimex derivative	Laquinimod	Increases NK cell activity and macrophage cytotoxicity and inhibits angiogenesis and reduces the secretion of TNF alpha.
Matrix metalloproteinase inhibitor	Minocycline	Inhibitory effect on 5-lipoxygenase and inhibits apoptosis (cell death) via attenuation of TNF-alpha, down regulating pro-inflammatory cytokine output
Immunomodulator	Oestriol	Immunomodulator
HMG-CoA reductase inhibitor	Simvastatin	HMG-CoA reductase inhibitor resulting Immunomodulation
Rapamycin analogue Cell cycle inhibitor	Temsirolimus (CCI 779)	Binding to its cytosolic receptor FKBP-12 the resulting complex inhibits the multifunctional serine–threonine kinase mTOR, attenuates growth factor induced proliferation of several nonimmune cells
Dihydro-orotate dehydrogenase inhibitor (pyrimidine synthesis)	Teriflunomide	Immunomodulatory drug inhibitingpyrimidine by blocking the enzymedihydro-orotate dehydrogenase.

Table 7: Treatment amyotrophic lateral sclerosis(Morrison, 2002; Rothstein, 1996)

Class of drug	Drug	Mechanism
Neurotrophic factors	Glial cell line derived neurotrophic factor (GDNF),cardiotrophin	Receptor agonists
Antioxidants	Lazaroids,selegiline,topiramate, N-acetyl cysteine.	Mimics Cu2+/Zn + superoxide metal chelators.
Antiglutamates	GYKI-52466, riluzole,gabapentin,L-threonine , amotrigine, dextromethorphan	NMDA, Non-NMDA (N-methy-D-aspartate) antagonists/release inhibitors
Combination Therapy	Riluzole + IGF-1, riluzole + BDNF, riluzole + gabapentin	Delays the onset of ventilator-dependence ortracheostomy by inhibitingglutamic-acid-uptake
Agents that boost mitochondrial function	Creatine	Increased availability of energy to injured nerve cells or blocks the chemical pathway that leads to cell death
Immunomodulatory and anti-inflammatory therapies	Cyclophosphamide cyclosporine,azathioprine, intravenous Ig	Specific T cell inhibitor, inhibit de novo purine synthesis, Oligosaccharides inhibitor.
Cholinergic drug	Physostigimine tetrahydroaminoacridine 3-4 Diaminopyridine	Agents acting on the cholinergic system.

Table 8: Treatment of multiple system atrophy (MSA)

Class of drug	Drug	Mechanism
For akinesia-rigidity	Levodopa+decarboxylase inhibitor	Act on dopaminergic receptor
For focal dystonia	Botulinum toxin	Inhibits acetycholine release to cause muscle paralysis
For orthostatic hypotension	Fludrocortisone , ephedrine, L-threo-DOPS, midodrine	Act on mineralocorticoid receptorwhich effect on RASS transported into the vesicles by the vesicular monoamine transporter in exchange for noradrenaline acting as sympathomimetic drugs.
For nocturnal polyuria	Desmopressin	Binds to V2 receptors in renal collecting ducts, increasing water reabsorption
Other therapies	Physiotherapy, speech therapy, occupational therapy,	Random mechanism

CONCLUSION

The future of neurodegenerative therapeutics development depends upon effective disease modification strategies centred on carefully investigated targets. Pharmaceutical research endeavour's that probe for a much deeper understanding of disease pathogenesis, and explain how adaptive or compensatory mechanisms might be engaged to delay disease onset or progression, will produce the needed breakthroughs. The prospects for new targets emerging out of the study of brain disease genes and their associated pathogenic pathways. The current crop of drug targets is based largely upon identified disease gene products and enzymes controlling their metabolism.New approaches are taken in consideration for managements of neurodegenerative disorder by neuro-scientist based on different pathological pathways.

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REFRENCES

Aarsland, D., Zaccai, J., & Brayne, C. (2005). A systematic review of prevalence studies of dementia in Parkinson's disease. Movement Disorders, 20(10), 1255-1263.

Arreguin, S., Nelson, P., Padway, S., Shirazi, M., & Pierpont, C. (2009). Dopamine complexes of iron in the etiology and pathogenesis of Parkinson's disease. Journal of inorganic biochemistry, 103(1), 87-93.

Bacman, S., Williams, S., Hernandez, D., & Moraes, C. (2007). Modulating mtDNA heteroplasmy by mitochondria-targeted restriction endonucleases in a 'differential multiple cleavage-site'model. Gene therapy, 14(18), 1309-1318.

Bonelli, R. M., Wenning, G. K., & Kapfhammer, H. P. (2004). Huntington's disease: present treatments and future therapeutic modalities. International clinical psychopharmacology, 19(2), 51-62.

Bossers, K., Meerhoff, G., Balesar, R., Van Dongen, J. W., Kruse, C. G., Swaab, D. F., & Verhaagen, J. (2009). Analysis of gene expression in Parkinson's disease: possible involvement of neurotrophic support and axon guidance in dopaminergic cell death. Brain Pathology, 19(1), 91-107.

Bredesen, D. E. (2008). Programmed cell death mechanisms in neurological disease. Current molecular medicine, 8(3), 173-186.

Brookmeyer, R., Johnson, E., Ziegler-Graham, K., & Arrighi, H. M. (2007). Forecasting the global burden of Alzheimer's disease. Alzheimer's & dementia, 3(3), 186-191.

Chinnery, P., Taylor, R., Diekert, K., Lill, R., Turnbull, D., & Lightowlers, R. (1999). Peptide nucleic acid delivery to human mitochondria. Gene therapy, 6(12), 1919-1928.

Chu, Y., Dodiya, H., Aebischer, P., Olanow, C. W., & Kordower, J. H. (2009). Alterations in lysosomal and proteasomal markers in Parkinson's disease: relationship to alpha-synuclein inclusions. Neurobiology of disease, 35(3), 385-398.

Cohen, J. A. (2009). The future of multiple sclerosis treatment. Journal of the neurological sciences, 277, S55-S61.
Crystal, H. A. (2008). Dementia with Lewy bodies. Emedicine. Retrieved from http://emedicine. medscape. com/article/1135041-overview.
De Lau, L. M., & Breteler, M. (2006). Epidemiology of Parkinson's disease. The Lancet Neurology, 5(6), 525-535.
Dickson, D. W. (2009). Neuropathology of non-Alzheimer degenerative disorders. Int J Clin Exp Pathol, 3(1), 1-23.
Ecroyd, H., & Carver, J. A. (2008). Unraveling the mysteries of protein folding and misfolding. IUBMB life, 60(12), 769-774.
Eliezer, D. (2009). Synuclein structure and function in Parkinson's disease Protein Folding and Misfolding: Neurodegenerative Diseases (pp. 159-174): Springer.
Esiri, M., Matthews, F., Brayne, C., Ince, P., Matthews, F., Xuereb, J.,McKeith, I. (2001). Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Lancet, 357(9251), 169-175.
Evidence, W. H. O. M. H., Team, R., & Project, D. C. P. (2006). Disease control priorities related to mental, neurological, developmental and substance abuse disorders: World Health Organization.
Fan, J., Hu, Z., Zeng, L., Lu, W., Tang, X., Zhang, J., & Li, T. (2008). Golgi apparatus and neurodegenerative diseases. International Journal of Developmental Neuroscience, 26(6), 523-534.
Fombonne, J., Rabizadeh, S., Banwait, S., Mehlen, P., & Bredesen, D. E. (2009). Selective vulnerability in Alzheimer's disease: Amyloid precursor protein and p75NTR interaction. Annals of neurology, 65(3), 294-303.
García Ruiz, P. (2004). [Prehistory of Parkinson's disease]. Neurologia (Barcelona, Spain), 19(10), 735-737.
Gardiner, J., Barton, D., Overall, R., & Marc, J. (2009). Neurotrophic support and oxidative stress: converging effects in the normal and diseased nervous system. The Neuroscientist, 15(1), 47-61.
Gonatas, N. K., Stieber, A., & Gonatas, J. O. (2006). Fragmentation of the Golgi apparatus in neurodegenerative diseases and cell death. Journal of the neurological sciences, 246(1), 21-30.
Guttmacher, A. E., Collins, F. S., Nussbaum, R. L., & Ellis, C. E. (2003). Alzheimer's disease and Parkinson's disease. New England Journal of Medicine, 348(14), 1356-1364.
Hebert, L. E., Scherr, P. A., Bienias, J. L., Bennett, D. A., & Evans, D. A. (2003). Alzheimer disease in the US population: prevalence estimates using the 2000 census. Archives of Neurology, 60(8), 1119.
Hirsch, E. C., & Hunot, S. (2009). Neuroinflammation in Parkinson's disease: a target for neuroprotection? The Lancet Neurology, 8(4), 382-397.
Hong-Qi, Y., Zhi-Kun, S., & Sheng-Di, C. (2012). Current advances in the treatment of Alzheimer's disease: focused on considerations targeting Aβ and tau. Translational neurodegeneration, 1(1), 1-12.
Hughes, A. J., Daniel, S. E., & Lees, A. J. (2001). Improved accuracy of clinical diagnosis of Lewy body Parkinson's disease. Neurology, 57(8), 1497-1499.
Jaeger, L. B., Dohgu, S., Sultana, R., Lynch, J. L., Owen, J. B., Erickson, M. A.,Butterfiled, D. A. (2009). Lipopolysaccharide alters the blood–brain barrier transport of amyloid β protein: A mechanism for inflammation in the progression of Alzheimer's disease. Brain, behavior, and immunity, 23(4), 507-517.
Jellinger, K. A. (2009). Recent advances in our understanding of neurodegeneration. Journal of neural transmission, 116(9), 1111-1162.
Koehler, P. J., & Keyser, A. (1997). Tremor in latin texts of dutch physicians: 16th-18th centuries. Movement Disorders, 12(5), 798-806.
Kramer, M. L., & Schulz-Schaeffer, W. J. (2007). Presynaptic α-synuclein aggregates, not Lewy bodies, cause neurodegeneration in dementia with Lewy bodies. The Journal of Neuroscience, 27(6), 1405-1410.
Kroemer, G., Galluzzi, L., Vandenabeele, P., Abrams, J., Alnemri, E. S., Baehrecke, E.,Green, D. (2008). Classification of cell death: recommendations of the Nomenclature Committee on Cell Death 2009. Cell Death & Differentiation, 16(1), 3-11.
Langa, K. M., Foster, N. L., & Larson, E. B. (2004). Mixed dementia. JAMA: the journal of the American Medical Association, 292(23), 2901-2908.
Lees, A. J. (2007). Unresolved issues relating to the shaking palsy on the celebration of James Parkinson's 250th birthday. Movement Disorders, 22(S17), S327-S334.
Li, W., Hoffman, P. N., Stirling, W., Price, D. L., & Lee, M. K. (2004). Axonal transport of human α-synuclein slows with aging but is not affected by familial Parkinson's disease-linked mutations. Journal of neurochemistry, 88(2), 401-410.
Lim, K.-L. (2007). Ubiquitin–proteasome system dysfunction in Parkinson's disease: current evidence and controversies. Expert review of proteomics, 4(6), 769-781.
Louneva, N., Cohen, J. W., Han, L.-Y., Talbot, K., Wilson, R. S., Bennett, D. A., Arnold, S. E. (2008). Caspase-3 is enriched in postsynaptic densities and increased in Alzheimer's disease. The American journal of pathology, 173(5), 1488-1495.

Lynch, M. A. (2009). Age-related neuroinflammatory changes negatively impact on neuronal function. Frontiers in aging neuroscience, 1.

Malhotra, J. D., & Kaufman, R. J. (2007). The endoplasmic reticulum and the unfolded protein response. Paper presented at the Seminars in cell & developmental biology.

Martinez-Vicente, M., Talloczy, Z., Kaushik, S., Massey, A. C., Mazzulli, J., Mosharov, E. V., Follenzi, A. (2008). Dopamine-modified α-synuclein blocks chaperone-mediated autophagy. The Journal of clinical investigation, 118(2), 777.

Mehta, A., Prabhakar, M., Kumar, P., Deshmukh, R., & Sharma, P. (2012). Excitotoxicity: Bridge to various triggers in neurodegenerative disorders. European journal of pharmacology.

Migliore, L., & Coppedè, F. (2009). Genetics, environmental factors and the emerging role of epigenetics in neurodegenerative diseases. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis, 667(1), 82-97.

Miller, R. L., James-Kracke, M., Sun, G. Y., & Sun, A. Y. (2009). Oxidative and inflammatory pathways in Parkinson's disease. Neurochemical research, 34(1), 55-65.

Miyoshi, K., Ohyagi, Y., Sakae, N., Motomura, K., Ma, L., Taniwaki, T.,Kira, J.-i. (2009). Enhancement of activation of caspases by presenilin 1 gene mutations and its inhibition by secretase inhibitors. Journal of Alzheimer's Disease, 16(3), 551-564.

Morfini, G. A., Burns, M., Binder, L. I., Kanaan, N. M., LaPointe, N., Bosco, D. A., Hayward, L. (2009). Axonal transport defects in neurodegenerative diseases. The Journal of Neuroscience, 29(41), 12776-12786.

Morris, A. M., Watzky, M. A., & Finke, R. G. (2009). Protein aggregation kinetics, mechanism, and curve-fitting: a review of the literature. Biochimica et Biophysica Acta (BBA)-Proteins & Proteomics, 1794(3), 375-397.

Morrison, K. E. (2002). Therapies in amyotrophic lateral sclerosis–beyond riluzole. Current opinion in pharmacology, 2(3), 302-309.

Muresan, V., Varvel, N. H., Lamb, B. T., & Muresan, Z. (2009). The cleavage products of amyloid-β precursor protein are sorted to distinct carrier vesicles that are independently transported within neurites. The Journal of Neuroscience, 29(11), 3565-3578.

Naderi, J., Somayajulu-Nitu, M., Mukerji, A., Sharda, P., Sikorska, M., Borowy-Borowski, H., Pandey, S. (2006). Water-soluble formulation of Coenzyme Q10 inhibits Bax-induced destabilization of mitochondria in mammalian cells. Apoptosis, 11(8), 1359-1369.

Nanjo, F., Goto, K., Seto, R., Suzuki, M., Sakai, M., & Hara, Y. (1996). Scavenging effects of tea catechins and their derivatives on 1, 1-diphenyl-2-picrylhydrazyl radical. Free Radical Biology and Medicine, 21(6), 895-902.

Olivares, D., Huang, X., Branden, L., Greig, N. H., & Rogers, J. T. (2009). Physiological and pathological role of alpha-synuclein in Parkinson's disease through iron mediated oxidative stress; the role of a putative iron-responsive element. International journal of molecular sciences, 10(3), 1226-1260.

Ovádi, J., & Orosz, F. (2009). Protein folding and misfolding: neurodegenerative diseases (Vol. 7): Springer.

Palop, J. J., Chin, J., & Mucke, L. (2006). A network dysfunction perspective on neurodegenerative diseases. Nature, 443(7113), 768-773.

Pan, T., Kondo, S., Le, W., & Jankovic, J. (2008). The role of autophagy-lysosome pathway in neurodegeneration associated with Parkinson's disease. Brain, 131(8), 1969-1978.

Pigino, G., Morfini, G., Atagi, Y., Deshpande, A., Yu, C., Jungbauer, L., Brady, S. (2009). Disruption of fast axonal transport is a pathogenic mechanism for intraneuronal amyloid beta. Proceedings of the National Academy of Sciences, 106(14), 5907-5912.

Praticò, D., & Sung, S. (2004). Lipid peroxidation and oxidative imbalance: early functional events in Alzheimer's disease. Journal of Alzheimer's Disease, 6(2), 171-175.

Priyadarshi, A., Khuder, S. A., Schaub, E. A., & Shrivastava, S. (2000). A meta-analysis of Parkinson's disease and exposure to pesticides. Neurotoxicology, 21(4), 435-440.

Prohovnik, I., Perl, D., Davis, K., Libow, L., Lesser, G., & Haroutunian, V. (2006). Dissociation of neuropathology from severity of dementia in late-onset Alzheimer disease. Neurology, 66(1), 49-55.

Quinn, L., & Busse, M. (2012). Development of physiotherapy guidance and treatment-based classifications for people with Huntington's disease. Neurodegenerative Disease Management, 2(1), 11-19.

Reddy, P. H. (2008). Mitochondrial medicine for aging and neurodegenerative diseases. Neuromolecular medicine, 10(4), 291-315.

Reddy, P. H., & Beal, M. F. (2008). Amyloid beta, mitochondrial dysfunction and synaptic damage: implications for cognitive decline in aging and Alzheimer's disease. Trends in molecular medicine, 14(2), 45-53.

Riley, K. P., Snowdon, D. A., & Markesbery, W. R. (2002). Alzheimer's neurofibrillary pathology and the spectrum of cognitive function: findings from the Nun Study. Annals of neurology, 51(5), 567-577.

Rothstein, J. D. (1996). Therapeutic horizons for amyotrophic lateral sclerosis. Current opinion in neurobiology, 6(5), 679-687.

Roy, S., Zhang, B., Lee, V. M.-Y., & Trojanowski, J. Q. (2005). Axonal transport defects: a common theme in neurodegenerative diseases. Acta neuropathologica, 109(1), 5-13.

Santpere, G., & Ferrer, I. (2009). Delineation of Early Changes in Cases with Progressive Supranuclear Palsy-Like Pathology. Astrocytes in Striatum are Primary Targets of Tau Phosphorylation and GFAP Oxidation. Brain Pathology, 19(2), 177-187.

Schindowski, K., Belarbi, K., & Buee, L. (2008). Neurotrophic factors in Alzheimer's disease: role of axonal transport. Genes, Brain and Behavior, 7(s1), 43-56.

Schneider, J. A., Arvanitakis, Z., Bang, W., & Bennett, D. A. (2007). Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology, 69(24), 2197-2204.

Schulz-Schaeffer, W. J. (2010). The synaptic pathology of α-synuclein aggregation in dementia with Lewy bodies, Parkinson's disease and Parkinson's disease dementia. Acta neuropathologica, 120(2), 131-143.

Steele, J. c., Richardson, J. C., & Olszewski, J. (1964). Progressive Supranuclear PalsyA Heterogeneous Degeneration Involving the Brain Stem, Basal Ganglia and Cerebellum With Vertical Gaze and Pseudobulbar Palsy, Nuchal Dystonia and Dementia. Archives of Neurology, 10(4), 333-359.

Stolp, H., & Dziegielewska, K. (2009). Review: role of developmental inflammation and blood–brain barrier dysfunction in neurodevelopmental and neurodegenerative diseases. Neuropathology and applied neurobiology, 35(2), 132-146.

Tapia-Arancibia, L., Aliaga, E., Silhol, M., & Arancibia, S. (2008). New insights into brain BDNF function in normal aging and Alzheimer disease. Brain research reviews, 59(1), 201-220.

Walker, F. O. (2007). Huntington's disease. The Lancet, 369(9557), 218-228.

Woodhouse, A., Dickson, T. C., West, A. K., McLean, C. A., & Vickers, J. C. (2006). No difference in expression of apoptosis-related proteins and apoptotic morphology in control, pathologically aged and Alzheimer's disease cases. Neurobiology of disease, 22(2), 323-333.

Yang, J.-L., Weissman, L., Bohr, V. A., & Mattson, M. P. (2008). Mitochondrial DNA damage and repair in neurodegenerative disorders. DNA repair, 7(7), 1110-1120.

Yang, Y., Ouyang, Y., Yang, L., Beal, M. F., McQuibban, A., Vogel, H., & Lu, B. (2008). Pink1 regulates mitochondrial dynamics through interaction with the fission/fusion machinery. Proceedings of the National Academy of Sciences, 105(19), 7070-7075.

Zheng, L., Kågedal, K., Dehvari, N., Benedikz, E., Cowburn, R., Marcusson, J., & Terman, A. (2009). Oxidative stress induces macroautophagy of amyloid β-protein and ensuing apoptosis. Free Radical Biology and Medicine, 46(3), 422-429.