Investigation of Neurodegeneration

Sydni McCall Ross

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____________________________
Sydni M Ross

Student Name (printed)

____________________________
Sydni Ross

Student Signature

_______ 4-26-22 _______

Date
Investigation of Neurodegeneration

by

Sydni McCall Ross

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Honors Capstone Director: Dr. Nathan Tenhundfeld

Associate Professor of Psychology

Student  Date

Director  Date

Department Chair  Date

Honors College Dean  Date
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Abstract

Alzheimer’s, Parkinson's, and multiple sclerosis are all major complex neurodegenerative disorders. Neurodegeneration results from nervous system cell deterioration thereby yielding severe cognitive, behavioral, and motor impairments which greatly diminish quality of life. This paper investigates the neurodegeneration of such diseases while highlighting current and novel therapeutic approaches, relevant molecular mechanisms, and risk factors to identify future directions. To treat and one day overcome these diseases, more must be understood.
Introduction

The economic cost of neurodegenerative diseases in 2020 alone was $655 billion USD as reported by the Alzheimer’s Association. Only treatments for associated symptoms exist today as no cure has yet been discovered. In 2016, neurodegenerative diseases were estimated to affect roughly 5-6 million people in the U.S. Three million citizens were on disability, and 273,000 deaths were reported. The economic burdens for 2016 for Alzheimer’s (AD) and Parkinson’s (PD) were put at $352billion and $54.7, respectively (Thorpe et al, 2021). As for multiple sclerosis (MS), the American Academy of Neurology reported a burden of $85.4 billion for 2019 (Bebo et al, 2022).

The etiology behind neurodegenerative disorders unfortunately remains largely unclear. There are risk factors, both biological and environmental, that have been linked to increased likelihood of developing AD, PD, or MS. These include age, climate, prior injury, nutrition, infection, familial inheritance, and sex. Relevant risk factors are discussed further below for each disease. As of today, these diseases can only be officially diagnosed post-mortem via autopsy. Technologies like CT, MRI, and PET scans can be used in support of a diagnosis, but better diagnostic methods are needed (Beach and Adler, 2019).

It is clear that AD, PD, and MS greatly diminish quality of life with progressive neurodegeneration that yields a cocktail of cognitive, behavioral, and motor impairments. Treatments today focus on alleviating symptoms as no cure is known. The diverse and complex pathophysiology of each disease presents as a tough opponent, however there are many shared underlying molecular processes and commonalities like protein aggregation. While the type of protein aggregate and affected anatomical location differs, important processes implicated in neurodegenerative research include proteolytic stress, the unfolded protein response (UPR),
ubiquitin-mediated degradation, oxidative stress, mitochondrial dysfunction, apoptosis, and neuroinflammation (Dugger and Dickson, 2017).
Alzheimer’s

AD is the most prevalent neurodegenerative disorder and form of dementia. It is a mixed proteinopathy hallmarked by beta-amyloid plaques, brain atrophy and tau neurofibrillary tangles. Misfolded beta amyloid (Ab), a derivative of amyloid precursor protein hydrolysis, accumulates into aggregates and toxic plaques. Tau, a microtubule protein, accumulates into insoluble neurofibrillary tangles. The basal neocortex and hippocampus are affected first followed by the rest of the cortex (Raskin et al, 2015).

Cognitive decline in AD has been linked to low levels of acetylcholine (ACh) resulting from loss of cholinergic neurons in the basal forebrain (Yiannopoulou and Papageorgiou, 2020). Mild symptoms of AD include confusion, memory loss, personality changes, depression, and more. This progresses to difficulties with activities in daily life such as difficulty walking, speaking, and bathing and may require the assistance of a caregiver. At this point, a patient will be diagnosed with dementia (Raskin et al, 2015). At this point, a patient will be diagnosed with dementia.

Risk factors of AD include aging, sex, genetics, injuries, and lifestyle choices. Obesity, smoking, and diet are all modifiable lifestyle choices which can increase AD risk. Women are at a higher risk than men. Traumatic brain injuries like concussions and strokes are other contributing factors (Edwards et al, 2019). To elaborate on genetic risk factors, the APOE gene allele ε4 has been associated with elevated risk of AD and has been linked to early onset. APOE is important for lipoprotein production and regulation. Other associated AD risk genes include ABCA7 which functions in APP regulation, and SORL1 which functions in Golgi to ER protein trafficking (Raskin et al, 2015).
Acetylcholinesterase inhibitors (AChEI) such as donepezil, galantamine, and rivastigmine are used to assist cognitive decline of AD. Memantine is another pharmaceutical commonly used which can be combined with AChEI use. For behavioral and psychological symptoms associated with AD, antipsychotics and antidepressants are primarily employed. Therapies targeting neuroprotective, anti-inflammatory, and metabolic molecules are currently being investigated (Yiannopoulou and Papageorgiou, 2020).

Reducing amyloid-beta production is of major interest in treatment of AD. There has been reported therapeutic potential for BACE inhibitors, y-secretase inhibitors, and alpha-secretase modulators. Anti-amyloid aggregation molecules like ELND005, KLVFF, and y-AApptides are also of interest for their potential in inhibiting Ab aggregation. As for preventing tau aggregation, ANAVEX2073 is being investigated. Tau aggregation inhibitors like TPI-287, BIB080, and TRX0237 have been reported in literature. Immunotherapeutic approaches to produce antibodies capable of targeting Ab and tau are also being investigated. Some of these antibodies being studied include BIIB092, RO7105705, and ABBV-8E12. Additionally, in the past decade, CAD106, GV1001, UB-311 and ACC-001 vaccines have moved to clinical trials. No new treatments for AD have been approved yet since 2003 (Yiannopoulou and Papageorgiou, 2020).
Parkinson’s

PD is a synucleinopathy marked by Lewy bodies composed of alpha-synuclein (SNCA) aggregates. Ubiquitin is another common aggregate protein found in PD. Misfolding of alpha-synuclein often occurs with post translational protein modifications. Lewy bodies are toxic and have been shown to contribute to neuronal membrane degeneration (Wilshusen and Mosely, 2014). Other mechanisms such as oxidative stress, neuroinflammation, mitochondrial dysfunction, and calcium imbalances have been implicated in neurodegeneration of PD (Aarsland et al, 2021).

Dopaminergic neurons are lost primarily from the substantia nigra pars compacta in PD. The affected nigrostriatal pathway controls movement and thus results in many of the known motor symptoms of PD like stiffness and tremors. Other symptoms include slow movements, impaired balance, speech and writing changes (Wilshusen and Mosely, 2014). Cognitive decline is frequently observed in later stages of PD but can occur at any point in the progression of the disease. This can affect attention, motivation, memory, planning, and visuospatial skills (Aarsland et al, 2021).

The risk of PD increases with age with the average age of onset being 60. Men were found to have a greater risk than women. Other risk factors including pesticide exposure of MPTP, melanoma cancer, methamphetamine use, severe brain injuries, obesity, diabetes, alcohol use, and hypertension have been reported for PD. Polymorphisms or changes in gene SLC2A9 have been identified as a major genetic risk factor (Ascherio and Schwarzschild, 2016). Other genes associated with increased risk include MAPT, GBA, LRRK2, and SNCA (Billingsley et al, 2018).
Dopaminergic treatment with dopamine agonists is commonly used to treat PD, however changes to this treatment have been linked to negative behavioral symptoms like impulse control loss. Pergolide, pramipexole, rotigotine, and apomorphine hydrochloride are some dopamine agonists available. Monoamine oxidase inhibitors like selegiline and rasagiline may also be used (Emamzadeh and Surguchov, 2018). For cognitive impairments seen in PD, deep brain stimulation of the subthalamic nucleus within the basal ganglia has been shown to be moderately effective. It was reported to improve hyperdopaminergic behavioral disorders. Cholinesterase inhibitors like rivastigmine are frequently used to improve psychotic effects. Additionally, electroconvulsive therapy has been linked to improved motor function in some case studies (Rektorova, 2019).

Regenerative treatments like gene therapies using viral vectors against PD have been carried out in animal models. This work has primarily centered on neuroprotection, neuromodulation, and dopamine restoration. Other novel approaches have focused on preventing and eliminating protein aggregates in PD using methods involving heat shock proteins and CRISPR, respectively (Ntetsika et al, 2021). Additionally, potential therapeutic targets for PD which have been implicated in recent research include mGLuR5 SVC2, ABL1, and GPR109A (Rai et al, 2021).
**Multiple Sclerosis**

Multiple sclerosis is a chronic central nervous system disease hallmarked by demyelination of both gray and white matter. Demyelination in MS occurs with damage to myelin sheaths surrounding neuronal axons. Its pathogenesis is multifaceted with auto-inflammatory and neurodegenerative mechanisms. It is believed that the inflammatory processes promote neurodegeneration in MS, though this relationship is not well understood (Friese et al, 2014). It is clear that neurodegeneration is a key in MS pathogenesis. Oxidative stress, mitochondrial dysfunction, ion channel disruptions, and oligodendrocyte apoptosis have been reported (Sandi et al, 2021). Furthermore, there is evidence of protein aggregation though it remains less understood than in PD and AD (David and Tayebi, 2014).

MS presents as relapsing or progressive. The majority of MS patients experience relapsing MS. Symptoms include limb weakness, tremors, sensory disturbances like numbness or burning, loss of motor control, and optic neuritis (Luessi et al, 2012). Cognitive impairment can affect episodic memory, processing speed, working memory, and visuospatial abilities. While cognitive impairment is common in MS patients, there is high variability of cognitive symptoms (Benedict et al, 2020). Behavioral changes, namely fatigue and depression, in a third of MS patients have also been reported (Heldner et al, 2017).

Risk factors of MS include obesity, radiation exposure, vitamin D deficiency, viral infection of Epstein-barr, smoking (Wei et al, 2021). Climate and geographical location are other recognized environmental risk factors. As for genetic risk factors, a fifth of MS patients have an afflicted family member, and the HLA allele DRB1*1501 has frequently been implicated in the genetic basis of MS. Other genome studies have revealed increased risk associated with CD6, CD58, IL12A, TNFRSF1A, PTGER4, CLEC16A, and IRF8 genes (Milo and Khana, 2010).
The majority of therapeutic approaches for MS target inflammation. Glatiramer acetate, natalizumab, teriflunomide, dimethyl fumarate, mitoxantrone, IFN-beta 1a, and fingolimod are approved medications for treatment of MS (Wei et al, 2021). More work to identify potential cognitive treatment routes for MS patients is needed (Benedict et al, 2020). Recently, more attention has shifted to address neurodegeneration in MS. CyPD, ASIC1 and TRPM4 have been additionally identified as potential therapeutic targets as they have demonstrated neuroprotective capabilities in mice models for MS (Friese et al, 2014). A novel therapeutic method of improving proteasome activation to assist degradation of aggregating proteins has been proposed. Recently, basson proteinopathy was discovered in MS rat models and believed to be a major contributor to neurodegeneration (Shattling et al, 2019).
Protein Aggregation

Proteinopathies are disorders of misfolding proteins which can result from mutations, physiological stressors, and protein production errors. The cellular response involves breaking down, refolding, or isolating misfolded proteins. Chaperones in the ER function to fold newly formed proteins from ribosomes. These molecules interact with and refold misfolded proteins. If unable to restore the correct or native state to the protein, it will be marked for ubiquitin proteasome degradation or be isolated to cellular compartments such as inclusion bodies. If cellular stress continues, apoptosis or programmed cell death is eventually triggered as neurons are non-mitotic and cannot clear protein abnormalities (Jellinger, 2010).

These misfolded proteins like SNCA and Ab can readily assume conformation with a high affinity for aggregation. From here, oligomerization and toxic fibril formation occurs which impairs natural cellular processes leading to cell death. Lowering the concentration of toxic protein aggregates is a current goal of research for which many strategies have been put forth. Some of these methods include employing antibodies, using interference RNA for gene silencing, preventing protein production, and chemically assisted degradation (Hyun and Shin 2021).
**Unfolded Protein Response (UPR)**

Cellular response to ER stress, caused by the protein aggregates, is the unfolded protein response (UPR) pathway. To regain homeostasis, the UPR response increases ER functionality by allowing it to take on higher loads and inhibiting protein production. The three main proteins functioning in the response are PERK, IRE1, and ATF6. In a simplified model of the UPR response, GRP78/BiP is a chaperone to which these molecules are bound to in stress-free environments. Grp78/BiP sequestration to the ER lumen is caused by misfolded protein stress and results in activation or oligomerization (Hotamisligil and Davis, 2014). The release of GRP78/BiP activates it against the misfolded protein aggregates. This sets in motion the following molecular cascades (Qu et al, 2021).

PERK, PKR-like eukaryotic initiation factor two alpha kinase, activates a subunit of the protein which functions in the inhibition of protein synthesis. Following this, the translation of ATF4 transcription factor is increased to increase chaperone production (Qu et al, 2021). IRE1 or inositol-requiring enzyme 1 functions similarly. It is a highly conserved protein that acts via the RIDD response and through XBP1, JNK, and ASK1 proteins. IRE1 splices XBP1 transcription factors to increase chaperone expression in the nucleus (Stone and Lin, 2015).

ATF6, also known as p90ATF6, is a membrane protein and transcription factor. It also functions in increasing chaperone concentration as a means of tackling ER stress. ATF6 is transferred to the Golgi complex where it is cleaved by S1P and S2P proteases. The resultant p50ATF6 enters the nucleus to activate genes important for ER stress relief (Stone and Lin, 2015). These described pathways are also involved in apoptotic signaling if ER stress persists. With PERK’s induction of ATF4, the ATF4 protein can activate CHOP/GADD153 to trigger cell
death in the case of persistent ER stress. IRE1, through TRAF25, can trigger apoptosis via JNK pathways (Qu et al, 2021).

There is evidence of UPR activation in neurodegeneration for AD, PD, and MS. Maladaptive PERK pathway resulting in loss of regulatory proteins has been observed in AD and PD. Interestingly, the same study reported that increased UPR sensitivity in mice models increased the likelihood of disease onset (Schepper and Hozemans, 2015). In MS, IRE1 and XP1 have been shown to not initiate UPR response in oligodendrocytes. Furthermore, while CHOP and PERK were able to successfully initiate apoptosis in various cell types, this was not observed in oligodendrocytes (Stone and Lin, 2015). More research to fully understand the specific UPR-related pathology behind neurodegeneration is needed.
**Ubiquitin-proteasome system**

The Ubiquitin-proteasome system (UPS) functions in proteolysis which is the clearance or degradation of proteins. It works by tagging proteins with ubiquitin for proteasome degradation. It helps relieve cellular ER stress generated by aggregating proteins. What proteins are not degraded by UPS, are degraded via the autophagy-lysosomal pathway (ALP). Ubiquitin, DUBs, 26S proteasome, enzyme E1, enzyme E2, and enzyme E3 make up the UPS. There are three main steps. Ubiquitin is activated by E1 and then conjugated to E2. Lastly, E3 transfers ubiquitin to the target protein. From there, DUBS or deubiquitinases remove the ubiquitin for 26S proteasome degradation of the target protein (Qu et al, 2021).

Many therapeutic approaches have focused on designing methods of assisted ubiquitin protein degradation to more efficiently clear protein aggregates. Approaches such as molecular glues, hydrophobic tagging, and use of autophagy targeting chimeras have shown promising results. All of these methods make use of UPS, and it is believed that these methods might have beneficial therapeutic effects for neurodegenerative diseases like AD and PD by clearing aggregating proteins (Hyun and Shin, 2021). Additionally, some recent work has pointed to a DUB/UPS14 inhibitor IU-1 for potential therapeutic efficacy if used intermittently. USPS14 has been shown to intervene in autophagy, though the mechanism is still unclear (Banerjee et al, 2020).
Oxidative Stress

Oxidative stress results from imbalance in reactive oxygen species (ROS), a subset of free radicals. Free radicals are unstable molecules which yield DNA damage and thereby to insoluble protein aggregation. This is an underlying process in neurodegeneration pathogenesis, but is also seen in normal aging, diabetes, and cancer (Quo et al, 2013). These ROS are produced in the antioxidant response to infection, injury, and xenobiotics. Some common ROS are superoxide anion, hydrogen peroxide, and hydrogen radical (Ray et al, 2012).

These free radicals are particularly damaging to mitochondria in the cell by damaging functional molecules within the mitochondrial respiratory chain. It also leads to dysfunction of the mitochondrial membrane through increased permeability which disrupts biochemical processes. Additionally, calcium ion homeostasis which is essential to cellular signaling is disrupted by ROS. These effects of oxidative stress have been observed in both PD and AD (Guo et al, 2013). Oxidative stress has also been shown to play a functionally similar role in MS (Adamczyk et al, 2017).

Research has suggested therapeutic potential for use of antioxidants and inflammatory mediators against oxidative stress. TNFR2 agonists have been shown to protect microglia and oligodendrocyte cells against damage by oxidative stress in MS models. Other proteins like PGC-1alpha and ceruloplasmin have also been implicated (Adamczyk et al, 2017). NOX1 inhibitors like ebselen and VAS2870 have demonstrated therapeutic effects in clinical studies for patients affected by AD and PD (Baru et al, 2019). Mitochondrial antioxidants like MitoQ and MitoPBN and pore inhibitors like Dimebon have been developed and tested in animal models (Reddy, 2011). More work is needed to develop to further characterize the activity of these molecules for therapeutic use in treatment of neurodegenerative diseases.
Conclusion

Alzheimer’s, Parkinson’s and multiple sclerosis are complex neurodegenerative diseases which result in a mixture of cognitive, behavioral, and physiological declines. The specific etiology remains unknown, though there are several contributing risk factors like age, injury, genetics, and nutrition. Several mechanisms underlie neurodegeneration which have been highlighted here and include proteolytic stress, protein aggregation, UPR, USP, oxidative stress, and mitochondrial dysfunction. Arduous research efforts continue towards generating new therapies and treatments. As a result, many therapeutic targets and methods have been identified for potential therapeutic use. Still more work is needed to fully understand the etiology and pathogenesis behind AD, PD, and MS to find better solutions.
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