

Biological mechanisms of parkinson's disease and alzheimer's disease



Compare and contrast the biological mechanisms underlying Parkinson's disease and Alzheimer's disease. Refer in your answer to recent experimental studies that have advanced understanding of the underlying causes and the brain pathology of these two disorders.

Alzheimer's (AD) is a neurological disorder characterised by cell death which causes memory loss and cognitive decline and other symptoms including dementia, cognitive, behavioural and psychiatric issues, typically Alzheimer's is linked to the degeneration of brain neurons specifically those in the cerebral cortex and the presence of neurofibrillary tangles and plaques containing beta-amyloid (β -amyloid). Parkinson's disease is a disorder of the nervous system that affects movement with the main symptoms being tremors, slow movement, stiff and inflexible muscles etc. Parkinson's (PD) is often linked to dopaminergic activity as well as Lewy bodies. Alzheimer's and Parkinson's are neurodegenerative disorders meaning that there is a gradual deterioration of the patient's abilities and their symptoms get harder to manage. These disorders typically occur later in life with an age onset of around 50+ yrs for most patients, however there can be an early onset e. g. Mohammed Ali who was diagnosed with Parkinson's at the age of 42. This essay examines the underlying biological mechanisms involved in Parkinson's and Alzheimer's disease as well as the similarities and differences between the two diseases.

Alois Alzheimer (1906) first noted the neuropathological and clinical description of features of Alzheimer's in a case study of a 51yr old woman Augusta D who showed symptoms of Alzheimer's disease such as memory impairment and disorientation. After Augusta's death a brain

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examination/autopsy was conducted, it was found that there were changes in neurofibril. Alois Alzheimer noted plaques and tangles of proteins in the cerebral cortex and the limbic system. The plaques contain the amyloid-beta protein and the tangles (axons and dendrites) are made up of tau, another protein. The identification of β -amyloid resulted in the formulation of the amyloid cascade hypothesis (ACH). The ACH suggests that the deposition of amyloid β is the pathological trigger for Alzheimer's which leads to the formation of neurofibrillary tangles, cell death and dementia. The general view is that mutations occur in genes that code for the amyloid precursor protein (APP), it is suggested that this mutation increases the development of amyloid- β ($A\beta$) particularly the ones that tend to aggregate. Support for the role of APP and tau comes from Lewis et al (2001), they found that transgenic mice show similar neurofibrillary degeneration when they overexpress 'mutant human tau and mutant human APP. They used mice with neurofibrillary tangles and motor disturbance, these mice were crossed with mice expressing mutant APP. They found that in transgenic mice overexpressing both mutant human APP and mutant human tau, neurofibrillary tangles are increased in the limbic system, whereas the structure and number of amyloid plaques remain unaltered. These results suggest that there is an interaction between $A\beta$ and tau and this interaction supports the similar interaction that occurs in Alzheimer's, it could also be argued that the alteration of APP processing occurs prior to tau alterations, suggesting that amyloid toxicity is tau dependent. Furthermore, the crossing of APP transgenic mice with apolipoprotein E (apoE) deficient mice reduces cerebral amyloid deposition in offspring (Bales et al., 1997). These findings support the idea that amyloid accumulation is the main influence of AD, <https://assignbuster.com/biological-mechanisms-of-parkinsons-disease-and-alzheimers-disease/>

however the disease process such as the tau tangles is a result of an imbalance between amyloid production and clearance. Also due to the studies use of rats it lacks population validity as the findings cannot be generalised to humans.

Compared to Alzheimer's, Parkinson's disease is brought on as a result of the degeneration of the nigrostriatal system. This system is a dopaminergic pathway, connecting the substantia nigra with the dorsal striatum. The degeneration of the system results in a near-disappearance of nigrostriatal dopaminergic neurons which decreases motor activity due to D2 receptors, the ones that do survive turn into abnormal structures called lewy bodies. These lewy bodies clusters use most of the dopamine secreted causing the brain to not function properly, resulting in the possible development of early Parkinson's disease. Support for the dopaminergic basis of Parkinson's comes from Dunnett and Bjorklund (1999), they used PET scans to assess cell loss in the brain, they found that there was dopamine cell loss before any symptoms appear, it is suggested that 'over 80%' of dopamine neurons have already died before diagnosis. Lewy bodies are formed from a protein called α -synuclein (α -syn) and are present in high numbers, α -synuclein is the mark of Parkinson's disease (Gitler et al, 2008). This is supported by Kordower et al (2008) they conducted a fetal transplantation into the striatum of individuals with Parkinson's, by using markers (staining) they were able to observe the structures affected. They found aggregated lewy body like structures that stained for α -synuclein and ubiquitin and non-aggregated α -synuclein in grafted nigral neuron had survived for 4 year after the transplantation, these are not normally see until middle age. They also

observed some unexpected findings, they found abnormal, aggregated proteins in implanted cells which is supported by the presence of ubiquitinated aggregates, some of which had the appearance of lewy bodies). Unfortunately, this study raises the question of whether Parkinson's is due to acute insult that leads to progressive neurodegeneration or if its an ongoing pathological process that affects previously health neurons. However, it could be argued that this unexpected find was due to graft failure caused by the Parkinson's or disease progression affecting dopaminergic and non-dopaminergic regions.

When considering Parkinson's and Alzheimer's disease, obvious differences are the areas of the brain in which the disease begins. Parkinson's has its beginning from the loss of dopamine-producing neurons in the substantia nigra region of the brain whereas, Alzheimer's disease has its genesis in the hippocampus, which is responsible for memories and spatial navigation. However, both Alzheimer's disease and Parkinson's disease are neurodegenerative diseases, caused by the loss of brain cells; in Parkinson's the dopamine producing cells and in Alzheimer's those associated with cognition and intellectual abilities are destroyed. Additionally, although these disorders genesis may originate from different parts in the brain it could be argued that Parkinson's ' parallels with the spread of brain pathology in Alzheimer's (Goedert, 2015), for example, in Parkinson's according to Braaks theory of progression (2003) lewy bodies are found first in brain stem, olfactory bulb, then spread upwards through the brain and Alzheimer's neuron loss initially occurs in the hippocampus, which is why memory loss is the initial symptom, it then spreads to the frontal, parietal and temporal

lobes of the cerebral cortex. Other systems such as the amygdala are also damaged, impacting on cognitive functions, for example, Destruction of the basal nucleus causes a decrease in acetylcholine levels, which makes the formation and retrieval of memories more difficult. Furthermore, both Alzheimer's and Parkinson's are caused by protein accumulation of protein aggregates resulting in progressive neuronal loss, suggesting a common underlying pathology. As stated, earlier Parkinson's is caused by Lewy bodies which are the product of the alpha-synuclein protein aggregation, where as Alzheimer's is caused by the deposition of the protein amyloid β which cause plaques and the accumulation/aggregation of the protein tau resulting in neurofibrillary tangles. The accumulation of these tangles results in cell degeneration, dysfunction and eventually death. Calderone et al (2016) compared the disease networks involved in both Alzheimer's and Parkinson's using a similarity matrix, they highlighted similarities and statistically analysed their significance. They found an 81% similarity between the network structures involved in AD and PD compared to other disorders such as Influenza (69% for AD and 68% for PD). However, it could be argued that biological network overlaps would always be present with AD and PD because these two disorders are associated with co-morbidities.

Within Alzheimer's there is also a genetic basis, it is often used to explain early onset Alzheimer's and its heritability. Further research by Lanoiselee et al (2006) identified APP, PSEN1 or PSEN2 gene mutations and aimed to show how these mutations lead to the accumulation of A β and early-onset familial Alzheimer's/dementia. They identified mutations in 170 early onset families with an onset of less than 65yrs and in 18 sporadic cases with an age of

onset below age 51. They found around 90 mutations throughout the whole sample that could be responsible for the early onsets of Alzheimer's, the evidence gained supports the idea of pathogenicity (ability of an organism to cause a disease), for this study pathogenicity is 77% suggesting that individuals who possess these mutations have around a 77% likelihood of developing Alzheimer's. However, in 10 of the 'sporadic cases' the parents showed an absence of the mutation suggesting that the mutation is present for the first time in that family member as a result of a variant in cells ('de novo'). Some of the mutations stated in the study where previous findings for example in the APP gene they found no novel mutation, but they included previously recorded mutations in 25 patients. These findings highlight the potential benefit of screening for Alzheimer's disease cases with an age of onset below 50, regarding APP, PSEN1 and PSEN2 genes. In comparison to Alzheimer's. Parkinson's has a lesser genetic origin compared to Alzheimers, however in more recent years studies are being conducted to find a genetic basis for Parkinson's. Researchers have discovered that gene mutations can also cause the onset of Parkinson's similarly to Alzheimer's, for example Palfreman (2015) studied an Italian family, he observed a 50% heritability of AD, of those 50% of the family diagnosed they possessed a mutation in the alpha synuclein gene. Support for this comes from the identification of the genes such as PINK1 and parkin. Liu et al, 2012 argues that mutations of PINK 1 and parkin result in mitochondrial impairment and damage which impacts on the quality of the mitochondrial control system. Parkin and PINK1 work together to regulate components of the transport system of the mitochondria, once PINK1 or Parkin are mutated the transports system is impaired and contributes to the loss of dopamine leading to symptoms of PD

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such as the inability to control movements. Their study suggests that these two genes work to regulate the transport system and thus regulate the quality of the mitochondria. It has also been found that parkin activates the UPS and has been shown to have a neuroprotective role (Petrucci et al. 2002). However, there isn't much research into the toxic effects of the accumulation of parkin and research conducted was inconclusive (Betarbet et al, 2005). It could be argued though the research shown that parkin may be involved in the pathogenesis of PD but that the mutations aren't enough to cause the disease.

One further aspect to consider in respect to the similarities between AD and PD is the role oxidative stress plays in the onset of these diseases. More recently oxidative stress has been identified as a key factor in the progression of Alzheimer's. In physiological conditions where there is an excess of reactive oxygen species (ROS), preoxidation occurs which damages DNA and proteins, leading to a decrease in the oxidase potency of mitochondrial cytochrome. Bringing about, metabolic aggravations and cell apoptosis (cell death). If the mitochondria are mutated, somatically or sporadically this can lead to increased ROS production (Yan et al, 2012). This is supported by Zhao et al (2018), they suggested that vitamin B2 (VB2) can be used as a treatment for Alzheimer's due to its anti-oxidative nature, it was found that VB2 created a noteworthy decrease in ROS and increases in the genes that protect oxidative damage from ROS in mice. This study suggests that VB2 treatment activates the Nrf2 pathway which represses Keap1 to control anti-oxidation, bringing about the release of antioxidant genes (CAT, SOD and GSH-Px) accordingly decreasing ROS and MDA,

subsequently the decrease in oxidative pressure enhances Alzheimer impairment. This study offers understanding into new neurological pathways engaged with Alzheimer's as it highlights the pathways affected by oxidative stress and how it has can play a role in the onset and development of Alzheimer's. However, it lacks generalisability to humans and thus further research is required. Increased amyloid- β also prompts oxidative stress, this in turn increases tau phosphorylation in the surrounding amyloid plaques (Puig et al, 1964). Similarly, to Alzheimer's, oxidative stress is also a factor in the onset and development of Parkinson's. Damage to the mitochondrial Complex I in the transport chain resulting in electron leaks which causes ROS generation, reduced Complex I activity was found in the brain tissue of participants with Parkinson's (Parker et al, 1989), suggesting that the

In conclusion, it is obvious to see that both Parkinson's and Alzheimer's both have similarities within each other for example, both diseases are affected by oxidative stress, and genetics. However, they both have origins in different areas of the brain which is why they have different symptoms for example, Alzheimer's show more memory-based symptoms whereas Parkinson's caused motor symptoms. It can also be seen that there is a stronger genetic component for Alzheimer's compared to Parkinson's. It could be argued that the similarities between the two diseases can explain their comorbidity.

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