Causes of parkinson's disease

Parkinson’s disease (PD) is caused by the progressive death of substantia nigral dopaminergic neurones, resulting in the reduction of caudate-putamen dopamine concentration in the basal ganglia. Insufficient DA produced from the substantia nigral dopaminergic neurones due to progressive degradation in PD patient’s results in motor neurone cell death. Afflicting just under 1% of the population over 60. Little was known about the pathophysiology of PD, with the classical pathological hallmarks of loss of nigrostriatal dopaminergic neurons and the presence of Lewy bodies (Dauer, 2003).

Though the first clinical description of the disease was written in 1817 – An essay on the Shaking Palsy by James Parkinson. Taking nearly 150 years to make real progress, the first milestone occurred in the 1960’s when striatal dopamine (DA) levels were discovered to be sharply reduced in PD patients (Garcia-Ruiz, 2014) linking PD to DA content of the basal ganglia. DA production occurs with the substantia nigra pars compacta uses the nigrostriatal pathway to transport dopamine via the dopamine transporter (DAT) controlled via a sodium gradient to the striatum. These co-dependant systems require dopamine production for motor movement; when the death of substantia nigral dopaminergic neurones occurs dopamine content in the basal ganglia is reduced and thus impairs motor function. Garcia-Ruiz (2014) rationale from his discovery was the two systems are linked as the stratum doesn’t produce dopamine indicating its source elsewhere, thus connecting substantia nigra pars compacta (a known producer of dopamine) in PD and that substantia nigra pars compacta neurone death is responsible for the pathophysiological symptoms of PD. Iravani (2005) states that when some

60% of nigral-striatal neurones have been lost the first motor abnormalities appear; resulting in diagnosis as late as 3 years after initial neurone death.

Neurodegeneration of substantia nigral dopaminergic neurones symptoms of can is managed. Levodopa (L-DOPA), the precursor to DA synthesis (making it a logical choice for using therapeutically) and DA agonist is able to cross the blood-brain barrier (BBB) via the LAT-1 (large amino acid transporter) where it is converted to dopamine via DOPA decarboxylase. This increases dopamine content in the brain and reduces symptoms such as motor skill deterioration. Levodopa also occurs in peripheral circulation resulting in peripheral dopamine concentration to increase causing a nauseous side effect, as a result levodopa of always given with carbidopa which inhibits the peripheral metabolism reducing this nausea (Dauer, 2003) also increases the bioavailability of L-DOPA in the CNS.

Lee (2009) an expert in PD, described PD it as a commonly diagnosed bradykinesia disorder characterised by severe pars-compacta nigral-cell loss and aggregated a-synuclein accumulation within cortical regions. Thought to be part of dopamine release and transport regulation, a-synuclein induces microtubule-associated protein fibrillation and within overexpression a reduction in neuronal responsiveness. This ties into the prion hypothesis, in which the misfolded protein a-synuclein can trigger aggregation of interconnected groups of neurones, thus resulting in Inflammation, oxidative stress, excitotoxicity and reduced responsiveness. Though his theory is contradicted by Leonidas (2012) who claims that there is insufficient evidence that consists of the idea that there is an overexpression of a-synuclein protein in PD brains; when mRNA studies show a decrease of SNCA

expression in PD nigra. Though Stefanis. L. does acknowledge there could be a rare familial and sporadic link of SNCA expression and PD, as α-synuclein is found within Lewy bodies which are a characteristic of PD.

Lewy bodies are aggregates of protein and are a classical sign of neurotoxicity, and closely associated with a-synuclein due to the radiating fibrillation of a-synuclein tying into Lee’s (2009) PD description. Lewy bodies also contain ubiquitin, a-B crystalline and neurofilament protein in an aggregated form. The a-synuclein interacts with DNA causing degradation (Power, 2017) and also Power observed α-synuclein and βIII Tubulin from Lewy bodies and n increased mitochondrial loss with neurones developing Lewy bodies, suggesting a link between Lewy body development and substantia nigral dopaminergic neurone death. Powers theory indirectly contradicts Leonidas’s theory on a-synuclein expression, as a-synuclein is required for Lewy body formation and thus leads to substantia nigral dopaminergic neuronal death Lee’s research does, however, support the Powers theory.

Dauer (2003) infers that it is possible that the misfolding of proteins which result in Lewy bodies could offer a level of neuroprotection by interfering with programmed cell death (PCD) and oxidative stress; thus slowing down neurodegeneration. Lewy bodies could interfere with Bax molecule formation (which there are elevated concentrations within PD patient’s) due to the changes in protein morphology, thus counteracting the overexpression of Bax (Dauer, 2003).

Though age is a significant risk factor for the development of PD, one toxin, in particular, can cause the disease to develop due to it targeting substantia nigral dopaminergic neurones. Siegel explains that though MTPT (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine) itself isn't toxic, though the active metabolite form MPP+ is. Though at the time (1999) the mechanism for MPP+ toxicity wasn't understood it was later described by Alexander (2004). MPP+ toxicity via the inhibition of the mitochondrial complex I resulting in inhibition of the respiratory chain and enhanced oxidative stress within SNc neurones resulting in PCD. MPTP is used in experimental parkinsonism as dosing marmosets via subcutaneous administration of MPTP 1 mg/kg for 3 consecutive days, which Iravani (2005) found to produce reproducible results. The use of MPTP on marmosets and the development of PD provides sufficient evidence that MPTP is connected to the development of PD, it also allows for research to be done on animals are they can be given the disorder within a 6 month period an allow for research into the causative factor behind PD and the regions of the CNS that are affected.

The expansion of understanding PD pathogenicity has grown over the last 25 years according to Schapira, as toxin research, postmortem investigations and gene deficits with familial PD have become general knowledge in consensus about the underlying mechanisms of cell death and neuronal loss. inflammatory change, mitochondrial dysfunction, oxidative stress, and altered protein formation are considered the main lead into understanding PD (Schapira, 2011). This ties into Dauer's theory on Lewy bodies, Lee's explantation on a-synuclein as they/were researching the leads mentioned by Schapira.

The causative reasons for Parkinson’s disease are thoroughly understood today compared to 1817, however, research is still underway to definitively understand the disorder. There is a clear understanding that (PD) is caused by the progressive death of substantia nigral dopaminergic neurones resulting in a reduced SNc dopamine content resulting in pathophysiological side effects. It is clear however that Lewy bodies are a classical characteristic of PD and are used in the diagnosis of the disorder, their true function is still under research. There is still some grey area of what causes the sudden initial death of theses neurones, though MPTP is linked to PD development via the study of marmosets. The research will continue to enhance a limited knowledge of the disorder and if there will ever be a possible way to regenerate those lost signalling pathways. Stem cell research on the cutting edge of neuronal regeneration as these unspecialised cells will eventually become neurones, replacing the one already loss to cell death. Though ethically there are issues around using stem cells, it is a case of the good out weights the bad.

References

Abeliovich. A, S. Y.-L. (2000). Mice Lacking α-Synuclein Display Functional Deficits in the Nigrostriatal Dopamine System. *Neuron, 25* (1), 239-252.

Alexander, G. E. (2004). BIology of Parkinson’s disease: pathogenesis and pathophysiology of a multisystem neurodegenerative disorder. *Dialogues in Clinical Neuroscience, 3* (6), 259-280.

Baba, M. N. (1998). Aggregation of alpha-synuclein in Lewy bodies of sporadic Parkinson’s disease and dementia with Lewy bodies. *The American Journal of Pathology, 152* (4), 879-884.

Bai-Yun Zeng, M. M. (2010). Morphological changes in serotoninergic neurites in the striatum and globus pallidus in levodopa primed MPTP treated common marmosets with dyskinesia. *Neurobiology Of Disease, 40* , 599-607. doi: 10. 1016/j. nbd. 2010. 08. 004

Barbeau, A. (1969). L-DOPA Therapy in Parkinson’s Disease: A Critical Review of Nine Year’s Experience. *Canadian Medical Association Journal, 101* (13), 59-68.

Chesselet, M.-F. (2008). In vivo alpha-synuclein overexpression in rodents: a useful model of Parkinson’s disease? *Experimental Neurology, 209* (1), 22-27. doi: 10. 1016/j. expneurol. 2007. 08. 006

Haber, D. D. (2001, July 1). Striatal Responses to Partial Dopaminergic Lesion: Evidence for Compensatory Sprouting. *Journal Of Neuroscience, 20* (13), 5102-5114.

Iria G. Dopeso-Reyes, A. J. (2014, December 14). Calbindin content and differential vulnerability of midbrain efferent dopaminergic neurons in macaques. doi: 10. 3389/fnana. 2014. 00146

Lees. A. J, H. J. (2009, June 13). Parkinson’s disease. *The Lancet, 373* , 2066.

Leonidas, S. (2012). α-Synuclein in Parkinson’s Disease. *Cold Spring Harbor Perspectives in Medicine, 2* (2). doi: http://doi. org/10. 1101/cshperspect. a009399

Mahmoud M. Iravani, E. S. (2005). A modified MPTP treatment regime produces reproducible partial nigrostriatal lesions in common marmosets. *European Journal Of Neuroscience, 21* , 841-854.

Marina Picillo, G. S. (2017). Association between dopaminergic dysfunction and anxiety in de novo Parkinson’s disease. *Parkinsonism and Related Disorders* . Retrieved from http://dx. doi. org/10. 1016/j. parkreldis. 2017. 02. 010

Pedro J. Garcia-Ruiz, K. R.-M. (2014). Non-motor symptoms of Parkinson’s disease A review…from the past. *Journal Of Neurological Sciences, 338* , 30-33. Retrieved from http://dx. doi. org/10. 1016/j. jns. 2014. 01. 002

Power, J. B. (2017). Lewy Bodies and the Mechanisms of Neuronal Cell Death in Parkinson’s Disease and Dementia with Lewy Bodies. *Brain Pathology, 27* (1), 3-12. doi: 10. 1111/bpa. 12344

Przedborski, V. J.-L. (2007). Protocol for the MPTP mouse model of Parkinson’s disease. *Nature Protocols, 2* , 141-151. doi: doi: 10. 1038/nprot. 2006. 342

Schapira, A. J. (2001). Etiology and pathogenesis of Parkinson’s disease. *Movement Disorders, 26* (6), 1049-1055. doi: 10. 1002/mds. 23732

Siegel G. J, A. B. (Neurochemistry: Molecular, Cellular and Medical Aspects). *MPTP-Induced Parkinsonian Syndrome* (6th ed.). Philadelphia: Lippincott-Raven. Retrieved from https://www. ncbi. nlm. nih. gov/books/NBK27974/

William Dauer, S. P. (2003). Parkinson’s Disease: Mechanisms and Models. *Neuron, 39* (6), 889-909. doi: http://dx. doi. org/10. 1016/S0896-6273(03)00568-3