Homeostasis And Parkinson’s Disease

Parkinson’s Disease

Parkinson’s disease is the second most common neurodegenerative condition globally (Soukup, Vanhauwaert, & Verstreken, 2018). It is caused by the preferential degradation of dopaminergic (DAergic) neurons in the substantia nigra pars compacta, part of the midbrain, causing dysfunctions such as rigidity, postural instability and tremors (Bisaglia, Greggio, Beltramini, & Bubacco, 2013). Studies have identified numerous causal genes and potential risk factors for Parkinson’s disease with the majority of these originating at the synapses between neurons (Soukup et al., 2018). Synapses are often located at a far distance from the cell body are the site of protein synthesis and degradation (Susmita & Ana Maria, 2015). The presence of synapse-specific mechanisms is important in the context of neurogenerative diseases as neurodegeneration is thought to originate at synaptic contact sites (Burke & O'Malley, 2013). Recent evidence suggests that the loss of synaptic homeostasis may be a key contributor to neurodegeneration and, hence, Parkinson’s disease (Soukup et al., 2018).

Homeostatic disruption of Parkinson’s Disease

Parkinson’s disease is the preferential death of a subset of neurons which utilise dopamine (DA) as a neurotransmitter for synaptic communication and are located in the midbrain (Bisaglia et al., 2013). DA can become a highly reactive molecule, leading to cytotoxicity if not properly metabolised and stored (Bisaglia et al., 2013). DAergic neurons comprise less than 1% of the neurons in the brain, however, DAergic pathways play a key role in both mental and physical functions (Chinta & Andersen, 2005).

DA is synthesised in the cytoplasm via tyrosine hydroxylase (TH) and aromatic amino acid decarboxylase (AADC) then isolated into synaptic vesicles by the vesicular monoamine transporter 2 (VMAT2) (Bisaglia et al., 2013).

Several of the genes involved in Parkinson’s disease encode proteins that are enhanced at the presynaptic compartment, namely ?-Synuclein, LRRK2, Synaptojanin (Synj1), Endophilin A1 (EndoA) and DNAJC6/Auxilin (Soukup et al., 2018). Additionally, ?-Synuclein is found aggregated in Lewy bodies in Parkinson’s disease for which the dominant mutations or triplications contribute to the disease (Hope et al., 2004). Research suggests that the aggregation of ?-Synuclein and other proteins may alter pathways that guard synaptic homeostasis (Kramer & Schulz-Schaeffer, 2007). For example, by blocking protein turnover systems and, hence, causing an excess of dysfunctional proteins and organelles (Kramer & Schulz-Schaeffer, 2007). The defects in pathways that regulate protein turnover at synapses, in addition to dysfunctional or aggregated proteins at synapses, contribute to poor synaptic function in Parkinson’s disease (Soukup et al., 2018). In paraffin-embedded tissue blots with Lewy body pathology, most of the ?-Synuclein aggregates cumulate at presynaptic terminals (Kramer & Schulz-Schaeffer, 2007), thereby presynaptic death occurs prior to neuronal death (Cheng, Ulane, & Burke, 2010). This affects the synaptic homeostasis and leads to neurodegeneration.

There are several genes involved in Parkinson's disease which encode proteins that are enhanced at the presynaptic terminal (Soukup et al., 2018). Mutations in these genes cause irregularities in synaptic mechanisms and, over time, cause defects in neurotransmitter release (Soukup et al., 2018). Hence, defects in synaptic function and mutations in presynaptic protein-encoding genes that mediate neurotransmitter release cause neurodegeneration (Soukup et al., 2018).

Protein homeostasis is controlled by various cellular mechanisms (Vijayan & Verstreken, 2017) and can be degraded by autophagy in Parkinson's disease. Autophagy has a key role in the removal of aggregated proteins and damaged organelles, namely mitochondria, which generally damage cells during stress (Zhang, Dong, Xu, & Xu, 2012). Although there are numerous types of autophagy by which proteins and organelles can be degraded, the commonality amongst all is that the proteins or organelles are delivered to the lysosome for degradation (Soukup et al., 2018).

Moreover, lysosomal dysfunction has been associated with neurodegeneration and are a key mechanism for maintaining synaptic homeostasis in Parkinson's disease (Mazzulli, Zunke, Isacson, Studer, & Krainc, 2016).

Autophagic dysfunction, as well as lysosomal dysfunction, lead to defects in intracellular degradation pathways and, hence, are often observed as disrupted in regards to Parkinson's disease (Soukup et al., 2018). Lysosomal dysfunction contributes to the accumulation of ?-Synuclein and other dysfunctional proteins susceptible to aggregation (Viktor et al., 2011).

In order to restore homeostasis in regard to Parkinson's disease, drugs that can reduce, arrest and delay the death of DAergic neurons are required. However, these are not readily available as neither the causes nor the mechanisms of DAergic neuronal dysfunction are fully understood (Bisaglia et al., 2013). Currently, the drug l-DOPA, a precursor with the ability to cross the blood-brain barrier, is used in order to replace the loss of DA (Bisaglia et al., 2013). Although this treatment does initially combat the symptoms of Parkinson's disease it loses its efficacy after several years, also; causing involuntary movements, queasiness and hypotension in some patients (Rajput et al., 2002). Further research into the protection of DAergic neurons is required in order to develop treatment methods that can restore synaptic homeostasis and prevent the progression of Parkinson's disease (Lynch-Day, Mao, Wang, Zhao, & Klionsky, 2012).

Précis

Parkinson's disease is caused by the preferential death of a subset of nerve cells, or neurons, in the midbrain. Generally, neurons communicate with each other at junctions referred to as synapses through neurotransmitters, or chemical messengers. Regarding Parkinson's disease, these neurons utilise dopamine (DA) as a neurotransmitter for synaptic communication. The activity of dopaminergic (DAergic) neurons is the basis of numerous physical and mental functions including voluntary movement, behaviour and cognition.

The functions of many genes involved with Parkinson's disease merge when regarding mechanisms of synaptic homeostasis, the phenomenon which prevents the nervous system from going haywire. Several genes involved with Parkinson's disease encode, i.e. are responsible for producing, proteins and organelles whose turnover at synapses cause neuronal

and synaptic dysfunctions. Over time, these dysfunctional proteins cause the failure of neurotransmitter release which disrupts the synaptic homeostasis and, hence, is a key contributor to Parkinson’s disease.

Moreover, mitochondrial homeostasis is also relevant to Parkinson’s disease. Mitochondria are organelles that, in this context, are imperative for synaptic calcium buffering and energy production which fuels events required for protein homeostasis. Mutations in the genes associated with Parkinson’s disease as well as associated environmental factors are known to cause mitochondrial dysfunction and, thereby, the pathogenesis of this disease.

Lysosomes are organelles that receive and degrade macromolecules from membrane trafficking pathways. Lysosomal dysfunction is linked with neurodegeneration and, with regards to Parkinson’s disease, is a key mechanism towards maintaining synaptic homeostasis.

Furthermore, autophagy is the process of self-degradation of cellular components, such as mitochondria, and has an essential role in the removal of organelles and proteins which have the potential to damage cells during stress. The dysfunction of this process leads to neurodegeneration and a homeostatic imbalance as it is essential for neuronal survival.

To conclude, Parkinson’s disease is not currently curable as it is a progressive disease, thus the current treatment, l-DOPA, only slows its progression but does not treat it. l-DOPA therapy is initially effective, however, commonly loses its efficacy after several years causing symptoms involuntary movement for patients.

References

1. Bisaglia, M., Greggio, E., Beltramini, M., & Bubacco, L. (2013). Dysfunction of dopamine homeostasis: clues in the hunt for novel Parkinson's disease therapies. FASEB journal : official publication of the Federation of American Societies for Experimental Biology, 27(6), 2101-2110. doi:10.1096/fj.12-226852
2. Burke, R. E., & O'Malley, K. (2013). Axon degeneration in Parkinson's disease. Experimental Neurology, 246, 72-83. doi:10.1016/j.expneurol.2012.01.011
3. Cheng, H. C., Ulane, C. M., & Burke, R. E. (2010). Clinical progression in Parkinson disease and the neurobiology of axons. Annals of Neurology, 67(6), 715-725. doi:10.1002/ana.21995
4. Chinta, S. J., & Andersen, J. K. (2005). Dopaminergic neurons. International Journal of Biochemistry and Cell Biology, 37(5), 942-946. doi:10.1016/j.biocel.2004.09.009
5. Hope, A. D., Myhre, R., Kachergus, J., Lincoln, S., Bisceglio, G., Hulihan, M., & Farrer, M. J. (2004). ?-Synuclein missense and multiplication mutations in autosomal dominant Parkinson’s disease. Neuroscience Letters, 367(1), 97-100. doi:10.1016/j.neulet.2004.05.100
6. Kramer, M. L., & Schulz-Schaeffer, W. J. (2007). Presynaptic ?-synuclein aggregates, not Lewy bodies, cause neurodegeneration in dementia with lewy bodies. Journal of Neuroscience, 27(6), 1405-1410. doi:10.1523/JNEUROSCI.4564-06.2007
7. Lynch-Day, M. A., Mao, K., Wang, K., Zhao, M., & Klionsky, D. J. (2012). The role of autophagy in Parkinson's disease. Cold Spring Harbor perspectives in medicine, 2(4), a009357-a009357. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22474616
8. Mazzulli, J. R., Zunke, F., Isacson, O., Studer, L., & Krainc, D. (2016). ?-

Synuclein–induced lysosomal dysfunction occurs through disruptions in protein trafficking in human midbrain synucleinopathy models. Proceedings of the National Academy of Sciences, 113(7), 1931. doi:10.1073/pnas.1520335113
9. Rajput, A. H., Fenton, M. E., Birdi, S., Macaulay, R., George, D., Rozdilsky, B., . . . Hornykiewicz, O. (2002). Clinical–Pathological study of levodopa complications. Movement Disorders, 17(2), 289-296. doi:10.1002/mds.10031
10. Soukup, S. F., Vanhauwaert, R., & Verstreken, P. (2018). Parkinson's disease: convergence on synaptic homeostasis. EMBO Journal, 37(18), n/a-n/a. doi:10.15252/embj.201898960
11. Susmita, K., & Ana Maria, C. (2015). Proteostasis and aging. Nature Medicine, 21(12), 1406. doi:10.1038/nm.4001
12. Vijayan, V., & Verstreken, P. (2017). Autophagy in the presynaptic compartment in health and disease. The Journal of cell biology, 216(7), 1895-1906. doi:10.1083/jcb.201611113
13. Viktor, I. K., Shinji, S., Maike, L., Farah, H. S., Esteban, A. R., Sara, I., . . . David, C. R. (2011). Lysosomal positioning coordinates cellular nutrient responses. Nature Cell Biology, 13(4), 453. doi:10.1038/ncb2204
14. Zhang, L., Dong, Y., Xu, X., & Xu, Z. (2012). The role of autophagy in Parkinson's disease. Neural regeneration research, 7(2), 141-145. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25767490