Parkinson's disease

PD is characterised by neurodegeneration of substantia nigra associated with synuclein and tau accumulation. The early symptoms are bradykinesia and muscle rigidity, late PD involves executive function and memory deficits because of the appearance of Lewy bodies. The degenerative process is not confined to the basal ganglia but also affects other parts of the brain

The neurochemical change of PD primarily affects basal ganglia, associated with a loss of dopaminergic neurons in the substantial nigra. The basal ganglia has two pathways to control movement that are highly related to dopamine, which are the direct pathway and the indirect pathway. The direct pathway starts with the D1 receptors on the striatum, and it projects GABA to substantial nigra/Globus pallidus internal segments, then they project GABA to thalamus, then thalamus project excited NT the supplementary motor area. there are two inhibitions in the direct pathway so disinhibition of the SMA therefore promotes the movement. And in the indirect pathway has three inhibit pathways so it suppresses the movement. The loss function of dopaminergic cells in PD leads to less activation of the direct pathway and more activation of the indirect pathway. This leads to bradykinesia. cholinergic neurones may also involved in affecting PD as well. Ach release from the striatum is strongly inhibited by dopamine, and it suggests that hyperactivity of these cholinergic neurons contributes to the symptoms of PD. It may cause tremors and rigidity in PD

Several drugs can be used to treat PD, and most of them can compensate for a loss of DAergic neurons in the SN. **L-DOPA** is the first-line treatment for PD. Dopamine can not cross the blood-brain barrier, therefore **L-DOPA** is given and is combined with a peripherally acting dopa decarboxylase inhibitor, such as **carbidopa** or benserazide, which reduces the dose needed by about 10-fold and diminishes the peripheral side effects. Carbidopa can not pass the blood-brain barrier so dopamine can be generated from L-DOPA only in the brain. Selegiline can be used to inhibit MAO-B, which only allows an increase in dopamine level in the brain and with fewer side effects like the cheese effect. In the late stage of PD, upregulating DA is no longer effective as there are so many neurons lost. So the **apomorphine** which is a D1 and D2 agonist could be used, and the peripheral D2 antagonist Domperidone is given as an adjunct. Besides, cholinergic interneurons of the corpus striatum are also involved in PD and HD. The poorly respond to levodopa in the late stage may be caused by a particular, reduction in acetylcholine due to degeneration of cholinergic structures, Accordingly, the cholinesterase inhibitor **rivastigmine** is efficacious for the treatment of dementia in Parkinson's disease(Kalia and Lang, 2015). Potential new treatments for PD at various stages of clinical trial are reviewed by Oertel and Schulz (2016). Active and passive immunisation against α-synuclein and inhibitors or modulators of α-synuclein aggregation may prevent the progression of the disease. Deep brain stimulation has therapeutic potential as well. Electrical stimulation of the subthalamic nuclei with implanted electrodes is used in severe cases, and can improve motor dysfunction in PD, but does not improve cognitive and other symptoms and does not stop the neurodegenerative process (Okun, 2012)

About 80% of patients show initial improvement with levodopa, particularly of rigidity and bradykinesia(Rang et al., 2015), However, there are significant unwanted side effects associated with this therapy. The two primary adverse effects are involuntary movements, which do not appear initially but develop in the majority of patients within 2 years of starting levodopa therapy. And the rapid fluctuations in clinical state, where bradykinesia and rigidity may suddenly worsen for anything from a few minutes to a few hours, and then improve again. This 'on-off effect' is not seen in untreated PD patients or with other anti-PD drugs, In addition to these slowly developing side effects, levodopa produces several acute effects, such as nausea, hypotension and some psychological effects because of alternation of dopamine reward system. Managing these unwanted effects is a crucial aspect of ongoing PD research. However, new potential treatments still do not

target the fundamental neurodegeneration associated with the disease. Therefore, preventing this neurodegeneration should be a primary focus in future PD studies, as it could fundamentally change the course of the disease and improve long-term outcomes for patients. neurodegeneration could be the initial target to treat PD and should play an important role in future studies.