LECTURE 05: MPTP Metabolism and PD Neurodegeneration Selectivity.

Since the initial discovery of MPTP-induced parkinsonism, much has been learned about the molecular pathway used by this toxin, as illustrated in Figure 4. Importantly, this knowledge enables investigators to use MPTP as a biological probe to explore the functions of PD genes and dissect the molecular events that occur during neurodegeneration of dopaminergic neurons. For example, mice mutant for PD genes (or other genes of possible relevance to dopaminergic neuronal death) can be injected with MPTP, and if these mice display markedly enhanced or suppressed dopaminergic neuronal death, one can then investigate which of the known molecular targets of MPTP are altered.

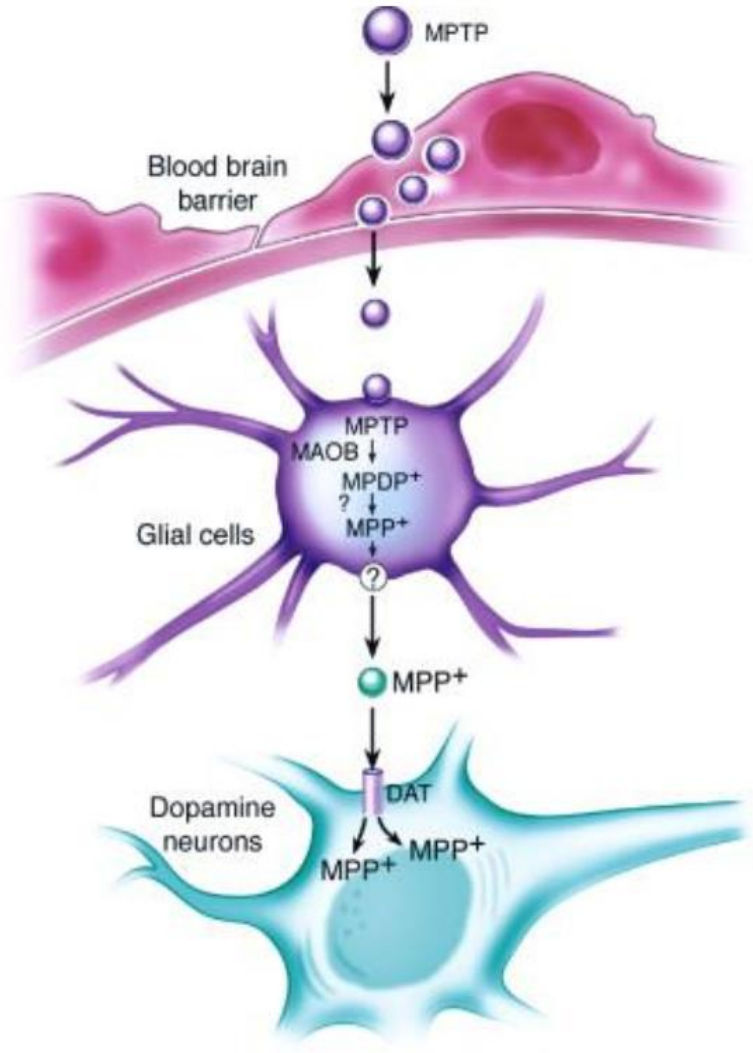

Figure 4.

Schematic Representation of MPTP Metabolism

- After systemic administration, MPTP crosses the blood-brain barrier.
- Once in the brain, MPTP is converted to 1-methyl-4-phenyl-2,3-dihydropyridinium (MPDP+) by monoamine oxidase B (MAO-B) within nondopaminergic cells, such as glial cells and serotonergic neurons, and then to MPP+ by an unknown mechanism (?).
- Thereafter, MPP+ is released, again by an unknown mechanism (?), into the extracellular space. MPP+ is concentrated into dopaminergic neurons via the dopamine transporter (DAT).
- Pharmacological inhibition or genetic deletion of DAT prevents MPTP-induced dopaminergic damage , demonstrating the obligatory character of this step in MPTP neurotoxicity.

Inside neurons , MPP+ can follow at least three routes:

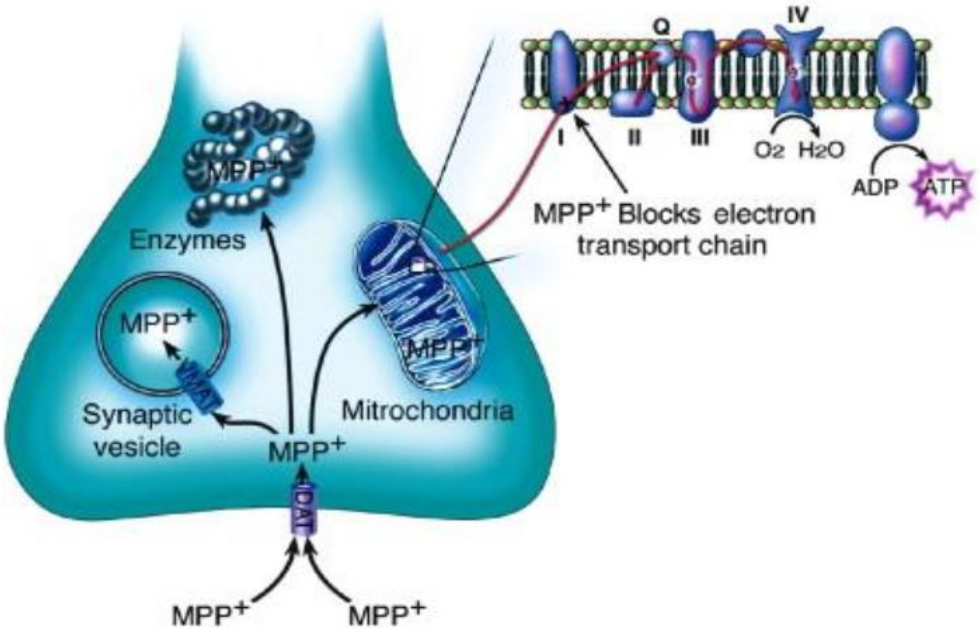

Figure 5.

Schematic Representation of MPP+ Intracellular Pathways

- Inside dopaminergic neurons, MPP+ can follow one of three routes: (1) concentration into mitochondria through an active process (toxic); (2) interaction with cytosolic enzymes (toxic); (3) sequestration into synaptic

vesicles via the vesicular monoamine transporters (VMAT; protective). Within the mitochondria, MPP+ blocks complex I (X), which interrupts the transfer of electrons from complex I to ubiquinone (Q). This perturbation enhances the production of reactive oxygen species and decreases the synthesis of ATP.

- In vitro experiments in mitochondria isolated from *whole brain*demonstrate that complex I activity must be inhibited by ~70% to significantly impair ATP production , but data from PD postmortem tissues demonstrate only a ~40% inhibition of complex I activity. Interestingly, in vitro experiments with *synaptic-derived* mitochondria demonstrate that significant ATP depletion results from as little as ~25% inhibition of complex I , indicating a much tighter functional relationship between complex I activity and ATP production in synaptic than in somatic mitochondria. Thus, mitochondria from phenotypically distinct neuronal populations may be differentially affected in PD, and the current approach of assessing mitochondrial function in specimens from whole tissue may not depict accurately abnormalities present in only a minority of cells.

Prolonged administration of low to moderate doses of MPTP to mice leads to morphologically defined apoptosis of SNpc dopaminergic neurons.

- Under this regimen of MPTP intoxication, Bax, a potent PCD agonist and member of the Bcl-2 family, is upregulated in SNpc dopaminergic neurons .
- Baxupregulation coincides with its translocation to mitochondria, mitochondrial release of cytochrome c (an electron carrier and a mediator of PCD), and activation of caspases 9 and 3. At the same time, PCD antagonists such as Bcl-2 are downregulated in the SNpc . Consistent with these observations, Bax null and Bcl-2 transgenic mice are both resistant to MPTP neurotoxicity .

MPTP causes oxidative damage to DNA , which may be important in inducing Bax via p53 activation.

- The tumor suppressor protein p53 is one of the few molecules known to regulate Bax expression and is activated by DNA damage.
- Furthermore, pharmacological inhibition of p53 attenuates MPTP-induced Baxupregulation and the subsequent SNpc dopaminergic neuron death , and p53 null mice are resistant to MPTP-induced neurodegeneration .

Activation of the JNK pathway following DNA damage is required in vitro for Bax mitochondrial translocation and the ensuing recruitment of the mitochondrial apoptotic pathway. Activation of the JNK pathway follows MPTP administration and pharmacological blockade of JNK results in marked attenuation of MPTP-induced SNpc dopaminergic cell death.

MPTP administration also leads to the accumulation and nitration of α-synuclein in the cytosol of SNpc dopaminergic neurons , and ablation of α-synuclein in mutant mice prevents MPTP-induced dopaminergic neurodegeneration. While it is not clear whether α-synuclein plays any direct role in regulating PCD, the expression of mutant α-synuclein in cell cultures may promote apoptosis, and cytochrome c has been reported to stimulate in vitro aggregation of α-synuclein. Collectively, these data demonstrate that the activation of PCD is instrumental in MPTP toxicity. They also suggest that PCD alterations in PD postmortem samples are of pathological significance and that targeting specific PCD molecules may be a valuable neuroprotective strategy for the treatment of PD.

Prevention

- Exercise in middle age reduces the risk of Parkinson's disease later in life.
- Caffeine also appears protective with a greater decrease in risk occurring with a larger intake of caffeinated beverages such as coffee.

- Although tobacco smoke causes adverse health effects, decreases life expectancy and quality of life, it may reduce the risk of PD by a third when compared to non-smokers. The basis for this effect is not known, but possibilities include an effect of nicotine as a dopamine stimulant Tobacco smoke contains compounds that act as MAO inhibitors that also might contribute to this effect.

- Antioxidants, such as vitamins C and D, have been proposed to protect against the disease but results of studies have been contradictory and no positive effect has been proven. The results regarding fat and fatty acids have been contradictory, with various studies reporting protective effects, risk-increasing effects or no effects. Also, there have been preliminary indications of a possible protective role of estrogens and anti-inflammatory drugs.

Management

There is no cure for Parkinson's disease, but medications, surgery and multidisciplinary management can provide relief from the symptoms. The main families of drugs useful for treating motor symptoms are levodopa (usually combined with a dopa decarboxylase inhibitor or COMT inhibitor which does not cross the blood–brain barrier), dopamine agonists and MAO-B inhibitors. The stage of the disease determines which group is most useful. Two stages are usually distinguished: an initial stage in which the individual with PD has already developed some disability for which he needs pharmacological treatment, then a second stage in which an individual develops motor complications related to levodopa usage. Treatment in the initial stage aims for an optimal tradeoff between good symptom control and side-effects resulting from improvement of dopaminergic function. The start of levodopa (or L-DOPA) treatment may be delayed by using other medications such as MAO-B inhibitors and dopamine agonists, in the hope of delaying the onset of dyskinesias. In the second stage the aim is to reduce symptoms while controlling fluctuations of the response to medication. Sudden withdrawals from medication or overuse have to be managed When medications are not enough to control symptoms, surgery and deep brain stimulation can be of use.In the final stages of the disease, palliative care is provided to improve quality of life.

Levodopa

Levodopa has been the most widely used treatment for over 30 years. L-DOPA is converted into dopamine in the dopaminergic neurons by dopa decarboxylase. Since motor symptoms are produced by a lack of dopamine in the substantianigra, the administration of L-DOPA temporarily diminishes the motor symptoms.

Only 5–10% of L-DOPA crosses the blood–brain barrier. The remainder is often metabolized to dopamine elsewhere, causing a variety of side effects including nausea, dyskinesias and joint stiffness. Carbidopaand benserazide are peripheral dopa decarboxylase inhibitors, which help to prevent the metabolism of L-DOPA before it reaches the dopaminergic neurons,

therefore reducing side effects and increasingbioavailability. They are generally given as combination preparations with levodopa.

Existing preparations are carbidopa/levodopa (co-careldopa) and benserazide/levodopa (co-beneldopa). Levodopa has been related to dopamine dysregulation syndrome, which is a compulsive overuse of the medication, and punding.

There are controlled release versions of levodopa in the form intravenous and intestinal infusions that spread out the effect of the medication. These slow-release levodopa preparations have not shown an increased control of motor symptoms or motor complications when compared to immediate release preparations.

Tolcapone inhibits the COMT enzyme, which degrades dopamine, thereby prolonging the effects of levodopa.It has been used to complement levodopa; however, its usefulness is limited by possible side effects such as liver damage. A similarly effective drug, entacapone, has not been shown to cause significant alterations of liver function. Licensed preparations of entacapone contain entacapone alone or in combination with carbidopa and levodopa.

Levodopa preparations lead in the long term to the development of motor complications characterized by involuntary movements called dyskinesias and fluctuations in the response to medication.When this occurs a person with PD can change from phases with good response to medication and few symptoms ("on" state), to phases with no response to medication and significant motor symptoms ("off" state). For this reason, levodopa doses are kept as low as possible while maintaining functionality. Delaying the initiation of therapy with levodopa by using alternatives (dopamine agonists and MAO-B inhibitors) is common practice. A former strategy to reduce motor complications was to withdraw L-DOPA medication for some time. This is discouraged now, since it can bring dangerous side effects such as neuroleptic malignant syndrome. Most people with PD will eventually need levodopa and later develop motor side effects.

Dopamine agonists

Several dopamine agonists that bind to dopaminergic post-synaptic receptors in the brain have similar effects to levodopa.These were initially used for individuals experiencing on-off fluctuations and dyskinesias as a complementary therapy to levodopa; they are now mainly used on their own as an initial therapy for motor symptoms with the aim of delaying motor complications.[5458] When used in late PD they are useful at reducing the off periods. Dopamine agonists include bromocriptine, pergolide, pramipexole, ropinirole, piribedil, cabergoline, apomorphine and lisuride.

Dopamine agonists produce significant, although usually mild, side effects including drowsiness, hallucinations, insomnia, nausea and constipation. Sometimes side effects appear even at a minimal clinically effective dose, leading the physician to search for a different drug. Compared with levodopa, dopamine agonists may delay motor complications of medication use but are less effective at controlling symptoms.Nevertheless,

they are usually effective enough to manage symptoms in the initial years.They tend to be more expensive than levodopa.Dyskinesias due to dopamine agonists are rare in younger people who have PD, but along with other side effects, become more common with age at onset.Thus dopamine agonists are the preferred initial treatment for earlier onset, as opposed to levodopa in later onset.Agonists have been related to impulse control disorders (such as compulsive sexual activity and eating, and pathological gambling and shopping) even more strongly than levodopa.

Apomorphine, a non-orally administered dopamine agonist, may be used to reduce off periods and dyskinesia in late PD. It is administered by intermittent injections or continuous subcutaneous infusions. Since secondary effects such as confusion and hallucinations are common, individuals receiving apomorphine treatment should be closely monitored. Two dopamine agonists that are administered through skin patches (lisuride and rotigotine) and are useful for people in the initial stages and possibly to control off states in those in the advanced state.

MAO-B inhibitors

MAO-B inhibitors (selegiline and rasagiline) increase the level of dopamine in the basal ganglia by blocking its metabolism. They inhibit monoamine oxidase B (MAO-B) which breaks down dopamine secreted by the dopaminergic neurons. The reduction in MAO-B activity results in increased L-DOPA in the striatum. Like dopamine agonists, MAO-B inhibitors used as monotherapy improve motor symptoms and delay the need for levodopa in early disease, but produce more adverse effects and are less effective than levodopa. There are few studies of their effectiveness in the advanced stage, although results suggest that they are useful to reduce fluctuations between on and off periods. An initial study indicated that selegiline in combination with levodopa increased the risk of death, but this was later disproven.

Other drugs

Other drugs such as amantadine and anticholinergics may be useful as treatment of motor symptoms. However, the evidence supporting them lacks quality, so they are not first choice treatments.[54] In addition to motor symptoms, PD is accompanied by a diverse range of symptoms. A number of drugs have been used to treat some of these problems. Examples are the use of quetiapine for psychosis, cholinesterase inhibitors for dementia, and modafinil for daytime sleepiness.A 2010 meta-analysis found that non-steroidal anti-inflammatory drugs (apart from aspirin), have been associated with at least a 15 percent (higher in long-term and regular users) reduction of incidence of the development of Parkinson's disease.

Surgery

Treating motor symptoms with surgery was once a common practice, but since the discovery of levodopa, the number of operations declined. Studies in the past few decades have led to great improvements in surgical techniques, so that surgery is again being used in people with advanced PD for whom drug therapy is no longer sufficient. Surgery for PD can be divided in two main groups: lesional and deep brain stimulation (DBS). Target areas for DBS or lesions include the thalamus, the globuspallidus or the subthalamic nucleus.Deep brain stimulation (DBS) is the most commonly used surgical treatment, developed in the 1980s by Alim-Louis Benabid and others. It involves the implantation of a medical device called a neurostimulator which sends electrical impulses to specific parts of the brain. DBS is recommended for people who have PD with motor fluctuations and tremor inadequately controlled by medication, or to those who are intolerant to medication, as long as they do not have severe neuropsychiatric problems. Other, less common, surgical therapies involve intentional formation of lesions to suppress overactivity of specific subcortical areas. For example, pallidotomy involves surgical destruction of the globuspallidus to control dyskinesia.

Rehabilitation

Exercise programs are recommended in people with Parkinson's disease. There is some evidence that speech or mobility problems can improve with rehabilitation, although studies are scarce and of low quality. Regular physical exercise with or without physiotherapy can be beneficial to maintain and improve mobility, flexibility, strength, gait speed, and quality of life. When an exercise program is performed under the supervision of a physiotherapist, there are more improvements in motor symptoms, mental and emotional functions, daily living activities, and quality of life compared to a self-supervised exercise program at home. In terms of improving flexibility and range of motion for people experiencing rigidity, generalized relaxation techniques such as gentle rocking have been found to decrease excessive muscle tension. Other effective techniques to promote relaxation include slow rotational movements of the extremities and trunk, rhythmic initiation, diaphragmatic breathing, and meditation techniques. As for gait and addressing the challenges associated with the disease such as hypokinesia (slowness of movement), shuffling and decreased arm swing; physiotherapists have a variety of strategies to improve functional mobility and safety. Areas of interest with respect to gait during rehabilitation programs focus on but are not limited to improving gait speed, base of support, stride length, trunk and arm swing movement. Strategies include utilizing assistive equipment (pole walking and treadmill walking), verbal cueing (manual, visual and auditory), exercises (marching and PNF patterns) and altering environments (surfaces, inputs, open vs. closed).Strengthening exercises have shown improvements in strength and motor function for people with primary muscular weakness and weakness related to inactivity with mild to moderate Parkinson’s disease. However, reports show a significant interaction between strength and the time the

medications was taken. Therefore, it is recommended that people with PD should perform exercises 45 minutes to one hour after medications, when they are at their best.[68] Also, due to the forward flexed posture, and respiratory dysfunctions in advanced Parkinson's disease, deep diaphragmatic breathing exercises are beneficial in improving chest wall mobility and vital capacity.Exercise may improve constipation.

One of the most widely practiced treatments for speech disorders associated with Parkinson's disease is the Lee Silverman voice treatment (LSVT).[6370] Speech therapy and specifically LSVT may improve speech. Occupational therapy (OT) aims to promote health and quality of life by helping people with the disease to participate in as many of their daily living activities as possible. There have been few studies on the effectiveness of OT and their quality is poor, although there is some indication that it may improve motor skills and quality of life for the duration of the therapy.

Palliative care

Palliative care is specialized medical care for people with serious illnesses, including Parkinson's. The goal of this speciality is to improve quality of life for both the person suffering from Parkinson's and the family by providing relief from the symptoms, pain, and stress of illnesses. As Parkinson's is not a curable disease, all treatments are focused on slowing decline and improving quality of life, and are therefore palliative in nature.

Palliative care should be involved earlier, rather than later in the disease course.Palliative care specialists can help with physical symptoms, emotional factors such as loss of function and jobs, depression, fear, and existential concerns.

Along with offering emotional support to both the patient and family, palliative care serves an important role in addressing goals of care. People with Parkinson's may have many difficult decisions to make as the disease progresses such as wishes for feeding tube, non-invasive ventilator, and tracheostomy; wishes for or against cardiopulmonary resuscitation; and when to use hospice care. Palliative care team members can help answer questions and guide people with Parkinson's on these complex and emotional topics to help them make the best decision based on their own values.