Drugs to Treat Neurodegeneration

Key Concepts in Neurotransmitter Function

Different neurotransmitters have unique roles in the CNS, influencing treatment strategies:

- **Neurotransmitter Synthesis:** enzymes and transporters; important for Parkinson's treatment, less so for Alzheimer's.
- **Storage:** vesicles and transporters; explain the action of drugs like cocaine and amphetamines.
- **Release Mechanisms:** release of neurotransmitters can be modulated through various channels (sodium, potassium, calcium)
- **Receptor Types:** presynaptic and postsynaptic receptors have different roles; ligand-gated and GPCR; signalling pathways; excitation vs inhibition
- **Inactivation Processes:** metabolism enzymes and uptake transporters; differences between neurotransmitters like acetylcholine (inactivated in the synaptic cleft) and dopamine (reuptake and repackaging).

Parkinson's Disease: Historical Context

Parkinson's disease was first identified in 1817 by English clinician James Parkinson. It is a chronic, progressive, neurological degenerative disease involving the disorder of muscle movement. The disease is characterised by the degeneration of dopaminergic neurons in the substantia nigra, which is named for the presence of neuromelanin that gives it a dark appearance.

Neurotransmitter Interplay in Parkinson's Disease

The interaction of neurotransmitters is crucial for coordinated movement:

- **Dopamine:** Acts as a tonic inhibitor, reducing excessive movement.
- **Acetylcholine:** Provides excitatory input, increasing movement.
- **GABA:** Functions as an inhibitory neurotransmitter, also reducing movement.

When these neurotransmitters do not work in concert, motor control is disrupted, leading to symptoms of Parkinson's disease.

Symptoms and Progression of Parkinson's Disease

Parkinson's disease is characterised by:

- Tremors
- Rigidity of limbs
- Bradykinesia (slowness of movement)
- Impairment of postural reflexes

- Impassive facial expression
- Monotonous and hypophonic speech
- Decreased manual dexterity

However, Parkinson's is not solely a motor disorder. Dopamine also plays a role in:

- Cognition
- Depression and anxiety
- Olfactory function (loss of smell)
- Sleep disturbances
- Fatigue and pain
- Bowel and bladder issues
- Sexual dysfunction

Pathophysiology of Parkinson's Disease

Multi-system neurological disorder which affects cognitive processes, emotion and autonomic function. Key features of Parkinson's disease include:

- Reduced dopamine levels
- Formation of Lewy bodies, which are aggregates of misfolded proteins

These features highlight the overlap in protein homeostasis issues between Parkinson's and other diseases, where beta-amyloid plaques are a hallmark of Alzheimer's.

Current Treatments and Research

While there is no cure for Parkinson's disease, significant advancements have been made in understanding and treating the condition.

Palliative Treatment Approach

Parkinson's disease management focuses on palliative care rather than curative treatment, as the underlying neurodegenerative processes cannot be halted. The primary goal is to alleviate symptoms and improve the quality of life for patients. Drugs provide symptomatic relief.

Restoring Dopamine Levels

Since dopamine-producing neurons are dying, treatment strategies aim to restore dopamine levels through various methods:

- Increasing dopamine synthesis
- Enhancing dopaminergic release
- Using dopamine receptor agonists
- Reducing dopamine metabolism to prolong its presence in the synaptic cleft

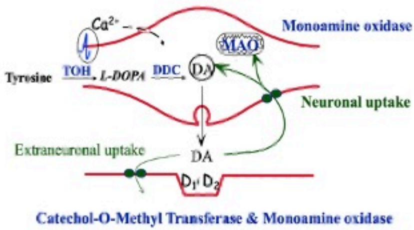
Dopaminergic Agonists

Dopamine itself cannot be administered as it does not cross the blood-brain barrier. Instead, dopaminergic agonists that can cross this barrier are used. However, these agonists bind to all types of dopaminergic receptors, leading to potential side effects.

Neurotransmission Pathways

The biochemical pathways involved in dopamine production include:

- Tyrosine is converted to L-Dopa by the enzyme tyrosine hydroxylase.
- L-Dopa is then converted to dopamine by dopa decarboxylase.
- Dopamine release requires an action potential and calcium influx.
- Dopamine binds to D1-like or D2-like receptors, which are categorised into five subtypes.
- Dopamine is metabolised by catechol-O-methyltransferase and monoamine oxidase.



Historical Context of Dopamine Discovery

Synthesis and Isolation of L-DOPA:

- D.L-DOPA was first synthesised in 1911 by Casimir Funk, a Polish biochemist who also coined the term "vitamin."
- L-DOPA was not seen as biologically useful at the time and was considered toxic
    - Marcus Guggenheim tested L-DOPA on himself and experienced violent vomiting. The vomiting occurred because L-DOPA is converted to dopamine in the body, and dopamine acts as an emetic.

Carlsson's Discovery:

- Carlsson's research on reserpine, a drug introduced in the mid-1950s to treat schizophrenia, led to his discovery.
- Reserpine was quickly replaced due to severe side effects, including the induction of parkinsonian symptoms.

L-DOPA as Treatment:

- Carlsson injected animals with L-DOPA, as noradrenaline and dopamine do not cross the blood–brain barrier.
- Within 15 minutes of the injection, the animals regained normal motor function.
- 5-hydroxytryptophan (a precursor of serotonin) did not reverse catatonia, indicating the specific role of L-DOPA in reversing symptoms.

Challenges with L-Dopa

L-Dopa is a precursor to dopamine but is primarily converted to dopamine in the gut, leading to side effects like vomiting. To mitigate this, peripheral dopa decarboxylase inhibitors (e.g., carbidopa) are used, which do not cross the blood-brain barrier, allowing L-Dopa to effectively increase dopamine levels in the brain.

Combination Therapy

The combination of L-Dopa and peripheral dopa decarboxylase inhibitors is known as levodopa therapy. Levodopa is an amino acid isomer that results in over 90% metabolism in the periphery, requiring large doses. This approach is the first line of treatment and allows for controlled release, improving symptoms such as rigidity and tremors. However, the therapy has a short half-life (1-2 hours), leading to an "on-off" phenomenon where patients may choose when to take their medication based on their activities. However, this therapy requires some functional dopaminergic neurons.

Long-Term Considerations

As Parkinson's disease progresses, the effectiveness of levodopa therapy may decline due to ongoing neurodegeneration. Patients may experience a paradox where increased dopamine production could potentially accelerate neuronal death. The disease typically manifests over decades, and treatment decisions must balance quality of life against potential long-term outcomes. Solutions include increasing the dose or incorporating other drugs.

Adverse Effects of Levodopa

- Peripheral:
  - Anorexia, nausea & vomiting
  - Tachycardia & ventricular dysrhythmias
  - Orthostatic hypotension
  - Pupil dilation (avoid in patients with glaucoma)
- Central:
  - Visual & auditory hallucinations, abnormal motor movements
  - Mood changes, depression, anxiety