Parkinson's disease

Pathophysiology

Degeneration of dopaminergic neurones in the substantia nigra, pars compacta[1]

Balance of dopaminergic and cholinergic activity in the extra-pyramidal system determines activating outflow to motor cortex

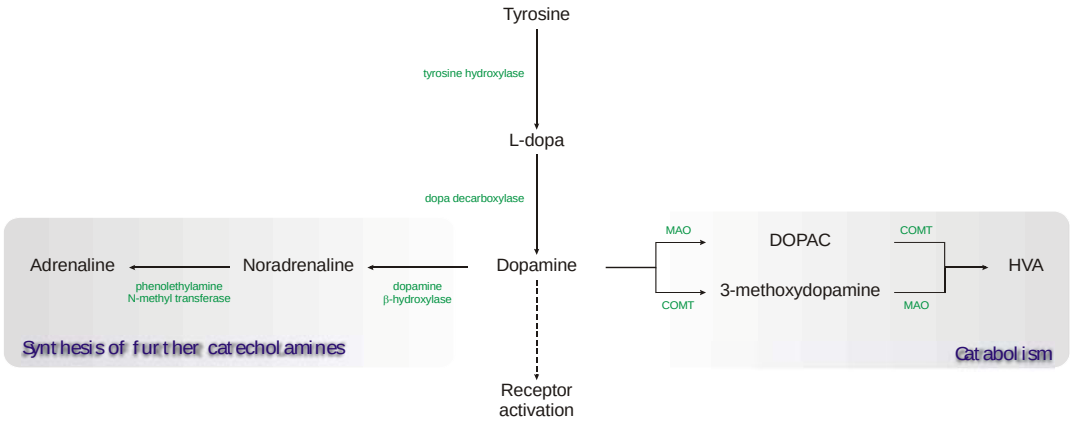
- Dopamine enhances
- ACh suppresses

In Parkinson's disease, a relative dopaminergic deficit causes the clinical features of 'TRAP'

- **T**remor ('pill-rolling', absent in 20-30%)
- **R**igidity ('lead pipe', esp. arms)[2]
- **A**kinesia/bradykinesia (esp. arms)
- **P**ostural reflex loss, gait disturbance

- Usually asymmetrical (cf. drug-induced: symmetrical)

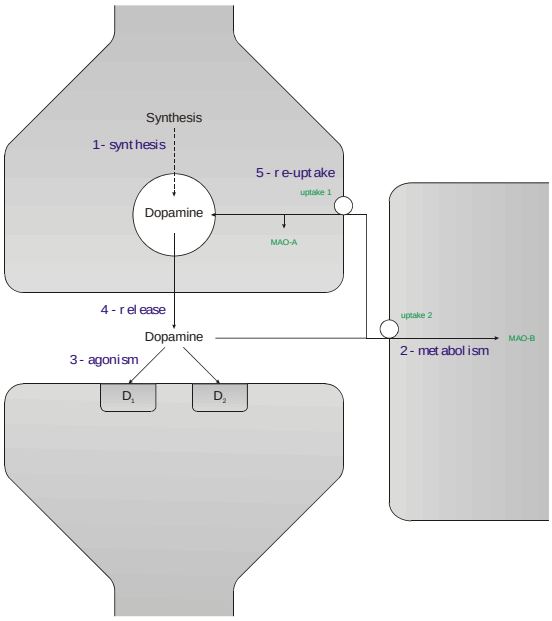
Overview of dopamine metabolism



Release pathway

[1] Note that Parkinsonism refers to the classical clinical features regardless of aetiology; Parkinson's disease is idiopathic Parkinsonism.

[2] Cogwheeling = rigidity with superimposed tremor



Dopamine receptors

At least 5 dopamine receptors have been cloned to date ($D_{1\text{-}5}$), but only D_1 and D_2 are of significance in Parkinsonism.

D_2 receptor is principal target for anti-Parkinsonian drugs. Chronic D_1 stimulation also appears to be beneficial – paradoxically so, since

- Both subtypes have opposite effects on the cAMP second messenger system (D_1 is G_s-coupled and stimulates adenylate cyclase, D_2 is $G_{i/o}$-coupled and inhibits it).
- Both subtypes have different spatial localization. D_1 is mostly found in the vasculature, whereas D_2 is concentrated in the areas shown later.

Consequent rationale for pharmacological management

Pharmacological treatment **cannot cure** Parkinson's disease – this would require replacing lost neurones. It can, however, **improve motor function through restoring DA/ACh balance** by

- Restoring dopaminergic activity
  - 1: replenish neuronal dopamine — L-dopa
  - 2: inhibit dopamine metabolism — MAO-B: selegiline; COMT: entacapone
  - 3: stimulate postsynaptic DA receptors — DA agonists
  - 4: stimulate dopamine release — amantadine
  - 5: inhibit dopamine re-uptake — amantadine
- Reducing cholinergic activity

Disease modification refers to delaying the progression of neuronal degeneration. Such an effect has been proposed for selegiline but has never been proven.

Drug classes

L-dopa (=levodopa) and dopa-decarboxylase inhibitors (DDC-Is)

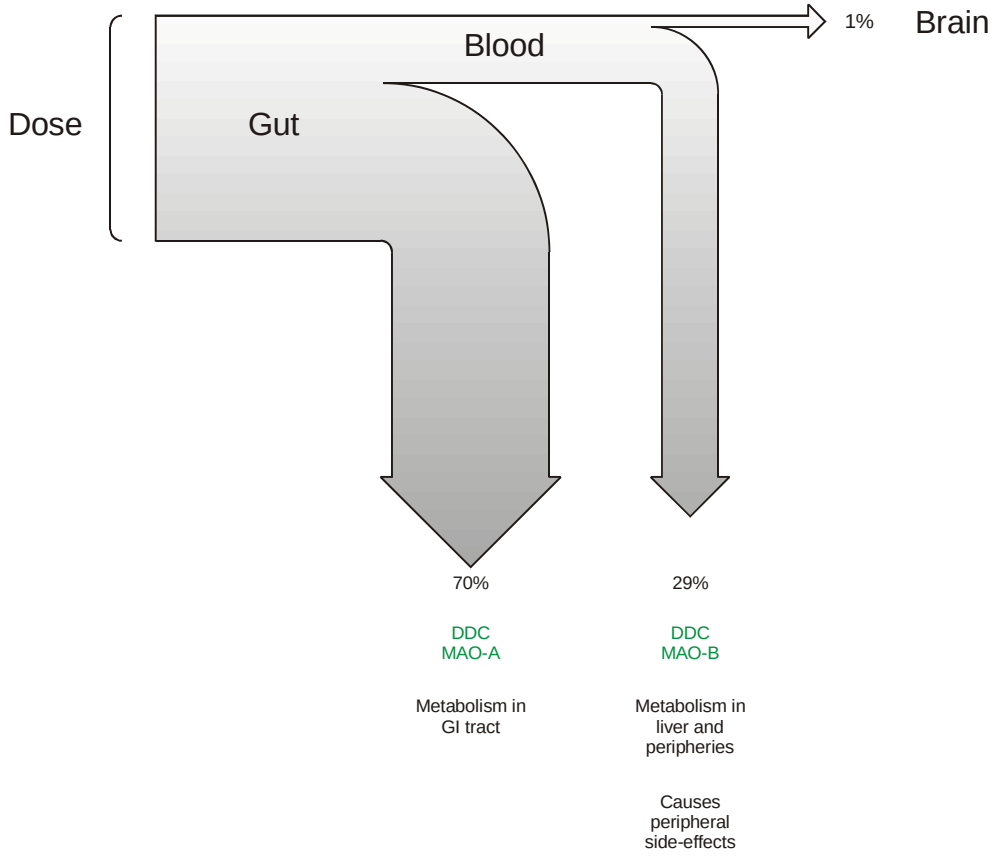
Why not give dopamine itself?

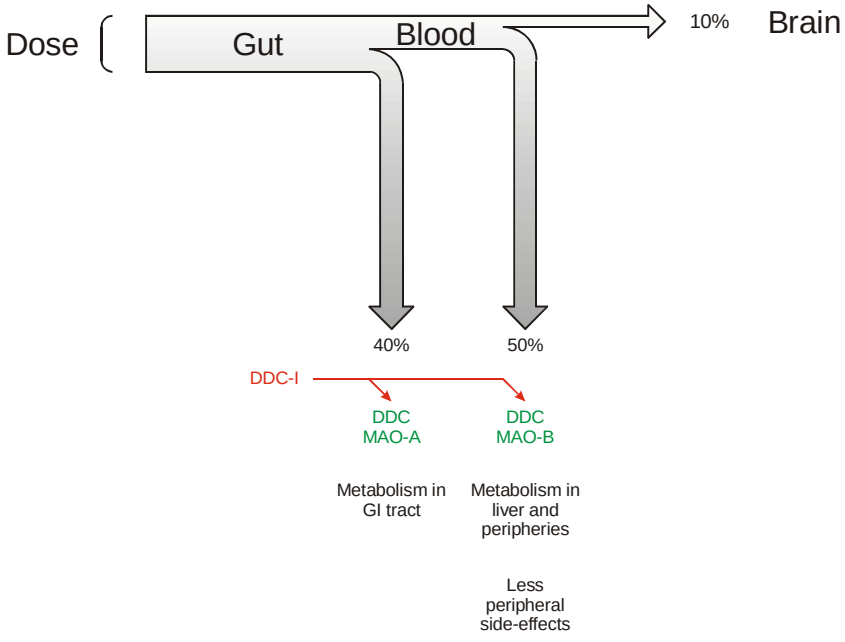
- Rapid GI/liver/blood metabolism by MAO and COMT
- Dopamine is poorly lipid soluble and cannot traverse the blood-brain barrier; L-dopa enters through the neural amino-acid transporter

Why give a DDC-I as well?

- 99% of L-dopa is converted to dopamine prematurely by peripheral DDC, causing side-effects of nausea, postural hypotension and cardiac arrhythmias
- Merely 1% enters the brain to be converted to dopamine

- Would have to give huge doses with consequently prominent side-effects
- DDC-Is (carbidopa, benserazide) do not cross the blood-brain barrier and selectively inhibit the extracerebral metabolism of L-dopa. Advantages:
    - Higher efficacy
    - Higher tolerability
    - Smoother clinical response with a more rapid onset





Indications

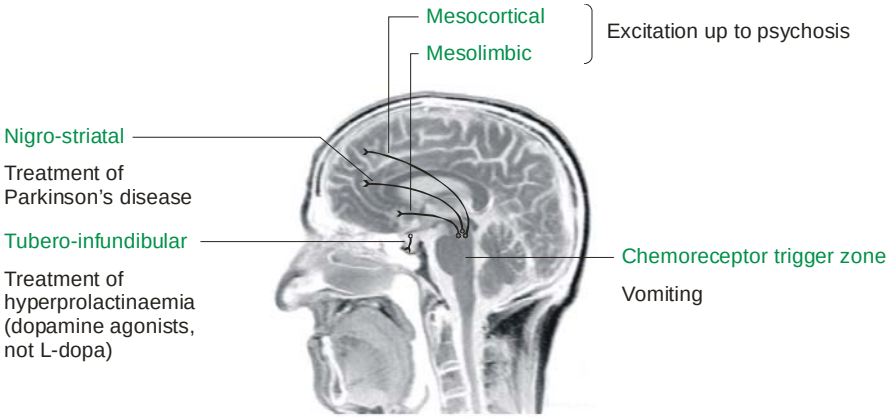
- Most potent treatment available, and treatment of choice for idiopathic Parkinson's disease. Over 75% of patients regain normal or near-normal physical activity. Usually slow response over 6-18 months and then maintained for up to 2 years followed by gradual decline. After 8 years, 50% have choreo-athetoid dyskinesia and end-dose akinesia.
- The ELLDOPA (Early vs. Late L-dopa) trial has shown that disease progression is not influenced by L-dopa therapy. Consequently, instigation of therapy should depend on symptomatology and quality of life.
- Less valuable in
    - Elderly patients or those with longstanding disease, who may not tolerate a dose large enough to overcome the deficit.
    - Post-encephalitic Parkinsonism
    - Parkinsonism due to degenerative brain disease (e.g. multiple system atrophy)
    - Neuroleptic-induced Parkinsonism. Instead, withdraw the offending drug and give antimuscarinics.
- A duodenal gel formulation provides a more constant L-dopa plasma level because it circumvents irregular gastric emptying and unpredictable small bowel absorption. It is an alternative to IV L-dopa, which is impractical as L-dopa is hydrophobic and requires large liquid volumes to dissolve. The duodenal formulation requires a percutaneous tube and portable pump, and is an advanced treatment for patients with severe motor fluctuations or dyskinesia.

Preparations
Oral

Co-careldopa (Sinemet®)	= L-dopa + carbidopa (4:1 or 10:1)
Co-beneldopa (Madopar®)	= L-dopa + benserazide (4:1)

Duodenal
Co-careldopa (Duodopa®)

Adverse effects
Central
Enhanced dopaminergic action is not confined to the nigro-striatal tract.

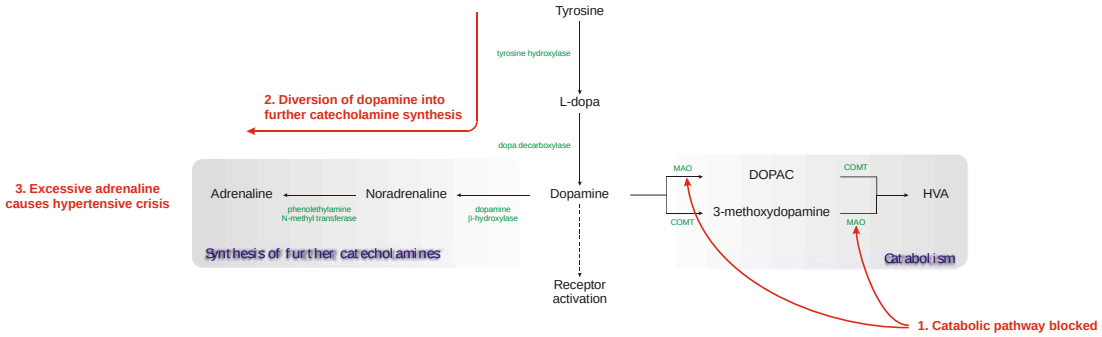


Note that the chemoreceptor trigger zone is sensitive to substances outside the blood-brain barrier; vomiting is therefore not a purely central side-effect.

Peripheral
Postural hypotension through D_1 activity.

Thus up-titrate the dose until the best trade-off between decreasing symptoms and increasing side-effects is reached.

Interactions
Remember the interaction between L-dopa and non-selective MAO-Is:



Pharmacokinetics
$t_{1/2}$ = 90min

Dopamine agonists

Classification

- Ergot-derived (ergolinic)
  - Bromocriptine
  - Pergolide (D_1 and D_2)
  - Cabergoline
- Non-ergot derived (non-ergolinic)
  - Ropinirole
  - Apomorphine (D_1 and D_2)
  - Pramipexole (D_2 and D_3)
  - Rotigotine

Adverse effects

- Dopamine dysregulation syndrome
  - Uncommon disorder
  - Use of any dopaminergic medication, esp. dopamine agonists
  - Behavioural disturbance including hypersexuality, pathological gambling and stereotypic motor acts
  - Management: wean drug

Bromocriptine
Most commonly used ergot-derived agonist

Indications

- Has no advantage over L-dopa and is used
  - When L-dopa alone is no longer adequate to control symptoms
  - When L-dopa is associated with intolerable side-effects
- Useful for akinetic periods and on-off phenomena (has a longer $t_{1/2}$ of 5h and hence a smoother action than levodopa)

Adverse effects

- Akin to L-dopa
- Also a weak α-blocker, hence more marked postural hypotension
- All ergot derivatives carry a risk of retroperitoneal/pulmonary/pericardial/heart valve fibrosis (5-HT_{2B} overstimulation; regurgitant valve lesions)[3]
  - Obtain ESR/crea/CXR ± lung function tests before starting
  - Monitor for abdo pain/tenderness, SOB/cough/CP or features of heart failure
  - Progression of fibrosis can be prevented by early diagnosis and cessation of drug treatment

Pergolide
Very similar, but also stimulates D_1.

Cabergoline

[3] ZANETTI, R. ET AL. (2007): Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *NEJM* **356**:39-46.
SCHADE, R. ET AL. (2007): Dopamine agonists and the risk of cardiac-valve regurgitation. *NEJM* **356**:29-38.

Extra-long half-life of 80h, thus suitable for once daily or even twice weekly dosing, but clinical experience is still limited.

Ropinirole
Newer drug with similar side-effect profile. D_{1-3} agonist.

Indications
- As an adjunct to L-dopa
- As monotherapy in young patients at risk of developing disabling dyskinesias with long-term therapy

Apomorphine
Morphine derivative that is a full D_1 and D_2 agonist; lacks activity at opioid receptors.

Indications
- Useful for stabilizing patients with unpredictable 'off' periods with L-dopa

Adverse effects
- Potent emetic[4]; thus need to give domperidone (DA antagonist that does not cross the blood-brain barrier) for 3 days before initiating therapy, then tailed off over weeks
- Rare but well-described: haemolytic anaemia
- Needs to be given by SC injection[5]/infusion under Consultant supervision. This route allows for fast onset and abortion of an 'off' period

Rotigotine
- Neupro® is a transdermal patch, avoids fluctuating dopaminergic stimulation

Monoamine oxidase inhibitors (MAO-Is)
The MAO enzyme exists in two isoforms:

	Central location	Peripheral location	Substrate
MAO-A	Neurons	Liver, sympathetic neurons	Principally 5HT, also NorAdr/Adr/DA
MAO-B	Glia	Gut	Principally phenylethylamine, also NorAdr/Adr/DA

In Parkinson's disease, the nigrostriatal neurons and their MAO-A activity are lost. Therefore DA is predominantly catabolised by MAO-B in the glia. MAO-B blockade can thus boost prevailing DA concentration.

Selegiline
Selective irreversible inhibitor of MAO-B

Indications
- Adjunct to L-dopa in severe Parkinsonism to reduce end-of-dose deterioration
  - Can halve the L-dopa requirement
- Controversies
  - Delayed need for L-dopa treatment/disease progression through early selegiline? – untrue
  - Increased mortality with combination of selegiline and L-dopa? – UKPRG (1995) trial suggests so, but used a flawed method of data collection and analysis

Rasagiline
Selective irreversible inhibitor of MAO-B

Indications
- Monotherapy (TEMPO)
- Adjunct to L-dopa (LARGO)

[4] Famously used by a murderer in an Agatha Christie novel who drank poisoned tea with her victim and then injected herself with apomorphine to vomit up the poison.
[5] 'Penjet' devices available, i.e. like insulin

Catechyl-O-methyl transferase inhibitors (COMT-Is)
Inhibit an alternative enzyme involved in the breakdown of dopamine. Theoretically more attractive than MAO-Is since COMT also catabolises L-dopa.

The original compound, **tolcapone**, is only used with extreme caution due to potential hepatotoxicity and NMS.

Entacapone (Comtess®) was subsequently introduced

Indications
- Adjunct to L-dopa therapy in patients with end-of-dose deterioration
- Available as a combined formulation: Stalevo® = L-dopa + carbidopa + entacapone
    - Minimises number of tablets
    - Ensures entacapone maximally effective as taken at same time as L-dopa

Amantadine
Developed as an antiviral agent to treat influenza, amantadine was noticed to improve Parkinsonian symptomatology by chance.

Mechanism: increases synthesis and release of dopamine by acting as an NMDA antagonist; reduces re-uptake of dopamine

Less effective than L-dopa but more than anticholinergics
Mild improvement in all 3 major symptoms

Adverse effects
- Relatively free from side-effects (ankle oedema, mild D_2 effects), but
    - Only a small proportion of patients derive benefit
    - Tolerance occurs

Antimuscarinic agents
E.g. benzhexol, procyclidine, orphenadrine

Generally less useful than levodopa
Greater effect on tremor and rigidity than on bradykinesia

Possible indications
- Predominant tremor
- Post-encephalitic or drug-induced Parkinsonism[6]
- Drooling (sialorrhoea)

Adverse effects
Typically anticholinergic: dry mouth, blurred vision, mydriasis, tachycardia, constipation, urinary retention, erectile impotence

Pharmacological management in context

1. Conservative measures
    - Speech therapy
    - Physiotherapy
    - Occupational therapy

2. Pharmacological measures
    - Commence drug therapy once symptoms impact significantly on quality of life
    - Mainstay of treatment remains L-dopa + DDC inhibitor
        - Rapid, marked improvement
        - Especially bradykinesia and rigidity; tremor less well controlled
        - Use lowest effective dose and titrate up gradually
    - After several years of L-dopa therapy, side-effects usually supervene
        - Dopaminergic side-effects

[6] L-dopa is largely ineffective here: it would have to act at receptors which are already blocked. But don't give antimuscarinics in tardive dyskinesia (see antipsychotics) – they make it worse!

    - Peak-dose dyskinesia
    - End of dose akinesia with drug-resistant off periods
    - Random 'on-off' phenomena whose timing is unrelated to the dose schedule[7]
- Possible approaches
    - Modified release L-dopa
    - Frequent L-dopa doses
    - Add in selegiline (helps with end of dose deterioration)
    - Add in dopamine agonists
    - **Not** drug holidays – risk of NMS
- NICE guidelines
    - Options in early disease: L-dopa, dopamine agonists, MAO-B inhibitors
    - Options in later disease: dopamine agonists, MAO-B inhibitors, COMT inhibitors

3. Non-pharmacological measures
    - Considered in patients who (NICE guidelines)
        - Have motor complications that are refractory to best medical treatment
        - Are biologically fit with no clinically significant active co-morbidity
        - Are levodopa responsive
        - Have no clinically significant active mental health problems, for example, depression or dementia
    - Stereotactic neurosurgery
        - In PD, neuronal activity is abnormally increased in the subthalamic nucleus and the globus pallidus pars interna
        - Deep brain stimulation (DBS) involves the implantation of electrodes into one or other of these areas bilaterally, connected to an implantable pulse generator. High frequency stimulation of the above areas induces a functional lesion. This is preferable to ablative surgery since
            - It is in principle reversible
            - It can be performed bilaterally with relative safety
            - Stimulation parameters can be adjusted and optimised after implantation
        - Benefits
            - On average 60% of dopaminergic drug doses can be replaced with DBS
            - 10% of subjects no longer require any L-dopa
            - Off-periods and dyskinesias are reduced by 60-70%
        - Drawbacks
            - Invasive
            - Potential psychiatric sequelae
    - Future perspectives
        - Intraputaminal implantation of retinal pigment epithelium (RPE) cells, which produce L-dopa and can be isolated from human eyes post mortem
        - Intrastriatal infusion of a viral vector containing the gene for human L-amino acid decarboxylase

[7] One possible mechanism is receptor downregulation