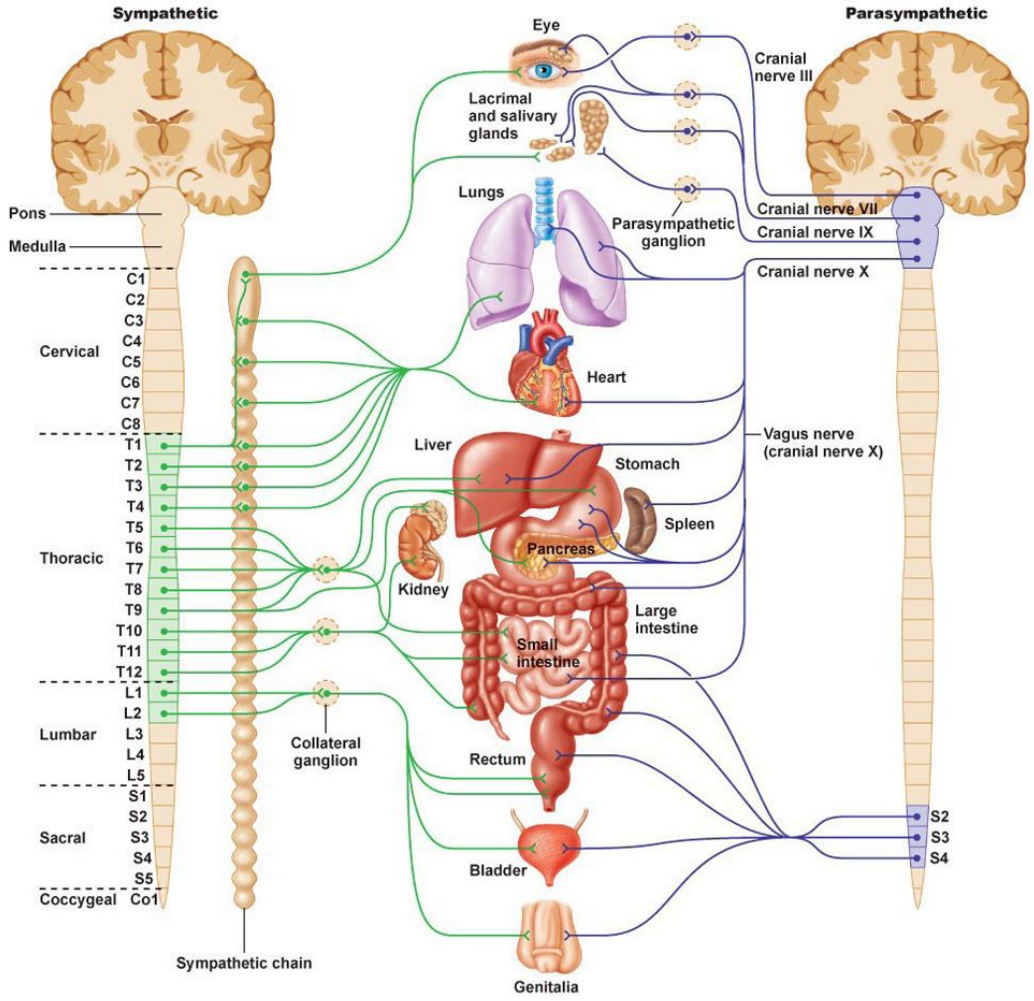
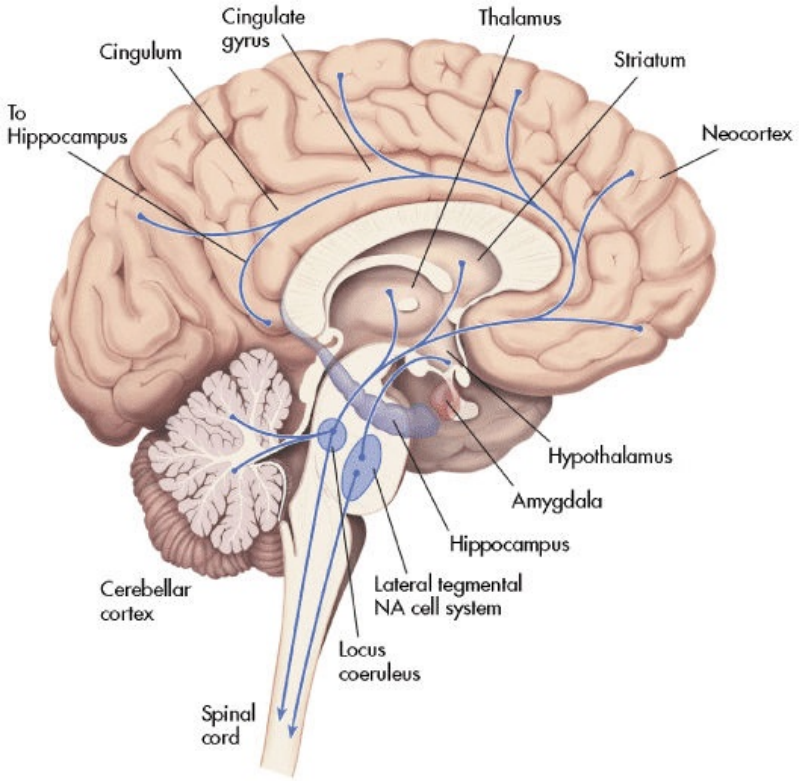
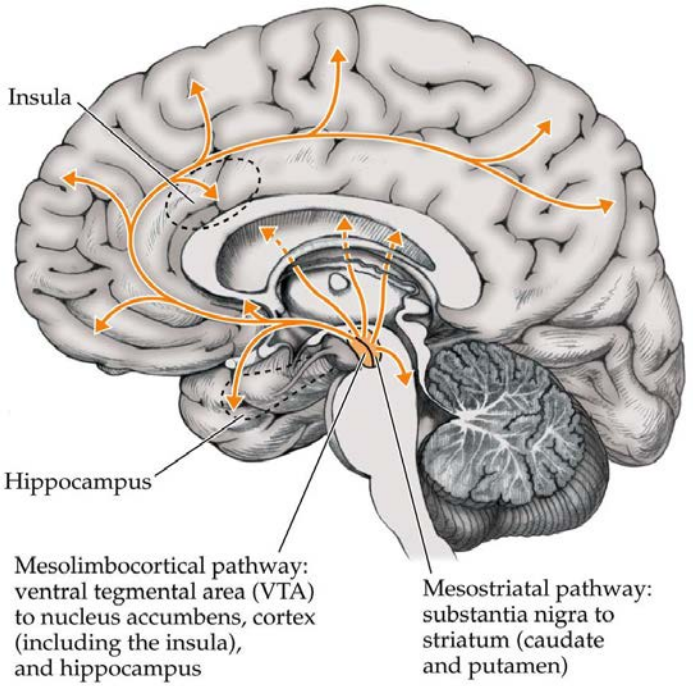
CATECHOLAMINEGIC TRANSMISSION

AUTONOMIC NERVOUS SYSTEM

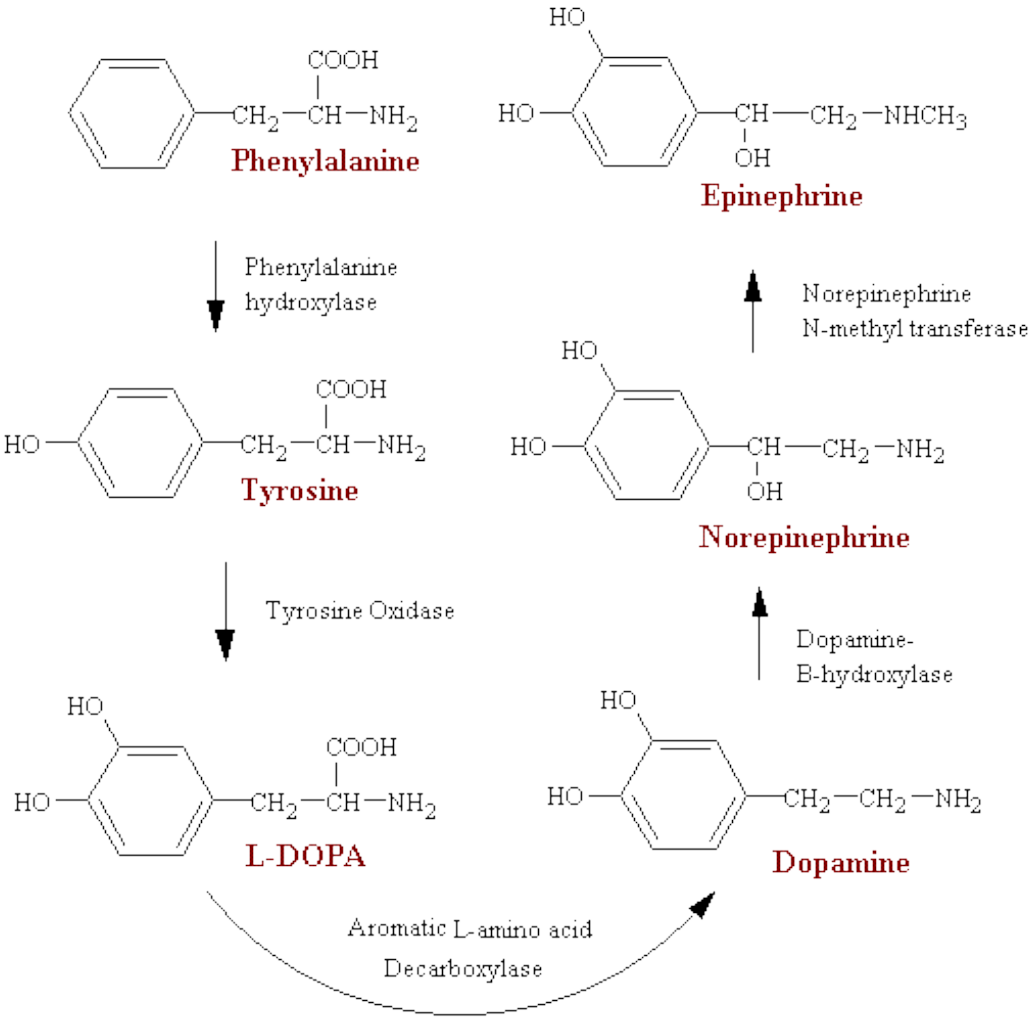


CATECHOLAMINERGIC PATHWAYS

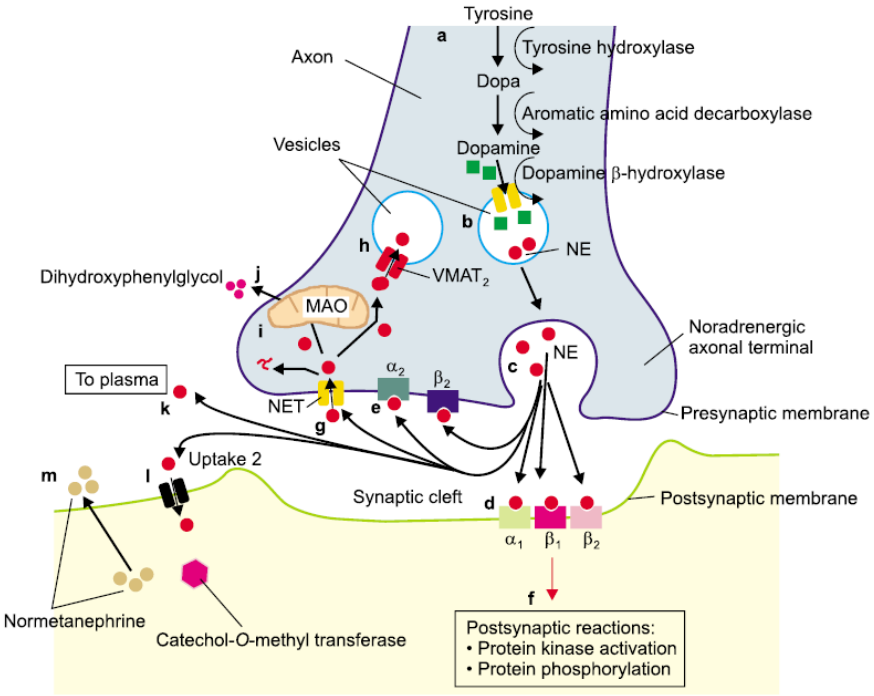




CATECHOLAMINE BIOSYNTHESIS PATHWAY

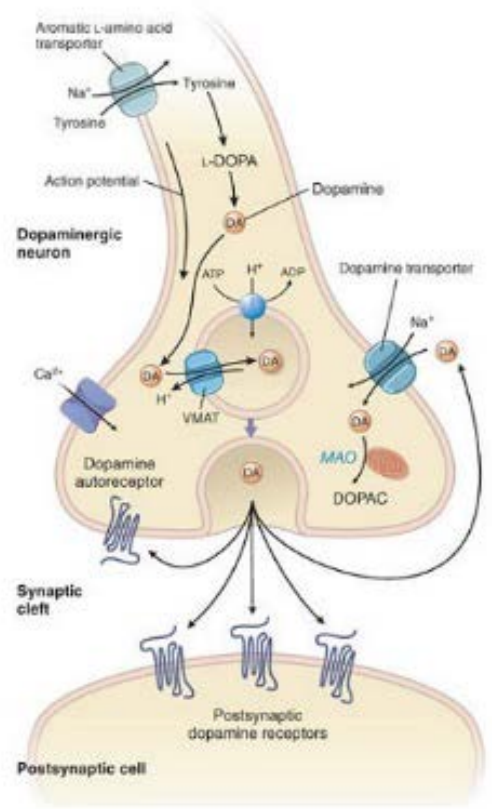


NOREPINEPHRINE STORAGE-RELEASE-REUPTAKE-INACTIVATION



- Diagram of a noradrenergic axonal terminal showing the release and reuptake of norepinephrine (NE). **a**. NE is synthesized from tyrosine via hydroxylation to form dihydroxyphenylalanine (Dopa), decarboxylation to form dopamine, and hydroxylation to form NE, and **b** stored in vesicles. **c**. As a result of an appropriate stimulus (not shown), NE is released into the synaptic cleft. **d**. Released NE activates the adrenergic receptors located on the postsynaptic membrane (α_1, β_1 and β_2) and also the **e** presynaptic membrane (α_2 and β_2) and causes **f** postsynaptic reactions such as protein kinase activation and protein phosphorylation. **g**. The NET is responsible for reuptake of NE in the synaptic cleft and terminates its action. **h**. After reuptake by the NET, a small portion of the NE is restored in vesicles (following uptake by the vesicular amine transporter$_2$, VMAT$_2$); **i** the rest is metabolized in the mitochondria by the enzyme monoamine oxidase (MAO), and **j** the end product dihydroxyphenylglycol (DHPG) is released into the circulation. **k**. A small portion of the synaptic NE leaks into the circulation, or **l** is taken up by another system (uptake$_2$) and **m** metabolized to form normetanephrine (NMN)

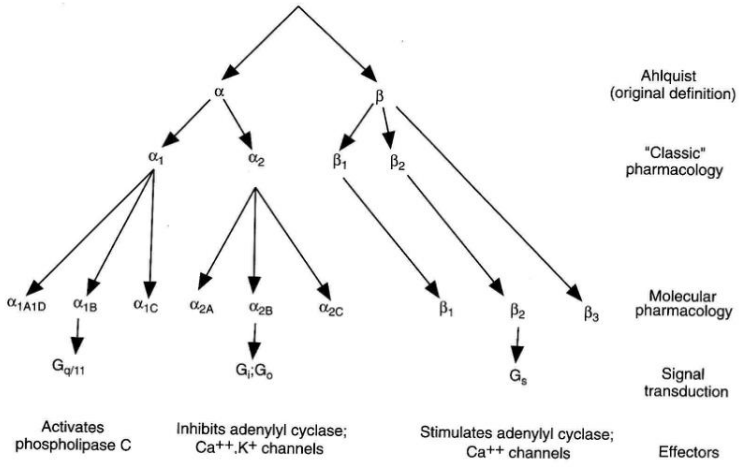
DOPAMINE STORAGE-RELEASE-REUPTAKE-INACTIVATION

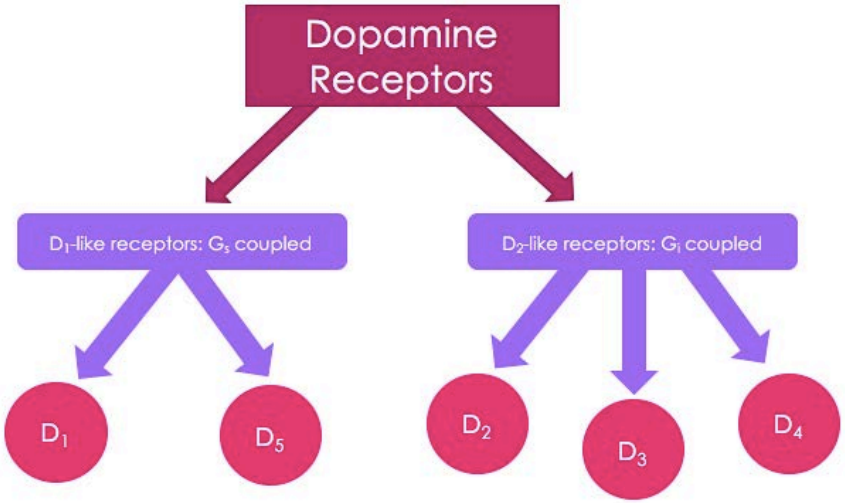


- Dopamine (DA) is synthesized from tyrosine in the cytoplasm of the neuron and then transported into secretory vesicles for storage and release. Two separate molecular pumps are required for the transport of DA into synaptic vesicles. A proton ATPase concentrates protons in the vesicle, creating an electrochemical gradient characterized by a low intravesicular pH (i.e., a high proton concentration) and an electropositive vesicle interior. This gradient is exploited by a proton antiporter, the vesicular monoamine transporter (VMAT), which allows protons to move down the gradient (out of the vesicle) while simultaneously transporting DA into the vesicle against its concentration gradient. Upon nerve cell stimulation, the DA storage vesicles fuse with the plasma membrane in a Ca^{2+}-dependent manner, releasing DA into the synaptic cleft. In the cleft, DA can bind to both postsynaptic DA receptors and presynaptic DA autoreceptors

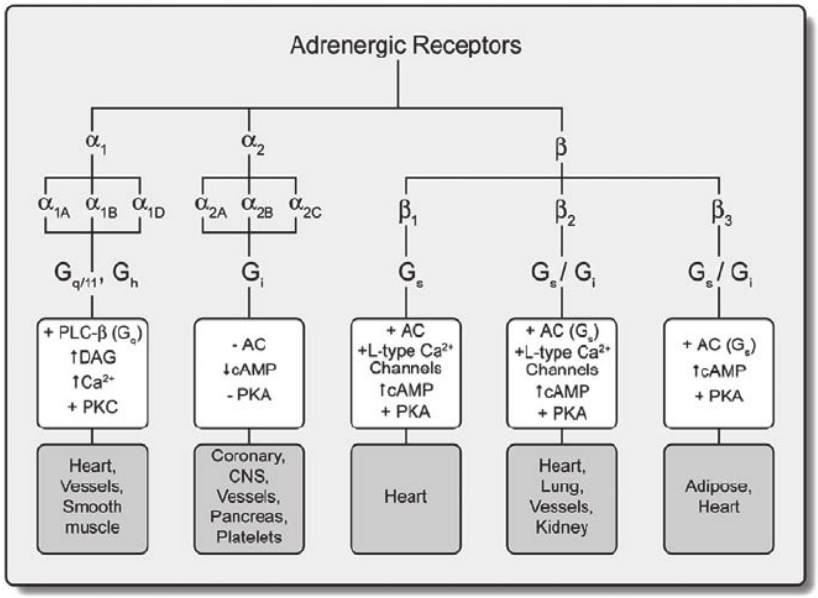
CATECHOLAMINE RECEPTORS

Adrenoreceptors





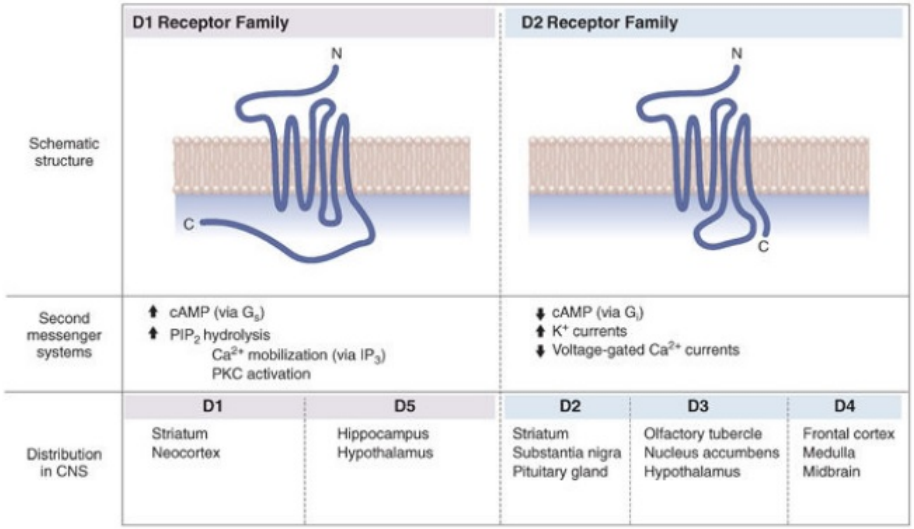
ADRENERGIC RECEPTORS



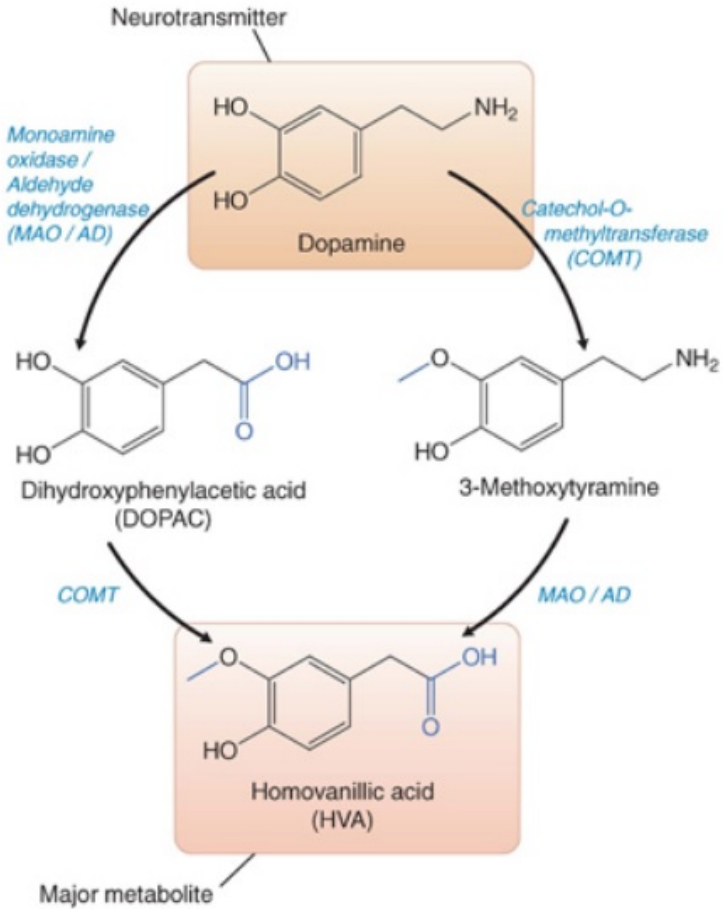
Receptor	Subtype	Function in cognition	Localization of function
α_1	α_{1A}	Improve spatial learning (Doze et al., 2011)	Hippocampus
	α_{1B}	Improve fear learning (Nalepa et al., 2013)	Amygdala
	α_{1D}	Improve working memory and attention (Mishima et al., 2004)	Prefrontal cortex
α_2	α_{2A}	Impair spatial and fear learning (Gamache et al., 2012; Warner and Drugan, 2012; Zoladz et al., 2013; Torkaman-Boutorabi et al., 2014)	Hippocampus
		Improve working memory (Arnsten and Goldman-Rakic, 1985, 1987; Arnsten et al., 1988)	Prefrontal cortex
	α_{2B}	Unknown	–
	α_{2C}	Unknown	–
β	β_1	Improve auditory fear memory (Qu et al., 2008)	Administration into amygdala
		Impair spatial reference memory	Hippocampus
	β_2	Improve memory retrieval (Introini-Collison et al., 1991)	Administration into amygdala
		Improves fear memory (Zhou et al., 2013)	Administration into prefrontal cortex
		Improve auditory fear memory (Qu et al., 2008)	Administration into amygdala
	β_3	unknown	–

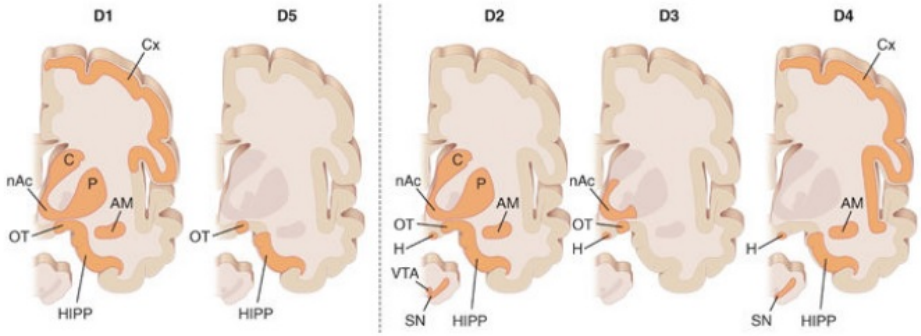
DOPAMINERGIC RECEPTORS

Dopamine receptors				
D1-like - Gαs coupled		**D2-like** - Gαi/o coupled		
D1	**D5**	**D2**	**D3**	**D4**
Substantia nigra Nucleus accumbens Olfactory bulb Lower levels: Cerebellum Hippocampus Thalamus Kidney	Substantia nigra Hypothalamus Kidney Heart Sympathetic ganglia	Substantia nigra Nucleus accumbens Ventral tegemental area Lower levels: Heart Blood vessels Adrenal glands Sympathetic ganglia	Olfactory bulb Nucleus accumbens	Heart Blood vessels Substantia nigra Hippocampus Amygdala Gastrointestinal tract



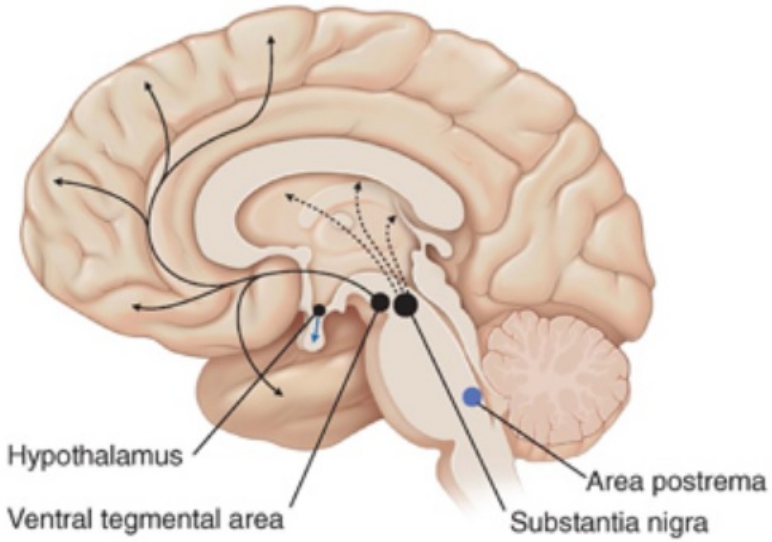
DOPAMINERGIC TRASMISSION

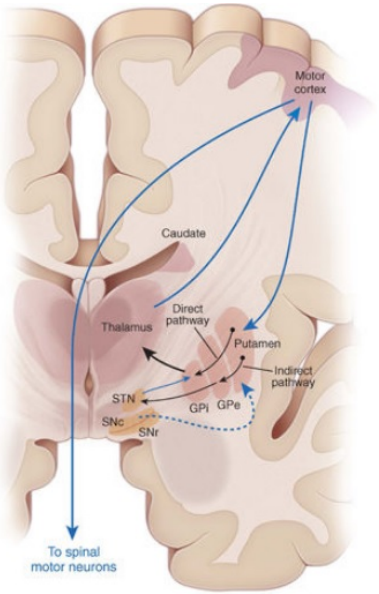


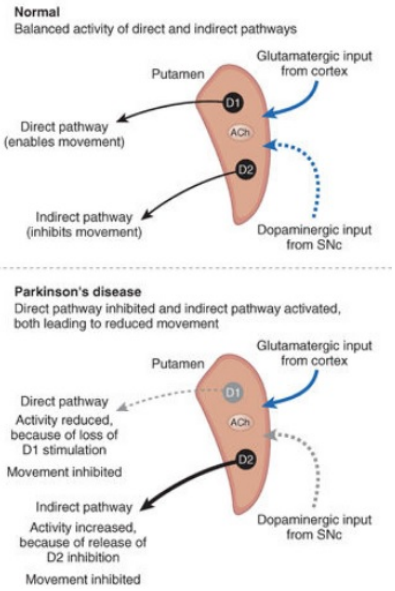


AM: Amygdala;
C: Caudate;
Cx: Cerebral cortex;
H: Hypothalamus;
Hipp: Hippocampus;
nAc: Nucleus accumbens;
OT: Olfactory Tubecles;
P: Putamen;
SN: Substantia Nigra;
VTA: Ventral Tegmental Area

DOPAMINERGIC TRASMISSION







DOPAMINERGIC TRASMISSION

- Dopaminergic transmission
  - Dopamine is a neurotransmitter as well as being the precursor for noradrenaline. It is degraded in a similar fashion to noradrenaline, giving rise mainly to dihydroxyphenylacetic acid and homovanillic acid, which are excreted in the urine
  - There are four main dopaminergic pathways
    - Nigrostriatal pathway, important in motor control
    - Mesolimbic pathway, running from groups of cells in the midbrain to parts of the limbic system, especially the nucleus accumbens, involved in emotion and drug-induced reward
    - Mesocortical pathway, running from the midbrain to the cortex, involved in emotion
    - Tuberohypophyseal neurons, running from the hypothalamus to the pituitary gland, whose secretions they regulate
  - There are five dopamine receptor subtypes an all belong to the family of G protein-coupled transmembrane receptors. D_1 and D_5 receptors link through G_s to stimulate adenylyl cyclase and activation of protein kinase A (PKA). PKA mediates many of the effects of D_1 and D_5 receptors by phosphorylating a wide array of proteins, including voltage-activated sodium, potassium and calcium channels as well as ionotropic glutamate and GABA receptors. D_2, D_3, and D_4 receptors link through G_i/G_o and activate potassium channels as well as inhibiting calcium channels and adenylyl cyclase
  - Parkinson’s disease is associated with a deficiency of nigrostriatal dopaminergic neurons.
  - Hormone release from the anterior pituitary gland is regulated by dopamine, especially prolactin release (inhibited) and growth hormone release (stimulated).
  - Dopamine acts on the chemoreceptor trigger zone to cause nausea and vomiting

NEURODEGENERATIVE DISEASES

NEURODEGENERATIVE DISEASES

- Neurodegenerative diseases
  - Alzheimer's disease (AD) and other dementias
  - Parkinson's disease (PD) and PD-related disorders
  - Prion disease
  - Motor neurone diseases (MND)
    - Amyotrophic lateral sclerosis (ALS)
  - Huntington's disease (HD)
  - Spinocerebellar ataxia (SCA)
  - Spinal muscular atrophy (SMA)

NEURODEGENERATIVE DISEASES

- Neurodegenerative diseases represent a large group of neurological disorders with heterogeneous clinical and pathological expressions affecting specific subsets of neurons in specific functional anatomic systems; they arise for unknown reasons and progress in a relentless manner

NEURODEGENERATIVE DISEASES

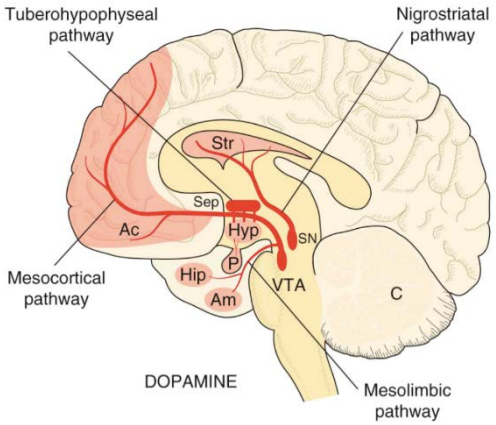
- Neurodegenerative diseases
  - Protein misfolding
  - Excitoxicity
  - Oxidative stress
    - Necrosis
    - Apoptosis

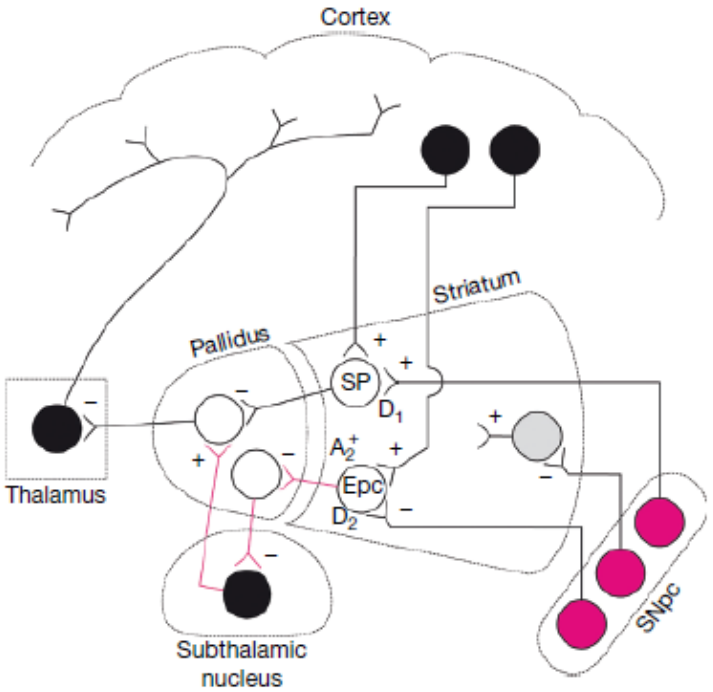
NEURODEGENERATIVE DISEASES

- Parkinson’s disease
  - Worldwide incidence estimates of Parkinson disease range from 5 to >35 new cases per 100,000 individuals yearly
  - Parkinson disease is rare before 50 years of age, but the incidence increases 5–10-fold from the sixth to the ninth decade of life. The global prevalence, conservatively estimated at 0.3% overall, likewise increases sharply with age to >3% in those >80 years of age
  - Mortality is not increased in the first decade after disease onset, but increases thereafter, eventually doubling compared with the general population
  - Parkinson disease is twice as common in men than in women in most populations

NEURODEGENERATIVE DISEASES

- Parkinson's disease
  - The chief symptoms are:
    - Suppression of voluntary movements (bradykinesia)
    - Tremor at rest
    - Muscle rigidity
    - A variable degree of cognitive impairment





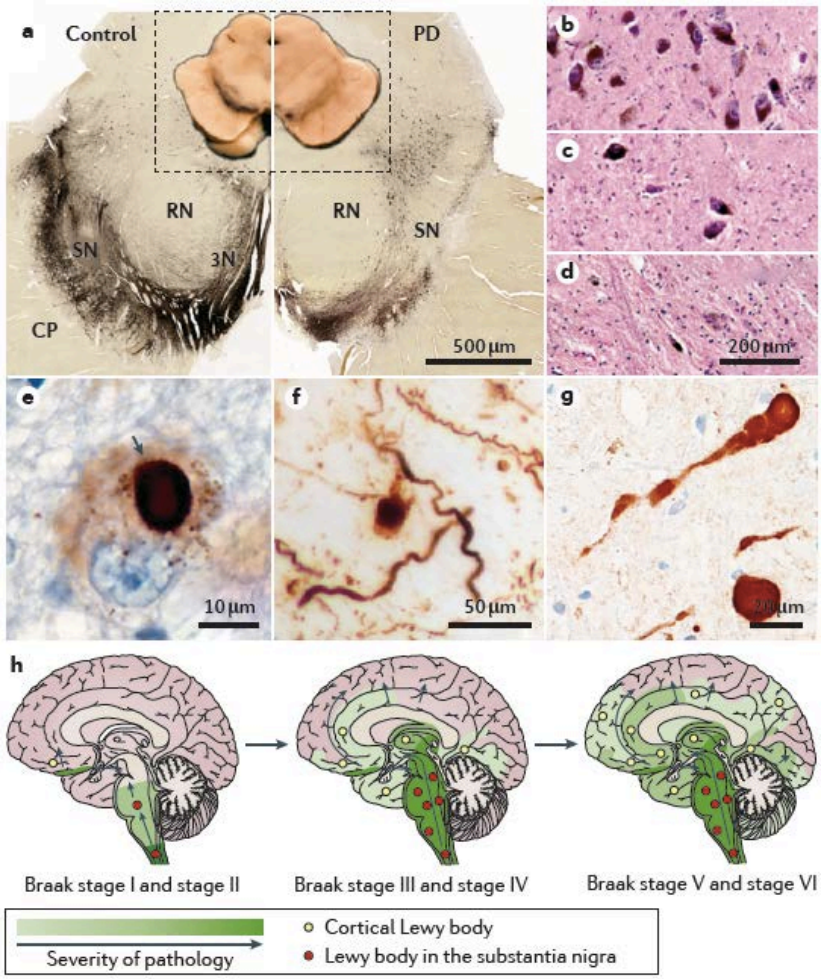
NEURODEGENERATIVE DISEASES

- Parkinson’s disease
  - Loss of dopaminergic neurons
    - Parkinson’s disease affects the basal ganglia associated with a loss of dopaminergic neurons in the substantia nigra and degeneration of nerve terminals in the striatum
    - Cholinergic interneurons of the corpus striatum are also involved in PD. Acetylcholine release from the striatum is strongly inhibited by dopamine, and it is suggested that hyperactivity of these cholinergic neurons contributes to the symptoms of PD
    - Parkinson’s disease is a disorder of motor control associated with deficiency of dopamine in the nigrostriatal pathway

NEURODEGENERATIVE DISEASES

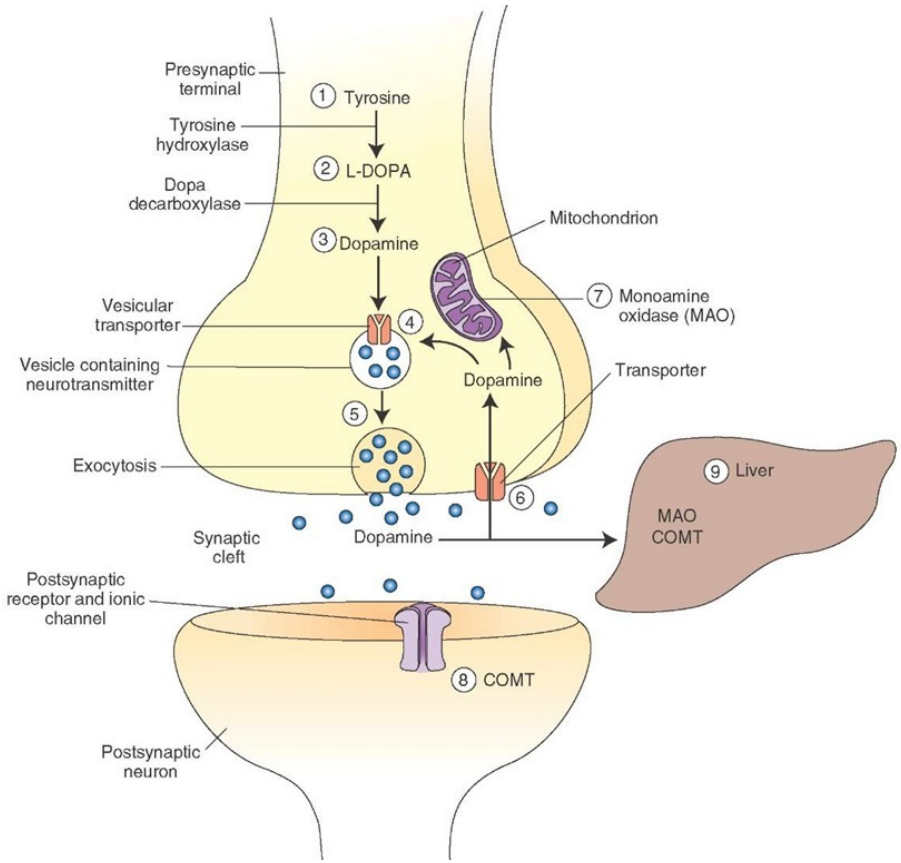
- Parkinson's disease
  - Pathogenesis of Parkinson's disease
    - As with other neurodegenerative disorders, the neuronal damage in PD is caused by protein misfolding and aggregation, aided and abetted by
      - Excitotoxicity
      - Mitochondrial dysfunction
      - Oxidative stress
      - Inflammation
      - Apoptosis
    - Parkinson's disease is associated with the development of intracellular protein aggregates known as Lewy bodies in various parts of the brain. They consist largely of α-synuclein, a synaptic protein, present in large amounts in normal brains
      - It is believed that misfolding and aggregation renders the protein resistant to degradation within cells, causing it to pile up in Lewy bodies
      - It is possible that the normal function of α-synuclein is related to synaptic vesicle recycling, and that the misfolded form loses this functionality, with the result that vesicular storage of dopamine is impaired. This may lead to an increase in cytosolic dopamine, degradation of which produces reactive oxygen species and hence neurotoxicity
    - Neurotoxins
      - It is possible that dopamine itself could be the culprit, because oxidation of dopamine gives rise to potentially toxic metabolites

NEURODEGENERATIVE DISEASES



NEURODEGENERATIVE DISEASES

- Dopaminergic transmission
  - The steps involved in the synthesis, removal, and metabolism of dopamine

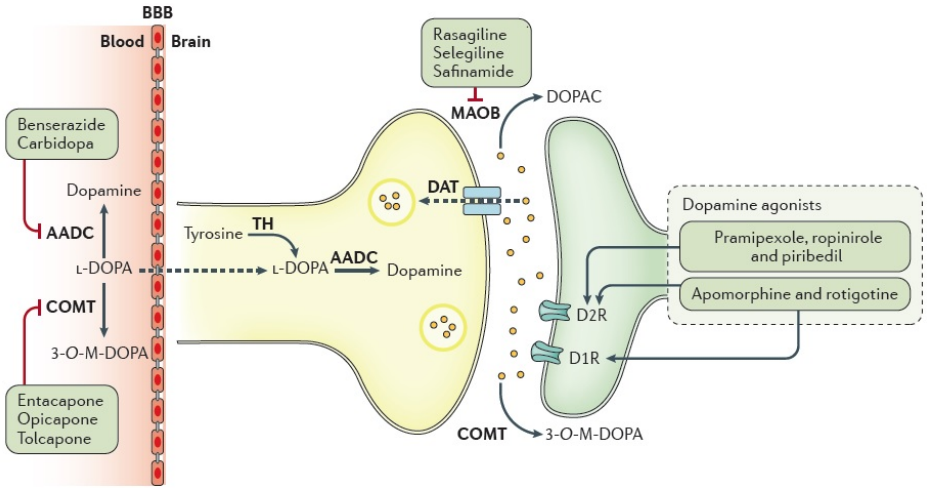


NEURODEGENERATIVE DISEASES

- Dopaminergic transmission
  - Effects of drugs on dopaminergic transmission
    - Many drugs affect dopamine transmission directly by either blocking or stimulating its receptors
    - Several drugs of clinical importance act indirectly increasing the synaptic concentration of dopamine by blocking its uptake or metabolism

NEURODEGENERATIVE DISEASES

- Parkinson's disease
  - Drug Treatment of Parkinson's disease
    - None of the drugs used to treat PD affects the progression of the disease
      - Levodopa (often in combination with carbidopa and entacapone)
      - Dopamine agonists (e.g. pramipexole, ropinirole, bromocriptine)
      - Monoamine oxidase-B (MAO-B) inhibitors (e.g. selegiline, rasagiline)
      - Muscarinic ACh receptor antagonists (e.g. orphenadrine, procyclidine and trihexyphenidyl)

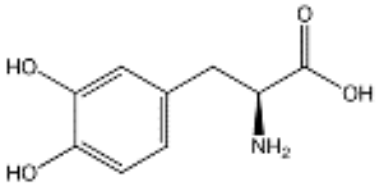


AADC: aromatic amino acid decarboxylase
COMT: catechol-O-methyltransferarse
MAOB: monoamine oxidase type B
BBB: blood-brain barrier
DAT: dopamine transporter
DOPAC: 3,4-dioxy-phenyacetic acid
3-O-M-DOPA: 3-O-methyl-DOPA
TH: tyrosine hydroxylase

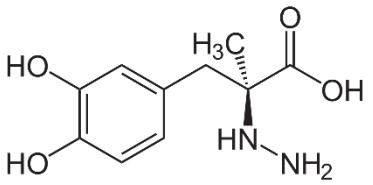
DRUG TREATMENT OF PARKINSON'S DISEASE

[Carbidopa and Levodopa for Parkinson's Disease - YouTube]

Levodopa



Carbidopa



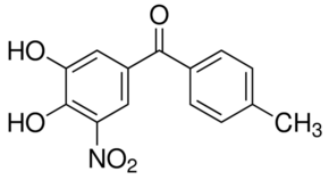
NEURODEGENERATIVE DISEASES

- Parkinson’s disease
  - Drug Treatment of Parkinson’s disease
    - Levodopa
      - Levodopa is the first-line treatment for PD 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
      - Conversion to dopamine in the periphery, which would otherwise account for about 95% of the levodopa dose and cause troublesome side effects, is largely prevented by the decarboxylase inhibitor
      - Decarboxylation occurs rapidly within the brain, because the decarboxylase inhibitors (e.g. carbidopa) do not penetrate the blood–brain barrier
      - The therapeutic effectiveness of levodopa decreases as the disease advances
      - Combination of levodopa plus a dopa decarboxylase inhibitor with a catechol-O-methyl transferase (COMT) inhibitor (e.g. entacapone or tolcapone) to inhibit its degradation, is used in patients troubled by ‘end of dose’ motor fluctuations

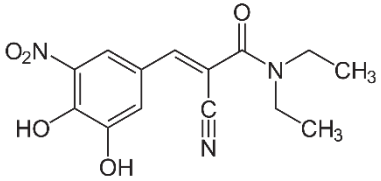
DRUG TREATMENT OF PARKINSON'S DISEASE

[COMT Inhibitors for Parkinson's Disease - YouTube]

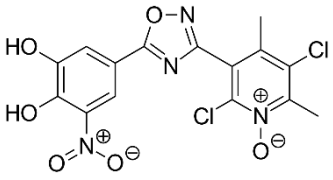
Tolcapone



Entacapone



Opicapone



NEURODEGENERATIVE DISEASES

- Parkinson’s disease
  - Drug Treatment of Parkinson’s disease
    - Levodopa
      - Pharmacokinetic
        - It is well absorbed from the small intestine, a process that relies on active transport, although much of it is inactivated by MAO in the wall of the intestine.
        - The plasma half-life is short (about 2 h)
        - Oral and subcutaneous slow release preparations have been developed
        - Conversion to dopamine in the periphery, which would otherwise account for about 95% of the levodopa dose and cause troublesome side effects, is largely prevented by the decarboxylase inhibitor
      - Therapeutic effectiveness
        - About 80% of patients show initial improvement with levodopa, particularly of rigidity and bradykinesia, and about 20% are restored virtually to normal motor function. As time progresses, the effectiveness of levodopa gradually declines
        - Overall, levodopa increases the life expectancy of PD patients, probably as a result of improved motor function, although some symptoms (e.g. dysphagia, cognitive decline) are not improved

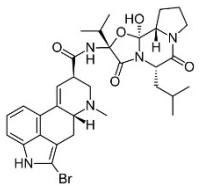
NEURODEGENERATIVE DISEASES

- Parkinson’s disease
  - Drug Treatment of Parkinson’s disease
    - Levodopa
      - Unwanted effects
        - Involuntary movements (dyskinesia), which do not appear initially but develop in the majority of patients within 2 years of starting levodopa therapy. These movements usually affect the face and limbs, and can become very severe
          - Levodopa is short acting, and the fluctuating plasma concentration of the drug may favour the development of dyskinesia
        - 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
          - On–off effect
            - As with the dyskinesia, the problem seems to reflect the fluctuating plasma concentration of levodopa, and it is suggested that as the disease advances, the ability of neurons to store dopamine is lost, so the therapeutic benefit of levodopa depends increasingly on the continuous formation of extraneuronal dopamine, which requires a continuous supply of levodopa
        - Nausea and anorexia
        - Hypotension
        - Psychological effects

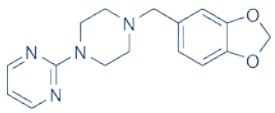
DRUG TREATMENT OF PARKINSON'S DISEASE

Dopamine Receptor Agonists for Parkinson's Disease

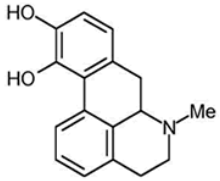
Bromocriptine



Piribedil



Apomorphine



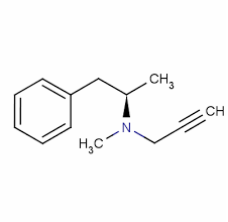
NEURODEGENERATIVE DISEASES

- Parkinson’s disease
  - Drug Treatment of Parkinson’s disease
    - Dopamine Agonists
      - Bromocriptine, pergolide and cabergoline exhibit slight selectivity for $D_{2/3}$ over D_1 receptors
        - Though effective in controlling the symptoms of PD, their usefulness is limited by side effects, such as nausea and vomiting, and somnolence and a risk of fibrotic reactions in the lungs, retroperitoneum and pericardium
        - These disadvantages have led to the replacement of these drugs by pramipexole and ropinirole and piribedil, which are $D_{2/3}$ selective and better tolerated, and do not show the fluctuations in efficacy associated with levodopa. They do, however, cause somnolence and sometimes hallucinations, and recent evidence suggests that they may predispose to compulsive behaviours, such as excessive gambling, over-eating and sexual excess, related to the ‘reward’ functions of dopamine
        - A disadvantage of current dopamine agonists is their short plasma half-life (6–8 h), requiring three-times daily dosage, though slow-release once-daily formulations are now available
          - Rotigotine
          - Apomorphine

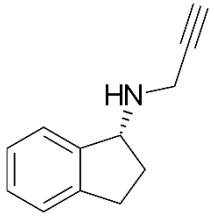
DRUG TREATMENT OF PARKINSON'S DISEASE

MAO Inhibitors for Parkinson's Disease - YouTube

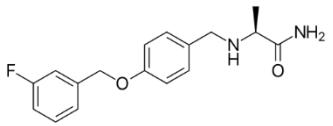
Selegeline



Rasageline



Safinamide



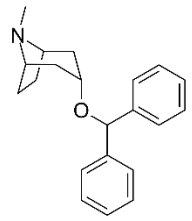
NEURODEGENERATIVE DISEASES

- Parkinson’s disease
  - Drug Treatment of Parkinson’s disease
    - MAO-B Inhibitors
      - Selegiline is a selective MAO-B inhibitor, which lacks the unwanted peripheral effects of non-selective MAO inhibitors
        - Inhibition of MAO-B protects dopamine from extraneuronal degradation and was initially used as an adjunct to levodopa. Long-term trials showed that the combination of selegiline and levodopa was more effective than levodopa alone in relieving symptoms and prolonging life
        - Selegiline is metabolised to amphetamine, and sometimes causes excitement, anxiety and insomnia
      - Rasagiline, a very similar drug, does not have this unwanted effect, and may somewhat retard disease progression, as well alleviating symptoms.
      - Safinamide, undergoing clinical trials, is a new drug that inhibits both MAO-B and dopamine reuptake

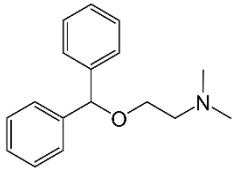
DRUG TREATMENT OF PARKINSON'S DISEASE

[Muscarinic Receptor Antagonists for Parkinson's Disease - YouTube]

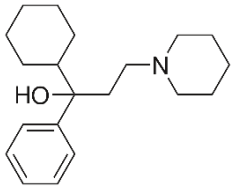
Benztropine



Diphenhydramine



Trihexyphenidyl



NEURODEGENERATIVE DISEASES

- Parkinson’s disease
  - Drug Treatment of Parkinson’s disease
    - Acetylcholine antagonists
      - For more than a century, until levodopa was discovered, atropine and related drugs were the main form of treatment for PD
      - The side effects of muscarinic antagonists – dry mouth, constipation, impaired vision, urinary retention – are troublesome, and they are now rarely used, except to treat parkinsonian symptoms in patients receiving antipsychotic drugs

NEURODEGENERATIVE DISEASES

- Parkinson's disease
  - Drug Treatment of Parkinson's disease
    - Other Drugs Used in Parkinson's disease
      - Amantadine
        - Many possible mechanisms for its action have been suggested based on neurochemical evidence of increased dopamine release, inhibition of amine uptake or a direct action on dopamine receptors. More recently block of N-Methyl-d-Aspartate glutamate receptors (NMDA) by stabilising closed states of the channel has been described and this may be a novel target for antiparkinsonian drugs
        - Amantadine is less effective than levodopa or bromocriptine in treating PD is but it is effective in reducing the dyskinesia induced by prolonged levodopa treatment

NEURODEGENERATIVE DISEASES

- Parkinson's disease
  - Drug Treatment of Parkinson's disease
    - New Pharmacological Approaches
      - Potential new treatments for PD include adenosine A_{2A} receptor antagonists (e.g. istradefylline and preladenant), 5-HT_{1A} antagonists (e.g. sarizotan) and glutamate receptor antagonists or negative allosteric modulators (acting at mGluR5, AMPA or NMDA receptors) as well as new, improved COMT inhibitors
    - New Therapeutic Approaches
      - Neural Transplantation
      - Gene Therapy
      - Brain Stimulation