PARKINSONS DISEASE

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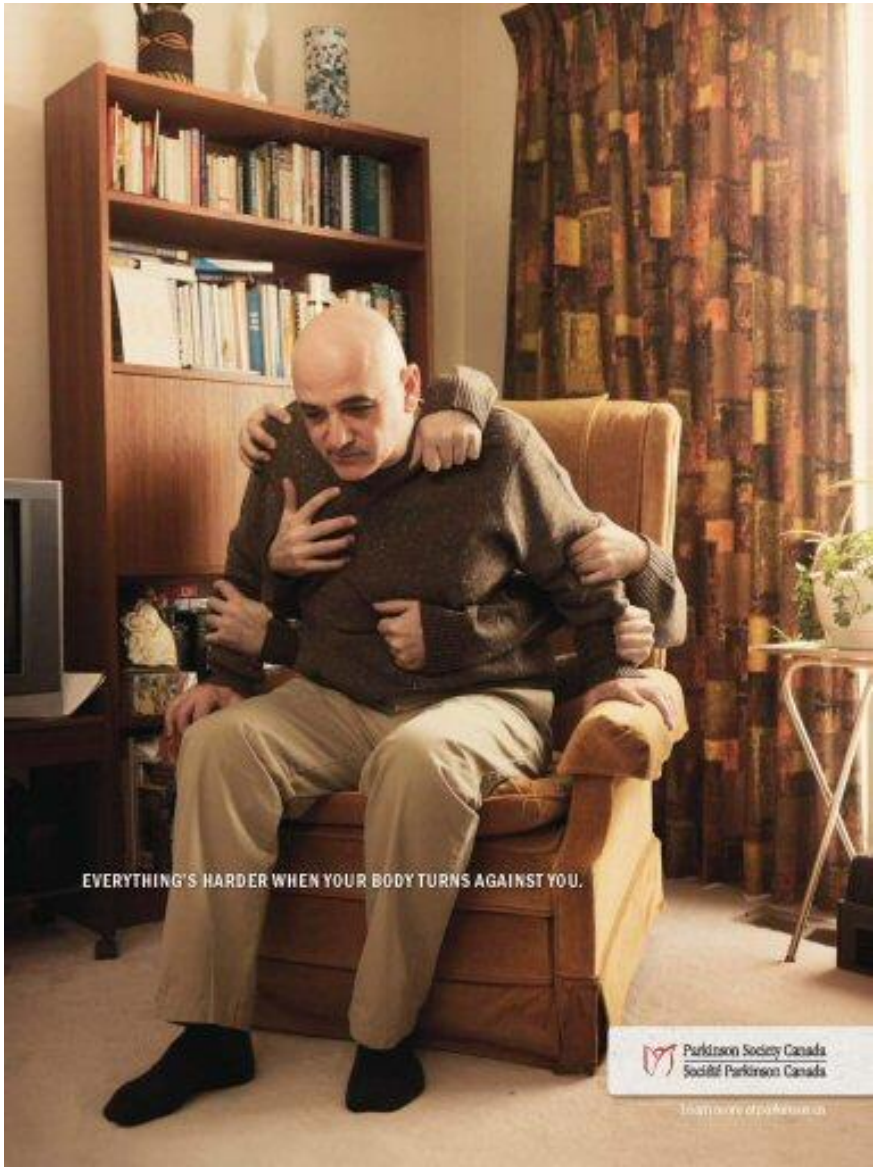
THOUGHT OF THE DAY

Seeking Answers

- How do we find the answers to the questions that arise in daily practice?
- In order to keep up to date, need to read 29 articles a day, 365 days a year (Didsbury, 2003)
- Or find someone who has found and summarized the relevant data for you

Parkinson's Disease



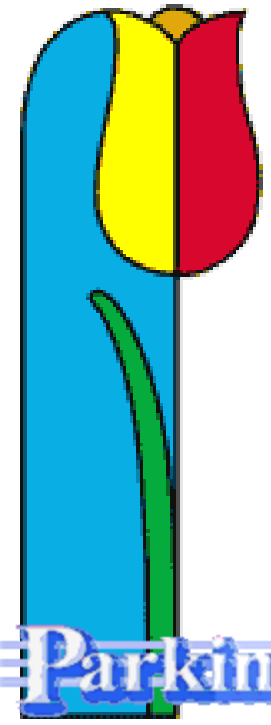
My Experience

Your Experience

Parkinson's Australia

What is Parkinson's Disease?

- A degenerative brain disorder affecting movement
- Symptoms caused by the deficiency of a chemical in the brain called Dopamine; **why** it happens, nobody knows
- Not fatal but progressive and incurable and, with time, severely affects quality of life
- Currently there is no one specific test to diagnose Parkinson's Disease – diagnosis is a combination of symptoms exhibited and eliminating other possible causes



Parkinson's Australia

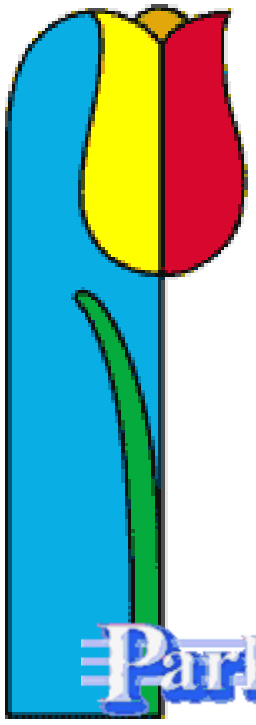
Symptoms of Parkinson's Disease

Tremor (shaking usually starts on one side of the body, often in the hand or finger)

Rigidity (stiffness where the limbs feel like lead)

Akinesia (difficulty in initiating movement and slowness of movement)

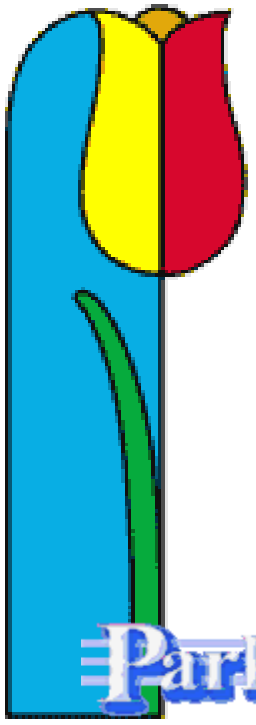
Problems with balance



Parkinson's Australia

Facts about Parkinson's Disease

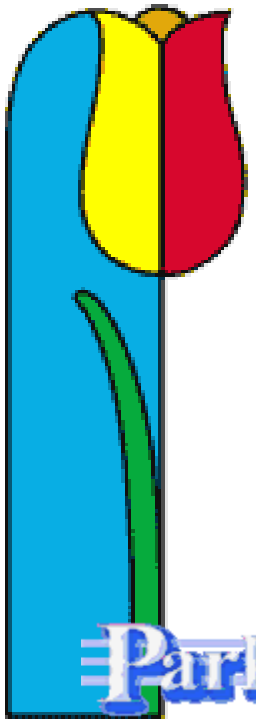
- Medicines effective for only a limited period. They then become less effective or cause disabling side-effects
- Stress intensifies symptoms and counteracts the benefit of medicines
- People also often suffer from depression, severe anxiety and emotional turmoil
- Even with severe symptoms, there is little impairment to the intellect
- Environmental and genetic factors may play a part in the development of Parkinson's Disease



Parkinson's Australia

Treatment of Parkinson's Disease

- **Medicines** - Can control symptoms effectively for 5 to10 years in most people before disabling side-effects appear and control then becomes less effective
- **Surgery** - Deep Brain Stimulation (DBS) is an alternative to earlier forms of surgery where lesions are cut in the area of the brain that controls fine movement of the limbs to stop shaking
- Even if surgery is successful, it only relieves symptoms for a period of time; it does not halt progression of the disease



Parkinson's Australia

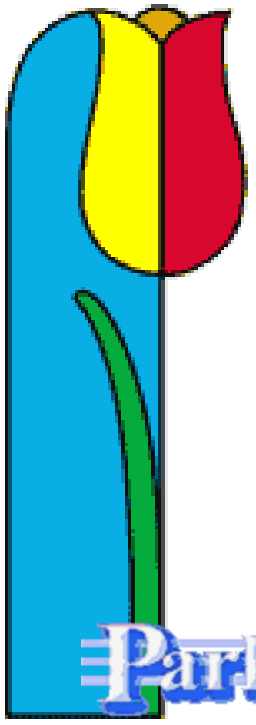
Towards

Understanding

Learning

Improving

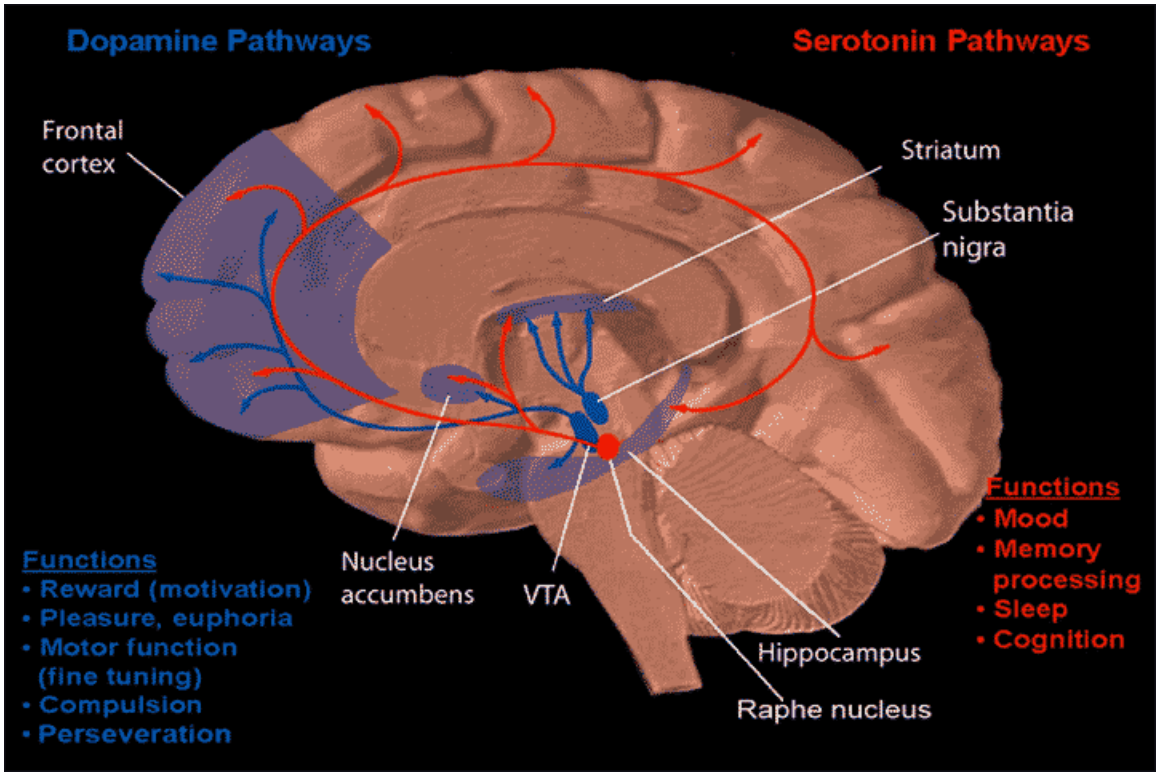
Parkinson's



Parkinson's Australia

Parkinson's Disease

- The basal ganglia, through the action of dopamine, are responsible for planning and controlling automatic movements of the body, such as pointing with a finger, pulling on a sock, writing or walking. If the basal ganglia are not working properly, as in Parkinson's disease patients, all aspects of movement are impaired, resulting in the characteristic features of the disease ≅ slowness of movement, stiffness and effort required to move a limb and, often, tremor.



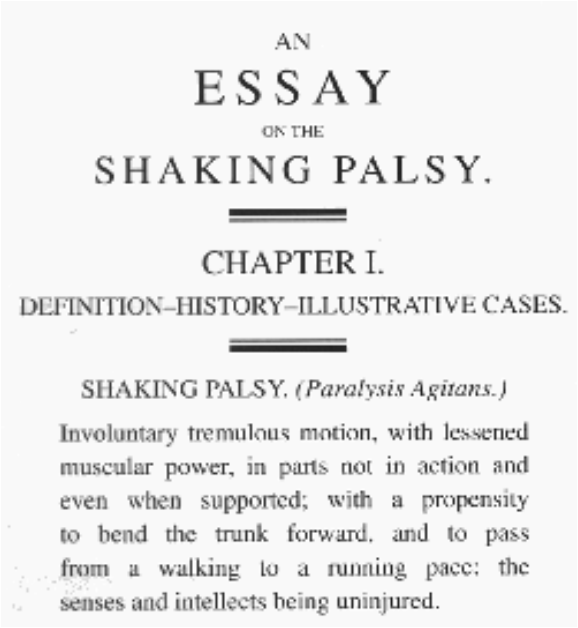
- Dopamine levels in the brain's substantia nigra do normally fall with ageing. However, they have to fall to one-fifth of normal values for the symptoms and signs of parkinsonism to emerge.

History

- James Parkinson (1755-1824), while best remembered for the disease state named after him by Charcot, was a man of many talents and interests.

- Publishing on chemistry, paleontology and other diverse topics, he was, early in his career, a social activist
- His efforts in this area were enough to result in his arrest and appearance before The Privy Council in London on at least one occasion.
- In collaboration with his son, who was a surgeon, he also offered the first description, in the English language, of a ruptured appendix.

History of Parkinson's Disease



AN

ESSAY

ON THE

SHAKING PALSY.

CHAPTER I.

DEFINITION–HISTORY–ILLUSTRATIVE CASES.

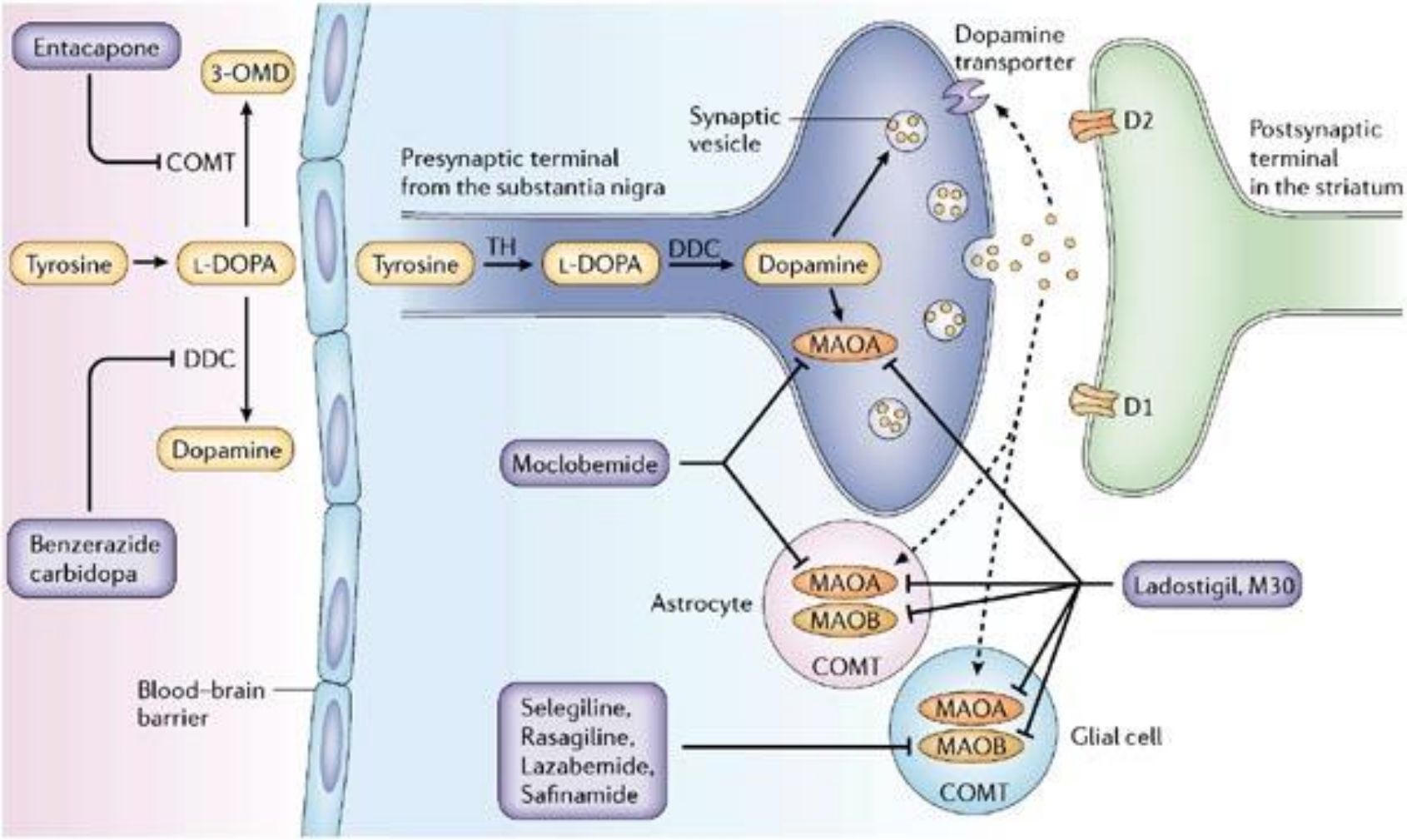
SHAKING PALSY. *(Paralysis Agitans.)*

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.

- His small but famous publication, "Essay on the Shaking Palsy", appeared in 1817, 7 years before his death in 1824.

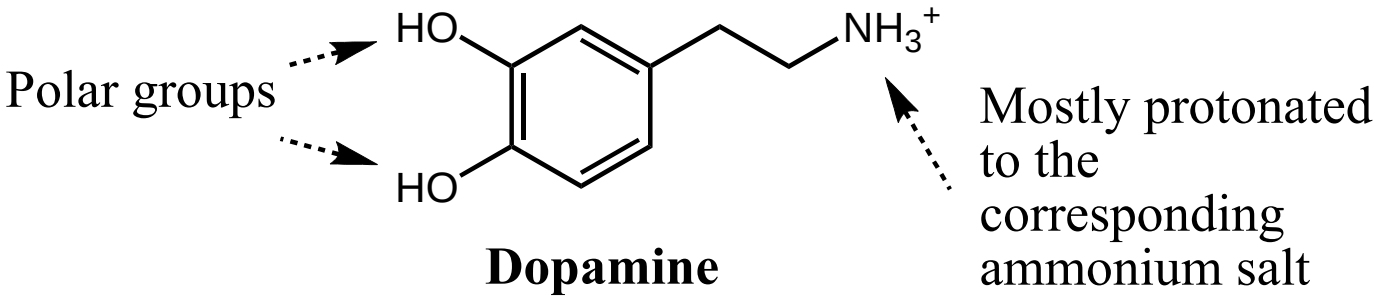
- The clinical description of 6 patients was a remarkable masterpiece testifying to his prodigious powers of observation for most of the 6 were never actually examined by Parkinson himself; rather, they were simply observed walking on the streets of London.

Summary of the Treatment of Parkinson's Disease



Treatment of Parkinson's Disease

- Since PD is related to a deficiency of dopamine, it would be appropriate to administer dopamine
- Problem: Dopamine does not cross BBB, since it is too polar



Dopamine

History of Treatment of PD

- Arvid Carlsson (b. January 25, 1923) a Swedish scientist who is best known for his work with the neurotransmitter dopamine and its effects in Parkinson's disease.

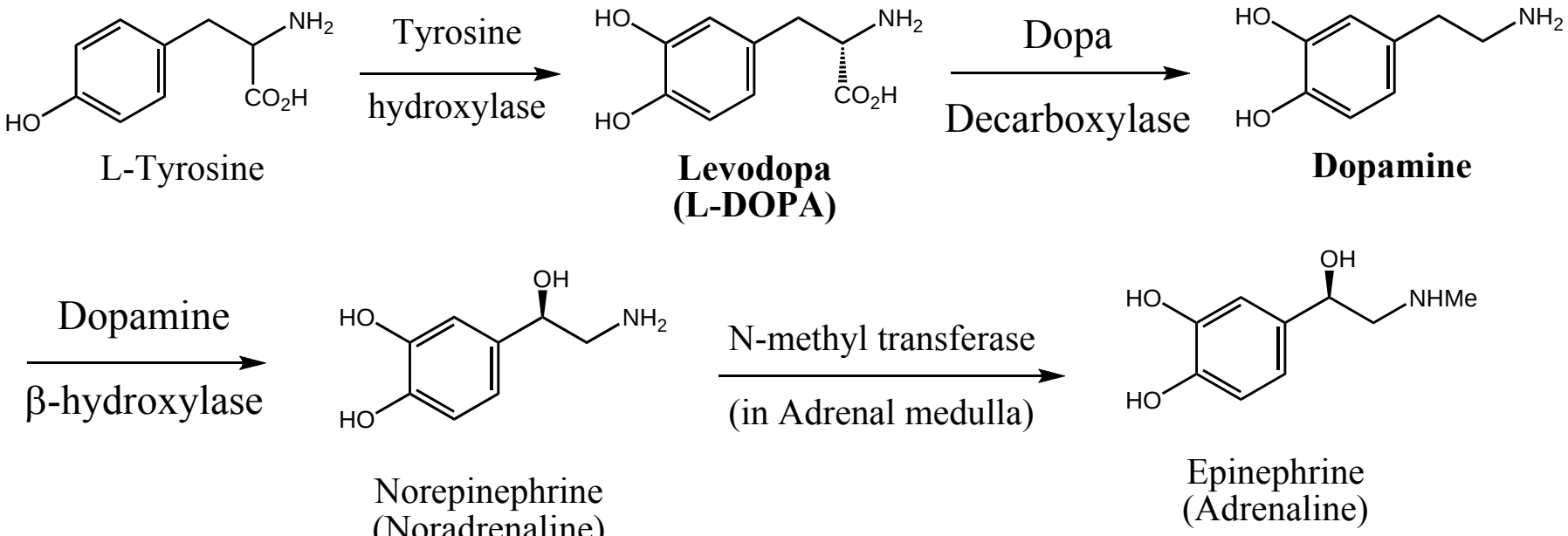
- Carlsson won the Nobel Prize in Physiology or Medicine in 2000 along with co-recipients Eric Kandel and Paul Greengard.

- In the 1950s, Carlsson demonstrated that dopamine was a neurotransmitter in the brain and not just a precursor for norepinephrine, as had been previously believed.
- He developed a method for measuring the amount of dopamine in brain tissues and found that dopamine levels in the basal ganglia, a brain area important for movement, were particularly high.

History of Treatment of PD

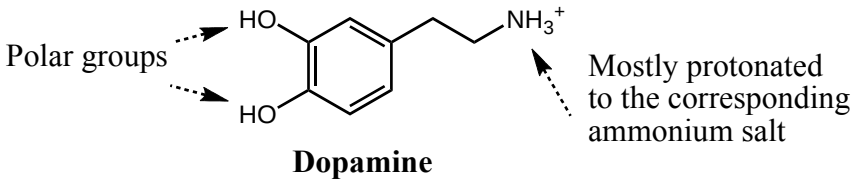
- Carlsson then showed that giving animals the drug reserpine caused a decrease in dopamine levels and a loss of movement control. These effects were similar to the symptoms of Parkinson's disease.
- By administering to these animals L-Dopa, a precursor to dopamine, he could alleviate the symptoms. These findings led other doctors try L-Dopa with human Parkinson's patients and found it to alleviate some of the symptoms in the early stages of Parkinson's. L-Dopa is still today the cornerstone of Parkinson therapy.

Biosynthesis of Epinephrine

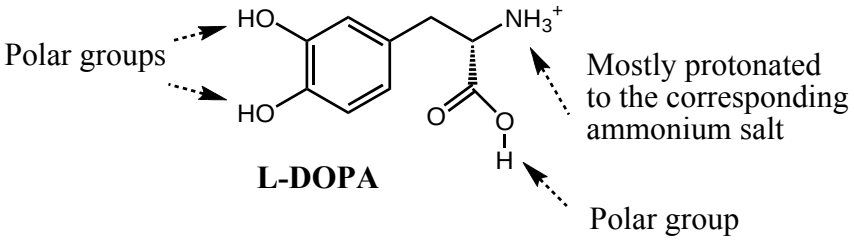


Wait a minute!

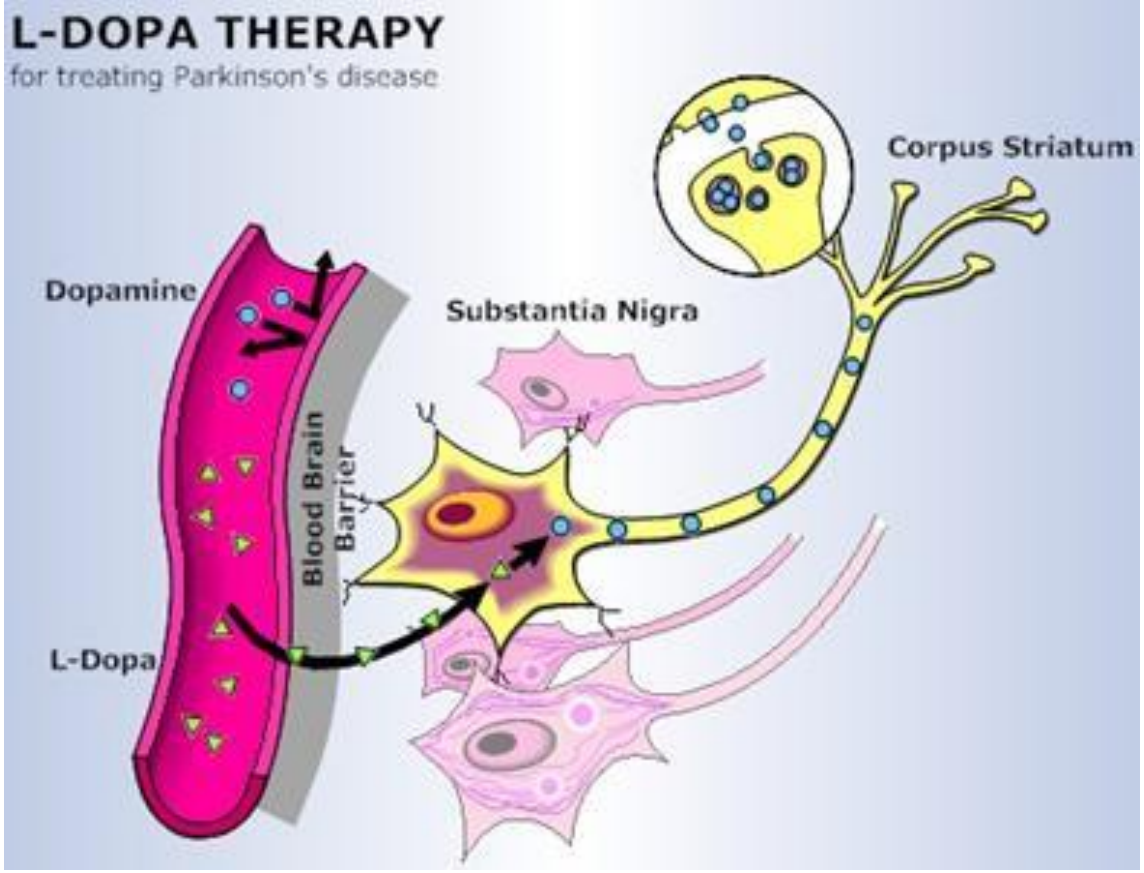
- If dopamine is too polar to cross the BBB, how can L-DOPA cross it?



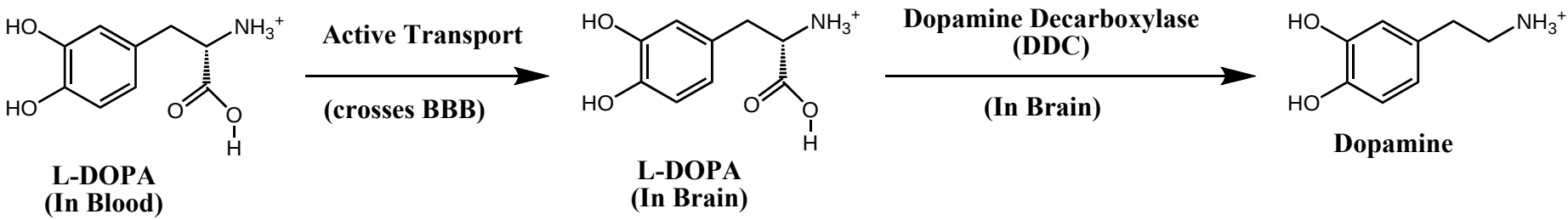
Dopamine



L-DOPA

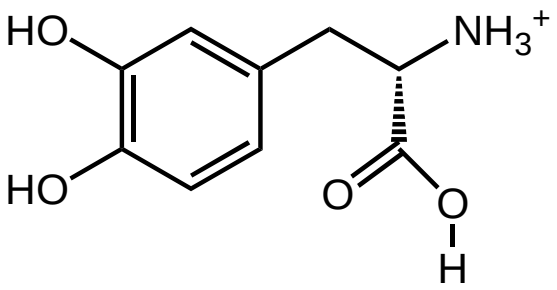


- L-DOPA is transported across the BBB by an amino acid transport system (same one used for tyrosine and phenylalanine)
- Once across, L-DOPA is decarboxylated to dopamine by Dopa Decarboxylase (DDC).

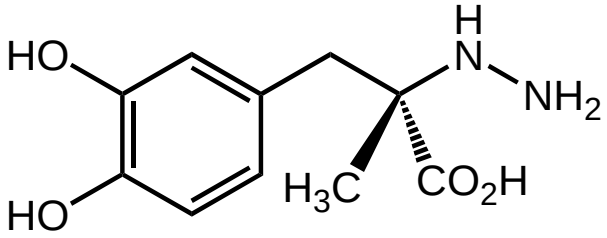


•This is an example of a “prodrug”, that is, a molecule that is a precursor to the drug and is converted to the actual drug at an appropriate place in the body.

- In actual practice, L-DOPA is almost always coadminstered together with an inhibitor of aromatic L-amino acid decarboxylase, so it doesn't get converted to dopamine before it crosses the BBB.
- The inhibitor commonly used is carbidopa, which does not cross the BBB itself.
- The inhibitor also prevents undesirable side effects of dopamine release into the PNS, including nausea.



L-DOPA



Carbidopa

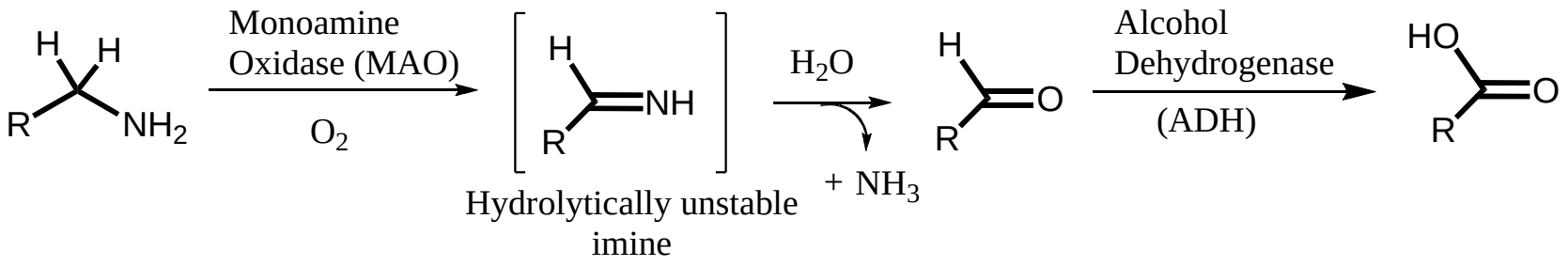
SINEMET

(CARBIDOPA-LEVODOPA)

DESCRIPTION

SINEMET* (Carbidopa-Levodopa) is a combination of carbidopa and levodopa for the treatment of Parkinson's disease and syndrome.

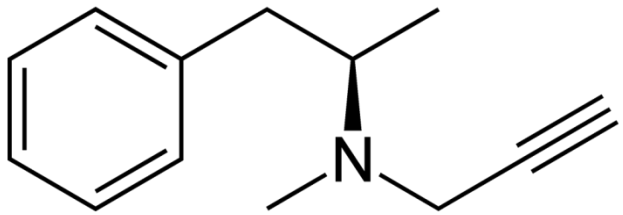
Treatment of Parkinson's Disease: Monoamine Oxidase Inhibitors (MAOI's)



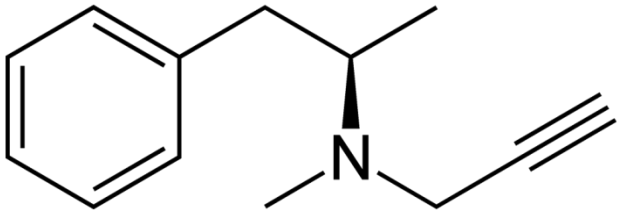
As shown above, monoamine oxidase is an enzyme that catalyzes the destruction of primary amines (such as dopamine,norepinephrine, seritonin) and secondary amines.

The type B isoform of MAO (MAO-B) is primarily responsible for metabolism of dopamine.

Inhibitor of MAO-B



- Selegiline (l-deprenyl, Eldepryl® or Anipryl® veterinary) is a drug used for the treatment of early-stage Parkinson's disease and senile dementia.
- In normal clinical doses it is a selective irreversible MAO-B inhibitor.
- Rasagiline is the new baby



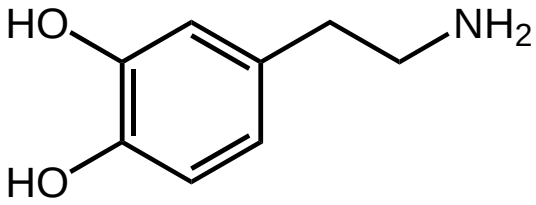
- In late stage Parkinson’s Disease, Selegiline is usually added to levodopa to prolong and enhance its effect

DOPAMINE AGONISTS

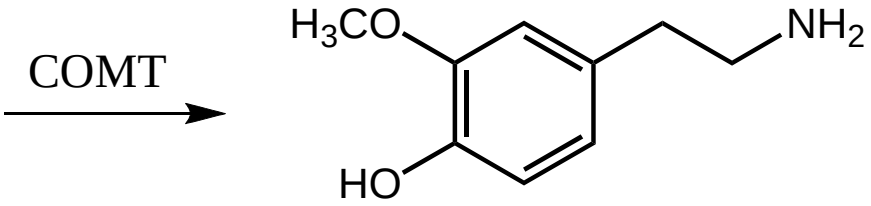
- 1.Pramipexole
- 2.Ropinirole

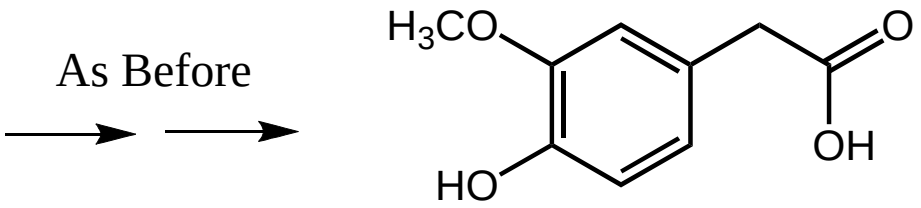
AMANTIDINE ?

Metabolism of Dopamine via Catachol-O-Methyl Transferase (COMT)

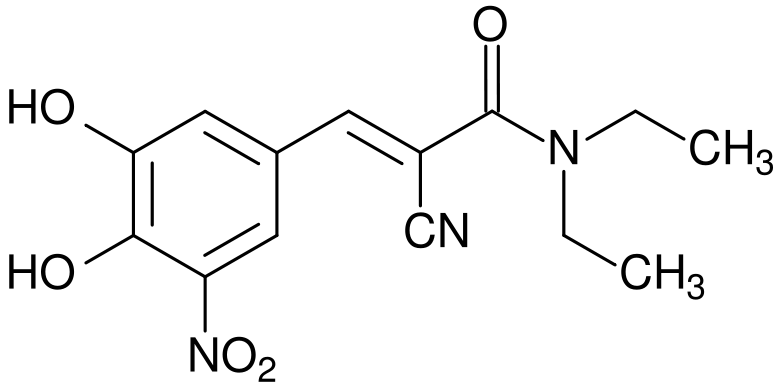


Dopamine

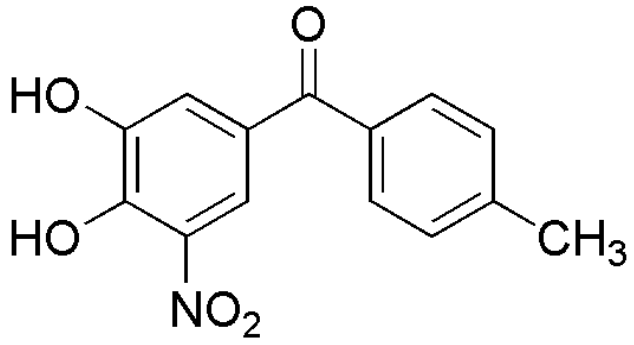




Inhibitors of COMT

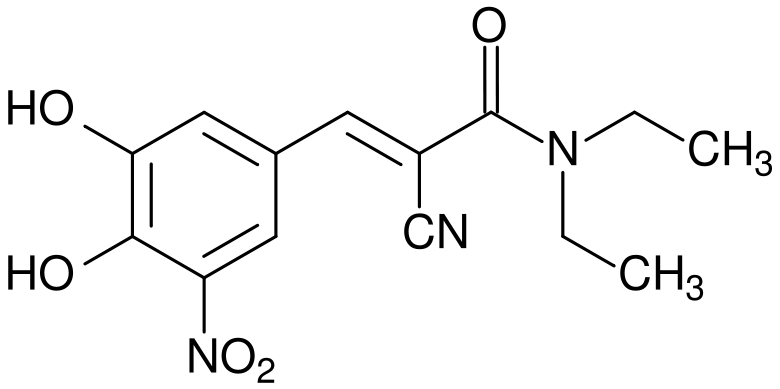


Entacapone



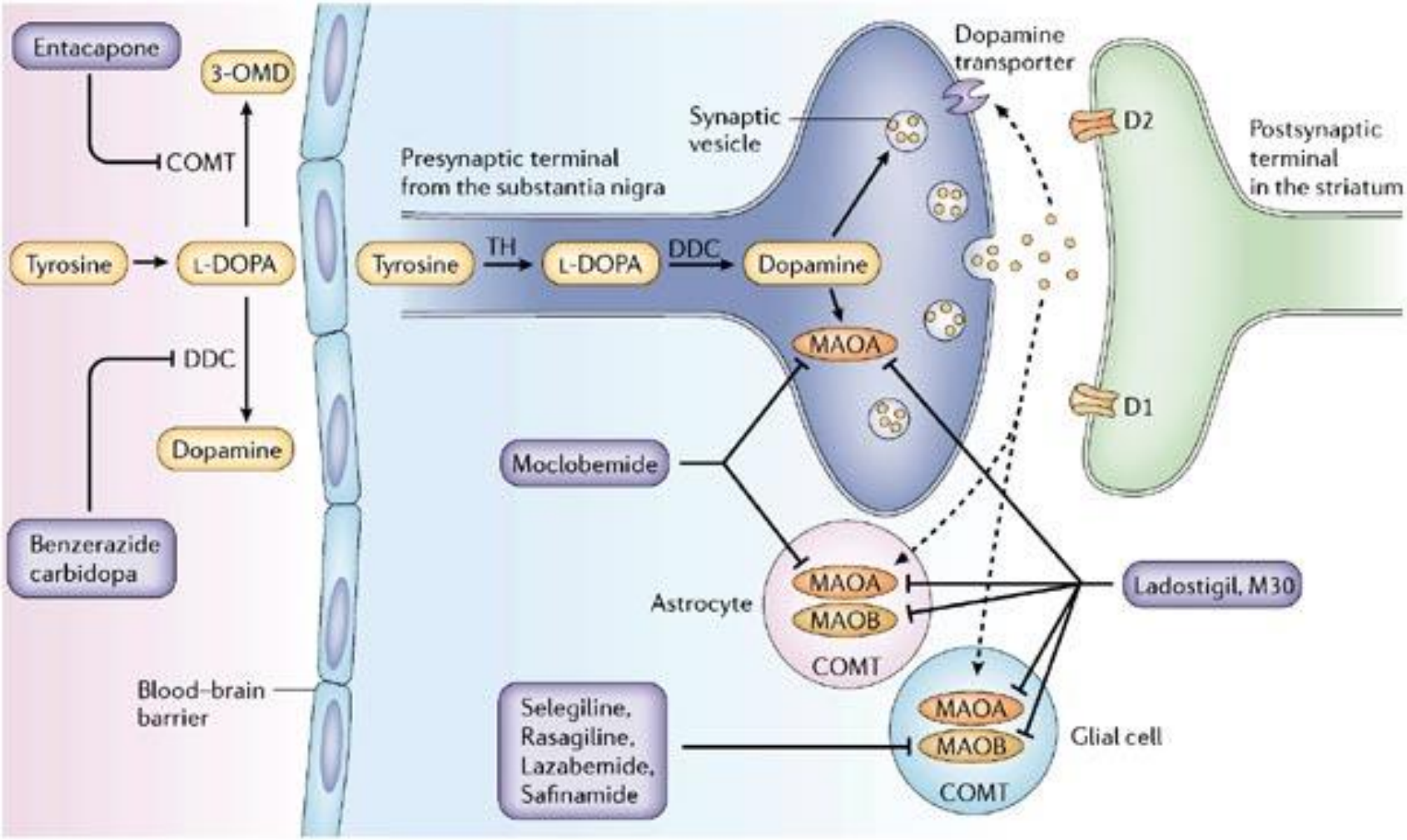
Tolcapone

Inhibitors of COMT



- Entacapone is marketed by Novartis as Comtan in the US
- Stalevo is a combination of Levodopa, Carbidopa, and Entacapone

Summary of the Treatment of Parkinson's Disease



Summary

- Entacapone and rasagiline should be offered to reduce off time (Level A)
- Pergolide, pramipexole, ropinirole and tolcapone should be considered to reduce off time (Level B)

Summary

- Sustained release carbidopa/levodopa and bromocriptine may be disregarded to reduce off time (Level C)
- Amantadine may be considered to reduce dyskinesia (Level C)

Summary

- Sustained release carbidopa/levodopa and bromocriptine may be disregarded to reduce off time (Level C)
- Amantadine may be considered to reduce dyskinesia (Level C)

Surgical Treatment of PD

- Resurgence in surgical approaches
- Deep brain stimulation (DBS)
  - Most commonly performed surgery for PD in North America
  - Uses an implanted electrode connected to an implantable pulse generator (IPG) that delivers electrical current to a targeted brain nucleus

Summary

- DBS of the STN may be considered to improve motor function and reduce off time, dyskinesia, and medication usage (Level C)

Summary

- Not enough evidence to support or refute the efficacy of DBS of the GPi or VIM nucleus of the thalamus in reducing off time, dyskinesia, or medication usage, or to improve motor function (Level U)

Recommendations for Factors Predicting Improvement after DBS

- Pre-operative response to levodopa should be considered as a factor predictive of outcome after DBS of the STN (Level B)

Recommendations for Factors Predicting Improvement after DBS

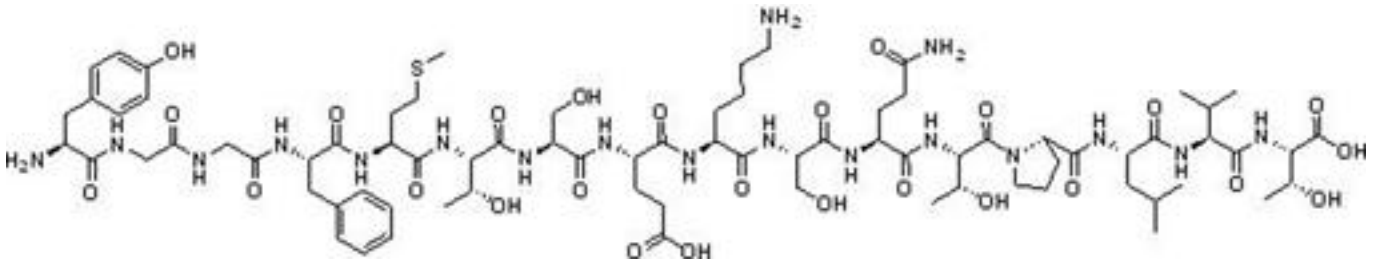
- Age and duration of PD may be considered as factors predictive of outcome after DBS of the STN. Younger patients with shorter disease durations may possibly have improvement greater than that of older patients with longer disease durations (Level C).

Recommendations for Factors Predicting Improvement after DBS

- Insufficient evidence to make any recommendations about factors predictive of improvement after DBS of the GPi or VIM nucleus of the thalamus in PD patients (Level U)

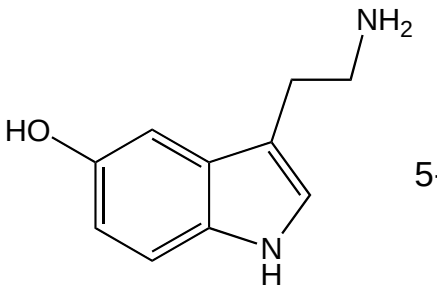
Thanks for your participation!

Endorphin



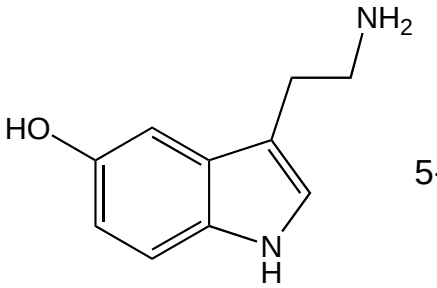
- Endorphins (or more correctly Endomorphines) are endogenous opioid biochemical compounds. They are peptides produced by the pituitary gland and the hypothalamus in vertebrates, and they resemble the opiates in their abilities to produce analgesia and a sense of well-being. In other words, they might work as "natural pain killers." Using drugs may increase the effects of the endorphins.

Serotonin



5-Hydroxytryptamine, or 5-HT

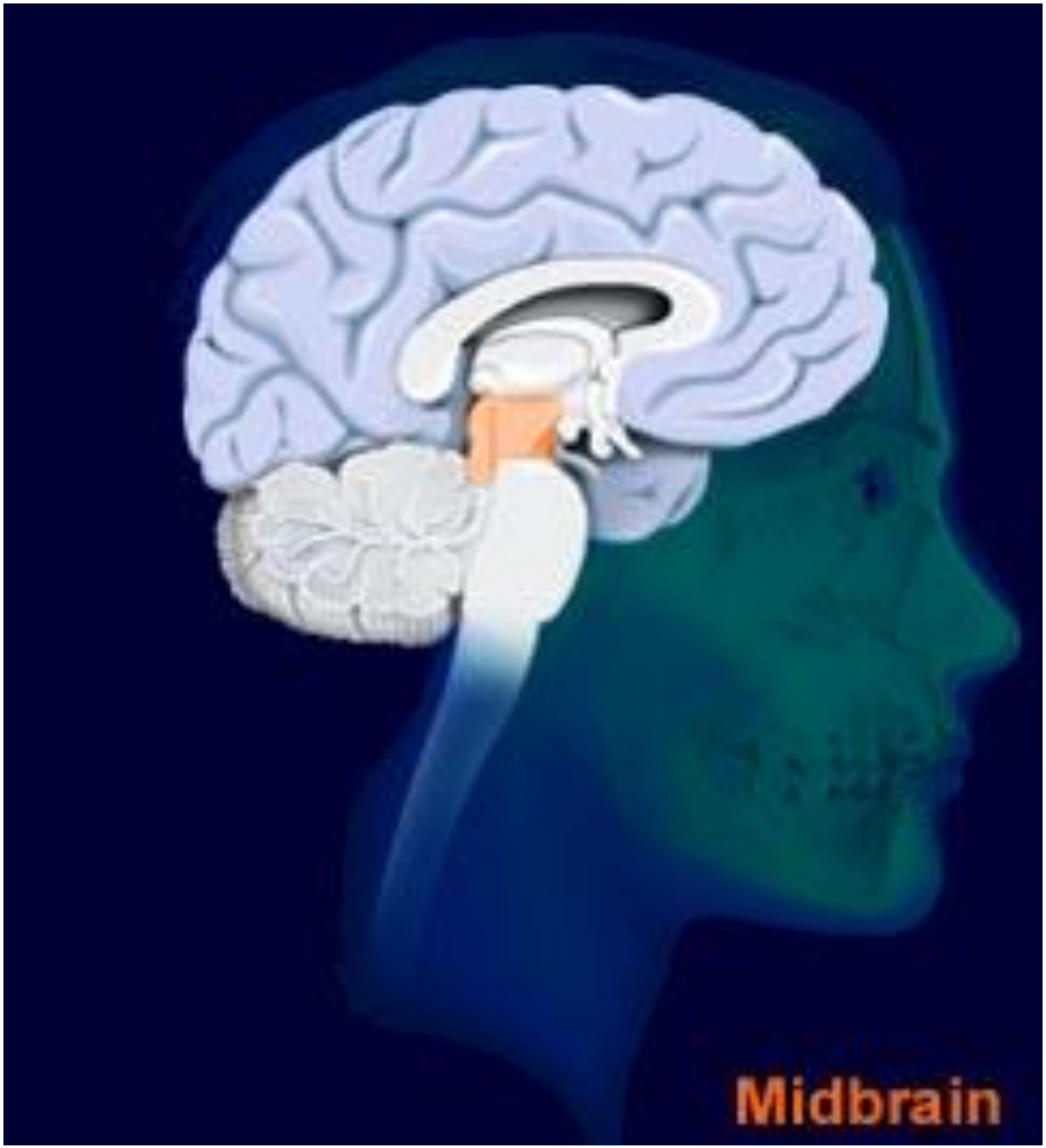
- Although the CNS contains less than 2% of the total serotonin in the body, serotonin plays a very important role in a range of brain functions. It is synthesized from the amino acid tryptophan.
- Within the brain, serotonin is localised mainly in nerve pathways emerging from the raphe nuclei, a group of nuclei at the centre of the reticular formation in the Midbrain, pons and medulla.
- These serotonergic pathways spread extensively throughout the brainstem, the cerebral cortex and the spinal cord.

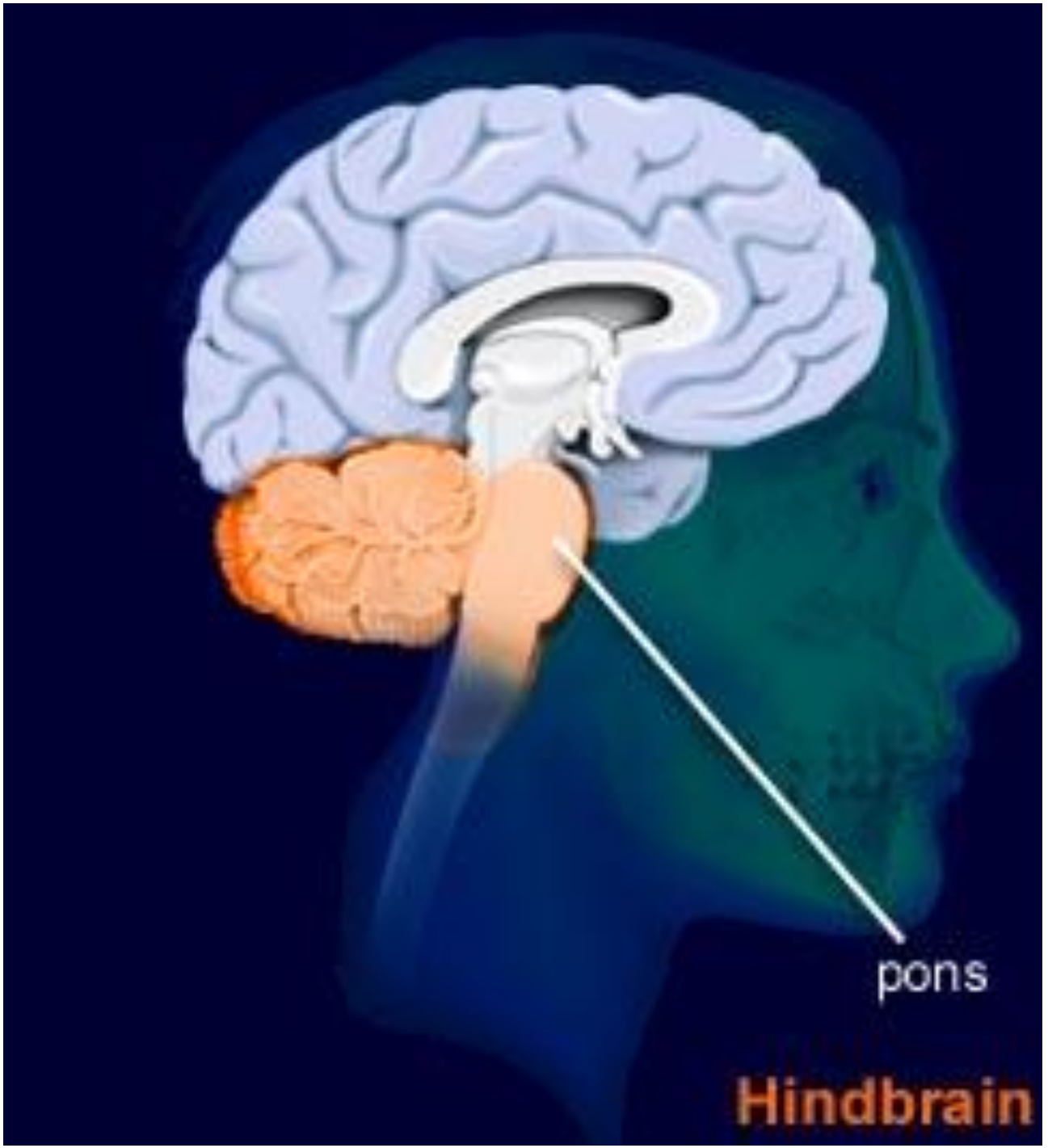


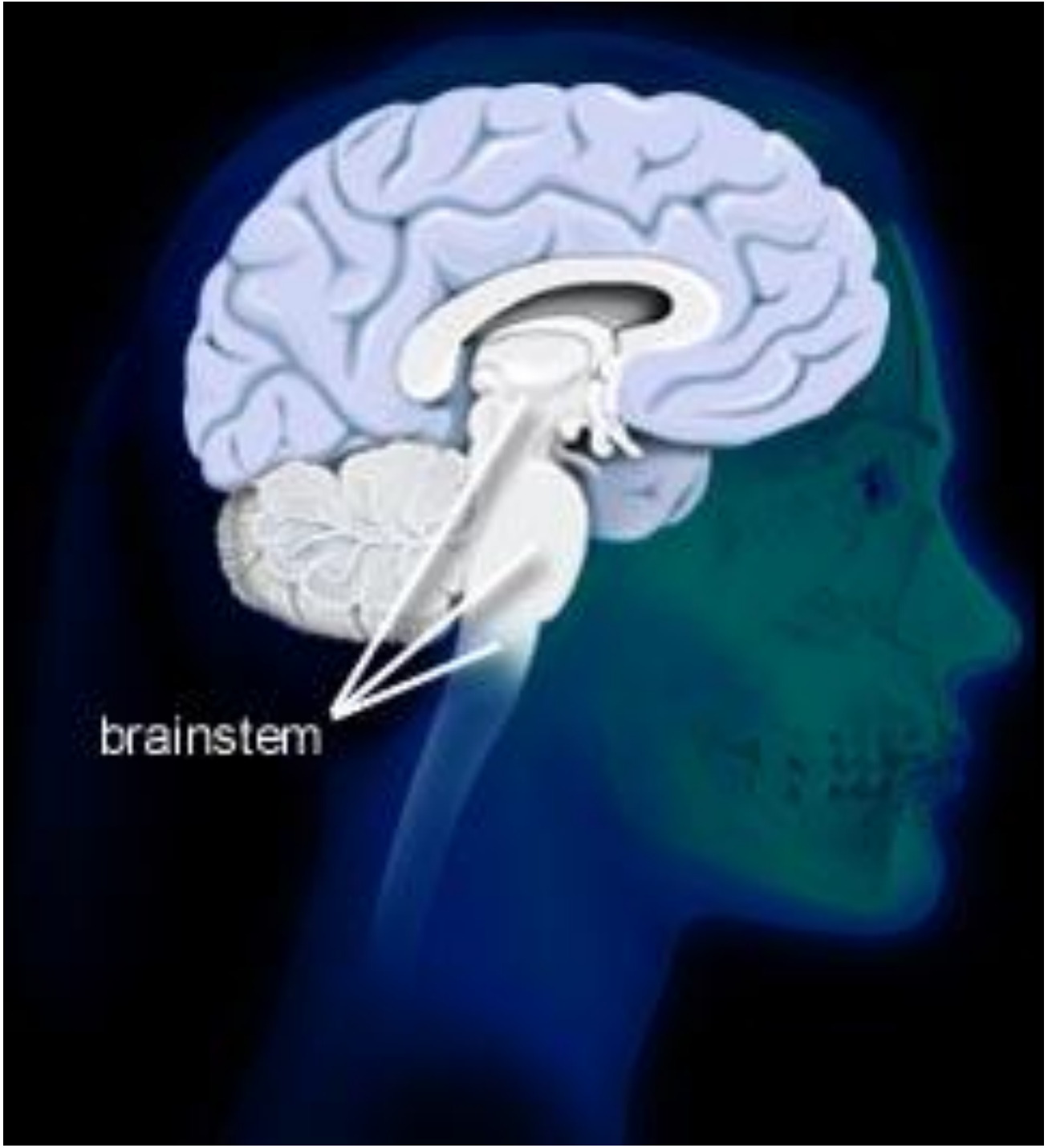
5-Hydroxytryptamine, or 5-HT

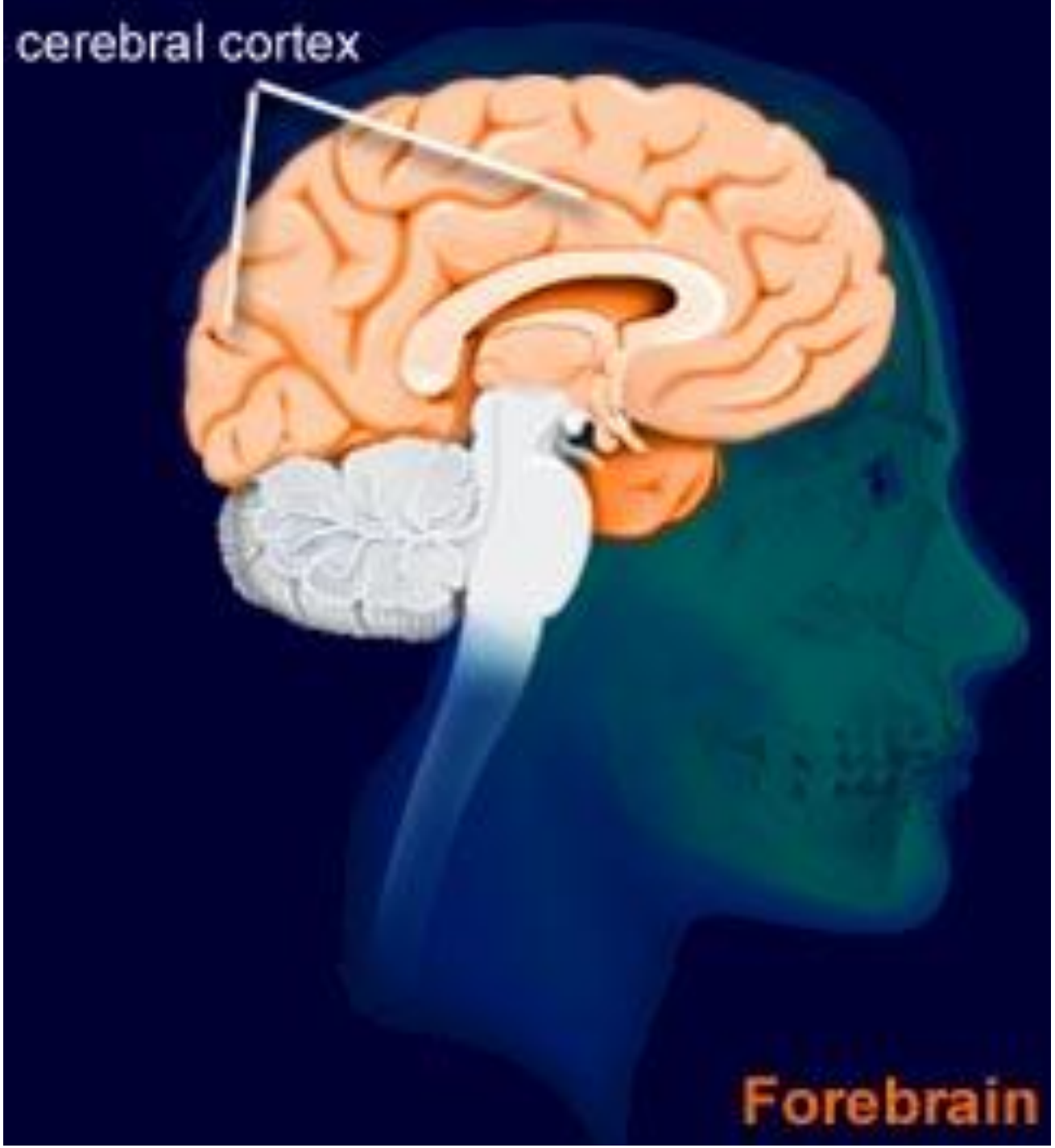
Serotonin

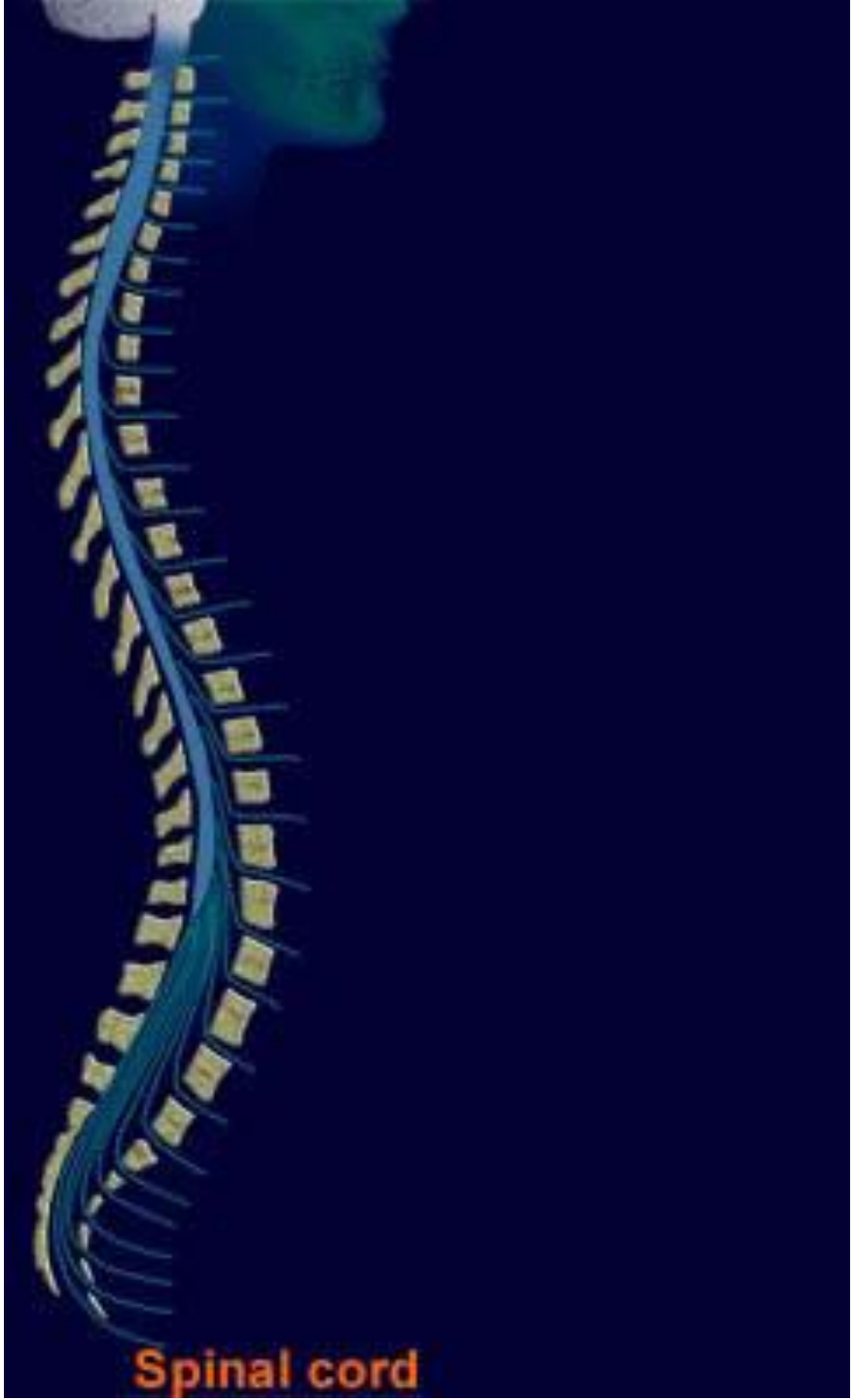
- In addition to mood control, serotonin has been linked with a wide variety of functions, including the regulation of sleep, pain perception, body temperature, blood pressure and hormonal activity.
- Outside the brain, serotonin exerts a number of important effects, particularly involving the gastrointestinal and cardiovascular systems.

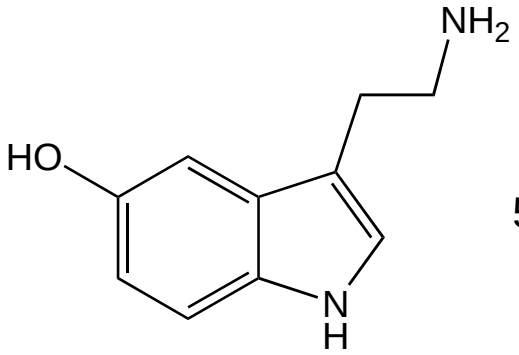

Midbrain


pons
Hindbrain


brainstem


cerebral cortex
Forebrain


Spinal cord



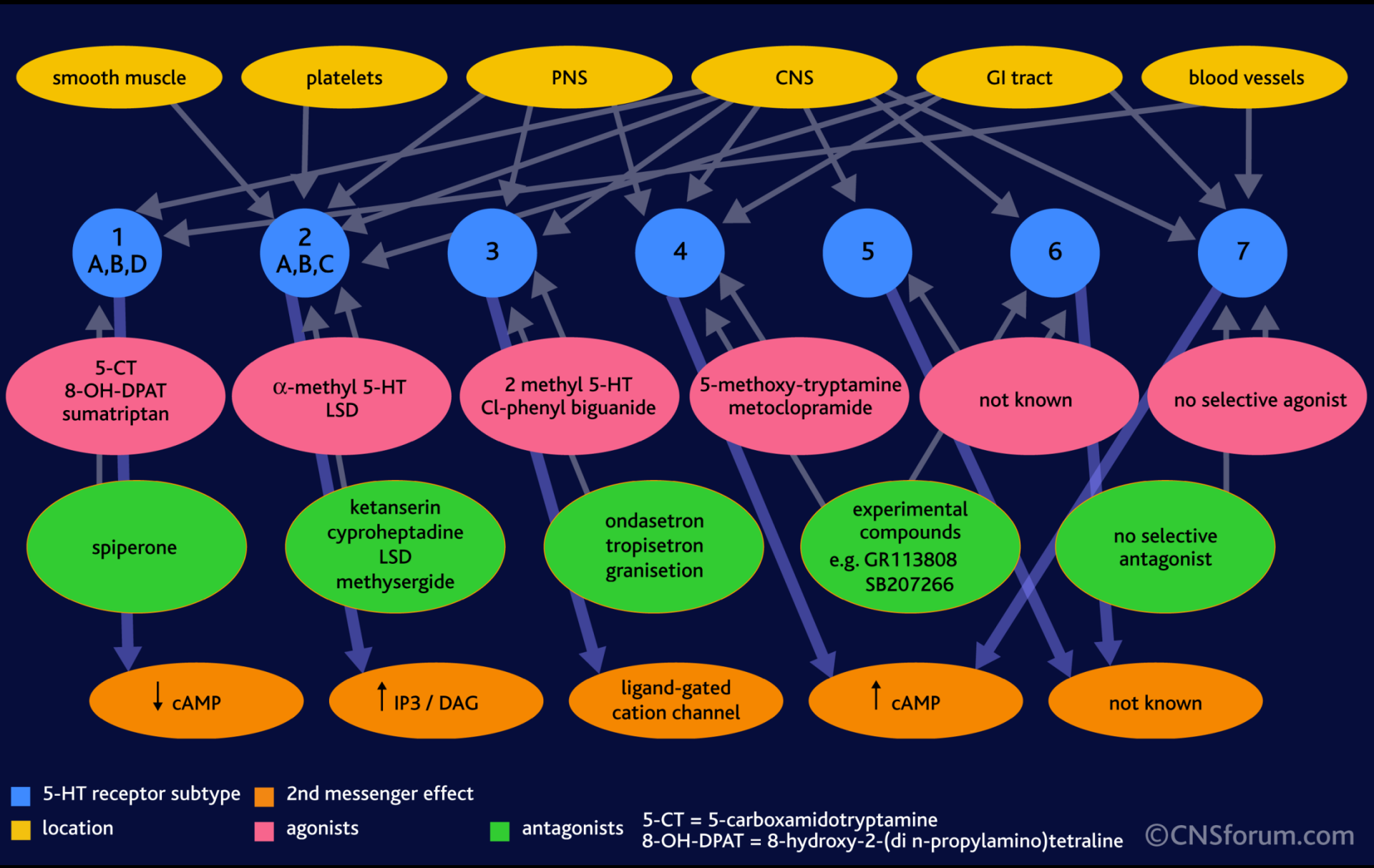
5-Hydroxytryptamine, or 5-HT

Serotonin

- In the central nervous system, serotonin is believed to play an important role in the regulation of body temperature, mood, sleep, vomiting, sexuality, and appetite.
- Low levels of serotonin have been associated with several disorders, namely clinical depression, obsessive-compulsive disorder (OCD), migraine, irritable bowel syndrome, tinnitus, fibromyalgia, bipolar disorder, and anxiety disorders.
- If neurons of the brainstem that make serotonin—serotonergic neurons—are abnormal, there is a risk of sudden infant death syndrome (SIDS) in an infant.

Understanding Serotonin

- The pharmacology of 5-HT is extremely complex, with its actions being mediated by a large and diverse range of 5-HT receptors.
- At least seven different receptor "families" are known to exist, each located in different parts of the body and triggering different responses.
- As with all neurotransmitters, the effects of 5-HT on the human mood and state of mind, and its role in consciousness, are very difficult to ascertain.


smooth muscle
platelets
PNS
CNS
GI tract
blood vessels
1 A,B,D
2 A,B,C
3
4
5
6
7
5-CT 8-OH-DPAT sumatriptan
α-methyl 5-HT LSD
2 methyl 5-HT Cl-phenyl biguanide
5-methoxy-tryptamine metoclopramide
not known
no selective agonist
spiperone
ketanserin cyproheptadine LSD methysergide
ondasetron tropisetron granisetion
experimental compounds e.g. GR113808 SB207266
no selective antagonist
↓ cAMP
↑ IP3 / DAG
ligand-gated cation channel
↑ cAMP
not known
5-HT receptor subtype
location
2nd messenger effect
agonists
antagonists
5-CT = 5-carboxamidotryptamine
8-OH-DPAT = 8-hydroxy-2-(di n-propylamino)tetraline
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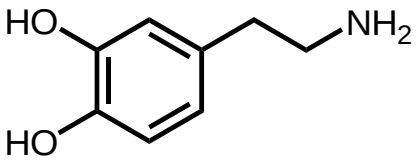
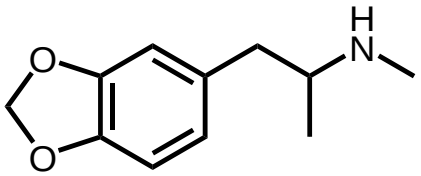
Understanding Serotonin

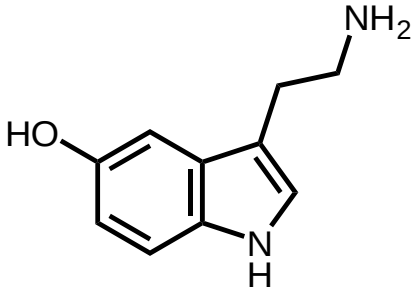
- Serotonergic action is terminated primarily via uptake of 5-HT from the synapse. This is through the specific monoamine transporter for 5-HT, 5-HT reuptake transporter, on the presynaptic neuron.
- Various agents can inhibit 5-HT reuptake including MDMA (ecstasy), cocaine, tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs).
- Recent research suggests that serotonin plays an important role in liver regeneration and acts as a mitogen (induces cell division) throughout the body.



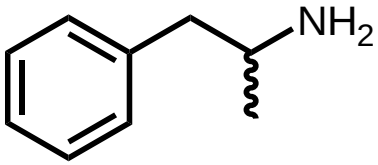
Dopamine



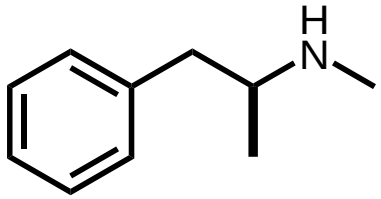
Methylenedioxymethamphetamine
(MDMA, ecstasy)



Serotonin



Amphetamine



Methamphetamine