Dopamine

Dopamine is classified as a **low molecular weight neurotransmitter** (class II: amines) and belongs to the group of catecholamines. It also functions as a **neurohormone** – its release from the hypothalamus inhibits the secretion of prolactinu from the adenohypophysis. Circulating dopamine acts as a **β-1-sympathomimetic** and, when administered intravenously, causes an increase in systolic blood pressure and an acceleration of the heart rate. It does not cross the blood-brain barrier, and its circulation in the blood therefore does not affect brain function. Its formation also occurs in other organs of the body.

neurons and adrenal medulla

catecholamine

5 types of G-protein coupled dopaminergic receptors

Synthesis and degradation

It is synthesized from non-essential tyrosine or essential amino acid – phenylalanine. First, (L-DOPA) is formed by attachment of the OH group of tyrosine hydroxylase. DOPA-decarboxylase then decarboxylates to form **dopamine**. It is a precursor of noradrenaline (by hydroxylation) and adrenaline (from noradrenaline by N-methylation).

Dopamine shares **degradation** with catecholamines: it is degraded by monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT). MAO is found both in synaptic terminals and in the liver, where it breaks down circulating catecholamines[1]. The final metabolite is homovanillic acid (HVA - homovanillic acid).

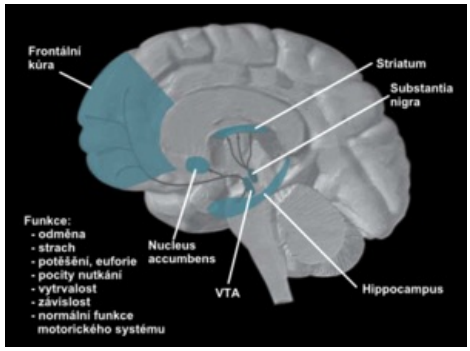
Functions in the brain

Dopamine is usually **inhibitory**. Dopaminergic neurons are found in several areas of the brain:

1. **Nigrostriatal system**, in which neurons from the **substantia nigra** project to the **corpus striatum** (a common name for the caudate nucleus and putamen). Dopaminergic neurons have a dual effect on the putamen:
    1. They stimulate **D_1** dopamine receptors, which **inhibit globus pallidus internus** (GPi) via direct GABAergic receptors (**direct pathway**).
    2. They inhibit **D_2** receptors, which in turn also **inhibit GPi**. Inhibition here limits excitatory glutamate signals from the ncl. subthalamicus to GPi (**indirect pathway**).
    - The balance between this inhibition and excitation maintains the normal function of the motor system. **In Parkinson's disease** the supply of dopamine to the putamen is interrupted, which *increases the activity of the GABAergic (inhibitory) GPi* though a direct and indirect pathway. Its excessive inhibitory activity to the thalamus then violates movement control and *hypertonic-hypokinetic syndrome* occurs.
2. **A mesocortical system** , that sends fibers **from the ventral tegmental area** (VTA – ventral tegmental area) **to the nucleus accumbens** and limbic subcortical structures.
    - Here it plays a role in reward, fear, pleasure and addiction mechanisms.

Other effects in the body

- **The arcuate nuclei of the hypothalamus** release dopamine into the adenohypophysis,where it regulates *the release of prolaktin*. Dopamine reduces its secretion up to 10×[2].
- It has been found that in the **retina** it is released by amacrine cells along with other neurotransmitters. Dopamine also has an inhibitory effect here.
- Dopamine is also produced in the **kidneys**, where it inhibits Na+/K+ ATPase by phosphorylating it and thus increases natriuresis. The second effect is renal vasodilation.[3]
- Dopamine is secreted by the **adrenal medulla**. The physiological effects in the circulation are unknown[3]. **Intravenous application** causes an increase in systolic pressure while maintaining the same diastolic pressure (it's a β-1-sympatomimetic). This is used in *the treatment of cardiogenic and traumatic shock*.



Dopamine Pathways. In the brain, dopamine plays an important role in the regulation of reward and movement. As part of the reward pathway, dopamine is manufactured in nerve cell bodies located within the ventral tegmental area (VTA) and is released in the nucleus accumbens and the prefrontal cortex. Its motor functions are linked to a separate pathway, with cell bodies in the substantia nigra that manufacture and release dopamine into the striatum.

Connection with diseases

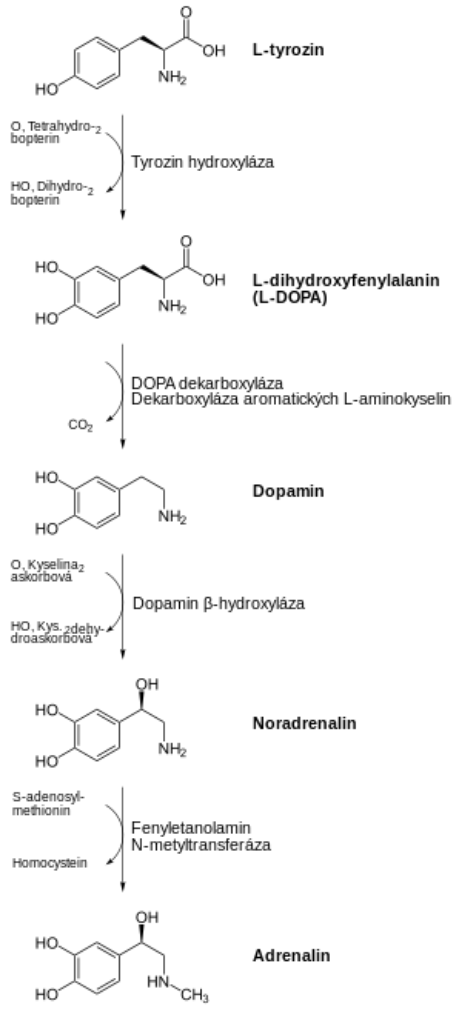
Parkinson's syndrome (parkinsonism)

Parkinson's syndrome is associated with **damage to the function of substantia nigra neurons**. These neurons send their fibers to the striatum (primarily to its part of the putamen). Decreasing the supply of

dopamine to the putamen by both the direct and indirect pathways *increases the activity of the GABAergic (inhibitory) GPi*. Its excessive inhibitory activity to the thalamus then disrupts movement control.

The disease is characterized by muscle rigidity (increased muscle tone), involuntary resting tremor (3–6 cycles per second[2]), akinesia (problems initiating movement), and postural instability. Therefore, it is also called as **hypokinetic-hypertonic syndrome**. Parkinsonian tremors occur even at rest, and thus differ from cerebellar tremors, which are intentional and occur only when performing movements.

Akinesia (trouble initiating movement) is probably caused by a reduction in dopamine production in the nucleus accumbens in the limbic system[2]. This will cause a deterioration in the ability to show the will to move. Akinesia often bothers patients with Parkinson's syndrome more than tremors and muscle rigidity, because they have to make a great effort to concentrate their will to initiate movements (often to the limit of their abilities).



Biosynthesis of catecholamines adrenaline (epinephrine) and noradrenaline (norepinephrine), intermediates DOPA and dopamine

Note: Parkinson's syndrome is a neurological syndrome that can arise from a variety of etiologies. Parkinson's disease is the most common cause (so-called primary parkinsonian syndrome). Among others, ponstencephalitic (e.g. after the Spanish flu), atherosclerotic (by ischemia of the substantia nigra), after CO poisoning or methanol poisoning, iatrogenic (by long-term administration of neuroleptics) or as part of other neurodegenerations (e.g. progressive supranuclear palsy).

🔎 *For more information see Parkinson's syndrome.*

Treatment of Parkinson's syndrome

L-DOPA (levodopa)

Administration of the dopamine precursor L-DOPA to patients with Parkinson's disease alleviates a number of symptoms. L-DOPA is probably *converted into dopamine* in the brain. Administering dopamine alone does not help, as it has difficulty crossing the blood-brain barrier.

L-deprenyl (selegiline)

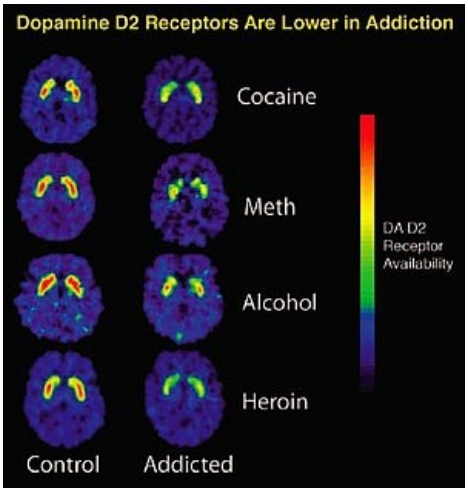
Another option for alleviating parkinsonian symptoms is the use of L-deprenyl. **It inhibits monoamine oxidase B (MAO-B)**, which is responsible for breaking down dopamine after its release. Inhibition of MAO-B will allow dopamine to persist longer in the basal ganglia region. Another effect, not yet understood, is the slowing down of the death of neurons in the substantia nigra[2].

🔎 *For more information see Antiparkinsonian.*

Schizophrenia

Although many factors contribute to the development of schizophrenia, it turns out that **a disorder of the mesocortical system** is responsible for at least some of the symptoms of schizophrenia. Reasons why dopamine may be involved in the development of schizophrenia:

- Amphetamine use causes an outpouring of dopamine and noradrenaline and induces psychosis similar to schizophrenia[3].
- Many drugs used to treat schizophrenia block dopamine D_2 receptors. Several recently invented drugs for the treatment of schizophrenia bind to dopamine D_4 receptors[3].
- Many patients with Parkinson's disease treated with L-DOPA develop schizophrenia-like symptoms[2]. L-DOPA reduces activity in various parts of the prefrontal lobes of the brain.
- Excess dopamine in schizophrenia may be produced by neurons in the ventral tegmental area (VTA). These neurons release dopamine into the medial and anterior regions of the limbic system and into the prefrontal lobes, which are centers for behavioral control.[2]
- The hippocampus in patients with schizophrenia is often reduced, especially in the dominant hemisphere[2].



The PET images show that repeated exposure to drugs depletes the brain's dopamine receptors, which are critical for one's ability to experience pleasure and reward.

🔎 *For more information see Schizophrenia.*

Depression

Evidence from clinical trials shows that depressed patients have lower amounts of homovanillic acid (HVA), the major metabolite of dopamine in the CNS. Using neuroimaging methods, it was further established that in depression, the ligand binds less to the dopamine transporter, while the ability to bind dopamine increases in the caudate nucleus and putamen. This suggests a functional deficiency of synaptic dopamine in depressed patients.[4]

Connection with addictive substances

Dopamine is produced in the **nucleus accumbens** – the center of reward, pleasure, laughter, addiction and fear. It is therefore not surprising that, regardless of other effects , the **increase in the amount of dopamine** availoble at D_3 receptors in the nucleus accumbens is linked to the use of addictive substances[3]. In this way, they directly stimulate **the reward system** in the brain.

With long-term use, there is a loss of dopamine receptors or a decrease in dopamine production, which leads to a reduced receptivity to normal pleasurable activities. Therefore, addicts often feel moody, lifeless and depressed. This forces them to use the addictive substance again to increase the amount of dopamine in their brain. And they are forced to gradually increase the dose, because a phenomenon called **tolerance** occurs.[5]

Links

Related articles

- Catecholamines
- Basal ganglia
- Parkinson's syndrome
- Parkinson's disease
- Antiparkinson drugs

Used literature

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References

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