

Dopamine Receptors

Dopamine is a monoamine catecholamine neurotransmitter belonging to the 7 transmembrane G protein-coupled receptors (GPCRs), which play an important role in the regulation of not only motor functions but also non-motor functions such as motivation, cognition, emotion, and neuroendocrine secretion.

Dopamine acts on dopamine receptors to regulate motor and non-motor function in a specific manner. The existence of dopamine receptors was revealed in 1972 and it was indicated that dopamine stimulates adenylyl cyclase (AC) activity. There are five types of dopamine receptors, which include D1, D2, D3, D4, and D5.

Keabian et al classified dopamine receptors into 2 families, D1-like receptor and D2-like receptor, on the basis of pharmacologic properties and the ability to regulate cAMP (cyclic adenosine monophosphate) generation.

Dopamine receptors are expressed in the central nervous system, specifically in the hippocampal dentate gyrus and subventricular zone.

In the human central nervous system (CNS), the relative density of DA receptors is $D1 > D2 > D3 > D5 > D4$.

D1 and D5 receptors mostly involved in post synaptic excitation. D2, D3, and D4 receptors are involved in both pre-and postsynaptic inhibition.

Each receptor has a different function.

The function of each dopamine receptor:

- D1: memory, attention, impulse control, regulation of reward system and locomotion
- D2: locomotion, attention, sleep, memory, learning
- D3: cognition, impulse control, attention, sleep
- D4: cognition, impulse control, attention, sleep
- D5: decision making, cognition, attention, renin secretion

D1 and D5 receptors couple to G stimulatory sites and activate adenylyl cyclase. The activation of adenylyl cyclase leads to the production of the second

messenger cAMP, which leads to the production of protein kinase A (PKA) which leads to further transcription in the nucleus.

D2 through D4 receptors couple to G inhibitory sites, which inhibit adenylyl cyclase and activate K⁺ channels.

D1 and D5 receptors have high density in the striatum, nucleus accumbens, olfactory bulb, and substantia nigra. These receptors are essential in regulating the reward system, motor activity, memory, and learning. D1 and D5 receptors, along with stimulating adenylyl cyclase, also activate phospholipase C, which leads to the induction of intracellular calcium release and activation of protein kinase C.

D2, D3, and D4 receptors are expressed mainly in the striatum, as well as the external globus pallidus, core of nucleus accumbens, hippocampus, amygdala, and cerebral cortex. These receptors also affect the postsynaptic receptor-mediated extrapyramidal activity. D2-D4 receptors are important in the signaling for the survival of human dopamine neurons and neuronal development.

Dopamine receptor classification, localization, and their functions.

| Receptors | D1 | D5 | D2 | D3 | D4 |
|-----------|--|--|---|--------------------------------------|---|
| Location | Striatum, nucleus accumbens. Olfactory bulb, amygdala hippocampus, substantia nigra Hypothalamus, frontal cortex | Cortex, substantia nigra, hypothalamus | Striatum, Olfactory bulb, cerebral cortex | Striatum, islands of Calleja, cortex | Frontal cortex, amygdala, hypothalamus, nucleus accumbens |
| Type | Gs-coupled | Gs-coupled | Gi-coupled | Gi-coupled | Gi-coupled |
| Mechanism | Increased intracellular level of cAMP by activated adenylyl cyclase | Adenylyl cyclase↑ | Decreased intracellular level of cAMP by inhibition of adenylyl cyclase | Adenylyl cyclase↓ | Adenylyl cyclase↓ |
| Function | Locomotion, | Cognition, | Learning and | Cognition, | Cognition, |

| Receptors | D1 | D5 | D2 | D3 | D4 |
|-----------|---|---|---|--|--|
| | learning and memory, attention, impulse control, sleep, regulation of reward system | attention, decision making, motor learning, renin secretion | memory, attention, sleep, regulates mood, emotional stability in the limbic system, movement control in basal ganglia | attention, impulse control, sleep, regulation of food intake, regulation of locomotor functions. | impulse control, attention, sleep, reproductive behaviour, involved in pain process. |

Sites for further reading

1. Dopamine: Receptors, Functions, Synthesis, Pathways, Locations and Mental Disorders: Review of Literatures by Getinet Ayano*
Journal of Mental Disorders Treatment 2016, 2:2
2. J Exp Neurosci. 2018; 12: 1179069518779829. Physiological and Functional Basis of Dopamine Receptors and Their Role in Neurogenesis: Possible Implication for Parkinson's disease
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3. Biochemistry, Dopamine Receptor Last Update: March 19, 2020.
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Compiled and prepared