[Template:Other uses](/wiki/Template:Other_uses" \o "Template:Other uses) [Template:Good article](/wiki/Template:Good_article) [Template:Use dmy dates](/wiki/Template:Use_dmy_dates) [Template:Infobox neurotransmitter](/wiki/Template:Infobox_neurotransmitter)

**Dopamine** (contracted from **3,4-dihydroxyphenethylamine**) is an [organic chemical](/wiki/Organic_compound) of the [catecholamine](/wiki/Catecholamine) and [phenethylamine](/wiki/Phenethylamine) families that plays several important roles in the brain and body. It is an [amine](/wiki/Amine) synthesized by removing a [carboxyl group](/wiki/C-terminus) from a molecule of its [precursor chemical](/wiki/Precursor_(chemistry)) [L-DOPA](/wiki/L-DOPA), which is [synthesized](/wiki/Biosynthesis) in the brain and kidneys. Dopamine is also synthesized in plants and most multicellular animals.

In the [brain](/wiki/Brain), dopamine functions as a [neurotransmitter](/wiki/Neurotransmitter)—a chemical released by [neurons](/wiki/Neuron) (nerve cells) to send signals to other nerve cells. The brain includes several distinct [dopamine pathways](/wiki/Dopaminergic_pathway), one of which plays a major role in [reward-motivated behavior](/wiki/Reward_system). Most types of reward increase the level of dopamine in the brain, and most [addictive](/wiki/Addiction) drugs increase dopamine neuronal activity. Other brain dopamine pathways are involved in [motor control](/wiki/Motor_system) and in controlling the release of various hormones. These pathways and [cell groups](/wiki/Dopaminergic_cell_groups) form a dopamine system which is [neuromodulatory](/wiki/Neuromodulation).

Outside the [central nervous system](/wiki/Central_nervous_system), dopamine functions in several parts of the [peripheral nervous system](/wiki/Peripheral_nervous_system) as a local [chemical messenger](/wiki/Neurotransmitter). In blood vessels, it inhibits [norepinephrine](/wiki/Norepinephrine) release and acts as a [vasodilator](/wiki/Vasodilator) (at normal concentrations); in the kidneys, it increases sodium excretion and urine output; in the [pancreas](/wiki/Pancreas), it reduces insulin production; in the digestive system, it reduces [gastrointestinal motility](/wiki/Gastrointestinal_physiology#Motility) and protects [intestinal mucosa](/wiki/Intestinal_mucosa); and in the immune system, it reduces the activity of [lymphocytes](/wiki/Lymphocytes). With the exception of the blood vessels, dopamine in each of these peripheral systems is synthesized locally and exerts its effects near the cells that release it.

Several important diseases of the nervous system are associated with dysfunctions of the dopamine system, and some of the key medications used to treat them work by altering the effects of dopamine. [Parkinson's disease](/wiki/Parkinson's_disease), a degenerative condition causing tremor and motor impairment, is caused by a loss of dopamine-secreting neurons in an area of the [midbrain](/wiki/Midbrain) called the [substantia nigra](/wiki/Substantia_nigra). Its metabolic precursor L-DOPA can be manufactured, and in its pure form marketed as *Levodopa* is the most widely used treatment for the condition. There is evidence that [schizophrenia](/wiki/Schizophrenia) involves altered levels of dopamine activity, and most [antipsychotic drugs](/wiki/Antipsychotic) used to treat this are [dopamine antagonists](/wiki/Dopamine_antagonist) which reduce dopamine activity.[[1]](#cite_note-1) Similar dopamine antagonist drugs are also some of the most effective [anti-nausea agents](/wiki/Antiemetic). [Restless legs syndrome](/wiki/Restless_legs_syndrome) and [attention deficit hyperactivity disorder](/wiki/Attention_deficit_hyperactivity_disorder) (ADHD) are associated with decreased dopamine activity.[[2]](#cite_note-2) [Dopaminergic](/wiki/Dopaminergic) [stimulants](/wiki/Sympathomimetic_drug) can be addictive in high doses, but some are used at lower doses to treat ADHD. Dopamine itself is available as a manufactured [medication](/wiki/Pharmaceutical_drug) for [intravenous injection](/wiki/Intravenous_therapy): although it cannot reach the brain from the bloodstream, its peripheral effects make it useful in the treatment of [heart failure](/wiki/Heart_failure) or [shock](/wiki/Shock_(circulatory)), especially in newborn babies. [Template:TOC limit](/wiki/Template:TOC_limit)

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## Structure[[edit](/index.php?title=(none)&action=edit&section=1)]

A dopamine molecule consists of a [catechol](/wiki/Catechol) structure (a [benzene](/wiki/Benzene) ring with two [hydroxyl](/wiki/Hydroxyl) side groups) with one [amine](/wiki/Amine) group attached via an [ethyl](/wiki/Ethyl_group) chain.<ref name=PubChem>[Template:Cite web](/wiki/Template:Cite_web)</ref> As such, dopamine is the simplest possible [catecholamine](/wiki/Catecholamine), a family that also includes the [neurotransmitters](/wiki/Neurotransmitter) [norepinephrine](/wiki/Norepinephrine) and [epinephrine](/wiki/Epinephrine).<ref name=Catecholamine>[Template:Cite web](/wiki/Template:Cite_web)</ref> The presence of a benzene ring with this amine attachment makes it a [substituted phenethylamine](/wiki/Substituted_phenethylamine), a family that includes numerous [psychoactive drugs](/wiki/Psychoactive_drug).<ref name=Phenethylamine>[Template:Cite web](/wiki/Template:Cite_web)</ref>

Like most [amines](/wiki/Amine), dopamine is an [organic base](/wiki/Organic_base).<ref name=Carter>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> As a [base](/wiki/Base_(chemistry)), it is generally [protonated](/wiki/Protonation) in [acidic](/wiki/Acid) environments (in an [acid-base reaction](/wiki/Acid-base_reaction)).<ref name=Carter/> The protonated form is highly water-soluble and relatively stable, but can become [oxidized](/wiki/Oxidation) if exposed to [oxygen](/wiki/Oxygen) or other [oxidants](/wiki/Oxidising_agent).<ref name=Carter/> In basic environments, dopamine is not protonated.<ref name=Carter/> In this [free base](/wiki/Free_base) form, it is less water-soluble and also more highly reactive.<ref name=Carter/> Because of the increased stability and water-solubility of the protonated form, dopamine is supplied for chemical or pharmaceutical use as dopamine hydrochloride—that is, the [hydrochloride](/wiki/Hydrochloride) [salt](/wiki/Salt_(chemistry)) that is created when dopamine is combined with [hydrochloric acid](/wiki/Hydrochloric_acid).<ref name=Carter/> In dry form, dopamine hydrochloride is a fine colorless powder.<ref name=Carter/> [Template:Multiple image](/wiki/Template:Multiple_image)

## Biochemistry[[edit](/index.php?title=(none)&action=edit&section=2)]

### Synthesis[[edit](/index.php?title=(none)&action=edit&section=3)]

[thumb|right|The reaction from L-DOPA to dopamine|alt=Diagram showing L-DOPA and dopamine molecular structures, with the reaction that connects them.](/wiki/File:L-DOPA-to-dopamine.svg)

Dopamine is [synthesized](/wiki/Biosynthesis) in a restricted set of cell types, mainly [neurons](/wiki/Neuron) and cells in the [medulla](/wiki/Adrenal_medulla) of the [adrenal glands](/wiki/Adrenal_gland).<ref name=Seeman/> The [metabolic pathway](/wiki/Metabolic_pathway) is:

L-Phenylalanine → L-Tyrosine → L-DOPA → Dopamine

The direct precursor of dopamine, [L-DOPA](/wiki/L-DOPA), can be synthesized indirectly from the [essential amino acid](/wiki/Essential_amino_acid) [phenylalanine](/wiki/Phenylalanine) or directly from the non-essential amino acid [tyrosine](/wiki/Tyrosine).<ref name=Musacchio/> These [amino acids](/wiki/Amino_acid) are found in nearly every [protein](/wiki/Protein) and so are readily available in [food](/wiki/Food), with tyrosine being the most common. Although dopamine is also found in many types of food, it is incapable of crossing the [blood–brain barrier](/wiki/Blood–brain_barrier) that surrounds and protects the brain.[[3]](#cite_note-3) It must therefore be synthesized inside the brain to perform its [neuronal activity](/wiki/Neurotransmission).[[3]](#cite_note-3) L-Phenylalanine is converted into L-tyrosine by the [enzyme](/wiki/Enzyme) [phenylalanine hydroxylase](/wiki/Phenylalanine_hydroxylase), with [molecular oxygen](/wiki/Allotropes_of_oxygen#Dioxygen) (O2) and [tetrahydrobiopterin](/wiki/Tetrahydrobiopterin) as [cofactors](/wiki/Cofactor_(biochemistry)). L-Tyrosine is converted into L-DOPA by the enzyme [tyrosine hydroxylase](/wiki/Tyrosine_hydroxylase), with tetrahydrobiopterin, O2, and [iron](/wiki/Ferrous) (Fe2+) as cofactors.<ref name=Musacchio>[Template:Cite book](/wiki/Template:Cite_book)</ref> L-DOPA is converted into dopamine by the enzyme [aromatic L-amino acid decarboxylase](/wiki/Aromatic_L-amino_acid_decarboxylase) (also known as DOPA decarboxylase), with [pyridoxal phosphate](/wiki/Pyridoxal_phosphate) as the cofactor.<ref name=Musacchio/>

Dopamine itself is used as precursor in the synthesis of the neurotransmitters (and hormones) [norepinephrine](/wiki/Norepinephrine) and [epinephrine](/wiki/Epinephrine).<ref name=Musacchio/> Dopamine is converted into norepinephrine by the enzyme [dopamine β-hydroxylase](/wiki/Dopamine_beta_hydroxylase), with O2 and [L-ascorbic acid](/wiki/Ascorbic_acid) as cofactors.<ref name=Musacchio/> Norepinephrine is converted into epinephrine by the enzyme [phenylethanolamine *N*-methyltransferase](/wiki/Phenylethanolamine_N-methyltransferase) with [*S*-adenosyl-L-methionine](/wiki/S-Adenosyl_methionine) as the cofactor.<ref name=Musacchio/>

Some of the cofactors also require their own synthesis.<ref name=Musacchio/> Deficiency in any required amino acid or cofactor can impair the synthesis of dopamine, norepinephrine, and epinephrine.<ref name=Musacchio/> [thumb|right|Primary pathways for dopamine metabolism  
MAO:](/wiki/File:Dopamine_metabolism_fncir-07-00102-g008.jpg) [Monoamine oxidase](/wiki/Monoamine_oxidase)  
COMT: [catechol-O-methyltransferase](/wiki/Catechol-O-methyltransferase)  
HVA: [Homovanillic acid](/wiki/Homovanillic_acid)|alt=Diagram of primary pathways of dopamine metabolism. The metabolism of dopamine into DOPAC (3,4-dihydroxyphenylacetic acid) and 3-MT (3-methoxytyramine) is followed by metabolism of these intermediate products into HVA (homovanillic acid) by the action of MAO (monoamine oxidase) and COMT (catechol-O-methyltransferase).

### Degradation[[edit](/index.php?title=(none)&action=edit&section=4)]

Dopamine is broken down into inactive [metabolites](/wiki/Metabolite) by a set of enzymes—[monoamine oxidase](/wiki/Monoamine_oxidase) (MAO), [catechol-*O*-methyl transferase](/wiki/Catechol-O-methyl_transferase) (COMT), and [aldehyde dehydrogenase](/wiki/Aldehyde_dehydrogenase), acting in sequence.<ref name=Eisenhofer>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> Both [isoforms](/wiki/Protein_isoform) of monoamine oxidase, [MAO-A](/wiki/Monoamine_oxidase_A) and [MAO-B](/wiki/Monoamine_oxidase_B), effectively metabolize dopamine.<ref name=Musacchio/> Different breakdown pathways exist but the main end-product is [homovanillic acid](/wiki/Homovanillic_acid), which has no known biological activity.<ref name=Eisenhofer/> From the bloodstream, homovanillic acid is filtered out by the kidneys and then excreted in the urine.<ref name=Eisenhofer/>

In clinical research on schizophrenia, measurements of homovanillic acid in [plasma](/wiki/Blood_plasma) have been used to estimate levels of dopamine activity in the brain. A difficulty in this approach however, is separating the high level of plasma homovanillic acid contributed by the metabolism of norepinephrine.[[4]](#cite_note-4)[[5]](#cite_note-5) Although dopamine is normally broken down by an [oxidoreductase](/wiki/Oxidoreductase) enzyme, it is also susceptible to [oxidation](/wiki/Oxidation) by direct reaction with oxygen, yielding [quinones](/wiki/Quinone) plus various [free radicals](/wiki/Radical_(chemistry)) as products.<ref name=Sulzer>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> The rate of oxidation can be increased by the presence of [ferric](/wiki/Ferric) iron or other factors. Quinones and free radicals produced by autoxidation of dopamine can [poison cells](/wiki/Neurotoxicity), and there is evidence that this mechanism may contribute to the cell loss that occurs in [Parkinson's disease](/wiki/Parkinson's_disease) and other conditions.[[6]](#cite_note-6)

## Functions[[edit](/index.php?title=(none)&action=edit&section=5)]

### Cellular effects[[edit](/index.php?title=(none)&action=edit&section=6)]

[Template:Main article](/wiki/Template:Main_article)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| [Primary targets](/wiki/Biological_target) of dopamine in the mammalian brain[[7]](#cite_note-7)[[8]](#cite_note-8) | | | | |
| **Family** | **Receptor** | **Gene** | **Type** | **Mechanism** |
| [D1-like](/wiki/D1-like_receptor) | [D1](/wiki/Dopamine_receptor_D1) | [Template:Gene](/wiki/Template:Gene) | [Gs](/wiki/Gs_alpha_subunit)-coupled. | Increase intracellular levels of [cAMP](/wiki/Cyclic_adenosine_monophosphate) by activating [adenylate cyclase](/wiki/Adenylate_cyclase). |
| [D5](/wiki/Dopamine_receptor_D5) | [Template:Gene](/wiki/Template:Gene) |
| [D2-like](/wiki/D2-like_receptor) | [D2](/wiki/Dopamine_receptor_D2) | [Template:Gene](/wiki/Template:Gene) | [Gi](/wiki/Gi_alpha_subunit)-coupled. | Decrease intracellular levels of [cAMP](/wiki/Cyclic_adenosine_monophosphate) by inhibiting [adenylate cyclase](/wiki/Adenylate_cyclase). |
| [D3](/wiki/Dopamine_receptor_D3) | [Template:Gene](/wiki/Template:Gene) |
| [D4](/wiki/Dopamine_receptor_D4) | [Template:Gene](/wiki/Template:Gene) |
| [TAAR](/wiki/Trace_amine-associated_receptor) | [TAAR1](/wiki/TAAR1) | [Template:Gene](/wiki/Template:Gene) | [Gs](/wiki/Gs_alpha_subunit)-coupled. [Gq](/wiki/Gq_alpha_subunit)-coupled. | Increase intracellular levels of [cAMP](/wiki/Cyclic_adenosine_monophosphate) and intracellular calcium concentration. |

Dopamine exerts its effects by binding to and activating [cell surface receptors](/wiki/Cell_surface_receptor).<ref name=Seeman/> In mammals, five subtypes of [dopamine receptors](/wiki/Dopamine_receptor) have been identified, labeled from D1 to D5.<ref name=Seeman>[Template:Cite book](/wiki/Template:Cite_book)</ref> All of them function as [metabotropic](/wiki/Metabotropic_receptor), [G protein-coupled receptors](/wiki/G_protein-coupled_receptor), meaning that they exert their effects via a complex [second messenger system](/wiki/Second_messenger_system).<ref name=Romanelli>[Template:Cite book](/wiki/Template:Cite_book)</ref> These receptors can be divided into two families, known as [D1-like](/wiki/D1-like_receptor) and [D2-like](/wiki/D2-like_receptor).<ref name=Seeman/> For receptors located on neurons in the nervous system, the ultimate effect of D1-like activation (D1 and D5) can be excitation (via opening of [sodium channels](/wiki/Sodium_channel)) or inhibition (via opening of [potassium channels](/wiki/Potassium_channel)); the ultimate effect of D2-like activation (D2, D3, and D4) is usually inhibition of the target neuron.<ref name=Romanelli/> Consequently, it is incorrect to describe dopamine itself as either excitatory or inhibitory: its effect on a target neuron depends on which types of receptors are present on the membrane of that neuron and on the internal responses of that neuron to the second messenger [cAMP](/wiki/Cyclic_adenosine_monophosphate).<ref name=Romanelli/> D1 receptors are the most numerous dopamine receptors in the human nervous system; D2 receptors are next; D3, D4, and D5 receptors are present at significantly lower levels.<ref name=Romanelli/>

#### Storage, release, and reuptake[[edit](/index.php?title=(none)&action=edit&section=7)]

[thumb|right|Dopamine processing in a synapse. After release dopamine can either be taken up again by the presynaptic terminal, or broken down by enzymes.  
TH:](/wiki/File:Synapse_dopaminergique.png) [tyrosine hydroxylase](/wiki/Tyrosine_hydroxylase)  
DOPA: [L-DOPA](/wiki/L-DOPA)  
DAT: [dopamine transporter](/wiki/Dopamine_transporter)  
DDC: [DOPA decarboxylase](/wiki/DOPA_decarboxylase)  
VMAT: [vesicular monoamine transporter 2](/wiki/Vesicular_monoamine_transporter_2)  
MAO: [Monoamine oxidase](/wiki/Monoamine_oxidase)  
COMT: [Catechol-O-methyl transferase](/wiki/Catechol-O-methyl_transferase)  
HVA: [Homovanillic acid](/wiki/Homovanillic_acid)|alt=Cartoon diagram of a dopaminergic synapse, showing the synthetic and metabolic mechanisms as well as the things that can happen after release. Inside the brain, dopamine functions as a [neurotransmitter](/wiki/Neurotransmitter) and [neuromodulator](/wiki/Neuromodulator), and is controlled by a set of mechanisms common to all [monoamine neurotransmitters](/wiki/Monoamine_neurotransmitter).<ref name=Seeman/> After synthesis, dopamine is transported from the [cytosol](/wiki/Cytosol) into [synaptic vesicles](/wiki/Vesicle_(biology_and_chemistry)) by a [solute carrier](/wiki/Solute_carrier_family)—a [vesicular monoamine transporter](/wiki/Vesicular_monoamine_transporter), [VMAT2](/wiki/Vesicular_monoamine_transporter_2).<ref name=Eiden>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> Dopamine is stored in these vesicles until it is ejected into the [synaptic cleft](/wiki/Chemical_synapse) through a process called [exocytosis](/wiki/Exocytosis). In most cases exocytosis is caused by [action potentials](/wiki/Action_potential), but it can also be caused by the activity of an intracellular [trace amine-associated receptor](/wiki/Trace_amine-associated_receptor), [TAAR1](/wiki/TAAR1).[[8]](#cite_note-8) TAAR1 is a high-affinity receptor for dopamine, [trace amines](/wiki/Trace_amine), and certain [substituted amphetamines](/wiki/Substituted_amphetamine) that is located along membranes in the intracellular milieu of the presynaptic cell;[[8]](#cite_note-8) activation of the receptor can regulate dopamine signaling by producing [reuptake inhibition](/wiki/Reuptake_inhibition) and [neurotransmitter efflux](/wiki/Transporter_reversal) and inhibiting neuronal firing through a diverse set of mechanisms.[[8]](#cite_note-8)[[9]](#cite_note-9) Once in the synapse, dopamine binds to and activates dopamine receptors.[[10]](#cite_note-10) These can be [postsynaptic](/wiki/Chemical_synapse) dopamine receptors, which are located on [dendrites](/wiki/Dendrite) (the postsynaptic neuron), or presynaptic [autoreceptors](/wiki/Autoreceptor) (e.g., the [D2sh](/wiki/Dopamine_receptor_D2#Isoforms) and presynaptic D3 receptors), which are located on the membrane of an [axon terminal](/wiki/Axon_terminal) (the presynaptic neuron).[[10]](#cite_note-10) After the postsynaptic neuron elicits an action potential, dopamine molecules quickly become unbound from their receptors. They are then absorbed back into the presynaptic cell, via [reuptake](/wiki/Reuptake) mediated either by the [dopamine transporter](/wiki/Dopamine_transporter) or by the [plasma membrane monoamine transporter](/wiki/Plasma_membrane_monoamine_transporter).<ref name=Torres>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> Once back in the cytosol, dopamine can either be broken down by a [monoamine oxidase](/wiki/Monoamine_oxidase) or repackaged into vesicles by VMAT2, making it available for future release.<ref name=Eiden/>

In the brain the level of extracellular dopamine is modulated by two mechanisms: [phasic and tonic transmission](/wiki/Sensory_receptor#Rate_of_adaptation).<ref name=Rice>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> Phasic dopamine release, like most neurotransmitter release in the nervous system, is driven directly by action potentials in the dopamine-containing cells.<ref name=Rice/> Tonic dopamine transmission occurs when small amounts of dopamine are released without being preceded by presynaptic action potentials.<ref name=Rice/> Tonic transmission is regulated by a variety of factors, including the activity of other neurons and neurotransmitter reuptake.<ref name=Rice/>

### {{Anchor|Functions in the brain}} Nervous system[[edit](/index.php?title=(none)&action=edit&section=8)]

[Template:Main article](/wiki/Template:Main_article) [thumb|Major dopamine pathways. As part of the reward pathway, dopamine is manufactured in nerve cell bodies located within the](/wiki/File:Dopamine_pathways.svg) [ventral tegmental area](/wiki/Ventral_tegmental_area) (VTA) and is released in the [nucleus accumbens](/wiki/Nucleus_accumbens) and the [prefrontal cortex](/wiki/Prefrontal_cortex). The motor functions of dopamine are linked to a separate pathway, with cell bodies in the [substantia nigra](/wiki/Substantia_nigra) that manufacture and release dopamine into the [dorsal striatum](/wiki/Dorsal_striatum).|alt=A labelled line drawing of dopamine pathways superimposed on a drawing of the human brain.

Inside the brain, dopamine plays important roles in [executive functions](/wiki/Executive_function), [motor control](/wiki/Motor_control), [motivation](/wiki/Motivation), [arousal](/wiki/Arousal), [reinforcement](/wiki/Reinforcement), and [reward](/wiki/Reward_system), as well as lower-level functions including [lactation](/wiki/Prolactin#Effects), [sexual gratification](/wiki/Sexual_gratification), and [nausea](/wiki/Nausea). The [dopaminergic cell groups](/wiki/Dopaminergic_cell_groups) and [pathways](/wiki/Dopaminergic_pathways) make up the dopamine system which is [neuromodulatory](/wiki/Neuromodulation).

[Dopaminergic](/wiki/Dopaminergic) neurons (dopamine-producing nerve cells) are comparatively few in number—a total of around 400,000 in the human brain<ref name=SchultzAnnRev>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>—and their [cell bodies](/wiki/Soma_(biology)) are confined in groups to a few relatively small brain areas.<ref name=Bjorklund/> However their [axons](/wiki/Axon) project to many other brain areas, and they exert powerful effects on their targets.<ref name=Bjorklund/> These [dopaminergic cell groups](/wiki/Dopaminergic_cell_groups) were first mapped in 1964 by [Annica Dahlström](/wiki/Annica_Dahlström) and Kjell Fuxe, who assigned them labels starting with the letter "A" (for "aminergic").<ref name=DahlstromFuxe>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> In their scheme, areas A1 through A7 contain the neurotransmitter [norepinephrine](/wiki/Norepinephrine), whereas A8 through A14 contain dopamine. The dopaminergic areas they identified are the [substantia nigra](/wiki/Substantia_nigra) (groups 8 and 9); the [ventral tegmental area](/wiki/Ventral_tegmental_area) (group 10); the posterior [hypothalamus](/wiki/Hypothalamus) (group 11); the [arcuate nucleus](/wiki/Arcuate_nucleus) (group 12); the [zona incerta](/wiki/Zona_incerta) (group 13) and the [periventricular nucleus](/wiki/Periventricular_nucleus) (group 14).<ref name=DahlstromFuxe/>

The [substantia nigra](/wiki/Substantia_nigra) is a small [midbrain](/wiki/Midbrain) area that forms a component of the [basal ganglia](/wiki/Basal_ganglia). This has two parts—an input area called the [pars compacta](/wiki/Pars_compacta) and an output area the [pars reticulata](/wiki/Pars_reticulata). The dopaminergic neurons are found mainly in the pars compacta (cell group A8) and nearby (group A9).<ref name=Bjorklund>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> In humans, the projection of dopaminergic neurons from the substantia nigra pars compacta to the [dorsal striatum](/wiki/Dorsal_striatum), termed the [*nigrostriatal pathway*](/wiki/Nigrostriatal_pathway), plays a significant role in the control of motor function and in learning new [motor skills](/wiki/Motor_skill).[[11]](#cite_note-11) These neurons are especially vulnerable to damage, and when a large number of them die, the result is a [parkinsonian syndrome](/wiki/Parkinsonism).[[12]](#cite_note-12) The [ventral tegmental area](/wiki/Ventral_tegmental_area) (VTA) is another midbrain area. The most prominent group of VTA dopaminergic neurons projects to the [prefrontal cortex](/wiki/Prefrontal_cortex) via the [mesocortical pathway](/wiki/Mesocortical_pathway) and another smaller group projects to the [nucleus accumbens](/wiki/Nucleus_accumbens) via the [mesolimbic pathway](/wiki/Mesolimbic_pathway). Together, these two pathways are collectively termed the [*mesocorticolimbic projection*](/wiki/Mesocorticolimbic_projection).[[11]](#cite_note-11) The VTA also sends dopaminergic projections to the [amygdala](/wiki/Amygdala), [cingulate gyrus](/wiki/Cingulate_gyrus), [hippocampus](/wiki/Hippocampus), and [olfactory bulb](/wiki/Olfactory_bulb).[[11]](#cite_note-11) Mesocorticolimbic neurons play a central role in reward and other aspects of motivation.[[11]](#cite_note-11) The posterior [hypothalamus](/wiki/Hypothalamus) has dopamine neurons that project to the spinal cord, but their function is not well established.<ref name=Paulus/> There is some evidence that pathology in this area plays a role in [restless legs syndrome](/wiki/Restless_legs_syndrome), a condition in which people have difficulty sleeping due to an overwhelming compulsion to constantly move parts of the body, especially the legs.<ref name=Paulus>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

The [arcuate nucleus](/wiki/Arcuate_nucleus) and the [periventricular nucleus](/wiki/Periventricular_nucleus) of the hypothalamus have dopamine neurons that form an important projection—the [*tuberoinfundibular pathway*](/wiki/Tuberoinfundibular_pathway) which goes to the [pituitary gland](/wiki/Pituitary_gland), where it influences the secretion of the hormone [prolactin](/wiki/Prolactin).<ref name=BenJonathan/> Dopamine is the primary [neuroendocrine](/wiki/Neuroendocrine) inhibitor of the secretion of [prolactin](/wiki/Prolactin) from the [anterior pituitary](/wiki/Anterior_pituitary) gland.<ref name=BenJonathan/> Dopamine produced by neurons in the arcuate nucleus is secreted into the [hypophyseal portal system](/wiki/Hypophyseal_portal_system) of the [median eminence](/wiki/Median_eminence), which supplies the [pituitary gland](/wiki/Pituitary_gland).<ref name=BenJonathan/> The [prolactin cells](/wiki/Prolactin_cell) that produce [prolactin](/wiki/Prolactin), in the absence of dopamine, secrete prolactin continuously; dopamine inhibits this secretion.<ref name=BenJonathan/> In the context of regulating prolactin secretion, dopamine is occasionally called prolactin-inhibiting factor, prolactin-inhibiting hormone, or prolactostatin.<ref name=BenJonathan>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

The [zona incerta](/wiki/Zona_incerta), grouped between the arcuate and periventricular nuclei, projects to several areas of the hypothalamus, and participates in the control of [gonadotropin-releasing hormone](/wiki/Gonadotropin-releasing_hormone), which is necessary to activate the development of the [male](/wiki/Male_reproductive_system) and [female reproductive systems](/wiki/Female_reproductive_system), following puberty.<ref name=BenJonathan/>

An additional group of dopamine-secreting neurons is found in the [retina](/wiki/Retina) of the eye.<ref name=Witkovsky/> These neurons are [amacrine cells](/wiki/Retina_amacrine_cell), meaning that they have no axons.<ref name=Witkovsky/> They release dopamine into the extracellular medium, and are specifically active during daylight hours, becoming silent at night.<ref name=Witkovsky/> This retinal dopamine acts to enhance the activity of [cone cells](/wiki/Cone_cell) in the retina while suppressing [rod cells](/wiki/Rod_cell)—the result is to increase sensitivity to color and contrast during bright light conditions, at the cost of reduced sensitivity when the light is dim.<ref name=Witkovsky>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

#### Basal ganglia[[edit](/index.php?title=(none)&action=edit&section=9)]

[thumb|right|300px|Main circuits of the](/wiki/File:Basal_ganglia_circuits.svg) [basal ganglia](/wiki/Basal_ganglia). The dopaminergic pathway from the [substantia nigra pars compacta](/wiki/Substantia_nigra_pars_compacta) to the [striatum](/wiki/Striatum) is shown in light blue.|alt=At the top, a line drawing of a side view of the human brain, with a cross section pulled out showing the basal ganglia structures in color near the center. At the bottom an expanded line drawing of the basal ganglia structures, showing outlines of each structure and broad arrows for their connection pathways.

The largest and most important sources of dopamine in the vertebrate brain are the [substantia nigra](/wiki/Substantia_nigra) and [ventral tegmental area](/wiki/Ventral_tegmental_area).<ref name=Bjorklund/> These structures are closely related to each other and functionally similar in many respects.<ref name=Bjorklund/> Both are components of the [basal ganglia](/wiki/Basal_ganglia), a complex network of structures located mainly at the base of the [forebrain](/wiki/Forebrain).<ref name=Bjorklund/> The largest component of the basal ganglia is the [striatum](/wiki/Striatum).<ref name=brs>[Template:Cite book](/wiki/Template:Cite_book)</ref> The substantia nigra sends a dopaminergic projection to the [dorsal striatum](/wiki/Dorsal_striatum), while the ventral tegmental area sends a similar type of dopaminergic projection to the [ventral striatum](/wiki/Ventral_striatum).<ref name=Bjorklund/>

Progress in understanding the functions of the basal ganglia has been slow.[[13]](#cite_note-13) The most popular hypotheses, broadly stated, propose that the basal ganglia play a central role in [action selection](/wiki/Action_selection).<ref name=chakravarthy>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> The action selection theory in its simplest form proposes that when a person or animal is in a situation where several behaviors are possible, activity in the basal ganglia determines which of them is executed, by releasing that response from inhibition while continuing to inhibit other motor systems that if activated would generate competing behaviors.<ref name=Floresco>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> Thus the basal ganglia, in this concept, are responsible for initiating behaviors, but not for determining the details of how they are carried out. In other words, they essentially form a decision-making system.<ref name=Floresco/>

The basal ganglia can be divided into several sectors, and each is involved in controlling particular types of actions.<ref name=Balleine>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> The ventral sector of the basal ganglia (containing the ventral striatum and ventral tegmental area) operates at the highest level of the hierarchy, selecting actions at the whole-organism level.<ref name=Floresco/> The dorsal sectors (containing the dorsal striatum and substantia nigra) operate at lower levels, selecting the specific muscles and movements that are used to implement a given behavior pattern.<ref name=Balleine/>

Dopamine contributes to the action selection process in at least two important ways. First, it sets the "threshold" for initiating actions.<ref name=chakravarthy/> The higher the level of dopamine activity, the lower the impetus required to evoke a given behavior.<ref name=chakravarthy/> As a consequence, high levels of dopamine lead to high levels of motor activity and [impulsive behavior](/wiki/Impulsivity); low levels of dopamine lead to [torpor](/wiki/Torpor) and slowed reactions.<ref name=chakravarthy/> [Parkinson's disease](/wiki/Parkinson's_disease), in which dopamine levels in the substantia nigra circuit are greatly reduced, is characterized by stiffness and difficulty initiating movement—however, when people with the disease are confronted with strong stimuli such as a serious threat, their reactions can be as vigorous as those of a healthy person.<ref name=Jankovic/> In the opposite direction, drugs that increase dopamine release, such as cocaine or amphetamine, can produce heightened levels of activity, including at the extreme, [psychomotor agitation](/wiki/Psychomotor_agitation) and [stereotyped movements](/wiki/Stereotypy).<ref name=Patti>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

The second important effect of dopamine is as a "teaching" signal.<ref name=chakravarthy/> When an action is followed by an increase in dopamine activity, the basal ganglia circuit is altered in a way that makes the same response easier to evoke when similar situations arise in the future.<ref name=chakravarthy/> This is a form of [operant conditioning](/wiki/Operant_conditioning), in which dopamine plays the role of a reward signal.<ref name=Floresco/>

#### Reward[[edit](/index.php?title=(none)&action=edit&section=10)]

[thumb|Illustration of dopaminergic reward structures](/wiki/File:Overview_of_reward_structures_in_the_human_brain.jpg) In the [reward system](/wiki/Reward_system), *reward* is the attractive and [motivational](/wiki/Motivation) property of a stimulus that induces [appetitive](/wiki/Appetite) behavior (also known as approach behavior) – and consummatory behavior.[[14]](#cite_note-14) A rewarding stimulus is one that has the potential to cause an approach to it and a choice to be made to consume it or not.[[14]](#cite_note-14) [Pleasure](/wiki/Pleasure), [learning](/wiki/Learning) (e.g., [classical](/wiki/Classical_conditioning) and [operant conditioning](/wiki/Operant_conditioning)), and approach behavior are the three main functions of reward.[[14]](#cite_note-14) As an aspect of reward, *pleasure* provides a definition of reward;[[14]](#cite_note-14) however, while all pleasurable stimuli are rewarding, not all rewarding stimuli are pleasurable (e.g., extrinstic rewards like money).[[14]](#cite_note-14)<ref name=Robinson>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> The motivational or desirable aspect of rewarding stimuli is reflected by the approach behavior that they induce, whereas the pleasurable component of intrinstic rewards is derived from the consummatory behavior that ensues upon acquiring them.[[14]](#cite_note-14) A neuropsychological model which distinguishes these two components of an intrinsically rewarding stimulus is the [incentive salience](/wiki/Incentive_salience) model, where "wanting" or desire (less commonly, "seeking"<ref name=Wright>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>) corresponds to appetitive or approach behavior while "liking" or pleasure corresponds to consummatory behavior.[[14]](#cite_note-14)[[15]](#cite_note-15)<ref name=Berridge2>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> In human [drug addicts](/wiki/Addiction), "wanting" becomes dissociated with "liking" as the desire to use an addictive drug increases, while the pleasure obtained from consuming it decreases due to [drug tolerance](/wiki/Drug_tolerance).[[15]](#cite_note-15) Within the brain, dopamine functions partly as a "global reward signal", where an initial phasic dopamine response to a rewarding stimulus encodes information about the [salience](/wiki/Salience_(neuroscience)), value, and context of a reward.[[14]](#cite_note-14) In the context of reward-related learning, dopamine also functions as a *reward prediction error* signal, that is, the degree to which the value of a reward is unexpected.<ref name=Schultz/> According to this hypothesis of [Wolfram Schultz](/wiki/Wolfram_Schultz), rewards that are expected do not produce a second phasic dopamine response in certain dopaminergic cells, but rewards that are unexpected, or greater than expected, produce a short-lasting increase in synaptic dopamine, whereas the omission of an expected reward actually causes dopamine release to drop below its background level.<ref name=Schultz/> The "prediction error" hypothesis has drawn particular interest from computational neuroscientists, because an influential computational-learning method known as [temporal difference learning](/wiki/Temporal_difference_learning) makes heavy use of a signal that encodes prediction error.<ref name=Schultz/> This confluence of theory and data has led to a fertile interaction between neuroscientists and computer scientists interested in [machine learning](/wiki/Machine_learning).<ref name=Schultz/>

Evidence from [microelectrode](/wiki/Microelectrode) recordings from the brains of animals shows that dopamine neurons in the ventral tegmental area (VTA) and substantia nigra are strongly activated by a wide variety of rewarding events.<ref name=Schultz>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> These reward-responsive dopamine neurons in the VTA and substantia nigra are crucial for reward-related cognition and serve as the central component of the [reward system](/wiki/Reward_system).[[15]](#cite_note-15)<ref name=Hikosaka>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>[[16]](#cite_note-16) The function of dopamine varies in each [axonal projection](/wiki/Axonal_projection) from the VTA and substantia nigra;[[15]](#cite_note-15) for example, the VTA–[nucleus accumbens shell](/wiki/Nucleus_accumbens_shell) projection assigns incentive salience ("want") to rewarding stimuli and its associated [cues](/wiki/Cue_reactivity), the VTA–[orbitofrontal cortex](/wiki/Orbitofrontal_cortex) projection updates the value of different goals in accordance with their incentive salience, the VTA–[amygdala](/wiki/Amygdala) and VTA–[hippocampus](/wiki/Hippocampus) projections mediate the consolidation of reward-related memories, and both the VTA–[nucleus accumbens core](/wiki/Nucleus_accumbens_core) and substantia nigra–[dorsal striatum](/wiki/Dorsal_striatum) pathways are involved in learning motor responses that facilitate the acquisition of rewarding stimuli.[[15]](#cite_note-15)[[17]](#cite_note-17) Some activity within the VTA dopaminergic projections appears to be associated with reward prediction as well.[[15]](#cite_note-15)[[17]](#cite_note-17) While dopamine has a central role in mediating "wanting" — associated with the appetitive or approach behavioral responses to rewarding stimuli, detailed studies have shown that dopamine cannot simply be equated with "liking" or pleasure, as reflected in the consummatory behavioral response.<ref name=Robinson/> Dopamine neurotransmission is involved in some but not all aspects of pleasure-related cognition, since [pleasure centers](/wiki/Pleasure_center) have been identified both within the dopamine system (i.e., [nucleus accumbens shell](/wiki/Nucleus_accumbens_shell)) and outside the dopamine system (i.e., [ventral pallidum](/wiki/Ventral_pallidum) and [parabrachial nucleus](/wiki/Parabrachial_nucleus)).[[18]](#cite_note-18) For example, [direct electrical stimulation](/wiki/Brain_stimulation_reward) of dopamine pathways, using electrodes implanted in the brain, is experienced as pleasurable, and many types of animals are willing to work to obtain it.<ref name=Wise/> [Antipsychotic drugs](/wiki/Antipsychotic_drug) used to treat [psychosis](/wiki/Psychosis) reduce dopamine levels and tend to cause [anhedonia](/wiki/Anhedonia), a diminished ability to experience pleasure.<ref name=Wise2>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> Many types of pleasurable experiences—such as sex, enjoying food, or playing video games—increase dopamine release.[[19]](#cite_note-19) All addictive drugs directly or indirectly affect dopamine neurotransmission in the nucleus accumbens;[[15]](#cite_note-15)<ref name=Wise/> these drugs increase drug "wanting", leading to compulsive drug use, when repeatedly taken in high doses, presumably through the [sensitization of incentive-salience](/wiki/Addiction#Reward_sensitization).[[20]](#cite_note-20) Drugs that increase dopamine release include [stimulants](/wiki/Stimulant) such as methamphetamine or cocaine. These produce increases in "wanting" behaviors, but do not greatly alter expressions of pleasure or change levels of satiation.<ref name=Berridge2/><ref name=Wise>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> However, [opiate](/wiki/Opiate) drugs such as heroin or morphine produce increases in expressions of "liking" and "wanting" behaviors.<ref name=Berridge2/> Moreover, animals in which the ventral tegmental dopamine system has been rendered inactive do not seek food, and will starve to death if left to themselves, but if food is placed in their mouths they will consume it and show expressions indicative of pleasure.<ref name=Salamone>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

### Outside the nervous system[[edit](/index.php?title=(none)&action=edit&section=11)]

Dopamine does not cross the [blood–brain barrier](/wiki/Blood–brain_barrier), so its synthesis and functions in peripheral areas are to a large degree independent of its synthesis and functions in the brain.[[3]](#cite_note-3) A substantial amount of dopamine circulates in the bloodstream, but its functions there are not entirely clear.<ref name=Eisenhofer/> Dopamine is found in blood plasma at levels comparable to those of [epinephrine](/wiki/Epinephrine), but in humans, over 95% of the dopamine in the plasma is in the form of dopamine [sulfate](/wiki/Sulfate), a conjugate produced by the enzyme [sulfotransferase 1A3/1A4](/wiki/SULT1A3) acting on free dopamine.<ref name=Eisenhofer/> The bulk of this dopamine sulfate is produced in the [mesentery](/wiki/Mesentery) that surrounds parts of the digestive system.<ref name=Eisenhofer/> The production of dopamine sulfate is thought to be a mechanism for detoxifying dopamine that is ingested as food or produced by the digestive process—levels in the plasma typically rise more than fifty-fold after a meal.<ref name=Eisenhofer/> Dopamine sulfate has no known biological functions and is excreted in urine.<ref name=Eisenhofer/>

The relatively small quantity of unconjugated dopamine in the bloodstream may be produced by the [sympathetic nervous system](/wiki/Sympathetic_nervous_system), the digestive system, or possibly other organs.<ref name=Eisenhofer/> It may act on dopamine receptors in peripheral tissues, or be metabolized, or be converted to [norepinephrine](/wiki/Norepinephrine) by the enzyme [dopamine beta hydroxylase](/wiki/Dopamine_beta_hydroxylase), which is released into the bloodstream by the [adrenal medulla](/wiki/Adrenal_medulla).<ref name=Eisenhofer/> Some dopamine receptors are located in the walls of arteries, where they act as a [vasodilator](/wiki/Vasodilation) and an inhibitor of [norepinephrine](/wiki/Norepinephrine) release.<ref name=Missale>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> These responses might be activated by dopamine released from the [carotid body](/wiki/Carotid_body) under conditions of low oxygen, but whether arterial dopamine receptors perform other biologically useful functions is not known.<ref name=Missale/>

Beyond its role in modulating blood flow, there are several peripheral systems in which dopamine circulates within a limited area and performs an [exocrine](/wiki/Exocrine_gland) or [paracrine](/wiki/Paracrine_signalling) function.<ref name=Eisenhofer/> The peripheral systems in which dopamine plays an important role include the [immune system](/wiki/Immune_system), the [kidneys](/wiki/Kidney) and the [pancreas](/wiki/Pancreas).

In the immune system dopamine acts upon receptors present on immune cells, especially [lymphocytes](/wiki/Lymphocyte).<ref name=Buttarelli>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> Dopamine can also affect immune cells in the [spleen](/wiki/Spleen), [bone marrow](/wiki/Bone_marrow), and [circulatory system](/wiki/Circulatory_system).[[21]](#cite_note-21) In addition, dopamine can be synthesized and released by immune cells themselves.<ref name=Buttarelli/> The main effect of dopamine on lymphocytes is to reduce their activation level. The functional significance of this system is unclear, but it affords a possible route for interactions between the nervous system and immune system, and may be relevant to some autoimmune disorders.[[21]](#cite_note-21) The renal dopaminergic system is located in the cells of the [nephron](/wiki/Nephron) in the kidney, where all subtypes of dopamine receptors are present.[[22]](#cite_note-22) Dopamine is also synthesized there, by [tubule](/wiki/Nephron) cells, and discharged into the [tubular fluid](/wiki/Tubular_fluid). Its actions include increasing the blood supply to the kidneys, increasing the [glomerular filtration rate](/wiki/Renal_function), and increasing the excretion of sodium in the urine. Hence, defects in renal dopamine function can lead to reduced sodium excretion and consequently result in the development of [high blood pressure](/wiki/Hypertension). There is strong evidence that faults in the production of dopamine or in the receptors can result in a number of pathologies including [oxidative stress](/wiki/Oxidative_stress), [edema](/wiki/Edema), and either genetic or essential hypertension. Oxidative stress can itself cause hypertension.[[23]](#cite_note-23) Defects in the system can also be caused by genetic factors or high blood pressure.[[24]](#cite_note-24) In the pancreas the role of dopamine is somewhat complex. The pancreas consists of two parts, an [exocrine](/wiki/Exocrine_component_of_pancreas) and an [endocrine](/wiki/Pancreatic_islets) component. The exocrine part synthesizes and secretes [digestive enzymes](/wiki/Digestive_enzymes) and other substances, including dopamine, into the [small intestine](/wiki/Small_intestine).<ref name=Rubi/> The function of this secreted dopamine after it enters the small intestine is not clearly established—the possibilities include protecting the intestinal mucosa from damage and reducing [gastrointestinal motility](/wiki/Gastrointestinal_motility) (the rate at which content moves through the digestive system).<ref name=Rubi>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

The [pancreatic islets](/wiki/Pancreatic_islets) make up the endocrine part of the pancreas, and synthesize and secrete hormones including [insulin](/wiki/Insulin) into the bloodstream.<ref name=Rubi/> There is evidence that the [beta cells](/wiki/Beta_cell) in the islets that synthesize insulin contain dopamine receptors, and that dopamine acts to reduce the amount of insulin they release.<ref name=Rubi/> The source of their dopamine input is not clearly established—it may come from dopamine that circulates in the bloodstream and derives from the sympathetic nervous system, or it may be synthesized locally by other types of pancreatic cells.<ref name=Rubi/>

## Medical uses[[edit](/index.php?title=(none)&action=edit&section=12)]

[thumb|upright=0.75|Dopamine HCl preparation, single dose vial for intravenous administration|alt=Dopamine HCl preparation, single dose vial for intravenous administration.](/wiki/File:Dopamine_HCl.JPG)

Dopamine as a manufactured [medication](/wiki/Pharmaceutical_drug) is sold under the trade names Intropin, Dopastat, and Revimine, among others, and is widely used: it is on the [World Health Organization's List of Essential Medicines](/wiki/World_Health_Organization's_List_of_Essential_Medicines).[[25]](#cite_note-25) It is most commonly used as a [stimulant drug](/wiki/Sympathomimetic_drug) in the treatment of severe [low blood pressure](/wiki/Hypotension), [slow heart rate](/wiki/Bradycardia), and [cardiac arrest](/wiki/Cardiac_arrest). It is especially important in treating these in [newborn infants](/wiki/Neonates).<ref name=Noori>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> It is given intravenously. Since the half-life of dopamine in [plasma](/wiki/Blood_plasma) is very short—approximately one minute in adults, two minutes in newborn infants and up to five minutes in preterm infants—it is usually given in a continuous [intravenous drip](/wiki/Intravenous_therapy) rather than a single injection.<ref name=BhattMehta>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

Its effects, depending on dosage, include an increase in sodium excretion by the kidneys, an increase in urine output, an increase in [heart rate](/wiki/Heart_rate), and an increase in [blood pressure](/wiki/Blood_pressure).<ref name=BhattMehta/> At low doses it acts through the [sympathetic nervous system](/wiki/Sympathetic_nervous_system) to increase [heart muscle contraction force](/wiki/Stroke_volume) and heart rate, thereby increasing [cardiac output](/wiki/Cardiac_output) and blood pressure.[[26]](#cite_note-26) Higher doses also cause [vasoconstriction](/wiki/Vasoconstriction) that further increases blood pressure.[[26]](#cite_note-26)[[27]](#cite_note-27) Older literature also describes very low doses thought to improve kidney function without other consequences, but recent reviews have concluded that doses at such low levels are not effective and may sometimes be harmful.[[28]](#cite_note-28) While some effects result from stimulation of dopamine receptors, the prominent cardiovascular effects result from dopamine acting at [α1](/wiki/Alpha-1_adrenergic_receptor), [β1](/wiki/Β1-adrenergic_receptor), and [β2](/wiki/Β2_receptor) [adrenergic receptors](/wiki/Adrenergic_receptor).[[29]](#cite_note-29)[[30]](#cite_note-30) [Side effects](/wiki/Side_effects) of dopamine include negative effects on [kidney function](/wiki/Renal_function) and [irregular heartbeats](/wiki/Cardiac_arrhythmias).[[26]](#cite_note-26) The [LD50](/wiki/Median_lethal_dose), or lethal dose which is expected to prove fatal in 50% of the population, has been found to be: 59 mg/kg (mouse; administered [intravenously](/wiki/Intravenously)); 950 mg/kg (mouse; administered [intraperitoneally](/wiki/Intraperitoneally)); 163 mg/kg (rat; administered intraperitoneally); 79 mg/kg (dog; administered intravenously).[[31]](#cite_note-31) A [fluorinated](/wiki/Fluorinated) form of L-DOPA known as [fluorodopa](/wiki/Fluorodopa) is available for use in [positron emission tomography](/wiki/Positron_emission_tomography) to assess the function of the nigrostriatal pathway.[[32]](#cite_note-32)

## Disease, disorders, and pharmacology[[edit](/index.php?title=(none)&action=edit&section=13)]

[Template:See also](/wiki/Template:See_also)

The dopamine system plays a central role in several significant medical conditions, including [Parkinson's disease](/wiki/Parkinson's_disease), [attention deficit hyperactivity disorder](/wiki/Attention_deficit_hyperactivity_disorder), [schizophrenia](/wiki/Schizophrenia), and [addiction](/wiki/Addiction). Aside from dopamine itself, there are many other important drugs that act on dopamine systems in various parts of the brain or body. Some are used for medical or recreational purposes, but [neurochemists](/wiki/Neurochemist) have also developed a variety of research drugs, some of which bind with high affinity to specific types of dopamine receptors and either [agonize](/wiki/Agonist) or [antagonize](/wiki/Receptor_antagonist) their effects, and many that affect other aspects of dopamine physiology,[[33]](#cite_note-33) including [dopamine transporter](/wiki/Dopamine_transporter) inhibitors, [VMAT](/wiki/Vesicular_monoamine_transporter) inhibitors, and [enzyme inhibitors](/wiki/Enzyme_inhibitors).

### Aging brain[[edit](/index.php?title=(none)&action=edit&section=14)]

[Template:Main article](/wiki/Template:Main_article) A number of studies have reported an age-related decline in dopamine synthesis and dopamine receptor density (i.e., the number of receptors) in the brain.[[34]](#cite_note-34) This decline has been shown to occur in the [striatum](/wiki/Striatum) and [extrastriatal](/wiki/Extrastriate_cortex) regions.[[35]](#cite_note-35) Decreases in the [D1](/wiki/Dopamine_receptor_D1), [D2](/wiki/Dopamine_receptor_D2), and [D3](/wiki/Dopamine_receptor_D3) receptors are well documented.[[36]](#cite_note-36)[[37]](#cite_note-37)[[38]](#cite_note-38) The reduction of dopamine with aging is thought to be responsible for many neurological symptoms that increase in frequency with age, such as decreased arm swing and increased [rigidity](/wiki/Rigidity_(neurology)).[[39]](#cite_note-39) Changes in dopamine levels may also cause age-related changes in cognitive flexibility.[[39]](#cite_note-39) Other neurotransmitters, such as [serotonin](/wiki/Serotonin) and [glutamate](/wiki/Glutamate) also show a decline in output with aging.[[38]](#cite_note-38)[[40]](#cite_note-40)

### Parkinson's disease[[edit](/index.php?title=(none)&action=edit&section=15)]

[Parkinson's disease](/wiki/Parkinson's_disease) is an age-related disorder characterized by [movement disorders](/wiki/Movement_disorder) such as stiffness of the body, slowing of movement, and trembling of limbs when they are not in use.<ref name=Jankovic>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> In advanced stages it progresses to [dementia](/wiki/Dementia) and eventually death.<ref name=Jankovic/> The main symptoms are caused by the loss of dopamine-secreting cells in the [substantia nigra](/wiki/Substantia_nigra).<ref name=Dickson>[Template:Cite book](/wiki/Template:Cite_book)</ref> These dopamine cells are especially vulnerable to damage, and a variety of insults, including [encephalitis](/wiki/Encephalitis) (as depicted in the book and movie "[Awakenings](/wiki/Awakenings)"), repeated sports-related [concussions](/wiki/Concussion), and some forms of chemical poisoning such as [MPTP](/wiki/MPTP), can lead to substantial cell loss, producing a [parkinsonian syndrome](/wiki/Parkinsonism) that is similar in its main features to Parkinson's disease.<ref name=Tuite>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> Most cases of Parkinson's disease, however, are [idiopathic](/wiki/Idiopathic), meaning that the cause of cell death cannot be identified.<ref name=Tuite/>

The most widely used treatment for parkinsonism is administration of [L-DOPA](/wiki/L-DOPA), the metabolic precursor for dopamine.[[3]](#cite_note-3) L-DOPA is converted to dopamine in the brain and various parts of the body by the enzyme [DOPA decarboxylase](/wiki/DOPA_decarboxylase).<ref name=Musacchio/> L-DOPA is used rather than dopamine itself because, unlike dopamine, it is capable of crossing the [blood-brain barrier](/wiki/Blood-brain_barrier).[[3]](#cite_note-3) It is often co-administered with an [enzyme inhibitor](/wiki/Enzyme_inhibitor) of peripheral [decarboxylation](/wiki/Decarboxylation) such as [carbidopa](/wiki/Carbidopa) or [benserazide](/wiki/Benserazide), to reduce the amount converted to dopamine in the periphery and thereby increase the amount of L-DOPA that enters the brain.[[3]](#cite_note-3) When L-DOPA is administered regularly over a long time period, a variety of unpleasant side effects such as [dyskinesia](/wiki/Dyskinesia) often begin to appear; even so, it is considered the best available long-term treatment option for most cases of Parkinson's disease.[[3]](#cite_note-3) L-DOPA treatment cannot restore the dopamine cells that have been lost, but it causes the remaining cells to produce more dopamine, thereby compensating for the loss to at least some degree.[[3]](#cite_note-3) In advanced stages the treatment begins to fail because the cell loss is so severe that the remaining ones cannot produce enough dopamine regardless of L-DOPA levels.[[3]](#cite_note-3) Other drugs that enhance dopamine function, such as [bromocryptine](/wiki/Bromocryptine) and [pergolide](/wiki/Pergolide), are also sometimes used to treat Parkinsonism, but in most cases L-DOPA appears to give the best trade-off between positive effects and negative side-effects.[[3]](#cite_note-3) Dopaminergic medications that are used to treat Parkinson's disease are sometimes associated with the development of a [dopamine dysregulation syndrome](/wiki/Dopamine_dysregulation_syndrome), which involves the overuse of dopaminergic medication and medication-induced compulsive engagement in [natural rewards](/wiki/Natural_reward) like gambling and sexual activity.[[41]](#cite_note-41)[[42]](#cite_note-42) The latter behaviors are similar to those observed in individuals with a [behavioral addiction](/wiki/Behavioral_addiction).[[41]](#cite_note-41)

### Drug addiction and psychostimulants[[edit](/index.php?title=(none)&action=edit&section=16)]

[Template:Main article](/wiki/Template:Main_article) [thumb|right|Cocaine increases dopamine levels by blocking](/wiki/File:DAT1_regulation.svg) [dopamine transporters](/wiki/Dopamine_transporter) (DAT), which transport dopamine back into a synaptic terminal after it has been emitted.|alt=Diagram describes the mechanisms by which cocaine and amphetamines reduce dopamine transporter activity.

[Cocaine](/wiki/Cocaine), [substituted amphetamines](/wiki/Substituted_amphetamine) (including [methamphetamine](/wiki/Methamphetamine)), [Adderall](/wiki/Adderall), [methylphenidate](/wiki/Methylphenidate) (marketed as Ritalin or Concerta), [MDMA](/wiki/MDMA) (ecstasy) and other [psychostimulants](/wiki/Stimulant) exert their effects primarily or partly by increasing dopamine levels in the brain by a variety of mechanisms.<ref name=Ghodse/> Cocaine and methylphenidate are [dopamine transporter](/wiki/Dopamine_transporter) blockers or [reuptake inhibitors](/wiki/Reuptake_inhibitor); they [non-competitively inhibit](/wiki/Non-competitive_inhibition) dopamine reuptake, resulting in increased dopamine concentrations in the synaptic cleft.<ref name=Heal>[Template:Cite journal](/wiki/Template:Cite_journal)</ref><ref name=Freye>[Template:Cite book](/wiki/Template:Cite_book)</ref>[Template:Rp](/wiki/Template:Rp) Like cocaine, substituted amphetamines and amphetamine also increase the concentration of dopamine in the [synaptic cleft](/wiki/Synaptic_cleft), but by different mechanisms.<ref name=Miller>[Template:Cite journal](/wiki/Template:Cite_journal)</ref><ref name=Freye/>[Template:Rp](/wiki/Template:Rp)

The effects of psychostimulants include increases in heart rate, body temperature, and sweating; improvements in alertness, attention, and endurance; increases in pleasure produced by rewarding events; but at higher doses agitation, anxiety, or even [loss of contact with reality](/wiki/Psychosis).<ref name=Ghodse>[Template:Cite book](/wiki/Template:Cite_book)</ref> Drugs in this group can have a high addiction potential, due to their activating effects on the dopamine-mediated reward system in the brain.<ref name=Ghodse/> However some can also be useful, at lower doses, for treating [attention deficit hyperactivity disorder](/wiki/Attention_deficit_hyperactivity_disorder) (ADHD) and [narcolepsy](/wiki/Narcolepsy).<ref name=Kimko/>[[43]](#cite_note-43) An important differentiating factor is the onset and duration of action.<ref name=Ghodse/> Cocaine can take effect in seconds if it is injected or inhaled in [free base](/wiki/Free_base) form; the effects last from 5 to 90 minutes.<ref name=Zimmerman>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> This rapid and brief action makes its effects easily perceived and consequently gives it high addiction potential.<ref name=Ghodse/> Methylphenidate taken in pill form, in contrast, can take two hours to reach peak levels in the bloodstream, and depending on formulation the effects can last for up to 12 hours.<ref name=Kimko>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> These slow and sustained actions reduce the addiction potential and make it more useful for treating ADHD.<ref name=Kimko/>

[thumb|right|](/wiki/File:Crystal_Meth_Rock.jpg)[Methamphetamine hydrochloride](/wiki/Methamphetamine#Physical_properties) also known as crystal meth|alt=A shiny translucent white crystal of methamphetamine, held between the ends of a finger and thumb A variety of addictive drugs produce an increase in reward-related dopamine activity.<ref name=Ghodse/> [Stimulants](/wiki/Stimulant) such as nicotine, cocaine and methamphetamine promote increased levels of dopamine which appear to be the primary factor in causing addiction. For other addictive drugs such as the [opioid](/wiki/Opioid) heroin, the increased levels of dopamine in the reward system may only play a minor role in addiction.<ref name=Nutt>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> When people addicted to stimulants go through withdrawal, they do not experience the physical suffering associated with [alcohol withdrawal](/wiki/Alcohol_withdrawal_syndrome) or [withdrawal](/wiki/Drug_withdrawal) from opiates; instead they experience [craving](/wiki/Craving_(withdrawal)), an intense desire for the drug characterized by [irritability](/wiki/Dysphoria), restlessness, and other arousal symptoms,<ref name=Sinha>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> brought about by [psychological dependence](/wiki/Psychological_dependence).

The dopamine system plays a crucial role in several aspects of addiction. At the earliest stage, genetic differences that alter the expression of dopamine receptors in the brain can predict whether a person will find stimulants appealing or aversive.<ref name=Volkow>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> Consumption of stimulants produces increases in brain dopamine levels that last from minutes to hours.<ref name=Ghodse/> Finally, the chronic elevation in dopamine that comes with repetitive high-dose stimulant consumption triggers a wide-ranging set of structural changes in the brain that are responsible for the behavioral abnormalities which characterize an addiction.[[44]](#cite_note-44) Treatment of stimulant addiction is very difficult, because even if consumption ceases, the craving that comes with psychological withdrawal does not.<ref name=Sinha/> Even when the craving seems to be extinct, it may re-emerge when faced with stimuli that are associated with the drug, such as friends, locations and situations.<ref name=Sinha/> [Association networks](/wiki/Cerebral_cortex#Association_areas) in the brain are greatly interlinked.[[45]](#cite_note-45)

### Psychosis and antipsychotic drugs[[edit](/index.php?title=(none)&action=edit&section=17)]

[Template:Main article](/wiki/Template:Main_article) Psychiatrists in the early 1950s discovered that a class of drugs known as [typical antipsychotics](/wiki/Typical_antipsychotic) (also known as major [tranquilizers](/wiki/Tranquilizer)), were often effective at reducing the [psychotic](/wiki/Psychotic) symptoms of [schizophrenia](/wiki/Schizophrenia).<ref name=Healy/> The introduction of the first widely used antipsychotic, [chlorpromazine](/wiki/Chlorpromazine) (Thorazine), in the 1950s, led to the release of many patients with schizophrenia from institutions in the years that followed.<ref name=Healy/> By the 1970s researchers understood that these typical antipsychotics worked as [antagonists](/wiki/Receptor_antagonists) on the [D2 receptors](/wiki/Dopamine_receptor_D2).<ref name=Healy/><ref name=Brunton>[Template:Cite book](/wiki/Template:Cite_book)</ref> This realization led to the so-called [dopamine hypothesis of schizophrenia](/wiki/Dopamine_hypothesis_of_schizophrenia), which postulates that schizophrenia is largely caused, by hyperactivity of brain dopamine systems.<ref name=Howes>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> The dopamine hypothesis drew additional support from the observation that psychotic symptoms were often intensified by dopamine-enhancing [stimulants](/wiki/Stimulant) such as [methamphetamine](/wiki/Methamphetamine), and that these drugs could also produce psychosis in healthy people if taken in large enough doses.<ref name=Howes/> In the following decades other [atypical antipsychotics](/wiki/Atypical_antipsychotics) that had fewer serious [side effects](/wiki/Side_effect) were developed.<ref name=Healy/> Many of these newer drugs do not act directly on dopamine receptors, but instead produce alterations in dopamine activity indirectly.<ref name=Horacek>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> These drugs were also used to treat other psychoses.<ref name=Healy>[Template:Cite book](/wiki/Template:Cite_book)</ref> [Antipsychotic drugs](/wiki/Antipsychotic_drugs) have a broadly suppressive effect on most types of active behavior, and particularly reduce the delusional and agitated behavior characteristic of overt psychosis.<ref name=Brunton/> There remains substantial dispute, however, about how much of an improvement the patient experiences on these drugs.<ref name=James/>

Later observations, however, have caused the dopamine hypothesis to lose popularity, at least in its simple original form.<ref name=Howes/> For one thing, patients with schizophrenia do not typically show measurably increased levels of brain dopamine activity.<ref name=Howes/> Also, other [dissociative](/wiki/Dissociative) drugs, notably [ketamine](/wiki/Ketamine) and [phencyclidine](/wiki/Phencyclidine) that act on [glutamate](/wiki/Glutamate) [NMDA receptors](/wiki/NMDA_receptor) (and not on dopamine receptors) can produce psychotic symptoms.<ref name=Howes/> Perhaps most importantly, those drugs that do reduce dopamine activity are a very imperfect treatment for schizophrenia: they only reduce a subset of symptoms, while producing severe short-term and long-term side effects.<ref name=Muench/> Even so, many psychiatrists and neuroscientists continue to believe that schizophrenia involves some sort of dopamine system dysfunction.<ref name=Healy/> As the "dopamine hypothesis" has evolved over time, however, the sorts of dysfunctions it postulates have tended to become increasingly subtle and complex.<ref name=Healy/>

However, the widespread use of antipsychotic drugs has long been controversial.<ref name=James>[Template:Cite web](/wiki/Template:Cite_web)</ref> There are several reasons for this. First, antipsychotic drugs are perceived as very aversive by people who have to take them, because they produce a general dullness of thought and suppress the ability to experience pleasure.<ref name=Lambert>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> Second, it is difficult to show that they act specifically against psychotic behaviors rather than merely suppressing all types of active behavior.<ref name=James/> Third, they can produce a range of serious side effects, including weight gain, diabetes, fatigue, sexual dysfunction, hormonal changes, and a type of serious [movement disorder](/wiki/Movement_disorder) known as [tardive dyskinesia](/wiki/Tardive_dyskinesia).<ref name=Muench>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> Some of these side effects may continue long after the cessation of drug use, or even permanently.<ref name=Muench/>

### Attention deficit hyperactivity disorder[[edit](/index.php?title=(none)&action=edit&section=18)]

Altered dopamine neurotransmission is implicated in [attention deficit hyperactivity disorder](/wiki/Attention_deficit_hyperactivity_disorder) (ADHD), a condition associated with impaired [cognitive control](/wiki/Cognitive_control), in turn leading to problems with regulating attention ([attentional control](/wiki/Attentional_control)), inhibiting behaviors ([inhibitory control](/wiki/Inhibitory_control)), and forgetting things or missing details ([working memory](/wiki/Working_memory)), among other problems.[[46]](#cite_note-46) There are genetic links between dopamine receptors, the dopamine transporter, and ADHD, in addition to links to other neurotransmitter receptors and transporters.<ref name=Wu>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> The most important relationship between dopamine and ADHD involves the drugs that are used to treat ADHD.<ref name=Berridge3/> Some of the most effective therapeutic agents for ADHD are psychostimulants such as [methylphenidate](/wiki/Methylphenidate) (Ritalin, Concerta) and [amphetamine](/wiki/Amphetamine) (Adderall, Dexedrine), drugs that increase both dopamine and norepinephrine levels in the brain.<ref name=Berridge3>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> The clinical effects of these psychostimulants in treating ADHD are mediated through the [indirect activation](/wiki/Indirect_agonist) of dopamine and norepinephrine receptors, specifically [dopamine receptor D1](/wiki/Dopamine_receptor_D1) and [adrenoceptor A2](/wiki/Alpha-2_adrenergic_receptor), in the [prefrontal cortex](/wiki/Prefrontal_cortex).[[46]](#cite_note-46)[[47]](#cite_note-47)[[48]](#cite_note-48)

### Pain[[edit](/index.php?title=(none)&action=edit&section=19)]

Dopamine plays a role in [pain](/wiki/Pain) processing in multiple levels of the [central nervous system](/wiki/Central_nervous_system) including the [spinal cord](/wiki/Spinal_cord), [periaqueductal gray](/wiki/Periaqueductal_gray), [thalamus](/wiki/Thalamus), [basal ganglia](/wiki/Basal_ganglia), and [cingulate cortex](/wiki/Cingulate_cortex).<ref name=Wood/> Decreased levels of dopamine have been associated with painful symptoms that frequently occur in [Parkinson's disease](/wiki/Parkinson's_disease).<ref name=Wood/> Abnormalities in dopaminergic neurotransmission also occur in several painful clinical conditions, including [burning mouth syndrome](/wiki/Burning_mouth_syndrome), [fibromyalgia](/wiki/Fibromyalgia), and [restless legs syndrome](/wiki/Restless_legs_syndrome).<ref name=Wood>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

### Nausea[[edit](/index.php?title=(none)&action=edit&section=20)]

[Nausea](/wiki/Nausea) and [vomiting](/wiki/Vomiting) are largely determined by activity in the [area postrema](/wiki/Area_postrema) in the [medulla](/wiki/Medulla_oblongata) of the [brainstem](/wiki/Brainstem), in a region known as the [chemoreceptor trigger zone](/wiki/Chemoreceptor_trigger_zone).<ref name=Flake>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> This area contains a large population of type D2 dopamine receptors.<ref name=Flake/> Consequently, drugs that activate D2 receptors have a high potential to cause nausea.<ref name=Flake/> This group includes some medications that are administered for [Parkinson's disease](/wiki/Parkinson's_disease), as well as other [dopamine agonists](/wiki/Dopamine_agonists) such as [apomorphine](/wiki/Apomorphine).<ref name=Connolly>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> In some cases, D2-receptor antagonists such as [metoclopramide](/wiki/Metoclopramide) are useful as [anti-nausea drugs](/wiki/Anti-emetics).<ref name=Flake/>

## Comparative biology and evolution[[edit](/index.php?title=(none)&action=edit&section=21)]

### Microorganisms[[edit](/index.php?title=(none)&action=edit&section=22)]

There are no reports of dopamine in [archaea](/wiki/Archaea), but it has been detected in some types of [bacteria](/wiki/Bacteria) and in the [protozoan](/wiki/Protozoa) called [*Tetrahymena*](/wiki/Tetrahymena).[[49]](#cite_note-49) Perhaps more importantly, there are types of bacteria that contain [homologs](/wiki/Homology_(biology)) of all the enzymes that animals use to synthesize dopamine.<ref name=Iyer/> It has been proposed that animals derived their dopamine-synthesizing machinery from bacteria, via [horizontal gene transfer](/wiki/Horizontal_gene_transfer) that may have occurred relatively late in evolutionary time, perhaps as a result of the [symbiotic](/wiki/Symbiotic) incorporation of bacteria into [eukaryotic](/wiki/Eukaryote) cells that gave rise to [mitochondria](/wiki/Mitochondrion).<ref name=Iyer>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

### Animals[[edit](/index.php?title=(none)&action=edit&section=23)]

Dopamine is used as a [neurotransmitter](/wiki/Neurotransmitter) in most multicellular animals.<ref name=Barron/> In [sponges](/wiki/Sponge) there is only a single report of the presence of dopamine, with no indication of its function;[[50]](#cite_note-50) however, dopamine has been reported in the nervous systems of many other [radially symmetric](/wiki/Symmetry_in_biology#radially_symmetric) species, including the [cnidarian](/wiki/Cnidarian) [jellyfish](/wiki/Jellyfish), [hydra](/wiki/Hydra_(genus)) and some [corals](/wiki/Coral).[[51]](#cite_note-51) This dates the emergence of dopamine as a neurotransmitter back to the earliest appearance of the nervous system, over 500 million years ago in the [Cambrian era](/wiki/Cambrian). Dopamine functions as a neurotransmitter in [vertebrates](/wiki/Vertebrate), [echinoderms](/wiki/Echinoderm), [arthropods](/wiki/Arthropod), [molluscs](/wiki/Mollusca), and several types of [worm](/wiki/Worm).<ref name=Cottrell>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>[[52]](#cite_note-52) In every type of animal that has been examined, dopamine has been seen to modify motor behavior.<ref name=Barron>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> In the [model organism](/wiki/Model_organism), [nematode](/wiki/Nematode) [*Caenorhabditis elegans*](/wiki/Caenorhabditis_elegans), it reduces [locomotion](/wiki/Animal_locomotion) and increases food-exploratory movements; in [flatworms](/wiki/Flatworm) it produces "screw-like" movements; in [leeches](/wiki/Leech) it inhibits swimming and promotes crawling. Across a wide range of vertebrates, dopamine has an "activating" effect on behavior-switching and response selection, comparable to its effect in mammals.<ref name=Barron/>

Dopamine has also consistently been shown to play a role in reward learning, in all animal groups.<ref name=Barron/> As in all [vertebrates](/wiki/Vertebrate) – [invertebrates](/wiki/Invertebrate) such as [roundworms](/wiki/Nematodes), [flatworms](/wiki/Flatworm), [molluscs](/wiki/Mollusc) and [common fruit flies](/wiki/Drosophila_melanogaster) can all be trained to repeat an action if it is consistently followed by an increase in dopamine levels.[[53]](#cite_note-53) It had long been believed that arthropods were an exception to this with dopamine being seen as having an adverse effect. Reward was seen to be mediated instead by [octopamine](/wiki/Octopamine_(neurotransmitter)), a neurotransmitter closely related to norepinephrine.<ref name=Waddell/> More recent studies however have shown that dopamine does play a part in reward learning in fruit flies. Also it has been found that the rewarding effect of octopamine is due to its activating a set of dopaminergic neurons not previously accessed in the research.<ref name=Waddell>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

### Plants[[edit](/index.php?title=(none)&action=edit&section=24)]

[thumb|right|Dopamine can be found in the](/wiki/File:Bananas_white_background_DS.jpg) [peel](/wiki/Banana_peel) and fruit pulp of [bananas](/wiki/Bananas).|alt=Photo of a bunch of bananas.

Many plants, including a variety of food plants, synthesize dopamine to varying degrees.<ref name=Kulma/> The highest concentrations have been observed in bananas—the fruit pulp of [red](/wiki/Red_banana) and [yellow bananas](/wiki/Cavendish_banana) contains dopamine at levels of 40 to 50 parts per million by weight.<ref name=Kulma/> Potatoes, avocados, broccoli, and Brussels sprouts may also contain dopamine at levels of 1 part per million or more; oranges, tomatoes, spinach, beans, and other plants contain measurable concentrations less than 1 part per million.<ref name=Kulma>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> The dopamine in plants is synthesized from the amino acid tyrosine, by biochemical mechanisms similar to those that animals use.<ref name=Kulma/> It can be metabolized in a variety of ways, producing [melanin](/wiki/Melanin) and a variety of [alkaloids](/wiki/Alkaloid) as byproducts.<ref name=Kulma/> The functions of plant catecholamines have not been clearly established, but there is evidence that they play a role in the response to stressors such as bacterial infection, act as growth-promoting factors in some situations, and modify the way that sugars are metabolized. The receptors that mediate these actions have not yet been identified, nor have the intracellular mechanisms that they activate.<ref name=Kulma/>

Dopamine consumed in food cannot act on the brain, because it cannot cross the [blood–brain barrier](/wiki/Blood–brain_barrier).[[3]](#cite_note-3) However, there are also a variety of plants that contain [L-DOPA](/wiki/L-DOPA), the metabolic precursor of dopamine.<ref name=Ingle>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> The highest concentrations are found in the leaves and bean pods of plants of the genus [*Mucuna*](/wiki/Mucuna), especially in [*Mucuna pruriens*](/wiki/Mucuna_pruriens) (velvet beans), which have been used as a source for L-DOPA as a drug.[[54]](#cite_note-54) Another plant containing substantial amounts of L-DOPA is [*Vicia faba*](/wiki/Vicia_faba), the plant that produces fava beans (also known as "broad beans"). The level of L-DOPA in the beans, however, is much lower than in the pod shells and other parts of the plant.[[55]](#cite_note-55) The seeds of [*Cassia*](/wiki/Cassia_(legume)) and [*Bauhinia*](/wiki/Bauhinia) trees also contain substantial amounts of L-DOPA.<ref name=Ingle/>

In a species of [marine](/wiki/Seawater) [green algae](/wiki/Green_algae) [*Ulvaria obscura*](/wiki/Ulvaria_obscura), a major component of some [algal blooms](/wiki/Algal_bloom), dopamine is present in very high concentrations, estimated at 4.4% of dry weight. There is evidence that this dopamine functions as an anti-[herbivore](/wiki/Herbivore) defense, reducing consumption by snails and [isopods](/wiki/Isopoda).[[56]](#cite_note-56)

### As a precursor for melanin[[edit](/index.php?title=(none)&action=edit&section=25)]

[Template:Anchor](/wiki/Template:Anchor)

[Melanins](/wiki/Melanin) are a family of dark-pigmented substances found in a wide range of organisms.<ref name=Simon/> Chemically they are closely related to dopamine, and there is a type of melanin, known as **dopamine-melanin**, that can be synthesized by oxidation of dopamine via the enzyme [tyrosinase](/wiki/Tyrosinase).<ref name=Simon>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> The melanin that darkens human skin is not of this type: it is synthesized by a pathway that uses [L-DOPA](/wiki/L-DOPA) as a precursor but not dopamine.<ref name=Simon/> However, there is substantial evidence that the [neuromelanin](/wiki/Neuromelanin) that gives a dark color to the brain's [substantia nigra](/wiki/Substantia_nigra) is at least in part dopamine-melanin.[[57]](#cite_note-57) Dopamine-derived melanin probably appears in at least some other biological systems as well. Some of the dopamine in plants is likely to be used as a precursor for dopamine-melanin.[[58]](#cite_note-58) The complex patterns that appear on butterfly wings, as well as black-and-white stripes on the bodies of insect larvae, are also thought to be caused by spatially structured accumulations of dopamine-melanin.[[59]](#cite_note-59)

## History and development[[edit](/index.php?title=(none)&action=edit&section=26)]

[Template:Main article](/wiki/Template:Main_article) Dopamine was first synthesized in 1910 by [George Barger](/wiki/George_Barger) and James Ewens at [Wellcome](/wiki/Wellcome_Trust) Laboratories in London, England[[60]](#cite_note-60) and first identified in the human brain by [Kathleen Montagu](/wiki/Kathleen_Montagu) in 1957. It was named dopamine because it is a [monoamine](/wiki/Monoamine) whose [precursor](/wiki/Precursor_chemical) in the Barger-Ewens synthesis is 3,4-**d**ihydr**o**xy**p**henyl**a**lanine (levodopa or [L-DOPA](/wiki/L-DOPA)). Dopamine's function as a neurotransmitter was first recognized in 1958 by [Arvid Carlsson](/wiki/Arvid_Carlsson) and [Nils-Åke Hillarp](/wiki/Nils-Åke_Hillarp) at the Laboratory for Chemical Pharmacology of the National Heart Institute of [Sweden](/wiki/Sweden).[[61]](#cite_note-61) Carlsson was awarded the 2000 [Nobel Prize in Physiology or Medicine](/wiki/Nobel_Prize_in_Physiology_or_Medicine) for showing that dopamine is not only a precursor of [norepinephrine](/wiki/Norepinephrine) (noradrenaline) and [epinephrine](/wiki/Epinephrine) (adrenaline), but is also itself a neurotransmitter.<ref name=Barondes>[Template:Cite book](/wiki/Template:Cite_book)</ref>

### Polydopamine[[edit](/index.php?title=(none)&action=edit&section=27)]

Research motivated by [adhesive](/wiki/Bioadhesive) [polyphenolic proteins](/wiki/Polyphenolic_protein) in [mussels](/wiki/Mussel) led to the discovery in 2007 that a wide variety of materials, if placed in a solution of dopamine at slightly basic [pH](/wiki/PH), will become coated with a layer of polymerized dopamine, often referred to as **polydopamine**.[[62]](#cite_note-62)<ref name=Dreyer>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> This polymerized dopamine forms by a spontaneous oxidation reaction, and is formally a type of [melanin](/wiki/Melanin).<ref name=Lynge>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> Synthesis usually involves reaction of dopamine hydrochloride with [Tris](/wiki/Tris) as a base in water. The structure of polydopamine is unknown.[[63]](#cite_note-63) Polydopamine coatings can form on objects ranging in size from [nanoparticles](/wiki/Nanoparticle) to large surfaces.<ref name=Lynge/> Polydopamine layers have chemical properties that have the potential to be extremely useful, and numerous studies have examined their possible applications.<ref name=Lynge/> At the simplest level, they can be used for protection against damage by light, or to form capsules for drug delivery.<ref name=Lynge/> At a more sophisticated level, their adhesive properties may make them useful as substrates for [biosensors](/wiki/Biosensor) or other biologically active macromolecules.<ref name=Lynge/>

## References[[edit](/index.php?title=(none)&action=edit&section=28)]

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