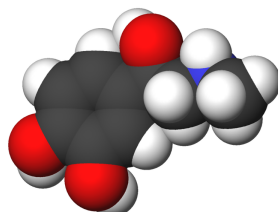
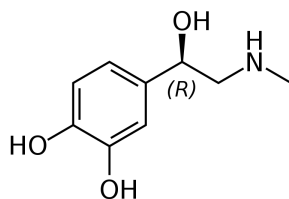


# Epinephrine

(*R*)-(-)-L-Epinephrine or (*R*)-(-)-L-adrenaline



### Systematic (IUPAC) name

(*R*)-4-(1-hydroxy-2-(methylamino)ethyl)benzene-1,2-diol

### Identifiers

<b>CAS number</b>	51-43-4 <sup>[1]</sup>
<b>ATC code</b>	A01 AD01 <sup>[2]</sup> B02 BC09 <sup>[3]</sup> C01 CA24 <sup>[4]</sup> R01 AA14 <sup>[5]</sup> R03 AA01 <sup>[6]</sup> S01 EA01 <sup>[7]</sup>
<b>PubChem</b>	CID 5816 <sup>[8]</sup>
<b>IUPHAR ligand ID</b>	509 <sup>[9]</sup>
<b>DrugBank</b>	DB00668 <sup>[10]</sup>
<b>ChemSpider</b>	5611 <sup>[11]</sup>

### Chemical data

<b>Formula</b>	$C_9H_{13}NO_3$
<b>Mol. mass</b>	183.204 g/mol
<b>SMILES</b>	eMolecules <sup>[12]</sup> & PubChem <sup>[13]</sup>

### Pharmacokinetic data

<b>Bioavailability</b>	Nil (oral)
<b>Metabolism</b>	adrenergic synapse (MAO and COMT)
<b>Half-life</b>	2 minutes
<b>Excretion</b>	Urine

### Therapeutic considerations

<b>Pregnancy cat.</b>	A(AU) C(US)
<b>Legal status</b>	Prescription Only (S4) (AU) POM (UK) <input type="checkbox"/> -only (US)
<b>Routes</b>	IV, IM, endotracheal, IC

✓ (what is this?) (verify) <sup>[14]</sup>

**Epinephrine** (also known as **adrenaline**) is a hormone and neurotransmitter.<sup>[15]</sup> It increases heart rate, contracts blood vessels, dilates air passages and participates in the fight-or-flight response of the sympathetic nervous system.<sup>[16]</sup> Chemically, epinephrine is a catecholamine, a monoamine produced only by the adrenal glands from the amino acids phenylalanine and tyrosine.

The term *adrenaline* is derived from the Latin roots *ad-* and *renes* and literally means *on the kidney*, in reference to the adrenal gland's anatomic location on the kidney. The Greek roots *epi-* and *nephros* have similar meanings, and give rise to *epinephrine*. The term *epinephrine* is often shortened to **epi** in medical jargon.<sup>[17]</sup>

Adrenal extracts containing adrenaline were first obtained by Polish physiologist Napoleon Cybulski in 1895. These extracts, which he called "nadnerczyna", contained epinephrine and other catecholamines.<sup>[18]</sup> Japanese chemist Jokichi Takamine and his assistant Keizo Uenaka independently discovered adrenaline in 1900.<sup>[19] [20]</sup> In 1901, Takamine successfully isolated and purified the hormone from the adrenal glands of sheep and oxen.<sup>[21]</sup> Adrenaline was first synthesized in the laboratory by Friedrich Stolz and Henry Drysdale Dakin, independently, in 1904.<sup>[20]</sup>

## Actions in the body

As a hormone, epinephrine acts on nearly all body tissues. Its actions vary by tissue type and tissue expression of adrenergic receptors. For example, epinephrine causes smooth muscle relaxation in the airways, but causes contraction of the smooth muscle that lines most arterioles.

Epinephrine acts by binding to a variety of adrenergic receptors. Adrenaline is a nonselective agonist of all adrenergic receptors, including  $\alpha_1$ ,  $\alpha_2$ ,  $\beta_1$ ,  $\beta_2$ , and  $\beta_3$  receptors.<sup>[22]</sup> Epinephrine's binding to these receptors triggers a number of metabolic changes. Binding to  $\alpha$ -adrenergic receptors inhibits insulin secretion by the pancreas, stimulates glycogenolysis in the liver and muscle, and stimulates glycolysis in muscle.<sup>[23]</sup>  $\beta$ -Adrenergic receptor binding triggers glucagon secretion in the pancreas, increased adrenocorticotropic hormone (ACTH) secretion by the pituitary gland, and increased lipolysis by adipose tissue. Together these effects lead to increased blood glucose and fatty acids, providing substrates for energy production within cells throughout the body.<sup>[23]</sup>

In addition to these metabolic changes, epinephrine also leads to broad alterations throughout all organ systems.

### Physiologic responses to epinephrine by organ

Organ	Effects
Heart	Increases heart rate
Lungs	Increases respiratory rate
Nearly all tissues	Vasoconstriction or vasodilation
Liver	Stimulates glycogenolysis
N/A, systemic	Triggers lipolysis
N/A, systemic	Muscles contraction

## Biosynthesis and regulation

Adrenaline is synthesized in the adrenal gland in an enzymatic pathway that converts the amino acid tyrosine into a series of intermediates and ultimately adrenaline. Tyrosine is first oxidized to L-DOPA, which is subsequently decarboxylated to give dopamine. Oxidation gives norepinephrine, which is methylated to give epinephrine.

Adrenaline is synthesized via methylation of the primary distal amine of noradrenaline by phenylethanolamine N-methyltransferase (PNMT) in the cytosol of adrenergic neurons and cells of the adrenal medulla (so-called chromaffin cells). PNMT is only found in the cytosol of cells of adrenal medullary cells. PNMT uses S-adenosylmethionine (SAME) as a cofactor to donate the methyl group to noradrenaline, creating adrenaline.

For noradrenaline to be acted upon by PNMT in the cytosol, it must first be shipped out of granules of the chromaffin cells. This may occur via the catecholamine-H<sup>+</sup> exchanger VMAT1. VMAT1 is also responsible for transporting newly synthesized adrenaline from the cytosol back into chromaffin granules in preparation for release.

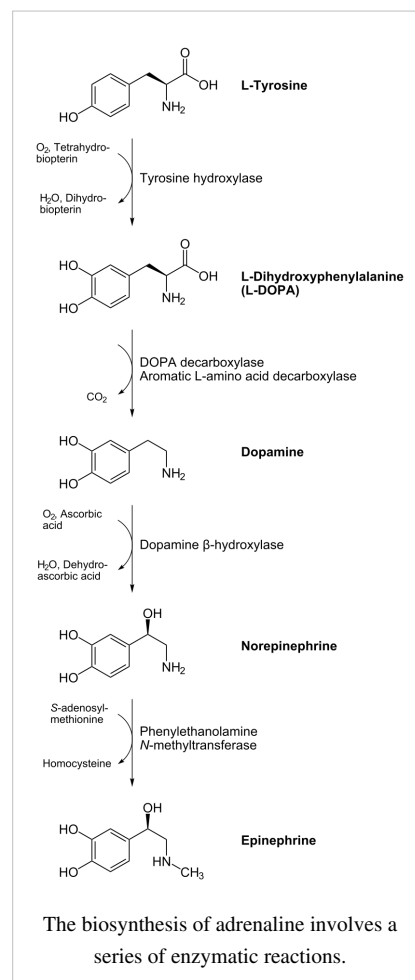
In liver cells, adrenaline binds to the  $\beta$ -Adrenergic receptor which changes conformation and helps Gs, a G protein, exchange GDP to GTP. This trimeric G protein dissociates to Gs alpha and Gs beta/gamma subunits. Gs alpha binds to adenylyl cyclase thus converting ATP into Cyclic AMP. Cyclic AMP binds to the regulatory subunit of Protein Kinase A: Protein kinase A phosphorylates Phosphorylase Kinase. Meanwhile, Gs beta/gamma binds to the calcium channel and allows calcium ions to enter the cytoplasm. Calcium ions bind to calmodulin proteins, a protein present in all eukaryotic cells, which then binds to Phosphorylase Kinase and finishes its activation. Phosphorylase Kinase phosphorylates Glycogen phosphorylase which then phosphorylates glycogen and converts it to glucose-6-phosphate.

## Regulation

The major physiologic triggers of adrenaline release center upon stresses such as physical threat, excitement, noise, bright lights, and high ambient temperature. All of these stimuli are processed in the central nervous system<sup>[24]</sup>.

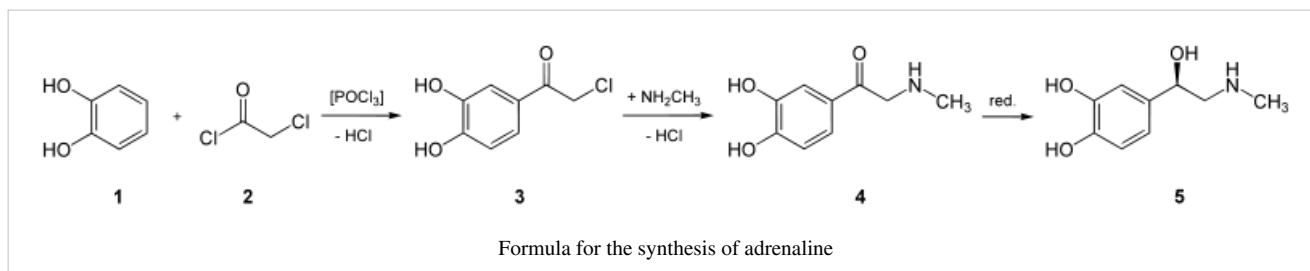
Adrenocorticotrophic hormone (ACTH) and the sympathetic nervous system stimulate the synthesis of adrenaline precursors by enhancing the activity of tyrosine hydroxylase and dopamine- $\beta$ -hydroxylase, two key enzymes involved in catecholamine synthesis. ACTH also stimulates the adrenal cortex to release cortisol, which increases the expression of PNMT in chromaffin cells, enhancing adrenaline synthesis. This is most often done in response to stress. The sympathetic nervous system, acting via splanchnic nerves to the adrenal medulla, stimulates the release of adrenaline. Acetylcholine released by preganglionic sympathetic fibers of these nerves acts on nicotinic acetylcholine receptors, causing cell depolarization and an influx of calcium through voltage-gated calcium channels. Calcium triggers the exocytosis of chromaffin granules and thus the release of adrenaline (and noradrenaline) into the bloodstream.

Adrenaline (as with noradrenaline) does exert negative feedback to down-regulate its own synthesis at the presynaptic alpha-2 adrenergic receptor. Abnormally elevated levels of adrenaline can occur in a variety of conditions, such as surreptitious epinephrine administration, pheochromocytoma, and other tumors of the sympathetic ganglia.



## Chemical synthesis

Epinephrine may be synthesized by the reaction of catechol with chloroacetyl chloride, followed by the reaction with methylamine to give the ketone, which is reduced to the desired hydroxy compound. The racemic mixture may be separated using tartaric acid.



## Therapeutic use

Epinephrine is available in a variety of preparations for the management of several medical conditions. Aqueous preparations of adrenaline are obtained by use of hydrochloric acid or tartaric acid, since it undergoes oxidation in the absence of acid medium. Borate salt is used in ophthalmology.

## Cardiac arrest

Adrenaline is used as a drug to treat cardiac arrest and other cardiac dysrhythmias resulting in diminished or absent cardiac output. Its actions are to increase peripheral resistance via  $\alpha_1$  receptor-dependent vasoconstriction and to increase cardiac output via its binding to  $\beta_1$  receptors.

## Shock and anaphylaxis

Due to its vasoconstrictive effects, adrenaline is the drug of choice for treating anaphylaxis. It is also useful in treating sepsis. Allergy<sup>[25]</sup> patients undergoing immunotherapy may receive an adrenaline rinse before the allergen extract is administered, thus reducing the immune response to the administered allergen. It is also used as a bronchodilator for asthma if specific  $\beta_2$  agonists are unavailable or ineffective.<sup>[26]</sup>

Because of various expression of  $\alpha_1$  or  $\beta_2$  receptors, depending on the patient, administration of adrenaline may *raise* or *lower* blood pressure, depending whether or not the net increase or decrease in peripheral resistance can balance the positive inotropic and chronotropic effects of adrenaline on the heart, effects which respectively increase the contractility and rate of the heart.



Epinephrine ampule, 1 mg (Suprarenin)

## Use in local anesthetics

Epinephrine is added to injectable forms of a number of local anesthetics, such as bupivacaine and lidocaine, as a vasoconstrictor to retard the absorption and therefore prolong the action of the anesthetic agent. Some of the adverse effects of local anesthetic use, such as apprehension, tachycardia and tremor, may be caused by epinephrine.<sup>[27]</sup>

## Autoinjectors

Epinephrine is available in an autoinjector delivery system. EpiPens, Anapens and Twinjects all use epinephrine as their active ingredient. Twinjects contain a second dose of epinephrine in a separate syringe and needle delivery system contained within the body of the autoinjector. The larger Twinject dose (0.3 mg) contains a third dose as well.

Though both *EpiPen* and *Twinject* are trademark names, common usage of the terms are drifting toward the generic context of any epinephrine autoinjector.

## Croup

Racemic epinephrine has historically been used for the treatment of croup.<sup>[28]</sup> <sup>[29]</sup> Racemic epinephrine is a 1:1 mixture of the dextrorotatory (D) and levorotatory (L) isomers of epinephrine.<sup>[30]</sup> The L form is the active component.<sup>[30]</sup> Racemic epinephrine works by stimulation of the  $\alpha$ -adrenergic receptors in the airway with resultant mucosal vasoconstriction and decreased subglottic edema and by stimulation of the  $\beta$ -adrenergic receptors with resultant relaxation of the bronchial smooth muscle.<sup>[29]</sup>

## Side effects and drug interactions

Adverse reactions to epinephrine include palpitations, tachycardia, arrhythmia, anxiety, headache, tremor, hypertension, and acute pulmonary edema.<sup>[31]</sup>

Use is contraindicated for patients on non-selective  $\beta$ -blockers because severe hypertension and even cerebral hemorrhage may result.<sup>[22]</sup> Although commonly believed that administration of epinephrine may cause heart failure by constricting coronary arteries, this is not the case. Coronary arteries only have  $\beta_2$  receptors, which cause vasodilation in the presence of epinephrine<sup>[32]</sup>. Even so, administering high-dose epinephrine has not been definitively proven to improve survival or neurologic outcomes in adult victims of cardiac arrest<sup>[33]</sup>.

## Measurement in biological fluids

Epinephrine may be quantitated in blood, plasma or serum as a diagnostic aid, to monitor therapeutic administration or to identify the causative agent in a potential poisoning victim. Endogenous plasma epinephrine concentrations in resting adults are normally less than 10 ng/L, but may increase by 10-fold during exercise and by 50-fold or more during times of stress. Pheochromocytoma patients often have plasma epinephrine levels of 1000-10,000 ng/L. Parenteral administration of epinephrine to acute-care cardiac patients can produce plasma concentrations of 10,000 to 100,000 ng/L.<sup>[34]</sup> <sup>[35]</sup>

## Use in full contact sports

In sports such as boxing, adrenaline chloride, usually a 1:1000 epinephrine solution, is used to still bleeding during matches.<sup>[36]</sup>

## Adrenaline junkie

*Adrenaline junkie* is a term used to describe somebody who appears to be addicted to epinephrine (endogenous) and such a person is sometimes described as getting a "high" from life. The term adrenaline junkie was popularly used in the 1991 movie *Point Break* to describe individuals who enjoyed dangerous activities (such as extreme sports e.g. BASE jumping) for the adrenaline "rush". Adrenaline junkies appear to favour stressful activities for the release of epinephrine as a stress response. Doing this may result in physical harm because of the potential danger. Whether or not the positive response is caused specifically by epinephrine is difficult to determine, as endorphins are also released during the fight-or-flight response to such activities.<sup>[37]</sup> <sup>[38]</sup>

## Terminology

This chemical is widely referred to as *adrenaline* outside of the United States; however, its United States Adopted Name and International Nonproprietary Name is *epinephrine*. *Epinephrine* was chosen because *adrenaline* bore too much similarity to the Parke, Davis & Co trademark *Adrenalin* (without the "e"), which was registered in the United States. The British Approved Name and European Pharmacopoeia term for this chemical is *adrenaline*, and is indeed now one of the few differences between the INN and BAN systems of names.<sup>[39]</sup>

Amongst American health professionals and scientists, the term epinephrine is used over adrenaline. However, it should be noted that pharmaceuticals that mimic the effects of epinephrine are often called *adrenergics*, and receptors for epinephrine are called adrenergic receptors or adrenoceptors.

## See also

- Anaphylaxis
- Adrenochrome
- Catechol-O-methyl transferase
- Adrenergic receptor

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## External links

- U.S. National Library of Medicine: Drug Information Portal - Epinephrine <sup>[40]</sup>

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