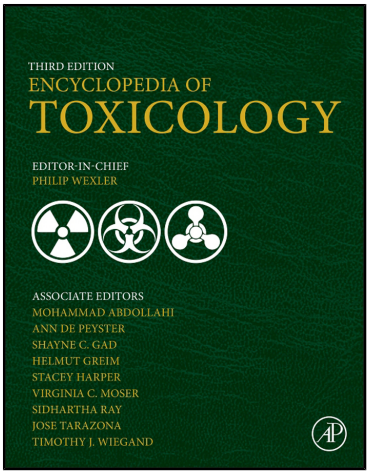

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Catecholamines

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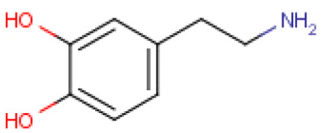
Description

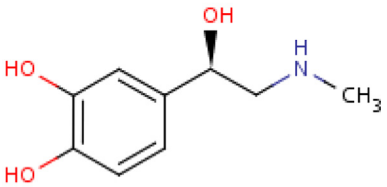
Catecholamine is the name of a group of compounds that contain a catechol nucleus (a benzene ring with two adjacent hydroxyl substituents) and an amine group. This group includes the mammalian neurotransmitters or hormones, such as dopamine, norepinephrine, and epinephrine, and non-mammalian compounds such as octopamine. Each compound has its own synonyms.

- Name: Dopamine
- Chemical Abstracts Service Registry Number: 51-61-6
- Synonyms: Pyrocatechol; 4-(2-Aminoethyl) pyrocatechol; 3-Hydroxytyramine; 3,4-Dihydroxyphenethylamine; 4-(2-Aminoethyl)-1,2-benzenediol; Dopastat
- Molecular Formula: $C_8H_{11}NO_2$
- Name: Epinephrine
- Chemical Abstracts Service Registry Number: 51-43-4
- Synonyms: Benzyl alcohol, Adrenalin, Epirenamine, Methylaminoethanolcatechol, Vasotonin
- Molecular Formula: $C_9H_{13}NO_3$
- Name: Norepinephrine
- Chemical Abstracts Service Registry Number: 51-41-2
- Synonyms: 4-(2-Amino-1-hydroxyethyl)-1,2-benzenediol; α-(Aminomethyl)-3,4-dihydroxybenzyl alcohol; 2-Amino-1-(3,4-dihydroxyphenyl)ethanol; 1-(3,4-Dihydroxyphenyl-2-aminoethanol; Noradrenaline.
- Molecular Formula: $C_8H_{11}NO_3$
- Chemical Structures:

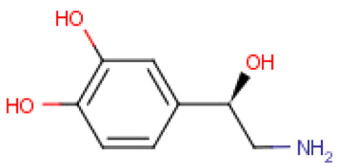
Dopamine



Epinephrine



Norepinephrine



Background

Catecholamines are endogenous neurotransmitters or hormones. Dopamine and norepinephrine are in the monoamine class. Catecholamines are synthesized in the brain, the adrenal medulla, and by some sympathetic nerve fibers. The biosynthesis of catecholamines begins with the hydroxylation of tyrosine by tyrosine hydroxylase to form L-dopa, which is decarboxylated by aromatic amino acid decarboxylase to form dopamine. Catecholamines are formed from dopamine by the enzyme dopamine beta-hydroxylase, and epinephrine is formed from norepinephrine by enzyme phenylethanolamine *N*-methyltransferase. Parkinson's disease is one of the most common neurodegenerative disorders and is characterized by the selective loss of dopaminergic neurons in the substantia nigra. Dopamine is widely distributed throughout the CNS and is involved in the control of movement. Dopamine is synthesized from the amino acid tyrosine. This amino acid is abundant in meats, dairy products, and soy. Tyrosine undergoes a series of enzymatic modifications to yield dopamine. The amount of dopamine that can be made is limited by the activity of the first enzyme in the synthesis chain – tyrosine hydroxylase. Cells that use dopamine as a neurotransmitter are referred to as dopaminergic. Norepinephrine is an important neurotransmitter in both the CNS and the sympathetic part of the autonomic nervous system. The hormone epinephrine acts together with the sympathetic nervous system to initiate the body's quick response to stressful stimuli.

Uses

Catecholamines are sympathomimetic drugs. Dopamine and norepinephrine are used as vasopressors (antihypotensives). Catecholamines are water-soluble and are 50%-bound to plasma proteins, and are always seen in the circulating blood. Epinephrine stimulates both the alpha- and beta-adrenergic systems, causes systemic vasoconstriction and gastrointestinal relaxation, stimulates the heart, and dilates bronchi and cerebral vessels. It is also used as a vasoconstrictor, cardiac stimulant, or bronchodilator to counter allergic reaction, anesthesia, and cardiac arrest. Epinephrine is used to treat severe allergic (anaphylactic) reactions because it can prevent or minimize the effects of histamine. It is also an antiglaucoma agent.

Environmental Fate and Behavior

Routes and Pathways

Catecholamines are mostly administered by intravenous injection or infusion. They have a very short half-life when circulating in the blood and are easily soluble in water. Epinephrine is available in nebulized racemic dosage form for inhalation.

Encyclopedia of Toxicology, Third Edition, 2014, 748–750

Intoxication from catecholamine usually results from iatrogenic overdoses, accidental intravenous administration, and the injection of solution intended for nebulization. High concentrations of dopamine present inside of a cell than there are vesicles to store it in, oxidative stress can occur and cause damage or death to the cell. It is thought that dopamine overload causes biochemical damage to cellular mitochondria, that provide the cell with all of the energy it requires to function, resulting in death of the cell. Catecholamines produced circulatory changes that reversed propofol anesthesia in animal models.

Toxicokinetics

Epinephrine is well absorbed after oral administration but is rapidly inactivated in the gut mucosa. When catecholamines were intravenously injected or infused, the onset of drug effect is rapid (within 5 min for dopamine and 3–10 min for epinephrine) and the duration of drug effect is short (10 min for dopamine, 1 or 2 min for norepinephrine, and 15 min to hours for epinephrine depending on route of administration). Exogenous catecholamines in the circulation are rapidly and efficiently taken up by adrenergic neurons. Catecholamines are metabolized by monoamine oxidase, which is localized largely in the outer membrane of neuronal mitochondria, and by catechol-*O*-methyl transferase, which is found in the cytoplasm of most animal tissues, particularly the kidneys and the liver.

The primary metabolites of dopamine are homovanillic acid and dihydroxyphenylacetic acid (75%) and norepinephrine (25%). The primary metabolites of epinephrine and norepinephrine are vanillylmandelic acid and 3-methoxy-4-hydroxyphenethyleneglycol. Catecholamine metabolites and their conjugates are excreted in urine.

Mechanism of Toxicity

Catecholamines are sympathomimetic drugs. These drugs increase heart rate and cardiac output and may produce cardiac arrhythmias. Administration of norepinephrine also results in increased peripheral vascular resistance. Both effects may cause serious systemic hypertension, which may cause cerebral hemorrhage. Reduced hepatic and renal blood flow may cause tissue ischemia, increase glycolysis, and serum lactic acidosis. In very high doses, a paranoid state may be induced. Recent studies have demonstrated that norepinephrine may enhance or inhibit immune function under certain conditions. Increased levels of catecholamines can also increase fat lipolysis and reduce adipogenesis.

Production of reactive oxygen species and formation of quinone during the metabolism of dopamine are involved in dopamine toxicity. Numerous *in vitro* and *in vivo* studies concerning dopamine-induced neurotoxicity have been reported in recent decades. The reactive oxygen species generated in the enzymatic oxidation or auto-oxidation of excess dopamine-induced neuronal damage and apoptotic cell death. Dopamine and its metabolites containing two hydroxyl residues exert cytotoxicity in dopaminergic neuronal cells mainly due to the generation of highly reactive dopamine quinones which are dopaminergic neuron-specific cytotoxic molecules. Dopamine quinones may irreversibly alter protein function through the formation of 5-cysteinyl-catechols on the proteins. The formation of dopamine quinone-alpha-synuclein consequently increases cytotoxic protofibrils and the covalent modification of tyrosine hydroxylase by dopamine quinones. The melanin-synthetic enzyme tyrosinase in the brain may rapidly oxidize excess amounts of cytosolic dopamine and prevent slowly progressive cell damage by auto-oxidation of dopamine, thus maintaining dopamine levels.

Acute and Short-Term Toxicity

Animal

Overdose of catecholamines may result in animal death. In test animals, there is evidence that death is the result of respiratory arrest caused by hypertension following overdose of epinephrine.

Human

At high infusion rates of dopamine, ventricular arrhythmias, and hypertension may occur. Nausea, vomiting, and angina pectoris are occasionally seen. Gangrene of the extremities may occur in patients with profound shock given large doses of dopamine for long periods of time. Norepinephrine may cause dose-related hypertension (sometimes indicated by headache), reflex bradycardia, increased peripheral vascular resistance, and decreased cardiac output. High doses of norepinephrine (in excess of 8–12 mg of base per min) cause intense vasoconstriction, which results in 'normal' blood pressure but decreased tissue perfusion. Local necrosis may result from perivascular infiltration and angina, mesenteric ischemia, and peripheral ischemia. Epinephrine may cause dose-related restlessness, anxiety, tremor, cardiac arrhythmias, palpitation, hypertension, weakness, dizziness, and headache. A sharp rise in blood pressure from over-dosage of epinephrine may cause cerebral hemorrhage and pulmonary edema. High catecholamine levels in blood are also associated with stress, due to psychological or environmental stressors.

Chronic Toxicity

Human

Prolonged use and repeated injection of epinephrine may lead to tolerance and local necrosis. Prolonged use of norepinephrine may cause edema, hemorrhage, focal myocarditis, necrosis of the intestine, or hepatic and renal necrosis. It may also cause plasma volume depletion, which may result in perpetuation of the shock state or recurrence of hypotension when the drug is discontinued. High levels of catecholamines may be also due to the low levels of monoamine oxidase A (MAO-A). MAO-A is one of the enzymes responsible for degradation of these neurotransmitters, and thus balance the levels of catecholamines.

Clinical Management

Basic and advanced life-support measures should be utilized as necessary. Treatment is directed at ameliorating tachycardias,

shock, cardiac arrhythmias, systemic hypertension, pulmonary edema, and lactic acidosis. In the case of severe toxicity, administration of a rapidly acting α-adrenergic blocking drug such as phentolamine may be considered. Glutathione is a scavenger for dopamine oxidation intermediates and it may provide complete protection against dopamine-mediated toxicity.

Ecotoxicology

Toxicity of catecholamines in a ciliated protozoan *Tetrahymena pyriformis* has been reported in a recent study. Catecholamines exhibited moderate acute toxicity to the protozoans. Dopamine showed toxic potential Effective Concentrations (EC_{10}) of 0.63 ppm in *T. pyriformis* and a higher concentration of dopamine inhibited the synthesis of adrenalin in these protozoans.

Disclaimer

The findings and conclusions in this report are those of the author and do not necessarily represent the views of the National Institute for Occupational Safety and Health, Center for Disease control and Prevention.

See also: Mode of Action; Occupational Exposure Limits; Monoamine Oxidase Inhibitors; Estrogens II: Catechol Estrogens.

Further Reading

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