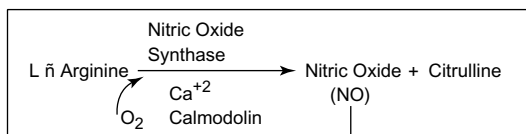
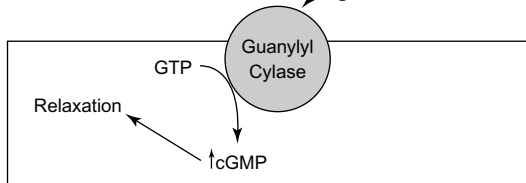


Action of Nitric Oxide

Vascular Endothelium

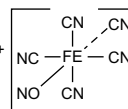


Vascular Smooth Muscle Cell

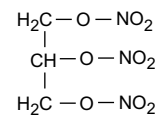


Drug Therapy to Increase NO

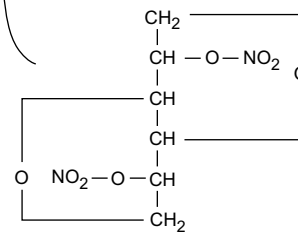
Nitroprusside



Nitroglycerin



Isosorbide Dinitrate



Nitric oxide (NO) is formed endogenously by the action of nitric oxide synthetase on L-arginine (**Figure**). This reaction, which occurs in vascular endothelial cells, requires molecular oxygen, calcium, and calmodulin. Nitric oxide is a nonpolar gas that does not require interaction with a surface receptor. After diffusion into vascular smooth muscle cells, NO activates guanylyl cyclase through nitrosylation. Guanylyl cyclase catalyzes the conversion of GTP to cGMP, which in turn mediates smooth muscle relaxation and thus vasodilation.

Organic compounds containing nitrate or nitroso moieties such as nitroglycerin, nitroprusside, and isosorbide dinitrate, undergo tissue catabolism or spontaneously decompose to yield nitric oxide. Unlike other vasodilators the effect of these compounds is independent of the state of autonomic innervation in the vascular system.

Nitroprusside is a potent balanced vasodilator. It is administered as a continuous rate IV infusion and results in an almost immediate decrease in systemic vascular resistance and systemic arterial blood pressure. The result is a decrease in ventricular filling pressure and a reduction in pulmonary capillary wedge pressure. Nitroprusside is used in the short-term management of acute, severe, life-threatening congestive heart failure (CHF), usually in combination with diuretics and dobutamine. It may also be used to treat an acute hypertensive crisis.

Nitroprusside is metabolized in the blood and tissue to cyanogen. Cyanogen is converted in the liver to thiocyanate, which is eliminated in feces, urine, and exhaled air. Cyanide toxicity can occur with prolonged administration of nitroprusside. An early indicator of cyanide toxicosis is metabolic acidosis. Plasma levels of thiocyanate should be monitored in dogs with renal insufficiency or when the drug is given for longer than 2 days. A plasma concentration of 10 mg/dl is considered toxic. Since nitroprusside is a potent vasodilator, blood pressure should be monitored intensively to prevent hypotension. Other side effects of therapy include

nausea, muscle twitching, and dizziness. Nitroprusside is degraded by light so bottles and IV lines should be wrapped in light protective covers.

Nitroglycerin is primarily a venodilator when it is administered transcutaneously. Its beneficial actions in CHF include a decrease in ventricular filling pressure and resolution of signs of pulmonary edema. Topical nitroglycerin is available as an ointment or patch for cutaneous application. The most common areas for application in veterinary patients are the groin, axilla, and pinna of the ear. Its onset of action is 1 hour, with a duration of action ranging from 2–12 hours. Nitroglycerin is metabolized in the liver by glutathione-organic nitrate reductase into more water soluble denitrated metabolites and inorganic nitrite. The liver has an enormous capacity to catalyze the reduction of organic nitrates. This transformation has important implications for oral bioavailability and duration of action. After topical administration, most of the drug bypasses the hepatic circulation because the liver receives only 20% of the cardiac output. Oral bioavailability is very low due to the large hepatic first pass effect. Controlled studies on the efficacy of nitroglycerin in canine and feline heart failure are lacking. Side effects of therapy include rash at the site of application and hypotension. Frequent repeated exposure to nitroglycerin leads to a decrease in the magnitude of its pharmacologic effect. Brief periods (overnight) of no therapy may be sufficient to avoid the development of tolerance.

Isosorbide Nitrate

Isosorbide dinitrate is metabolized in the liver by enzymatic denitration. Unlike nitroglycerin two of the major metabolites, isosorbide-2-mononitrate and isosorbide-5-mononitrate, have longer half lives than the parent drug. These active metabolites make it possible to administer isosorbide dinitrate orally to obtain therapeutic vasodilation.