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Nitroglycerin

by

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Paper IV

Abbreviations

NTG – Nitroglycerin, cGMP – cyclic guanosine mono phosphate, sGC – soluble guanylate cyclase, NO – nitric oxide, LDL - low density lipoproteins.

Contents

Abstract

Nitroglycerin has been used to treat angina pectoris and heart failure for over 130 years. It is accepted now that the main mechanism of its action is release of nitric oxide during bioactivation of nitroglycerin.
Nitric oxide has a series of protective effects in the vasculature, which are briefly described in this paper. Chen Z. et al described the exact mechanism of the nitroglycerin bioactivation in 2002. Another interesting phenomenon concerning to nitroglycerin is so called “nitrate” tolerance. Recent works give some insights on the underlying mechanisms of this effect. The goal of this paper is to give a brief overview of the current information about nitroglycerin: basic chemistry, biological effects, mechanism of biotransformation and nitroglycerin tolerance.

Introduction.

Alfred Nobel used nitroglycerin, which was originally synthesized by Ascanio Sobrero, for manufacture of dynamite. Soon, it was discovered that it is an effective drug for treatment of

angina pectoris and heart failure. It was W. Murrel, who first reported in 1879 that a 1 percent solution of nitroglycerin administered orally relieved angina and prevented subsequent attacks. However the mechanism of this drug remained a mistery for many years.
In the late 1970s and early 1980s, a series of articles was published that showed the role of nitric oxide in vasodilatation. It was suggested that biological effects of nitroglycerin are mediated by donation of NO. Precise mechanisms of nitroglycerin bioactivation were still unknown.
Last year Chen Z. et al has identified enzyme enzyme responsible for this process. They have identified this enzyme as mitochondrial aldehyde dehydrogenase.
The goal of this paper is to briefly review all the data about nitroglycerin chemistry, biotransformation and mechanism of action acquired during the 130 years since its discovery.

Protective roles of nitric oxide in vasculature

The role of nitric oxide as a signaling molecule in the cardiovascular system was discovered in the end of 20^{th} centure. Robert F Furchgott, Louis J Ignarro and Ferid Murad received Nobel Prize for their contribution to this discovery in 1998.
Endothelial cells are able to produce nitric oxide in the response to the certain stimuli: shear stress, bradykinin, acetylcholine, serotonin etc. NO oxide defuses through the vessel wall causing different effects. The main one is activation of soluble guanyl cyclase in smooth muscle cells. Activation of sGC causes increase of intracellular level of cGMP, which in its turn activate cGMP-dependent protein kinases, thich mediate vasorelaxation via phosphorylation of proteins that regulate intracellular Ca^{2+} levels (Lincoln TM, 2001, J Appl Physiol)
Vasorelaxation reduces ischemia and protects heart from overload.
During last couple decades several other vasoprotective effects of nitric oxide were discovered. Thus NO was shown to inhibit platelet aggregation by stimulation of CGMP production in human platelets, which causes decrease of intracellular calcium concentration. Nitric oxide was shown to inhibit leukocyte adhesion. The main mechanism of this process is inhibition of VCAM-1 expression.

Nitric oxide inhibits smooth muscle cells proliferation, which plays a key role in the narrowing the lumen of blood vessels in coronary artery disease and restenosis. Nitric oxide has as proapoptotic as antiapoptotic effects depending on the cell type. NO was shown to inhibit apoptosis of endothelial cells which could play protective role in different cardiovascular diseases.

NO oxide was shown to induce synthesis of ecSOD, which could contribute to its antioxidant activity. NO induces synthesis of ferritin as well. Ferritin chelates iron II, which prevents Fenton reaction. All these findings explain therapeutical effects of nitric oxide donors. Protective effects of nitric oxide in vasculature are summarized in figure 1.

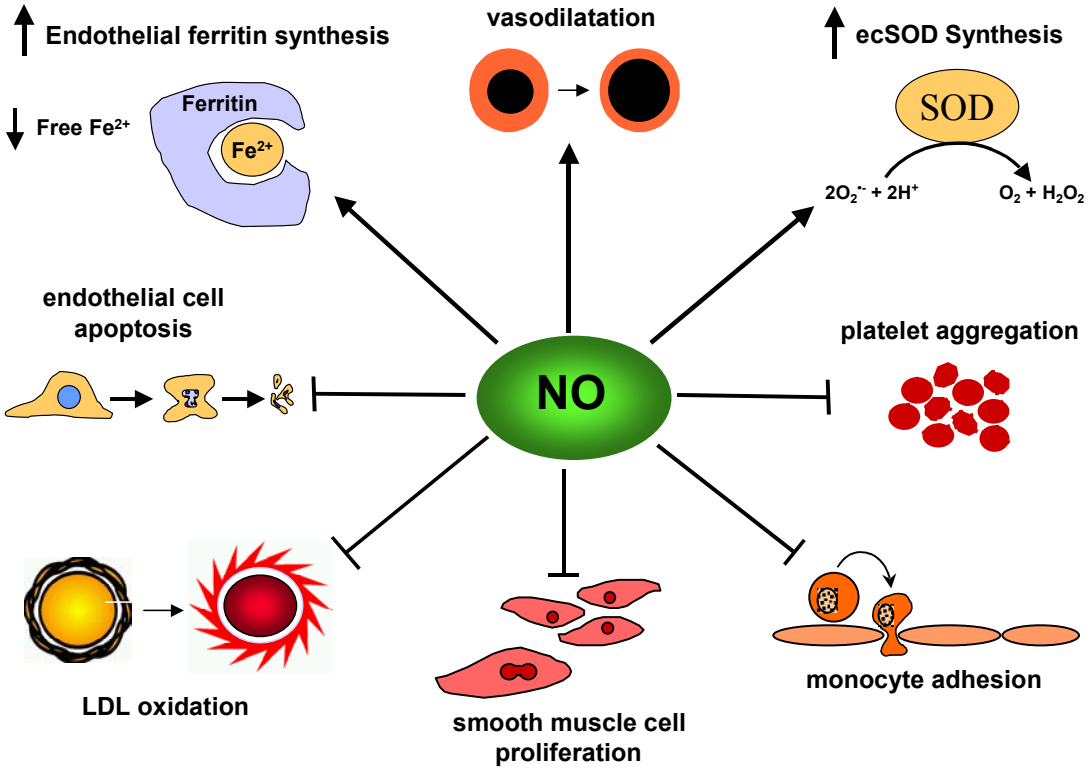

Fig 1. **Vasoprotective effects nitric oxide.** ⊣ - inhibition; → - induction. [author's slide]

Chemistry of nitroglycerin

The more accurate name for nitroglycerin is glyceryl trinitrate.

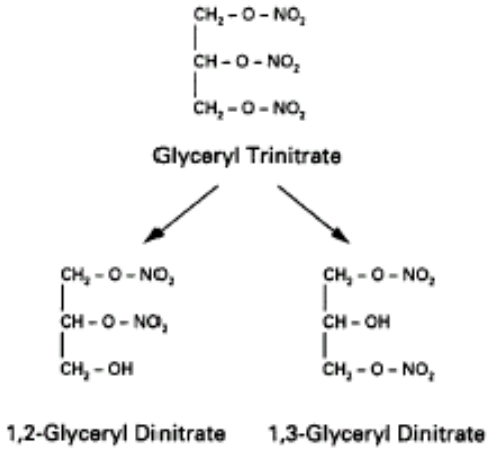

Fig. 2 Chemical structure of nitroglycerin and its biologically active metabolites

Pure nitroglycerin is a slightly oily yellowish liquid with a sweet, burning taste. It is very sensitive to shock, friction, elevation of temperature and sparks. Molecular weight: 227.11. Density: 1.13 at 15°C. Melting point: 13.2°C. Boiling point (at 760 mm Hg): Explodes at 218 degrees C (424.4 degrees F) Specific gravity: 1.59 at 20 degrees C (68 degrees F). Vapor density: 7.84. Vapor pressure at 20 degrees C (68 degrees F): 0.00026 mm Hg. Solubility: Slightly soluble in water; miscible with acetone, ether, benzene and other organic solvents.

Mechanism of nitroglycerin biotransformation

It took a while to understand the mechanism of nitroglycerin bioactivation. First it was shown that thiols or sulfhydryl-containing compounds are involved in this process [3]. Nitric oxide is a quite short living radical. Some part of NO that is produced in the cells immediately reacts with thiols to form nitrosothiols. S-nitrosothiols are considered to be one of the most important storage forms for NO.

Nitroglycerin biotransformation is tissue and cell and dose dependent, and it yields 1,2-glyceryl dinitrate, 1,3-glyceryl dinitrate, and NO (or S-nitrosothiols) in different amounts and ratios

It was only in 2002, when the exact mechanism of this process was determined [5]. Chen Z et al has purified a nitroglycerin reductase that catalyzes this process. They have identified this enzyme as mitochondrial aldehyde dehydrogenase (mtALDH). The mechanism of nitroglycerin biotransformation is shown on Fig 3.

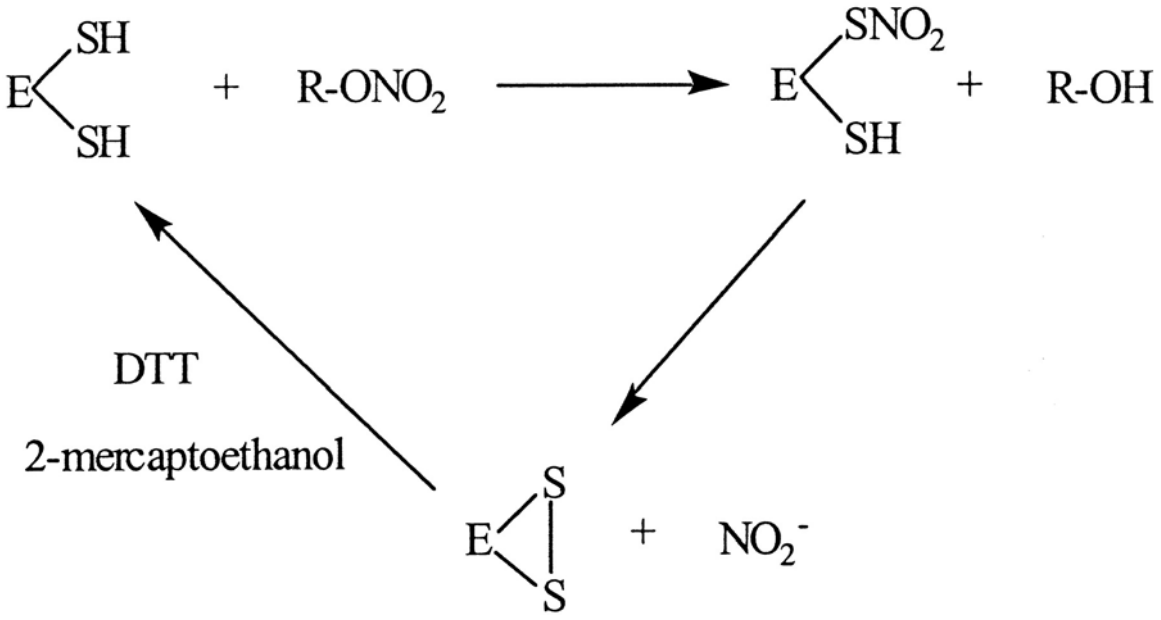

Fig 3 Nitroglycerin biotransformation [5]. E – mtALDH**. R-ONO**

Nitrate tolerance

Soon after nitroglycerin was first used in clinical practice, it was recognized that continuous treatment with this drug resulted in the development of tolerance. Progressive reduction of hemodynamic and antiaggregatory effects of nitroglycerin imposes the major limitation of efficiency of nitrate therapy for stable angina pectoris, congestive heart failure, and acute myocardial infarction.

There have been traditionally two main groups of hypotheses concerning the mechanism of nitrate tolerance. The “dispositional” (“metabolic” or “end-organ tolerance”) theory postulates that decrease of the effect of organic nitrates is caused by decreased biotransformation of nitrates.

According to "functional" theory the counterregulatory mechanisms that occur in response to nitrate therapy play the main role in nitrate tolerance. These mechanisms, that include neurohormonal activation and plasma volume expansion, have been termed "pseudotolerance. The main support for metabolic theory was observation that the effects of nitrates depend on the concentration of the thiols in the cells. According to Chen Z. thiols are required for reduction of mtALDH. Tolerance to nitroglycerine was explained simply by thiol utilization and depletion in the presence of excess nitroglycerin.

Medical usage of nitroglycerin

TRADE NAMES:

Nitro-bid®, Nitrostat®, Nitrogard®, NitroDur®, Nitrolingual®, Nitrol®, Tridil®

PHARMACOKINETICS:

Oral nitroglycerin undergoes significant first-pass metabolism and has less than 1% oral bioavailability. Nitroglycerin is readily absorbed through the sublingual mucosa as well as the skin. Nitroglycerin has a short half-life estimated at 1-4 minutes. The liver metabolizes nitroglycerin.

INDICATIONS:

1. Ischemic chest pain
2. Hypertension
3. Congestive heart failure

CONTRAINDICATIONS:

1. Known hypersensitivity to drug
2. Increased intracranial pressure
3. Hypovolemia
4. Hypotension
5. Known aortic valve stenosis

SIDE EFFECTS:

1. CNS: headache, dizziness, weakness
2. Cardiovascular: hypotension, reflex tachycardia, fainting

3. Gastrointestinal: nausea, vomiting, dry mouth

TOXIC EFFECTS:

1. Cardiovascular: hypotension, tachycardia, heart block
2. Respiratory: hyperpnea, dyspnea
3. Gastrointestinal: nausea, vomiting, anorexia
4. CNS: flushing, diaphoresis, dizziness, syncope, confusion, fever

Conclusions

This review discusses the wide spectrum of information available now about nitroglycerin. This drug has been used already for more than 130 years. A lot of data concerning nitroglycerin chemistry, bioactivation and mechanisms of action were acquired.

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