5. Nitric oxide donors

NO = potent, paracrine vasodilator
- Role in cell death (apoptosis)
- Neurotransmitter
- Produced from arginine (Arg) metabolism endogenously
- It is the active metabolite of any drug that release it (= the NO “donors”)
- Also available as a drug in itself
- EDFR (endothelium-derived relaxing factor) = mixture of NO + other VASODILATING molecules synthesized in vascular endothelium

NO donor = any molecule from which NO is released

<table>
<thead>
<tr>
<th>Agents related to NO</th>
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<tbody>
<tr>
<td><strong>Endogenous</strong></td>
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<tr>
<td>NOS activators (nitric oxide synthase)</td>
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<tr>
<td>ACh, Histamine</td>
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<tr>
<td>Family of cytoplasmic enzymes</td>
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</table>

- Endogenous NO release can happen when drugs stimulate the NOS enzymes
- They can be stimulated by
  - Cytokines
  - Ca2+ influx
  - Histamine
  - ACh
  - Muscarinic agonists
  - Other vasodilators e.g. bradykinin, hydralazine
- Different naturally occurring forms of NOS enzymes exist:
  - bNOS (epithelial)
  - cNOS (constitutive) – NOS1
  - eNOS (endothelial) – NOS3
  - iNOS (inducible) – NOS2
  - mNOS (macrophage)
  - nNOS (neuronal)
- After synthesis from arginine metabolism \( \rightarrow \) citrulline + NO (catalyzed by NOS), NO diffuses to surrounding tissues
- It is inactivated by Hb (hemoglobin)
- It is not “stored” in cells because it is a gas at body temperature and always diffuses around
- When a tissue/cell is ischemic, NO is formed from NO3- (nitrate ion)
Roles of NO:
1. Smooth muscle relaxation
2. Neurotransmitter (in apoptosis)
3. Inflammation
4. Cell adhesion

Smooth muscle relaxation
- Powerful vasodilator in all vascular beds
- Potent relaxant in most smooth muscles
- Mechanism:
  1. Activation of guanylyl cyclase
  2. Synthesis of cGMP
  3. Facilitation of dephosphorylation $\rightarrow$ inactivation of MLC (myosin-light-chain)
  4. This leads to relaxation of smooth muscles
- Clinical uses: CARDIOVASCULAR APPLICATION

Nitric oxide donors = used in hypertension and angina pectoris
**Angina pectoris:** strangle/pressure-like **pain** caused by cardiac ischemia

- Woman develop it later than men
- The defect that causes pain is inadequate O2 delivery for myocardial O2 requirements

**Ischemia:** Insufficient O2 in cardiac tissues (and other tissues, depending on the type)

The pain in angina pectoris is located:
- substernally (behind/below sternum)
- neck
- shoulders
- arms

2 main strategies of treatment of angina pectoris:
1. Reduction of oxygen demand/need
2. Increase of O2 delivery to myocardium

Drugs used in angina pectoris:
1. Vasodilators
   a. Nitrates (nitroprusside/nitroglycerin/isosorbide dinitrate/amyl nitrate)
   b. Calcium blockers (nifedipine, nimodipine, felodipine, amlodipine)
2. Cardiac depressants
   a. Calcium blockers (see above)
   b. Beta-blockers (propranolol)
3. Others
   a. Metabolism modifiers
   b. Rate inhibitors

**Nitrates (based on duration of action):**

1. Short – sublingual nitroglycerin
2. Intermediate – oral nitroglycerin
3. Long – transdermal nitroglycerin

Important terms to know

**Atherosclerotic angina:** angina associated with atheromatous (clog by atherosclerosis) plaques partially occlude one or more coronary arteries.

⇒ When cardiac work increased (e.g. in exercising, walking up stairs) there is an **obstruction flow** and **inadequate O2 delivery** ⇒ resulting in accumulation of metabolites like lactic acid (formed in anaerobic cases) ⇒ these metabolites + ischemia (insufficient O2) ⇒ lead to **STIMULATION OF MYOCARDIAL PAIN ENDINGS**

⇒ If a person rests for 15 min (aka reduces the cardiac work) the pain ends

⇒ 90% of all anginas are of this type!!!
**Variant/vasospastic angina**: Angina due to reversible spasms of coronary vessels, happens often during rest!

**Monday disease**: A disorder caused by chronic exposure to organic nitrates that (hopefully used to) happens at workplaces/factories and is due to the vasodilating effect of these chemicals. Symptoms: headache/tachycardia/dizziness

**Preload**: Filling pressure on heart
  - Dependent on **venous tone + blood volume**
  - Determines **end-diastolic volume** fiber length and tension

**Afterload**: Combined load of blood in ventricles (the EDV = end-diastolic volume) + arterial resistance during ventricular contraction
  - Dependent on vascular resistance + arterial stiffness
  - Determines **systolic fiber tension**

**Intramyocardial fiber tension**: Force exerted by myocardial fibers, especially ventricular ones (at any given time)
  - Primary determinant of myocardial O2 requirement!

**Myocardial re-vascularization**: Mechanical intervention to improve O2 delivery to myocardium (corrects coronary obstruction)

**Determinants of oxygen (O2) demand of heart**:

1. **Diastolic factors**
   1) Blood volume
   2) **Venous tone**.

2. **Systolic factors**
   1) Peripheral resistance.
   2) Heart rate and heart force.
   3) Ejection time.

All of these **increase** the intramyocardial fiber tension
  ➔ leading **increased** to myocardial O2 requirement

*: sympathetic discharge dependent
Mechanism of action of organic nitrates

- Release NO within smooth muscle cells through the action of
  - Mitochondrial enzyme aldehyde dehydrogenase 2 (ALDH2)
- NO then stimulates soluble cytoplasmic guanylyl cyclase → increasing the 2nd messenger cGMP (cyclic guanylyl monophosphate) → this stimulates the dephosphorylation of myosin-light-chain phosphate → leading to smooth muscle relaxation

Effects

- Venous dilation (= venodilation) is caused by smooth muscle relaxation through reduced preload (the filling pressure of the heart)
- Venodilation reduces cardiac output and cardiac size 😊
- Relaxation of arterial smooth muscles → increased flow through partially occluded epicardial coronary vessels (these are the left and right coronary arteries lying on the surface of heart, distributing blood flow to different regions of heart muscles)
- Arteriolar dilation of resistance vessels (= smaller arteries/arterioles, playing crucial role in regulation of bp.) → reduces afterload (= EDV + arterial resistance) → contributing to increase of ejection → further decrease of cardiac size 😊 → reduced peripheral resistance → decrease blood pressure 😊😊😊
- Increased coronary flow through collateral vessels (small branches of arteries formed over time in response to narrowed coronary arteries)
- Decreased diastolic heart size and fiber tension 😊

Overall reduction in myocardial fiber tension and O2 consumption → decreased O2 demand → decreased blood pressure leads to reflex tachycardia and increase of contraction force (= baroreceptor reflex mechanism)

Treatment strategies for angina pectoris

A. Increase O2 delivery
B. Decrease O2 demand

Traditional agents:
1. Nitrates
2. Ca2+ channel blockers
3. Beta-blockers

Newer drugs: Increase the efficiency of O2 utilization (by shifting the energy preference of heart from fatty acids to glucose)

1. pFOX inhibitors = partial fatty acid oxidation inhibitors
   - Ranolazine (inhibit late Na+ channels)
   - Trimetazidine
2. Selectively reducing heart rate and O2 requirement
   - Ivabradin (inhibit the funny current, no other hemodynamic effects)
Nitrates = Venodilators

1. Glyceryl trinitrate (Nitroglycerin)
2. Isosorbide dinitrate
3. Amyl nitrate
4. Nitroprusside
5. Hydralazine

<table>
<thead>
<tr>
<th>Organic nitrate</th>
<th>Formulations and types</th>
<th>Pharmacokinetic</th>
</tr>
</thead>
</table>
| Nitroglycerin/glyceryl trinitrate | Active component of dynamite  
Most important therapeutically  
Many available formulations depending on duration of action  
Short-acting: 10 min, sublingual  
Intermediate-acting: 20-40 min, oral  
Long-acting: 8-10 h, transdermal, prophylaxis  
Intravenous admin.: reduces platelet aggregation | Denitrated in liver/smooth muscle  
1. First into 2 dinitrates (glyceryl dinitrate) \(\rightarrow\) significant vasodilating effect  
2. Then into mononitrates \(\rightarrow\) less active  
90% first-pass metabolism  
Oral efficacy due to high levels of active metabolites  
Sublingual/transdermal efficacy due to unchanged drug because it avoids first-pass metabolism |
| Isosorbide dinitrate | Sublingual  
Oral | Rapidly denitrated in liver/smooth muscle to isosorbide mononitrate (active)  
Active metabolite avail. As separated drug too for oral use \(\rightarrow\) intermediate duration of action (4-6 h) |
| Amyl nitrate | Volatile  
Rapid-acting (inhaled) now rarely used /ultra-short acting | |

Soraya Jahedi Pharmacology 2019/2020
Effects on other organs

Relax smooth muscles of:
1. Bronchi
2. GI-tract
3. Genito-urinary tract

Clinical uses

Several formulations available:

<table>
<thead>
<tr>
<th>Agent</th>
<th>Formulation</th>
<th>Duration of action</th>
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</thead>
<tbody>
<tr>
<td>Nitroglycerin</td>
<td>Sublingual/spray for acute</td>
<td>10-20 min</td>
</tr>
<tr>
<td></td>
<td>anginal pain</td>
<td></td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>Sublingual</td>
<td>30 min</td>
</tr>
<tr>
<td>Both of the above</td>
<td>Oral</td>
<td>4-6 h</td>
</tr>
<tr>
<td></td>
<td>Sustained release</td>
<td>Longer than 4-6 h</td>
</tr>
<tr>
<td></td>
<td>Transdermalpatches/ointments</td>
<td>Maintain levels up to 24 h,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tolerance may develop –</td>
</tr>
<tr>
<td></td>
<td></td>
<td>change patch after 10 h</td>
</tr>
</tbody>
</table>

Side-effect profile

- Adverse drug reactions due to vasodilatory effect:
  1. Tachycardia (baroreceptor reflex mechanism)
  2. Orthostatic hypotension (direct cause of vasodilation)
  3. Throbbing headache (meningeal artery vasodilation)
- Monday disease
- Methemoglobinemia at high plasma concentrations (means too high amnt. Of type of Hb called methHb) \(\rightarrow\) caused by NITRITE (not nitraTES), nitrites can treat CN poisoning
- Drug-interaction with sildenafil (Viagra) = synergistic effect
  
  Increased synthesis of cGMP (NO donor) + inhibited breakdown of cGMP (Viagra) = potentially dangerous hypotension