Pharmacology 659

Drugs Acting Primarily on Smooth Muscle

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Types of Smooth Muscle

- Vascular
- Pulmonary
- Gastrointestinal
- Urinary Bladder and Ureters
- Uterus
- Other
Drugs Used to Treat “Erectile Dysfunction”
Phosphodiesterase Type 5 Inhibitors
Nitric Oxide

1. Nitric oxide (NO) is as a major signaling molecule in neurons and in the immune system, either acting within the cell in which it is produced or by penetrating cell membranes to affect adjacent cells.

2. NO has a half-life of only a few seconds in vivo. However, since it is soluble in both aqueous and lipid media, it readily diffuses through the cytoplasm and plasma membranes.
Nitric Oxide Synthase

Arginine

\[ \text{Arginine} \quad \overset{\text{NO}}{\longrightarrow} \quad \text{Citrulline} \]

\[ \text{Citrulline} + \text{NADPH} + \frac{1}{2} \text{O}_2 \rightarrow \text{Arginine} + \text{NADP} + \text{H}_2\text{O} \]
Nitric Oxide

3. NO has effects on neuronal transmission as well as on synaptic plasticity in the central nervous system. In the vasculature, NO reacts with iron in the active site of the enzyme guanylyl cyclase (GC), stimulating it to produce the intracellular mediator cyclic GMP (cGMP), that in turn enhances the release of neurotransmitters resulting in smooth muscle relaxation and vasodilation.
Synthesis and Metabolism of Nitric Oxide

- Arginine (Arg) is converted to nitric oxide (NO) by NOS III (eNOS), which is activated by calcium (Ca$^{2+}$) and calmodulin (CaM).
- NO activates soluble guanylyl cyclase (sGC), which converts GTP to cGMP.
- cGMP activates protein kinase G (PKG).
- Ca$^{2+}$ is released from the endoplasmic reticulum through IP$_3$R.
- NO is metabolized by PDE5 to GMP.
- ANP, BNP, and CNP release cGMP and inhibit PDE5.

Key proteins and molecules involved:
- NOS III (eNOS)
- sGC
- PDE5
- NO
- GTP
- cGMP
- IP$_3$R
- CaM
- Ca$^{2+}$

Endoplasmic reticulum (in red) and nuclear envelope (in blue) are also shown.
Nitric Oxide

4. NO may also be involved in the regulation of protein activity through S-nitrosylation.

5. In the extracellular milieu, NO reacts with oxygen and water to form nitrates and nitrites. NO toxicity is linked to its ability to combine with superoxide anions (O2–) to form peroxynitrite (ONOO–), an oxidizing free radical that can cause DNA fragmentation and lipid oxidation. In the mitochondria, ONOO– acts on the respiratory chain (I-IV) complex and manganese superoxide dismutase (MnSOD), to generate superoxide anions and hydrogen peroxide (H2O2), respectively.
Phosphodiesterase Type-5 Inhibitors

I. Sildenafil (Viagra®)
II. Tadalafil (Cialis®)
III. Vardenafil (Levitra®, Nuviva®)
Pharmacological Actions of Sildenafil

1. Smooth muscle relaxation and inflow of blood to the corpus cavernosum, which at recommended doses has no effect in the absence of sexual stimulation
2. Inhibition of platelet thrombus formation
3. Decreased blood pressure
Blood flow in human penis

A. Flaccid state
- Corpus cavernosum
- Skin
- Efferent vein
- Tunica albuginea
- Venous plexus
- Veins are compressed as cavernosa enlarge
- Cavemosal artery

B. Erect state
- Engorged cavernous spaces
Absorption and Metabolism of Sildenafil

1. rapidly absorbed after oral administration, with absolute bioavailability of about 40%.

2. eliminated predominantly by hepatic metabolism (mainly cytochrome P450 3A4) and is converted to an active metabolite with properties similar to the parent, sildenafil.

3. both sildenafil and the metabolite have terminal half lives of about 4 hours.
Therapeutic Uses of Sildenafil

1. Erectile dysfunction
2. Pulmonary hypertension
<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Percentage of Patients Reporting Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sildenafil (N=734)</td>
</tr>
<tr>
<td>Headache</td>
<td>16%</td>
</tr>
<tr>
<td>Flushing</td>
<td>10%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>7%</td>
</tr>
<tr>
<td>Nasal Congestion</td>
<td>4%</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>3%</td>
</tr>
<tr>
<td>Abnormal Vision†</td>
<td>3%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2%</td>
</tr>
<tr>
<td>Rash</td>
<td>2%</td>
</tr>
</tbody>
</table>

†Abnormal Vision: Mild and transient, predominantly color tinge to vision, but also increased sensitivity to light or blurred vision. In these studies, only one patient discontinued due to abnormal vision.
Precautions with the Use of Sildenafil

1. elderly patients (65 years or over) have a reduced clearance of sildenafil with plasma concentrations approximately 40% greater than those seen in younger volunteers (18-45 years)
2. patients with severe ($\text{CL}_{\text{cr}} = <30 \text{ ml/min}$) renal impairment, have a reduced sildenafil clearance
3. In patients with hepatic cirrhosis sildenafil clearance is reduced
4. Therefore, age $>65$, hepatic impairment and severe renal impairment are associated with increased plasma levels of sildenafil.
Phosphodiesterase Type 5 inhibitors should not be used with the following medications because very serious (possibly fatal) interactions may occur: nitrates (e.g., nitroglycerin, isosorbide), nitroprusside (or any "nitric oxide donor" drugs), recreational drugs called "poppers" containing amyl or butyl nitrite.
DRUGS AFFECTING UTERINE FUNCTION
Uterine Stimulants

• Induce abortion
• Induce or augment labor
• Prevent postpartum hemorrhage

Oxytocin
Prostaglandins
Ergot alkaloids
Antiprogestins (RU 486)
Uterine Relaxants

• Prevent or arrest preterm labor
• Reverse effects of uterine stimulants
• Facilitate intrauterine manipulations
• Relieve painful uterine contractions during menstruation
Uterine Relaxants

Beta-adrenergic blocking drugs
Prostaglandin synthesis inhibitors
NSAIDs
Magnesium sulfate
Oxytocin antagonists
I. Neurohypophyseal hormones

Hormones synthesized in the supraoptic and paraventricular hypothalamic nuclei

- Antidiuretic hormone (8-arginine vasopressin)
- Lypressin (8-lysine vasopressin, swine peptide)
- Oxytocin (milk ejecting peptide)
Antidiuretic hormone
(8-arginine vasopressin)

- Increases permeability of renal collecting duct to water
- Constricts vascular smooth muscle
- Regulates secretion of adrenocorticotropic hormone (ACTH)
Antidiuretic hormone
(8-arginine vasopressin)

- Acts as a neurotransmitter substance
- Central regulator of circulation, temperature, and other visceral functions
- Promoter of release of coagulation factor by vascular endothelium
Storage and Release

- Stored in granules in neurohypophysis and in the zona externa of the median eminence. These granules also incorporate dynorphin.
Storage and Release

- Sensory stimuli arising from the cervix and vagina induce secretion of oxytocin. This process is inhibited by ovarian relaxin. Stimulation of the breast also results in secretion of oxytocin.

- Increases in osmolality of plasma stimulates and ethanol inhibits the release of oxytocin.
Pharmacological Actions of Oxytocin

Uterus

- Stimulates both force and frequency of contraction of uterine smooth muscle.
- Actions dependent upon presence of estrogen
- Responsiveness of uterus increases markedly during the third trimester of pregnancy and is accompanied by an increase in the number of specific oxytocin receptors.
Pharmacological Actions of Oxytocin

Mammary Gland

- Causes contraction of the myoepithelium which forces milk from the alveolar channels into the large sinuses (milk ejection).

- Catecholamines inhibit milk ejection, but this process is not under control of the autonomic nervous system.
Pharmacological Actions of Oxytocin

Cardiovascular system

- Causes a marked, transient relaxation of vascular smooth muscle.
- Decreases systolic and especially diastolic blood pressure. Also causes flushing, reflex tachycardia, and an increase in limb blood flow.
Pharmacological Actions of Oxytocin

Cardiovascular system

- Inhibition of sympathetic preganglionic neurons and neurons in the caudal medulla.

- Highly efficacious constrictor of umbilical arteries and veins, suggesting a role in effecting their closure at birth.
Pharmacological Actions of Oxytocin

Absorption, metabolism and excretion

- Absorbed by any parenteral route.
- Can be administered by intranasal spray.
- Inactivated mainly in liver and kidneys.
- Metabolized by cystyl-aminopeptidase or oxytocinase in plasma.
Eicosanoids

- Prostaglandins
- Protacyclin
- Thromboxane A$_2$
- Leucotrienes
- Platelet-activating factor (PAF)
Parent Fatty Acids
- arachidonic acid
- eicosapentaenoic acid
- dihomo-$\gamma$-linolenic acid

- cytochrome P-450 monooxygenases
- cyclooxygenases
- 5-lipoxygenases

- epoxides
- prostaglandins and thromboxanes
- leukotrienes
Cyclooxygenase

Prostacyclin synthase

Thromboxane synthase

Arachidonic acid

Synthesis of prostaglandins
### Subtypes of Prostaglandin Receptors

<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>Endogenous Agonist</th>
<th>Rank Order of Potency</th>
<th>Signal Transduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>DP</td>
<td>PGD₂</td>
<td>D₂ &gt; E₂, F₂α, I₂, TXA₂</td>
<td></td>
</tr>
<tr>
<td>EP</td>
<td>PGE₂</td>
<td>E₂ &gt; I₂ ≥ F₂α &gt; D₂</td>
<td>PLC cAMP↑, cAMP↓</td>
</tr>
<tr>
<td>EP₁ EP₂</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EP₃</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FP</td>
<td>PGF₂α</td>
<td>F₂α &gt; D₂ &gt; E₂ &gt; I₂</td>
<td>PLC</td>
</tr>
<tr>
<td>IP</td>
<td>PGI₂</td>
<td>I₂ &gt; D₂, E₂, F₂α, TXA₂</td>
<td>cAMP↑</td>
</tr>
<tr>
<td>TP</td>
<td>TXA₂</td>
<td>TXA₂ &gt; D₂ &gt; F₂α E₂, I₂,</td>
<td>PLC</td>
</tr>
</tbody>
</table>
Actions of Prostaglandins upon the Uterus

- Prostaglandins are found in the female reproductive system (ovary, myometrium and menstrual fluid).
- Also found in seminal fluid in very high concentrations.
- At term and during labor prostaglandins rise in amniotic fluid, umbilical cord blood, and maternal blood.
Actions of Prostaglandins upon the Uterus

- During the last two trimesters of pregnancy, PGE$_2$ (dinoprostone, PROSTIN E$_2$) and PGF$_{2a}$ (carboprost, HEMOBATE) cause strong uterine contractions.

- Local instillation of prostaglandins can induce cervical ripening at doses that do not affect uterine motility.

- Major use is to induce midtrimester abortions.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprostadil (PGE$_1$)</td>
<td>Increased blood flow and oxygenation by vessel relaxation</td>
<td>Neonatal defects; interruption of aortic arch, pulmonary stenosis</td>
</tr>
<tr>
<td>Dinoprostone (PGE$_2$)</td>
<td>Increased uterine contraction</td>
<td>Abortifacient</td>
</tr>
<tr>
<td>Carboprost (15-Methyl PGE$_{2\alpha}$)</td>
<td>Increased uterine stimulation with other stimulants</td>
<td>Control uterine bleeding in postpartum hemorrhage</td>
</tr>
<tr>
<td>Iloprost (PGI$_2$ derivative – prostacyclin)</td>
<td>Reduced platelet hyperaggregation</td>
<td>Peripheral vascular disease</td>
</tr>
<tr>
<td>Misoprostol</td>
<td>Suppress gastric acid secretion</td>
<td>Heal gastric ulcers</td>
</tr>
</tbody>
</table>
Prostaglandin Toxicity

- Nausea and vomiting
- Diarrhea
- Hyperpyrexia
- Hypertension
Pharmacological Actions of the Ergot Alkaloids

- Increase force and frequency of contractions of the uterus which are followed by normal relaxation.
- At higher doses contractions are more forceful and prolonged and the resulting tone is greatly increased
Pharmacological Actions of the Ergot Alkaloids

- Stimulate the uterus at all times, but the gravid uterus is much more sensitive, and small doses given immediately post partum cause a marked uterine response without significant side effects.

- Can cause a severe peripheral vasoconstriction that can result in damage to the vascular epithelium as well as vascular stasis, thrombosis and gangrene.

- Use is associated with the development of retroperitoneal fibrosis, a rare disorder caused by an excess of fibrous tissue in the area just behind the stomach.
Pharmacological Actions of the Ergot Alkaloids

- Ergonovine and the synthetic methyl-ergonovine are the major ergot alkaloids that are used to stimulate the uterus.

- Ergotamine is used mainly to treat migraine headaches
Major Therapeutic Uses of Drugs that Stimulate Uterine Motility

- Induction of labor
- Augmentation of labor
- Reduction of postpartum bleeding (not an accepted contemporary use)
- Therapeutic abortion
- Antepartum test of uteroplacental insufficiency in high-risk pregnancies.
Migraine

• Affects 10% to 20% or the population
• Throbbing (usually unilateral) headache associated with nausea
• Photophobia
• Hyperacusis
• Polyuria
  Diarrhea
• “Aura” (usually visual, sensory and motor changes)
Migraine Pathogenesis

- Vascular
- Spreading depression of cortical electrical activity
- Serotonergic abnormalities
- Other: neurotransmitter systems, anatomical and autonomic
Acute Migraine Treatment

• Mild migraine
  Mild analgesics, combination analgesics, antiemetics

• Moderate migraine
  Combination analgesics, ergot alkaloid, sumatriptan (IMITREX)

• Severe migraine
  Ergot alkaloid, sumatriptan, prophylactic medications, antiemetics
Migraine Prophylaxis

• Tricyclic antidepressants
  ♦ Amitriptyline (ELAVIL)
• Serotonergic antagonists
  ♦ Methysergide (SANSERT)
• β-Adrenergic antagonists
  ♦ Propranolol (INDERAL)
• Monoamine oxidase inhibitors
  ♦ Phenelzine (NARDIL)