Eicosanoids

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Eicosanoids

Free radical attack
Isoprostanes

CYPs
EETs

HETEs
Leukotrienes
Lipoxins
(see Figure 37-2)

5-LOX inhibitors e.g., zileuton

Cyclooxygenase
Arachidonic Acid

COX-1
Aspirin and other NSAIDs e.g., ibuprofen

COX-2
Selective COX-2 inhibitors e.g., coxibs

Peroxidase

PGG₂

PGH₂

PGFs

PGI₂

L-PGDs
H-PGDs

mPGES
cPGES

PGD₂

PGE₂

EP₁, EP₂

EP₃, EP₄


COX-1
COX-2

Platelets, vascular smooth muscle, macrophages, kidney

Brain, kidney, vascular smooth muscle, platelets

Uterus, airways, vascular smooth muscle, eye

Mast cells, brain, airway

Endothelium, kidney, platelets, brain


DP₁, DP₂, CRTH₂

IP
Major pathways of prostanoid degradation

- TxA₂
- PGI₂

Non-enzymatic hydrolysis:
- 11-hydro-TXB₂ dehydrogenase
  - 11-dehydro-TXB₂
  - 2,3-dinor-TXB₂⁻
- β-oxidation
  - 2,3-dinor-6-keto PGF₁α⁻

11-keto reductase
- 9α11β-PGF₂

Prostaglandin dehydrogenase
- Δ¹³ reduction, β oxidation, α oxidation
  - PGE-M⁺
  - PGF-M⁺
  - PGD-M⁺
Prostanoid receptors and their primary signaling pathways
<table>
<thead>
<tr>
<th>RECEPTOR</th>
<th>LIGANDS 1° (2°)</th>
<th>PRIMARY COUPLING</th>
<th>MAJOR PHENOTYPE IN KNOCKOUT MICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>DP₁</td>
<td>PGD₁</td>
<td>G₄</td>
<td>↓ Allergic asthma</td>
</tr>
<tr>
<td>DP/CHRT₅</td>
<td>PGD₂ (15d-PGI₂)</td>
<td></td>
<td>↑ or ↓ Allergic airway inflammation</td>
</tr>
<tr>
<td>EP₁</td>
<td>PGE₂</td>
<td>G₄</td>
<td>↓ Response of colon to carcinogens</td>
</tr>
<tr>
<td>EP₂</td>
<td></td>
<td>G₄</td>
<td>Impaired ovulation and fertilization</td>
</tr>
<tr>
<td>EP₃, I–VI, e, f</td>
<td>PGE₂</td>
<td>G₃, G₁, G₄</td>
<td>Resistance to pyrogens ↓ Acute cutaneous inflammation</td>
</tr>
<tr>
<td>EP₄</td>
<td>PGE₁</td>
<td>G₄</td>
<td>Patent ductus arteriosus ↓ Bone mass/density in aged mice ↑ Bowel inflammatory response ↓ Colon carcinogenesis</td>
</tr>
<tr>
<td>FP₅,₆</td>
<td>PGF₂₀ (IsoPs)</td>
<td>G₄</td>
<td>Failure of parturition</td>
</tr>
<tr>
<td>IP</td>
<td>PGI₂ (PGE₂)</td>
<td>G₄</td>
<td>↑ Thrombotic response ↓ Response to vascular injury ↑ Atherosclerosis ↑ Cardiac fibrosis Salt-sensitive hypertension ↓ Joint inflammation</td>
</tr>
<tr>
<td>TP₄,₆</td>
<td>TxA₂ (IsoPs)</td>
<td>G₃, G₁, G₁₂₁₃, G₁₆</td>
<td>↑ Bleeding time ↓ Response to vascular injury ↓ Atherosclerosis ↑ Survival after cardiac allograft</td>
</tr>
<tr>
<td>BLT₁</td>
<td>LTB₁</td>
<td>G₁₂ G₃</td>
<td>Some suppression of inflammatory response</td>
</tr>
<tr>
<td>CysLT₁</td>
<td>LTD₄ (LTC₁/LTE₁)</td>
<td>G₄</td>
<td>↓ Innate and adaptive immune vascular permeability response ↑ Pulmonary inflammatory and fibrotic response</td>
</tr>
<tr>
<td>CysLT₂</td>
<td>LTC₄/LTD₄ (LTE₁)</td>
<td>G₄</td>
<td>↓ Pulmonary inflammatory and fibrotic response</td>
</tr>
</tbody>
</table>

This table lists the major classes of eicosanoid receptors and their signaling characteristics. Splice variants for EP₄, TP, and FP are indicated.
Eicosanoids Effects (Cont.)

- **Respiratory system**
  - **Contraction**
    - TXA2, PGF2α & PGD2
    - LTC4 & D4
      - Bronchoconstriction (1000 times of histamine)
      - ↑Secretion
      - Chemotaxis
  - **Relaxation**
    - PGE2 & PGI2

- **Reproductive system**
  - **Female**
    - ovulation, luteolysis, fertilization
    - PGE2 & PGF2α
    - Contraction of uterine
      - TXA2, PGF2α & Low concentration PGE2
    - Relaxation of uterine
      - PGI2, PGD2 & High concentration of PGE2
  - **Male**
    - Fertility & erection
Eicosanoids Effects (Cont.)

- **Nervous Systems**
  - Fever
    - PGE 2
    - interleukin-1
  - Sleep
    - PGD2: natural sleep
    - PGE2: wakefulness
  - Neurotransmission
    - ↓release of NE
      - PGE
  - Pain
    - PGE2 & PGI 2
      - Sensitization of peripheral nerve
      - Central sensitization
  - Eye
    - ↓intraocular pressure
      - PGE & PGF

- **Bone**
  - ↑bone turnover
    - PGE2
    - NSAIDs may be helpful in osteoporosis due to menopause
  - Effects of mechanical forces on bones
  - Bone fracture healing

- **Inflammation and Immunity**
  - vascular permeability
    - edema & leukocyte infiltration
      - PGE 2 & PGI 2
  - T & B-lymphocyte development
  - chemoattraction
    - PGD2 & LTB4
Eicosanoids (Clinical use)

- Abortion & Facilitation of Labor
  - Dinoprostone (PGE2)
  - Misoprostol (PGE1)
  - Carboprost (PGF2α)
  - Antiprogestins (mifepristone)

- Oxytocin
  - preeclampsia-eclampsia
  - cardiac and renal disorders
    - antidiuretic effect of oxytocin
    - Natriuretic effects of PGE2

- Dysmenorrhea
  - NSAIDs

- Erectile dysfunction
  - alprostadil (PGE1)

- Bartter’s syndrome
  - ↑ prostaglandins
  - low-to-normal blood pressure
  - ↓ sensitivity to angiotensin & hyperreninemia
  - ↑ aldosteronism, ↑ loss of K

- Cancer
  - oncogenic prostanoids: PGE 2
  - Proliferation, angiogenesis & invasion
  - NSAIDs: ↓ risk for cancers
Eicosanoids (Clinical use)

Pulmonary Hypertension
- PGI2
  - ↓ peripheral, pulmonary & coronary vascular resistance
  - after mitral valve surgery
  - portopulmonary hypertension
- Analogues
  - Epoprostenol (iv infusion)
  - Iloprost (inhalation & iv)
  - Treprostinil (SC or IV, longer T1/2)

Patent Ductus Arteriosus
- At birth: ↓ PGE2 → ductus arteriosus closure
- Inhibition of closure until surgery:
  - transposition of the great arteries
  - pulmonary atresia
  - pulmonary artery stenosis
  - alprostadil (PGE1)
- Induction of closure
- NSAIDs: indomethacin
Eicosanoids (Clinical use)

- **Glaucoma**
  - Latanoprost (PGF2α)

- **Cell-Mediated Transplant Rejection**
  - ↑PGI2, ↓TXA2, ↓Leukotriens
  - Corticosteroids
  - PGI2

- **Inflammation**
  - NSAIDs (Aspirin, Ibuprofen, ...)
  - Rheumatoid Arthritis
    - immune complexes
    - inflammatory response

- **GI protection**
  - Cytoprotective against NSAIDs induced gastritis
  - Misoprostol (PGE1)
Eicosanoids (Clinical use)

- **Platelet aggregation**
  - low-dose aspirin (81 mg/d)
    - ↓platelet COX-1
      - ↓TXA2 → ↓Platelet aggregation
    - NO effect on systemic COX-1 or COX-2
      - NO effect on PGI2
  - **selective COX-2 inhibitors**
    - NO effect on platelet TXA2 biosynthesis
    - ↓PGI2 synthesis → ↑Platelet aggregation

- **Asthma**
  - leukotriene-receptor inhibitors
    - Zafirlukast & montelukast
  - lipoxygenase inhibitor
    - Zileuton
  - ↓eicosanoid synthesis
    - Corticosteroids
  - ↓Release of eicosanoids, histamine & PAF: cromolyn
Dietary Manipulation of Eicosanoids

- dietary linoleic & \( \alpha \)-linolenic acids
  - Arachidonic acid (C20:4)
    - Corn, safflower & sunflower oils
  - linoleic acid (C18:2)

- Cold-water Fish oil (omega-3)
  - eicosapentaenoic (C20:5)
  - docosahexaenoic acids (C22:6)

Formation of TXA3 (inactive) instead of TXA2

- ↓ platelet aggregation
- leukocyte function, Inflammation & Cancer
- ↓ blood pressure & dyslipidemias
- myocardial infarction & sudden cardiac death
<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic Uses</th>
<th>Clinical Pharmacology and Tips</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prostanoids and Prostanoid Analogues: PGE$_1$/PGE$_2$</strong></td>
<td></td>
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<tr>
<td>Alprostadil (PGE$_1$)</td>
<td>• Erectile dysfunction</td>
<td>• Rapidly metabolized</td>
</tr>
<tr>
<td></td>
<td>• Temporary maintenance of patent ductus arteriosus in neonates</td>
<td>• Prolonged erection (4–6 h) in 4% of patients</td>
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<td></td>
<td></td>
<td>• Apnea in 10%–12% of neonates with congenital heart defects; ventilator assistance should be available during treatment</td>
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<tr>
<td>Misoprostol</td>
<td>• Protection from NSAID-induced gastric toxicity</td>
<td>• Contraindicated for use in pregnant women; women who may become pregnant must use birth control when taking misoprostol</td>
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<tr>
<td>(PGE$_1$ analogue)</td>
<td></td>
<td>• Combined with mifepristone to terminate early pregnancy</td>
</tr>
<tr>
<td>Dinoprostone (PGE$_2$)</td>
<td>• Labor induction</td>
<td>• Rapidly metabolized</td>
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<tr>
<td>Prostanoids and Prostanoid Analogues: PGI₂ (Prostacyclin)</td>
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<tr>
<td><strong>Epoprostenol (PGI₂)</strong></td>
<td>Pulmonary arterial hypertension</td>
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<tr>
<td>• Rapidly metabolized</td>
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<tr>
<td>• Administered by intravenous infusion</td>
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<tr>
<td>• Most common dose-limiting adverse effects are nausea, vomiting, headache, hypotension, and flushing</td>
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<tr>
<td><strong>Iloprost (PGI₂ analogue)</strong></td>
<td>Pulmonary arterial hypertension</td>
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<td>• Administered by inhalation</td>
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<tr>
<td>• Synthetic PGI₂ analogue with longer t&lt;sub&gt;1/2&lt;/sub&gt;</td>
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<td>• May increase risk of bleeding when used with anticoagulants or platelet inhibitors</td>
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<tr>
<td><strong>Treprostinil (PGI₂ analogue)</strong></td>
<td>Pulmonary arterial hypertension</td>
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<tr>
<td>• May be administered by subcutaneous/intravenous infusion or by inhalation</td>
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<tr>
<td>• Adverse events similar to Iloprost</td>
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<tr>
<td>Prostanoids and Prostanoid Analogues: PGF$_{2\alpha}$</td>
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<tr>
<td>Carboprost tromethamine</td>
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<tr>
<td>- Abortifacient (second trimester)</td>
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<td>- Postpartum hemorrhage</td>
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<tr>
<td>- Common adverse effects are vomiting, diarrhea, nausea, fever, flushing</td>
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<tr>
<td>Bimatoprost</td>
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<td></td>
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<tr>
<td>- Ocular hypertension</td>
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<td>- Open-angle glaucoma</td>
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<td>- Hypotrichosis of the eyelashes</td>
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<td>- Upper respiratory tract infections in about 10% of patients</td>
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<tr>
<td>- May cause changes in pigmentation and hair growth</td>
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<tr>
<td>Latanoprost</td>
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<td>- Open-angle glaucoma</td>
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<tr>
<td>- Increased iris pigmentation with time</td>
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<tr>
<td>Tafluprost</td>
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<tr>
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<td>- Open-angle glaucoma</td>
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<td>- Metabolized to active drug in the eye</td>
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<td>- May cause increased iris pigmentation</td>
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<tr>
<td>Travoprost</td>
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Synthesis and degradation of PAF