Autacoids III

EICOSANOIDS

(prostaglandins, thromboxanes, leukotrienes)

OBJECTIVES

1. Describe the pharmacology of prostaglandins and its clinical Implications
2. List the major clinical implications and toxicities of ergot alkaloids on the major organ systems

Eicosanoids

- **Eicosanoids** are produced from arachidonic acid, a 20-carbon polyunsaturated fatty acid (5,8,11,14-eicosatetraenoic acid)

- The eicosanoids are considered “autacoids"
  - They act on cells close to their site of production
  - They are rapidly degraded
- They have both intercellular signaling, & intracellular signal cascades

The Cyclooxygenase Pathway Prostanoids

Prostaglandin H_2 Synthase production of PGs, PGI_2 & TXA_2

PGH_2 synthase & Cyclooxygenase (COX) are used as synonyms

PG endoperoxides (PGG_2 & PGH_2) are more potent & long-acting than the PGs to which they decompose

TXA_2 formed mainly in platelets by TX synthase mediating vasoconstriction & platelet aggregation

PGI_2, formed mainly in endothelium by PGI synthase opposes TXA_2

The Cyclooxygenase Pathway

- Two isoforms of COX exists: **COX-1 (constitutive form) & COX-2 (inducible form)**
- COX-1 is constitutively expressed at low levels in many cell types
- COX-2 is constitutively expressed in kidney & CNS

- ✓ COX-2 gene transcription is stimulated by growth factors, cytokines, & endotoxins
- ❑ A COX-1 variant, named COX-3, plays a significant role in pain sensation in paracetamol-sensitive way

Prostaglandin receptors:

- Prostaglandins & related compounds are transported out of the cells that synthesize them.
- Most affect other cells by interacting with plasma membrane **G-protein coupled receptors**.

Depending on the cell type, the activated G-protein may stimulate or inhibit formation of **cAMP**, or may activate a phosphatidylinositol signal pathway leading to intracellular **Ca^{++}** release.

- Another prostaglandin receptor, designated **PPAR**□, is related to a family of nuclear

receptors with transcription factor activity.

Prostanoids Receptors

- Prostanoid receptors are AC/PLC **G-protein coupled Rs**
- Five main classes; **DP** (PGD_2), **FP** ($PGF_{2\alpha}$),**IP** (PGI_2),**TP** (TXA_2),& **EP** (PGE_2)

- Eicosanoid synthesis is activated by:
  - ✓ Pathological stimulus: tissue injury/disease
  - ✓ Transmitter release like BK, AngII, NE

Prostanoids Biologic Effects

Cardiovascular System

- **$PGI_2/D_2/E_2$** →dilation of arterioles, pre-capillary sphincters & post-capillary veins → increased blood flow & cardiac output
- **TXA_2** is a potent vasoconstrictor

- TXA_2 & ***PGI_2*** are potent platelet aggregation inducer & *inhibitor* respectively (blood fluidity)
- PGI_2 de-aggregate platelets clumps & reduces myocardial infarct size & ischemic organ damage
- **PGI_2, PGE_2, & NO** are simultaneously released from endothelium
- PGE_2 inhibits B- & T-lymphocyte activation & proliferation, inhibiting antibodies & lymphokines production

Prostanoids Biologic Effects

Smooth muscle:

- Bronchial muscle relaxation by PGE_2 &

PGI_2, but constriction by TXA_2, LTC_4 & LTD_4

- Human pregnant uterus is contracted by $PGE_{1/2}$, and $PGF_{2\alpha}$

GIT: PGE_s & PGI_2 inhibit gastric acid secretion & reduce pepsin content

- They increase bicarbonate, mucus & blood flow

- Increased electrolyte/water movement into intestinal lumen (diarrhea)
- TXA_2 is pro-ulcerogenic

Prostanoids Biologic Effects

Renal System

PGs enhance urine formation, natriuresis, & kaliuresis via action on renal blood flow & tubules

PGD_2, PGE_2, PGI_2 stimulate renin release

PGs inhibit water re-absorption under ADH effect

Nervous system

Hyperthermia by PGE_2, related pyrogen-induced fever

- Antipyretic action of ASA & NSAIDs is via inhibition of COX-1, -2 & -3

Algesia induction & pain sensitization to histamine, BK or mechanical stimuli

- Analgesic action of ASA & NSAIDs is via inhibition of COXs

The Lipoxygenase Pathway

- **Lipoxygenase**, catalze the addition of O_2 to double bond(s) of arachidonic acid forming hydroperoxy-eicosatetraenoic acid **(HPETE)**

- ✓ **5-, 12- & 15- lipoxygenases → 5-, 12- & 15-**HPETEs respectively
- ✓ 5-HPETE is converted to leukotriene-A_4 (LTA_4) , which in turn may be converted to various other **leukotrienes**

Leukotriens (Slow-Reacting Substance of Anaphylaxis, SRS-A)

Cysteinyl LTs ($LTC_4/D_4/E_4/F_4$) cause potent vasoconstriction & small airway constriction

- ➢ They increase tracheal mucus secretion

- They may be of role in immediate hypersensitivity & asthma, where corticosteroids are effective antiallergic via LTs inhibition (but NOT ASA)

LTB$_4$ produced from PMNLs has a potent chemotactic activity (Inflammation/damage)

- LTB_4 induce aggregation of PMNLs in joint diseases (gout, arthritis) & skin diseases (psoriasis)

The Epoxygenase Pathway

A cytochrome P450 epoxides double bonds of the precursor FA (arachidonate) into mono-epoxide FA; epoxy

eicosatetraenoic acids (EPETEs)
EPETEs are involved in vascular tone modulation, ion transport, hemostasis & hematopoiesis

Prostanoids
Therapeutic Uses

UTERINE STIMULATION

Dinoprostone (PGE_2): Prostin E_2 vaginal suppositories used to induce abortion between 12^{th} -20^{th} gestational weeks

- **Prostin E_2 oral tablets** for elective induction of labbour/obliged induction because of HTN, toxemia, intrauterine death

- Treatment of duration ≤ 18 hrs

➢ **Prostin E_2 vaginal gel** used for induction of labour at term or near term (I-2 mg intravaginal, repeated Q 6hrs according to response)

Prostanoids

Therapeutic Uses

UTERINE STIMULATION

Carboprost (15-methyl $PGF_{2\alpha}$)

Used by IM route for induction of abortion between 12^{th} -20^{th} gestational weeks

Used at a dose of 250 μg every 1-3 hrs

Dinoprost ($PGF_{2\alpha}$)

Injection form for intra-amniotic administration
Used to induce labour or abortion

Prostanoids

Therapeutic Uses

GIT

Misoprostol is a synthetic methyl ester analogue of PGE_1

- Used to prevent drug-induced gastric ulceration during

NSAIDs, corticosteroid or anticoagulant therapy

- It can be used alone or in combination with antacids for duodenal ulcer treatment
- Not used for pregnant women or whom are planning pregnancy

Prostanoids

Therapeutic Uses

Platelet Aggregation

Epoprostenol (PGI_2):
It is used as a heparin replacement in some hemodialysis patients
Used to prevent platelet aggregation in extracorporal circulation systems

Impotence

- **Alprostadil (PGE_1)**
  was used by in jection into corpora cavernosa to maintain erection

- ✓Replaced by PDE-V inhibitors

Leukotriens Therapeutic Importance

- ❑**LTs have no therapeutic uses, but LTs antagonists have**
- ❑**Anti-asthma medications**:
  - ✓ **5-Lipoxygenase** Inhibitors, e.g., zileutin
  - ✓**Leukotriene-receptor antagonists;** montelukast, & zafirlukast

Platelet-Activating factor (PAF)

PAF, another lipid-derived autacoid

Released from inflammatory cells & platelets by PLA_2, upon activation

It has a role in many types of inflammation, bronchial hyper-responsiveness, and delayed phase of asthma

PAF antagonists (receptor/production inhibition) are potential antiinflammatory & antiasthmatic drugs
Corticosteroids anti-inflammatory effect comprise PAF production inhibition

Peripheral Effect

Central Effects

Central Effects

Uterotonic Effects

THANK YOU