**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 H2 Synthase** production of PGs, PGI2 & TXA2

PGH2 synthase & Cyclooxygenase (COX) are used as synonyms

PG endoperoxides (PGG2 & PGH2) are more potent & long-acting than the PGs to which they decompose

TXA2 formed mainly in platelets by TX synthase mediating vasoconstriction & platelet aggregation

PGI2, formed mainly in endothelium by PGI synthase opposes TXA2

**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** (PGD2), **FP** (PGF2α),**IP** (PGI2),**TP** (TXA2),& **EP** (PGE2)
* Eicosanoid synthesis is activated by:
* Pathological stimulus: tissue injury/disease
* Transmitter release like BK, AngII, NE

**Prostanoids Biologic Effects
Cardiovascular System**

* **PGI2/D2/E2**→dilation of arterioles, pre-capillary sphincters & post-capillary veins → increased blood flow & cardiac output
* **TXA2** is a potent vasoconstrictor
* TXA2 & ***PGI2***are potent platelet aggregation inducer & *inhibitor* respectively (blood fluidity)
* PGI2 de-aggregate platelets clumps & reduces myocardial infarct size & ischemic organ damage
* **PGI2, PGE2, & NO** are simultaneously released from endothelium
* PGE2 inhibits B- & T-lymphocyte activation & proliferation, inhibiting antibodies & lymphokines production

**Prostanoids Biologic Effects**

**Smooth muscle:**

* Bronchial muscle relaxation by PGE2 & PGI2, but constriction by TXA2, LTC4 & LTD4
* Human pregnant uterus is contracted by PGE1/2, and PGF2α

**GIT:** PGEs & PGI2 inhibit gastric acid secretion & reduce pepsin content

* They increase bicarbonate, mucus & blood flow
* Increased electrolyte/water movement into intestinal lumen (diarrhea)
* TXA2 is pro-ulcerogenic

**Prostanoids Biologic Effects**

**Renal System**

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

PGD2, PGE2, PGI2 stimulate renin release

PGs inhibit water re-absorption under ADH effect

**Nervous system**

*Hyperthermia* by PGE2, 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 O2 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-A4 (LTA4) , which in turn may be converted to various other **leukotrienes**

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

**Cysteinyl LTs (LTC4/D4/E4/F4)** 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)

**LTB4** produced from PMNLs has a potent chemotactic activity (Inflammation/damage)

* LTB4 induce aggregation ofPMNLs 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 (PGE2): Prostin E2 vaginal suppositories used to induce abortion between 12th -20th gestational weeks

* **Prostin E2 oral tablets** for elective induction of labbour/obliged induction because of HTN, toxemia, intrauterine death
* Treatment of duration ≤ 18 hrs
* **Prostin E2 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 PGF2α)**

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

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

**Dinoprost (PGF2α)**

Injection form for intra-amniotic administration

Used to induce labour or abortion

**Prostanoids Therapeutic Uses
GIT**

Misoprostol is a synthetic methyl ester analogue of PGE1

* 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 (PGI2):**

It is used as a heparin replacement in some hemodialysis patients

Used to prevent platelet aggregation in extracorporal circulation systems

**Impotence**

* **Alprostadil (PGE1)** 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 PLA2, 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