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Arachidonic Acid Metabolites and Inflammation

Tuesday, February 12, 2008
10:00 AM

- Arachidonic Acid can be produced two ways
 - Via PLA to make lysophospholipid and arachidonic acid
 - Via PLC to make DAG and phosphoryl-R then DAG lipase to make arachidonic acid and monacylglycerol
 - Lipoxygenase pathway --> leukotrienes
 - LTB₄ - neutrophils
 - C₄, D₄, E₄ - mast cells
 - Glutathione-S transferase: C --> D
 - Cyclooxygenase pathway --> prostaglandins
 - PGI₂ - prostacyclin
 - PGE₂ - macrophages
 - Thromboxanes
 - Cell Specificity of Arachidonic Acid Derivatives
 - Neutrophils --> leukotrienes
 - M'phage/Monocyte --> PG and leukotrienes
 - Platelets --> Thromboxanes
 - Endothelial cells --> prostacyclin (PGI₂)
 - Balances btwn prostacyclin and thromboxanes
- Biological Functions of Arachidonic Acid Products
 - COX-derived products
 - PGE₂/PGI₂
 - Immunoregulatory
 - ◆ Inhibits immune cell activation
 - ◆ Inhibits cytokine production
 - ◆ Inhibits mast cell activation
 - Blocks platelet aggregation
 - Increases vasodilation
 - Stimulates adenylate cyclase
 - Thromboxanes
 - Causes vasoconstriction
 - Induces platelet aggregation
 - Lipoxygenase derived products
 - LTB₄
 - Neutrophil activation
 - ◆ Chemotaxis
 - ◆ Degranulation
 - Mast cell activation: degranulation
 - LTC₄, D₄, E₄
 - Smooth muscle contraction
 - Increased vascular permeability
- In vivo effects
 - Regulates thermostatic set point (fever)
 - Activated leukocytes -->
 - Endogenous pyrogens
 - Arachidonic acid in hypothalamus converted to PGE₂ (NSAIDs inhibit)
 - Leads to increased temperature
 - Vasomotor tone and sweating
 - Shivering

- Regulates pain (PGE2 interacts w/ pain receptors)
- Regulates blood flow
- Regulates leukocyte activity
- Rheumatoid arthritis
 - Altered IgG leads to fixation/activation of complements
 - Chemotaxis
 - Lysosomal enzymes and activated oxygen released
 - Collagenase, proteases, phospholipases destroy cartilage
 - Phospholipases releases arachidonic acid from membranes --> PG --> nerve sensitization and vasodilation
- Pharmacologic Regulation
 - Modulate PLA/C activity
 - Suppress the release of arachidonic acid (no substrate available)
 - Blocks both COX and LO-derived products
 - Modulate COX activity
 - Blocks COX-derived products
 - COX-1/COX-2 inhibitors
 - COX-1 constitutive activity
 - PGE2 in kidneys
 - Thromboxane A2 in platelets
 - PGI2 in gastric cells for protection
 - COX-2 inducible
 - Pro-inflammatory PGs and other mediators lead to
 - Inflammation
 - Modulate specific enzymes down-stream from COX
 - Thromboxane synthetase inhibitors
 - Modulate LO activity
 - Block 5-LO activity
 - Small molecule receptor antagonists for cysteinyl leukotrienes
- NSAIDs
 - Aspirin, IB, indomethacin, acetaminophen
 - COX-2 Inhibitors
 - -coxibs
 - Osteoarthritis, rheumatoid, primary dysmenorrhea, pain mgmt
 - Aspirin
 - Irreversible inhibition of COX by acetylation at active site
 - But b/c platelets don't reproduce and endothelial cells can make more COX, aspirin has an anti-thrombotic month --> reduced risk of heart attack/stroke
 - Aspirin inhibits platelet aggregation by blocking platelet thromboxane production
 - Blocks platelet COX for life of platelet b/c no new protein synthesis occurs
 - Can block endothelial cell-derived prostacyclin, but short-lived by cell produces new COX
 - Platelet activity blocked more than endothelial cell activity
 - Indomethacin, ibuprofen reversibly inhibit COX
- Lipid mediators of inflammation
 - COX1+2 --> prostaglandins (PGE2, PGI2)
 - COX-1: thromboxanes
 - 5-LO: LTB4, C4, D4
 - Vasodilation, increased vascular permeability, control of platelet aggregation, chemotaxis, pain, fever
 - Balance between
 - Endothelium COX-2 -->PGI2 --> anti-thrombotic
 - Platelets COX-1 --> TXB2 --> pro-thrombotic

- NSAIDs inhibits both, COXIBs inhibit COX-2
- Ibuprofen reversibly inhibits both leading to a balance, maybe a little anti-thrombotic
- COX-2 (vioxx) inhibits COX-2 favoring thrombosis --> cardiogenic effects and why vioxx was pulled
- Aspirin irreversibly inhibits both, but as discussed before, COX-2 is truly irreversible vs. COX-1 being produced by endothelial cells --> anti-thrombotic effects of aspirin