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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 --> luekotrienes
    - LTB4 - neutrophils
    - C4, D4, E4 - mast cells
    - Glutathione-S transferase: C --> D
  - Cycloxygenase pathway --> prostaglandins
    - PGI2 - prostacyclin
    - PGE2 - macrophages
    - Thromboxanes
  - Cell Specificity of Arachdonic 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 activaiton
        - 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
    - LTC,D,E
      - 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
        - Alterged IgG leads to fixation/activation of complements
        - Chemotaxis
        - Lysosomal enzymes and activated oxygen released
        - Collegenase, proteases, phopholipases 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
            - Aspiring 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 cellls --> anti-thrombotic effects of aspirin