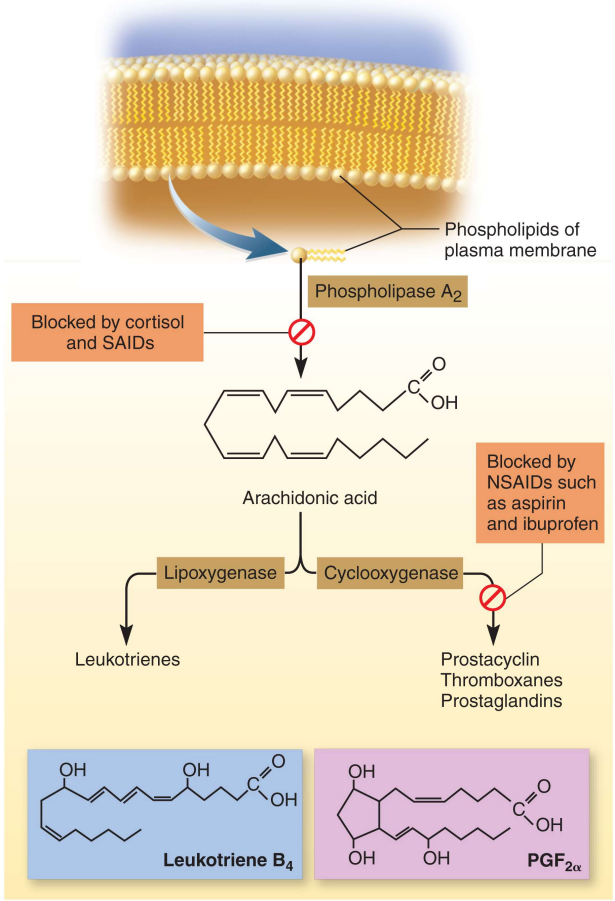
Chapter 18

Paracrine Secretions



Paracrine Secretions

- chemical messengers secreted from cell that don't enter blood but diffuse short distances to stimulate nearby cells (know this!)
  - unlike neurotransmitters not produced in neurons
  - unlike hormones not transported in blood to reach target tissue

Paracrine Secretions

- Note: single molecule may act as a hormone, paracrine, or even neurotransmitter in different situations (locations)
  - histamine
    - from mast cells in connective tissue
    - causes relaxation of blood vessel smooth muscle / paracrine
    - released from synaptic vesicles as neurotransmitter
  - nitric oxide
    - from endothelium of blood vessels, causes vasodilation / paracrine
    - Released from post synaptic neurons in CNS as a neuromodulator
  - catecholamines
    - diffuse from adrenal medulla to cortex / paracrine
    - Medulla releases catecholamines into blood / hormone
    - principle neurotransmitter for Sympathetic Nervous System

Eicosanoids = A Family of Paracrine Secretions

Eicosanoids – important family of paracrines (covered in C20)

- derived from fatty acid called arachidonic acid

- lipoxygenase converts arachidonic acid into leukotrienes
  - Leukotrienes // mediates allergic and inflammatory reactions

- cyclooxygenase converts arachidonic acid to three other types of eicosanoids (see next slide)

Eicosanoids = A Family of Paracrine Secretions

- cyclooxygenase converts arachidonic acid to three other types of eicosanoids

  - prostacyclin // inhibits blood clotting and vasoconstriction – normally present and coats inner lining of blood vessels

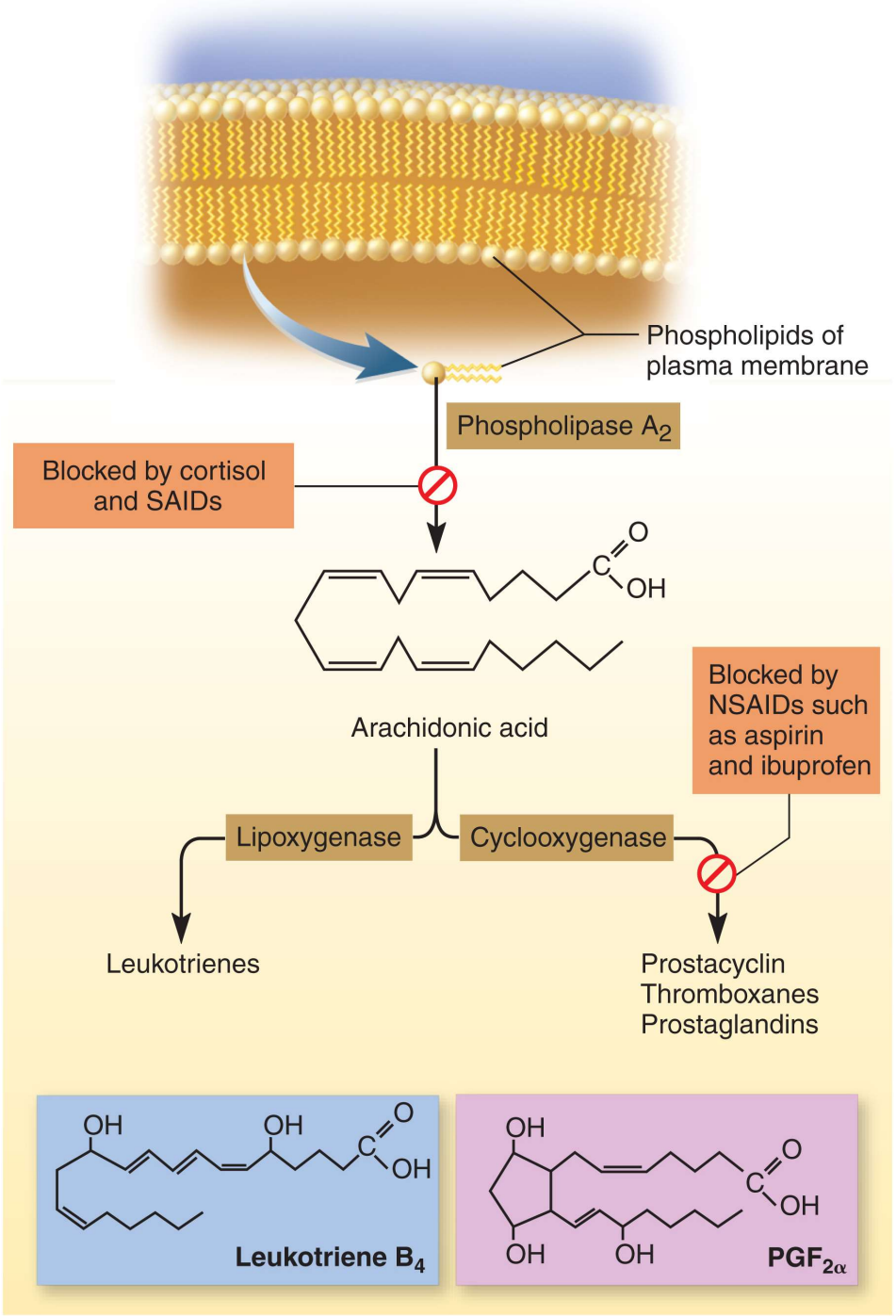
  - thromboxanes

    - produced by blood platelets after injury
    - overrides effect of prostacyclin
    - stimulates vasoconstriction and clotting

  - prostaglandins // multiple effects // includes:

    - PGE: relaxes smooth muscle in bladder, intestines, bronchioles, uterus and stimulates contraction of blood vessels
    - PGF: opposite effects

Eicosanoid Synthesis



Anti-Inflammatory Drugs

- These drugs are used to treat musculoskeletal disorders which result in inflammation (i.e. swelling, pain, redness, heat, limited mobility)
    - Arthritis, bursitis, spondylitis, gout, muscle strains
    - Acute stages of treatment use analgesics (block pain) and corticosteroids (blocks inflammation)
    - Corticosteroids not used for extended periods of time because of serious side affects
    - Nonsteroidal anti-inflammatory drugs (NSAID) maybe given at low doses for maintenance of treatment

NSAID

- Salicylates (e.g. aspirin) oldest drug in this category
  - Analgesic, anti-inflammatory, antipyretic effects
  - May cause gastric ulcerations or “silent bleeding” // due to blocking production of prostiglandins)
  - This NSAID said to be “non-select” because it inhibits all end products of metabolic pathways

NSAID

- New classes of drugs are “selective” NSAIDs
  - COX-1 (cyclooxygenase inhibitor 1) – in all tissues
  - COX-2 (cyclooxygenase inhibitor 2) – only at sites of inflammation
- Celebrex is a select NSAID that selectively inhibits cyclooxygenase-2 (COX-2) prostaglandin sysnthesis (COX-2 inhibitor)
  - Analgesic, anti-inflammatory, antipyretic effects
  - Celebrex does not inhibit COX-1
    - COX-1 enzymes regulates platelet aggregation therefore COX-1 inhibitors do not pose problem of silent bleeding or and fewer risks of gastric bleeding

NSAID

- Vioxx is also a COX-2 inhibitor
  - Removed from market in 2004
  - Twice the rate of myocardial infarctions and stroke when compared to placebo
  - Select COX-2 inhibitors stop synthesis of both good and bad prostaglandins with respect to the heart
    - Suppressing both types of prostaglandins as nonselective NSAIDs do actually helps the heart
    - Selective COX-2 inhibitors shut down the “good prostaglandins” / increasing risk of high blood pressure, atherosclerosis, and blood clotting
    - Note: Celebrex is still being prescribed