Ketone bodies and hormonal state
Essential Fatty acids

Metabolismo y Enfermedades Metabólicas
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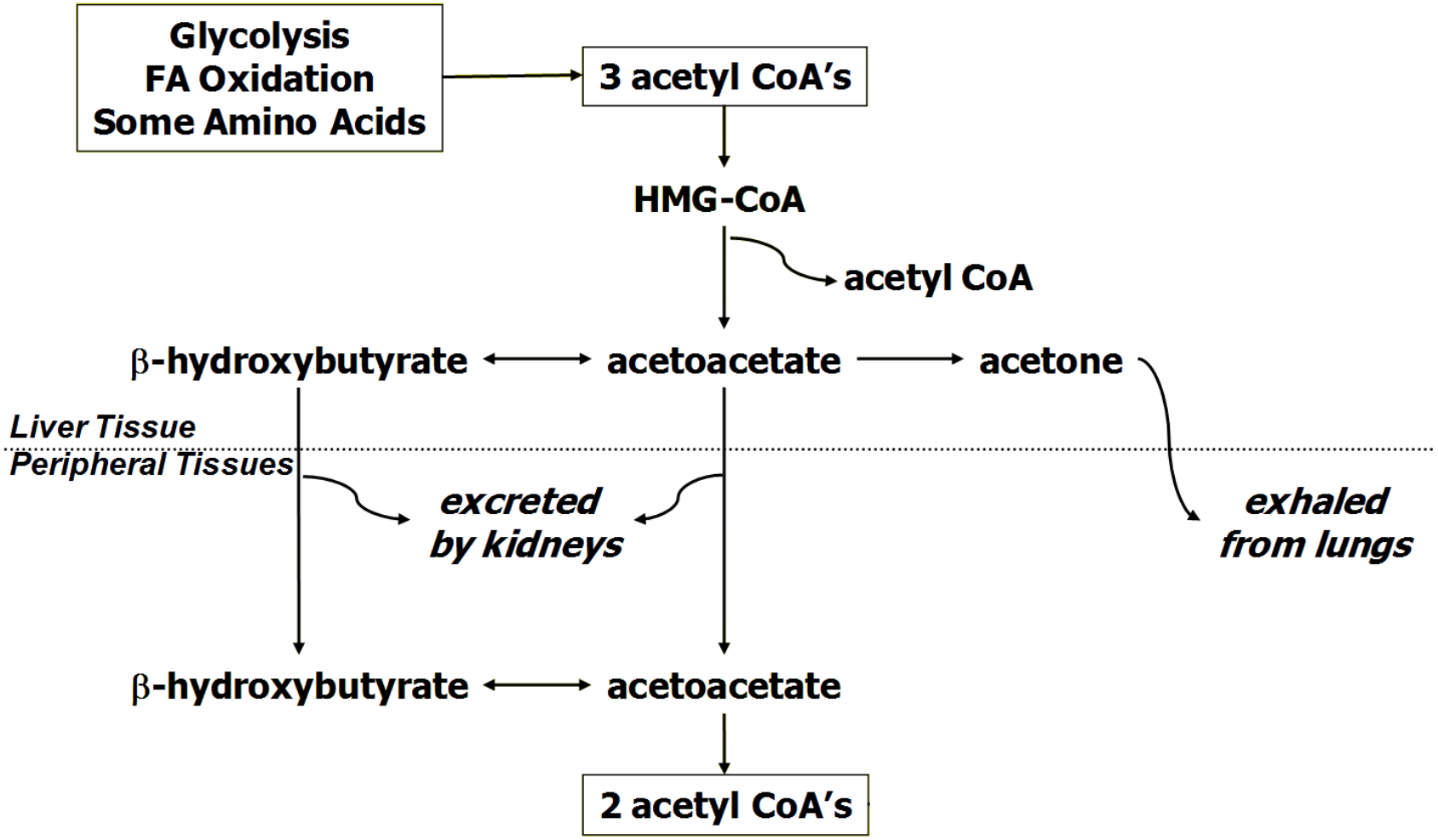
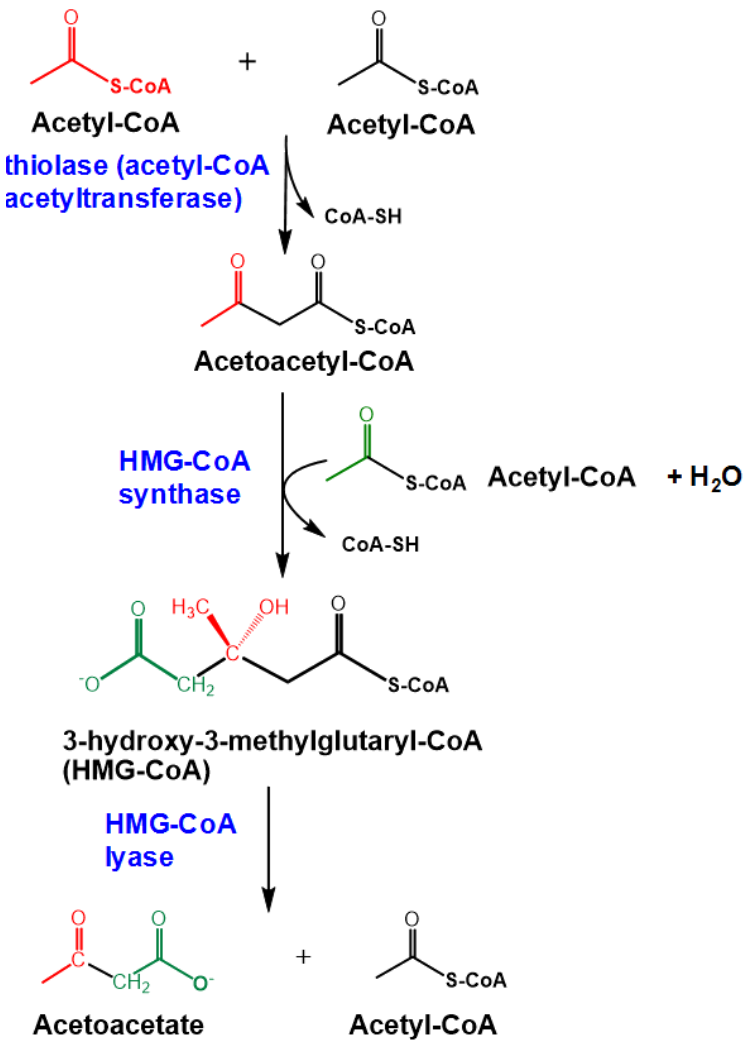
Ketone Bodies

Ketone Bodies in a Nutshell…

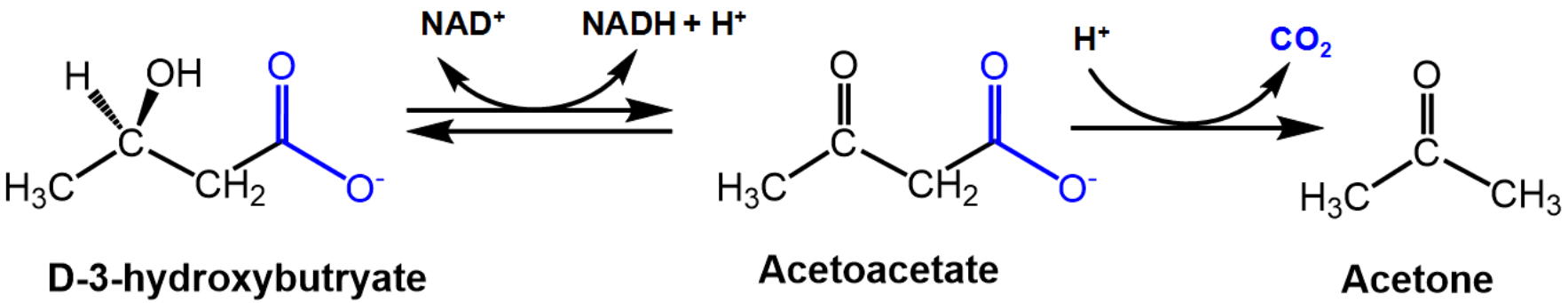


Synthesis of Acetoacetate



- Acetoacetate is made during starvation.
  - Initially, it feeds the periphery so the brain can have glucose.
  - After several weeks, it becomes the major source of energy for the brain too.
- Synthesis is a 3 step process
  - thiolase
  - HMG-CoA synthase
  - HMG-CoA lyase
- Makes HMG-CoA as an intermediate step

β-Hydroxybutyrate and Acetone



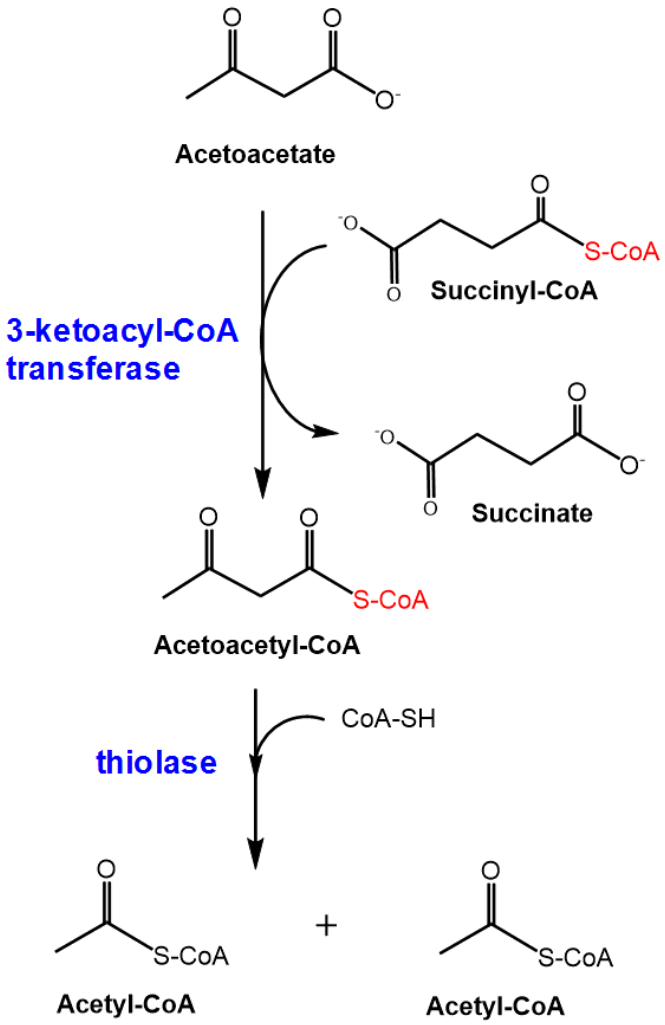
β-hydroxybutyrate Reaction

- Dehydrogenase
- Reversible and driven by mass action
- Excess excreted in urine

Acetone Reaction

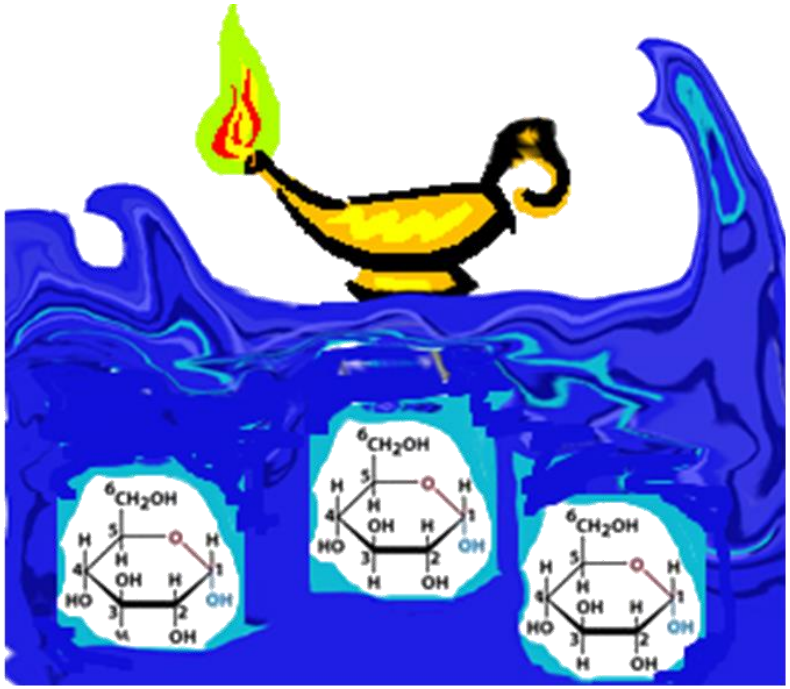
- Non-enzymatic reaction
- Irreversible
- Volatile: excess is exhaled

Peripheral Use of Ketone Bodies



- 2 steps (from acetoacetate)
  - 3-ketoacyl-CoA transferase
    - aka: succinyl CoA transferase
  - reversible thiolase
- Acetyl CoA is produced
  - can enter TCA
  - can enter FA synthesis
- **NOT the same steps** used to make the ketone bodies!
  - Liver lacks succinyl CoA transferase and therefore cannot use ketones for fuel
    - all the ketones are exported

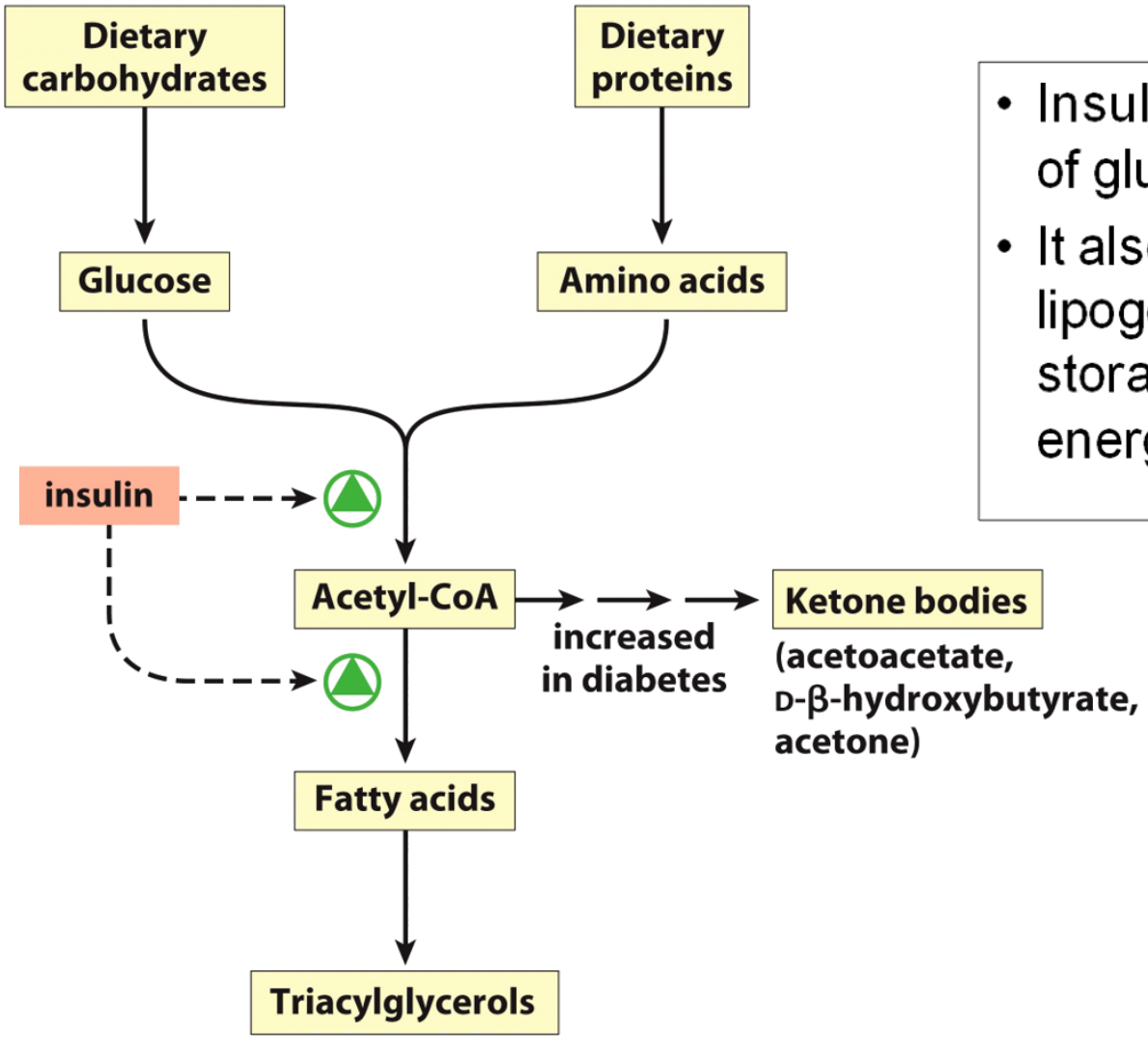
Fats Burn in a Sea of Carbohydrates



Liver gluconeogenesis progresses without alteration following reduction or loss of the insulin signal, releasing sugar in spite of high blood glucose levels. **The body reacts as though glucose was not present.**

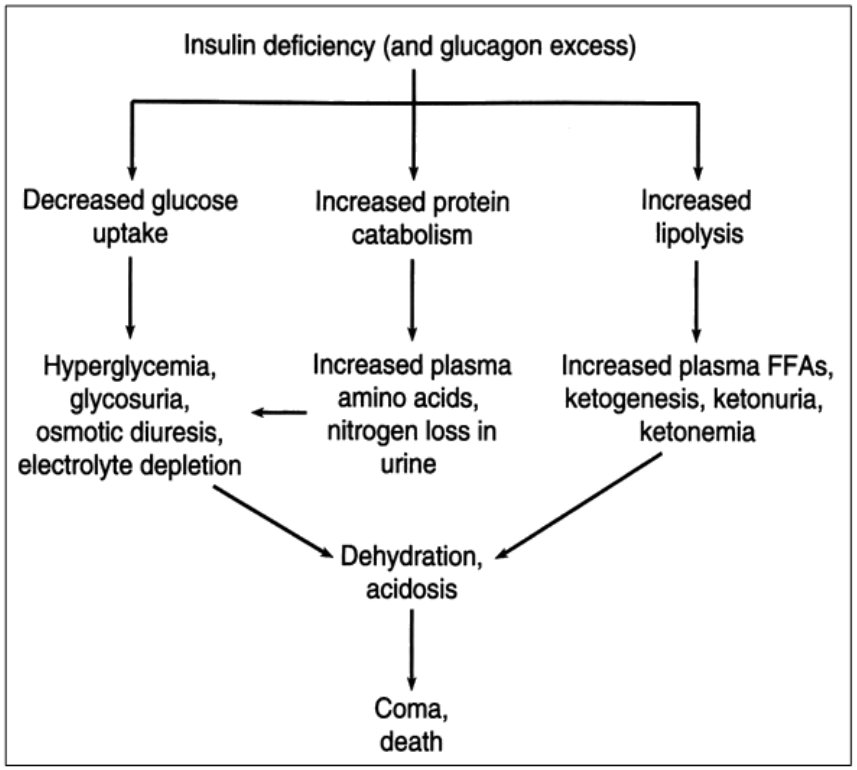
Massive amounts of fatty acids are released to the circulation and the liver converts these to ketone bodies. The high blood glucose levels lead to diuresis with loss of water, glucose, Na^+, and K^+, while the ketones lead to a pronounced fall in blood pH. Diabetic coma and death follow if effective treatment is not initiated.

Regulatory Effects of Insulin



- Insulin spurs uptake of glucose by tissues
- It also triggers lipogenesis – the storage of excess energy as fat

Overview of Diabetes Mellitus



Trivia: The word "mellitus" means **honeyed** in Latin. Ancient doctors tasted the excess glucose that spilled into the patient's urine for a diagnosis. By contrast, diabetes insipidus (a different disease altogether) has bland, watery urine.

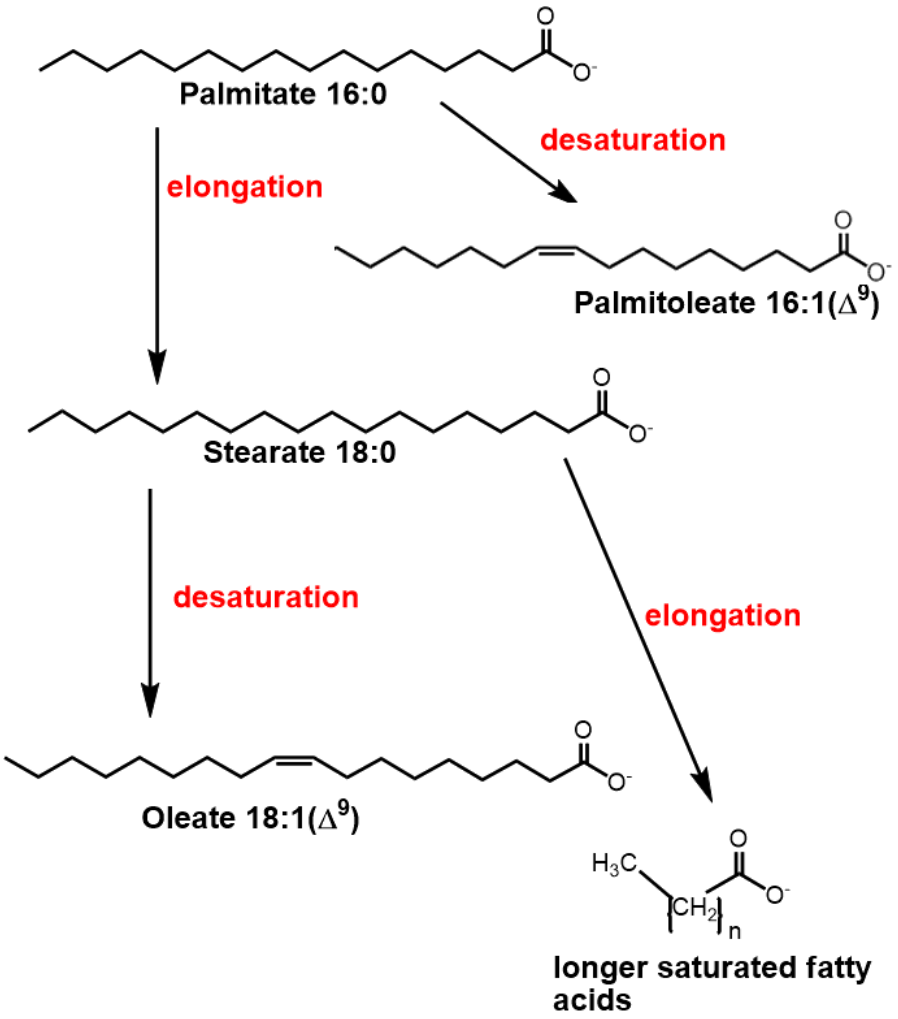
- **Incidence**: ~1 in 20 people in US
  - Second most common chronic health problem
- **Symptoms**: "The classic 3 P's"
  - Polyphagia (frequently eating)
  - Polyuria (large urine output)
  - Polydypsia (always thirsty)
- **Mechanism**: No *effective* insulin
  - Elevated serum glucose levels
  - **Ketosis** & dyslipidemia
- **Treatments**:
  - diet, exercise & weight loss
  - various glycemic control medicines
  - insulin

Fatty Acid Homeostasis

METABOLIC STATE OF PATIENT	INSULIN	GLUCAGON	PKA ACTIVITY	MALONYL COA LEVEL	FA SYNTHASE	HS LIPASE ACTIVITY	FA OXID	KETONE BODIES
eating	↑	↓	↓	↑	↑	↓	↓	↓
starvation	↓	↑	↑	↓	↓	↑	↑	↑

Essential Fatty Acids

Fatty Acid Elongation & Saturation



- FA Synthase makes palmitate (C16)
- Several enzymes then add double bonds
  - fatty acyl CoA desaturases
    - 4 versions: Δ^9, Δ^6, Δ^5, Δ^4
- Other enzymes elongate the chain
  - elongases
    - add 2 carbons at a time
    - occurs in the mitochondria and ER

Key Point!!!

Observation 1

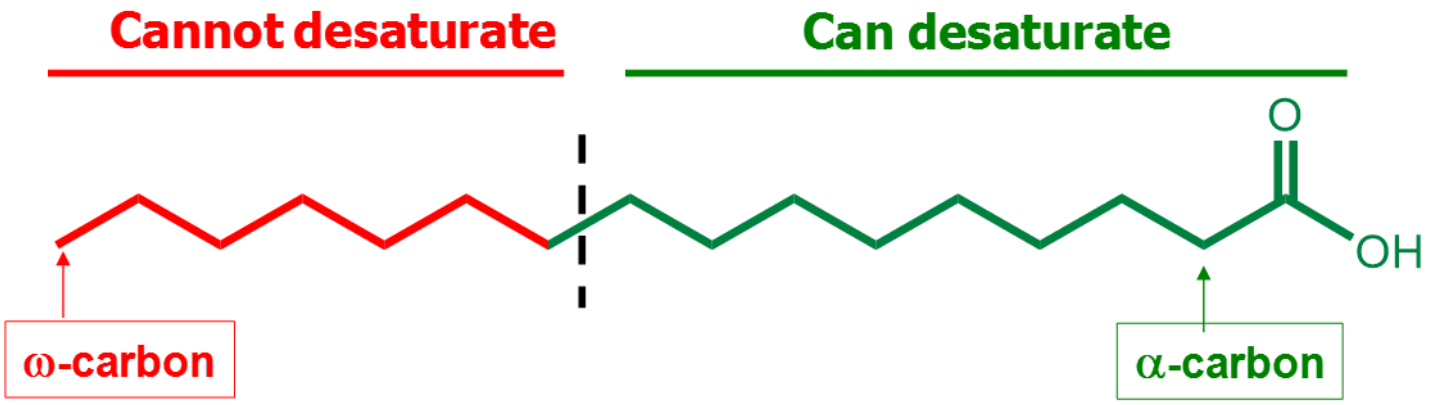
- Palmitic acid is the shortest FA available in mammals (C16)

Observation 2

- The Δ-9 bond is the farthest "desaturatable" site in mammals

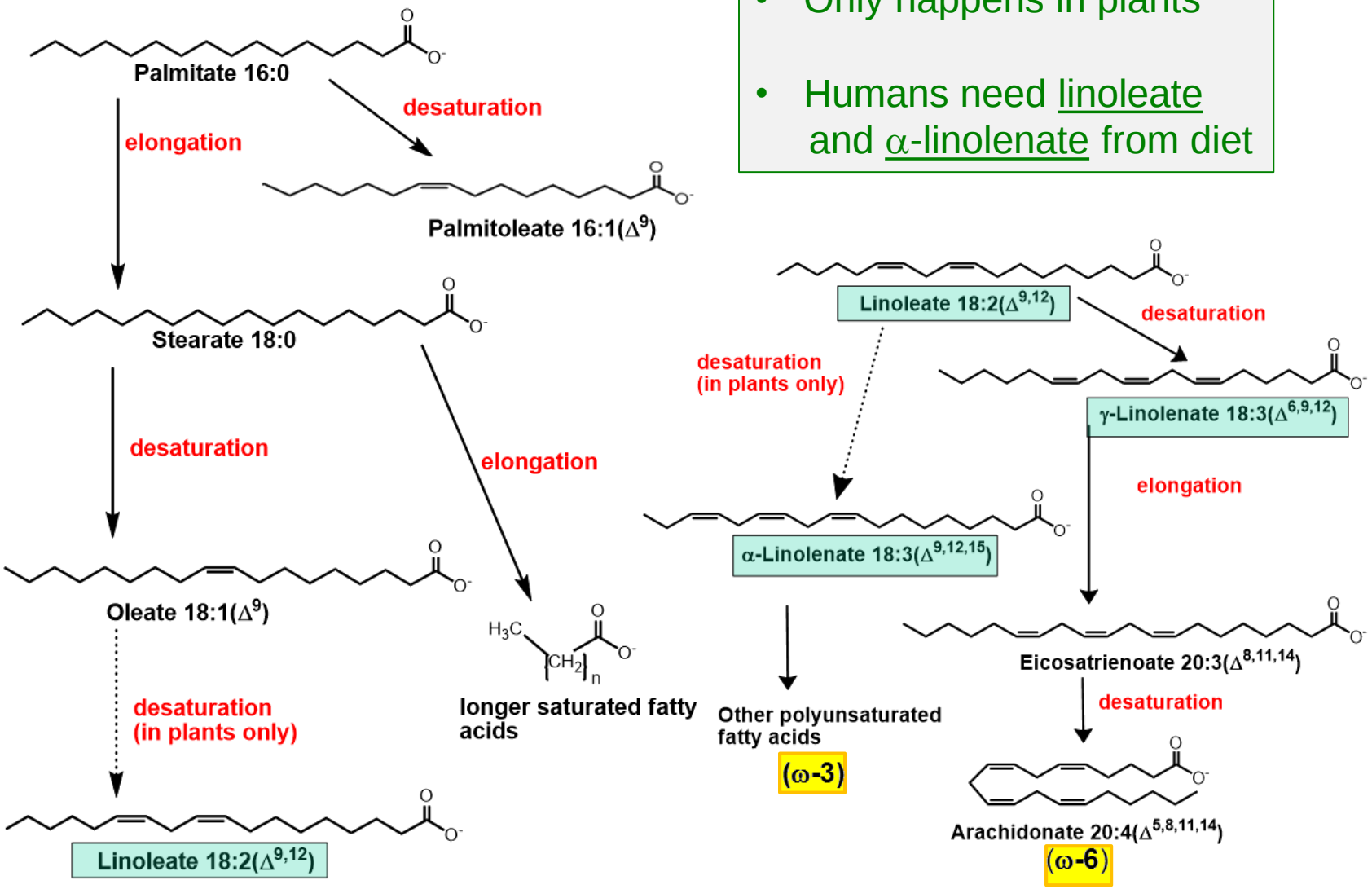
Therefore:

- Mammals **cannot** make double bonds in the last 6 bond positions of a fatty acid chain



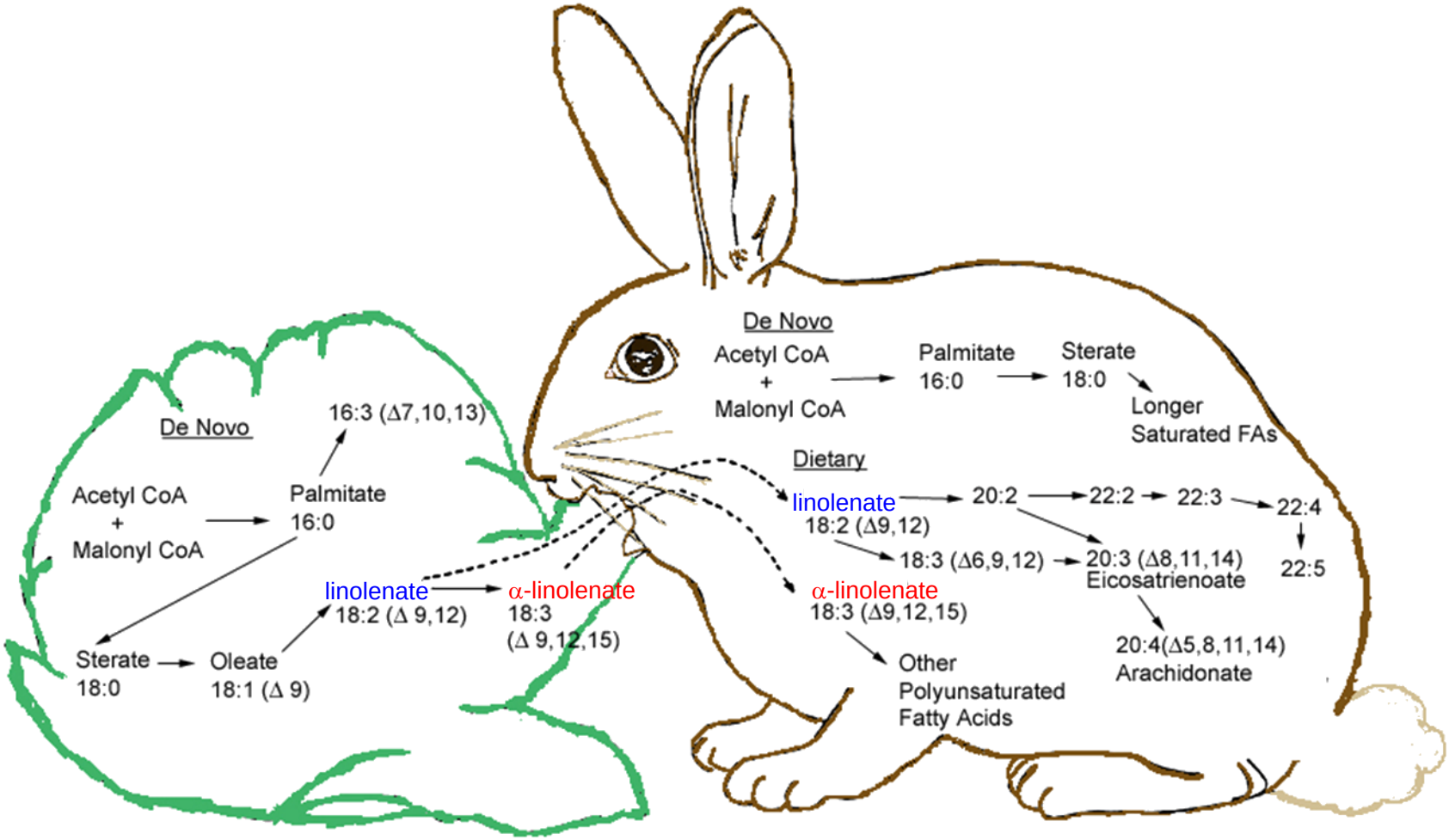
Making EFAs from Palmitic Acid

- Only happens in plants
- Humans need linoleate and α-linolenate from diet



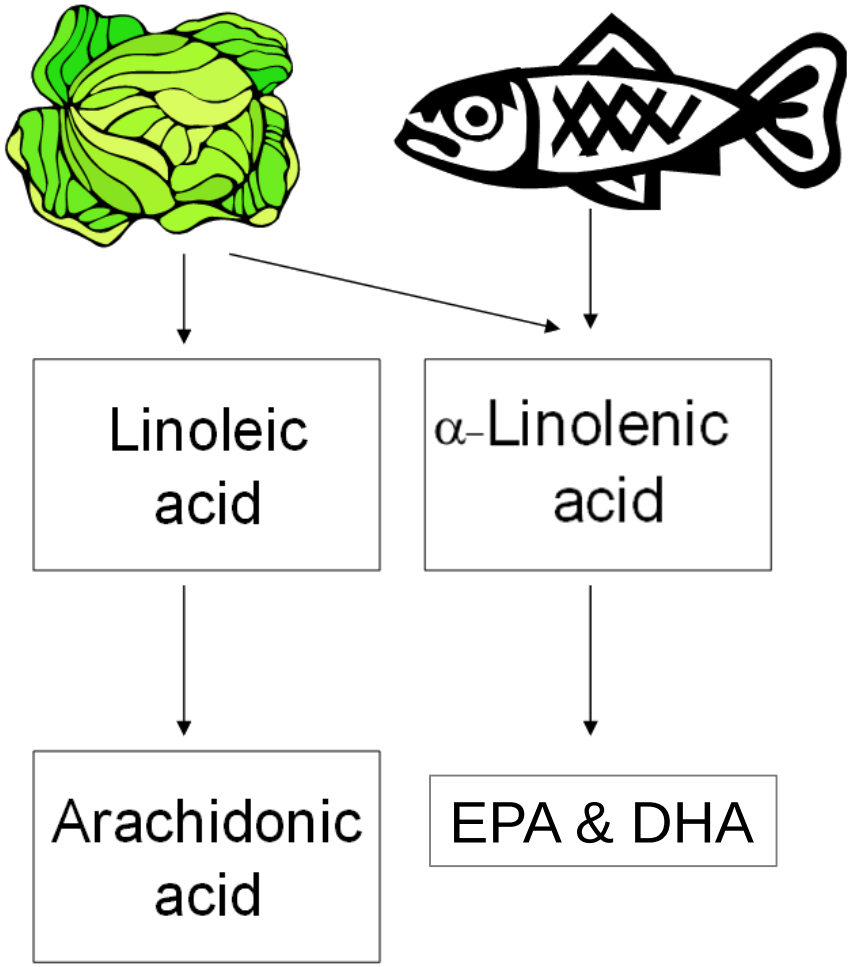
Getting EFAs from the Diet

Getting EFAs from the Diet



Important pathways of unsaturated fatty acid biosynthesis in plants and animals. Note the conversion of dietary 18:2 from plant sources to γ-18:3 and 20:4 in animals, and the further desaturation of plant derived α-18:3 by animals.

What Are Essential Fatty Acids?



- Two "Essential" FA's cannot be synthesized by humans
  - **Linoleic** acid (ω-6)
  - **α-Linolenic** acid (ω-3)
- Obtained from diet
  - Fish oils
  - Plant sources

Seven Countries Study (SCS)

Ancel Keys

Fish Oils and Epidemiology

- Different Diets
  - Danes eat "western" diet
  - Eskimos eat a lot of fish and fish oils
- Population Studies
  - Suggest fish oils help

Incidence of select diseases by population group

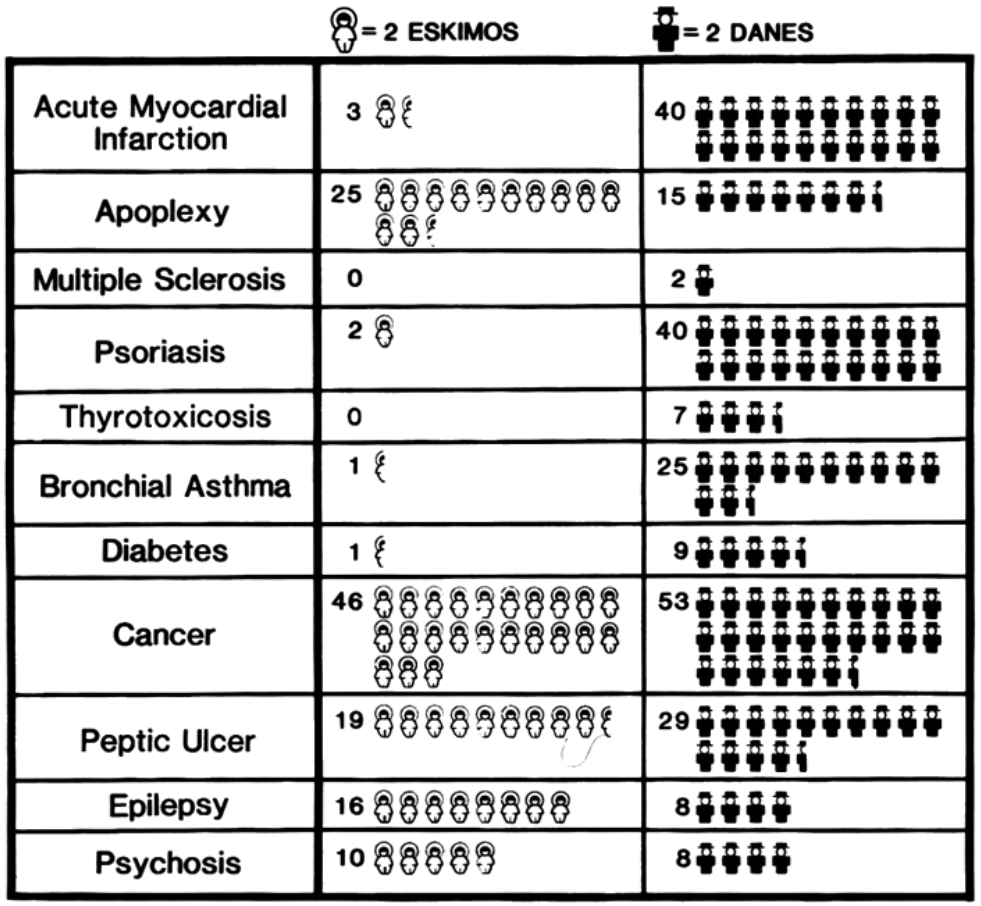
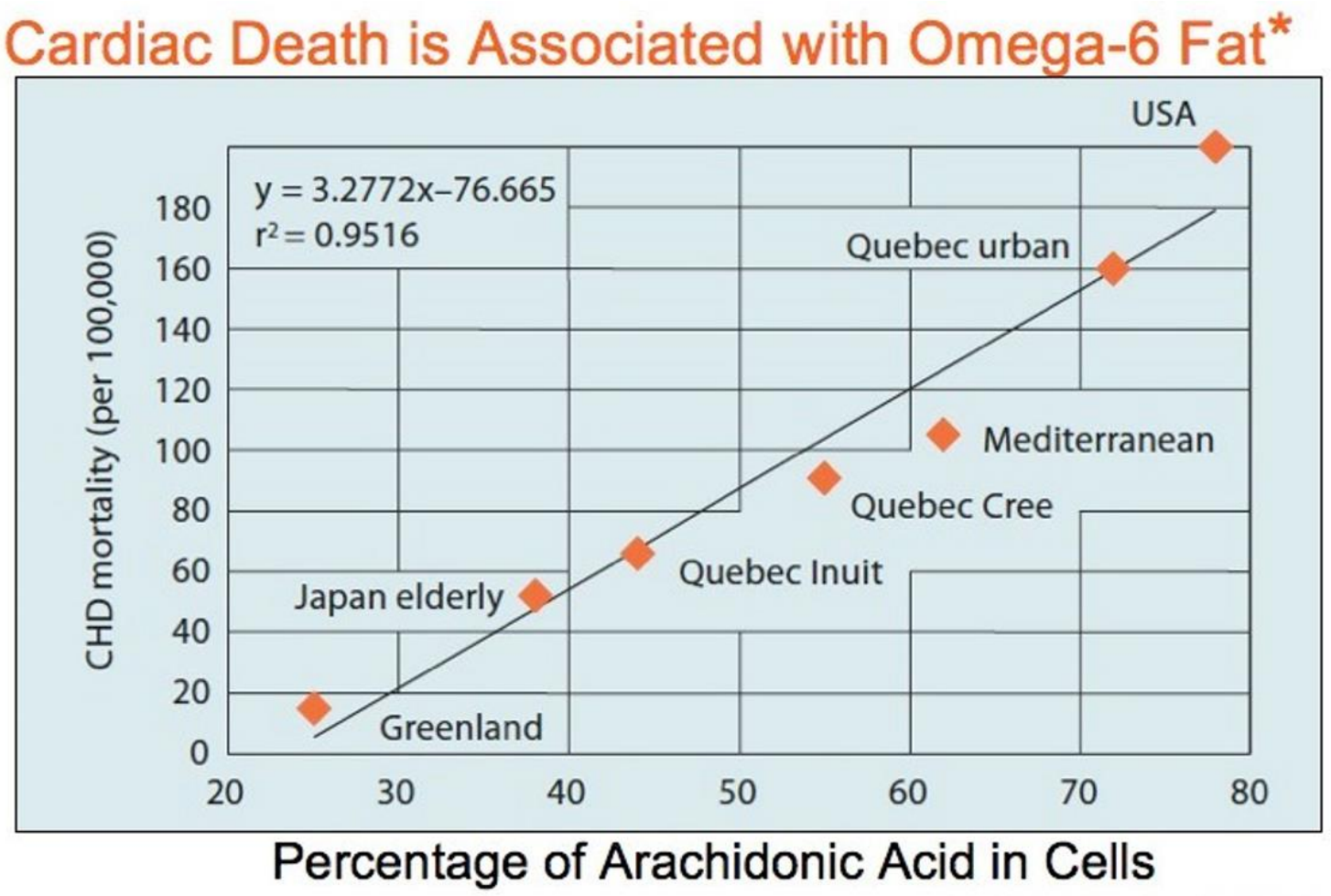
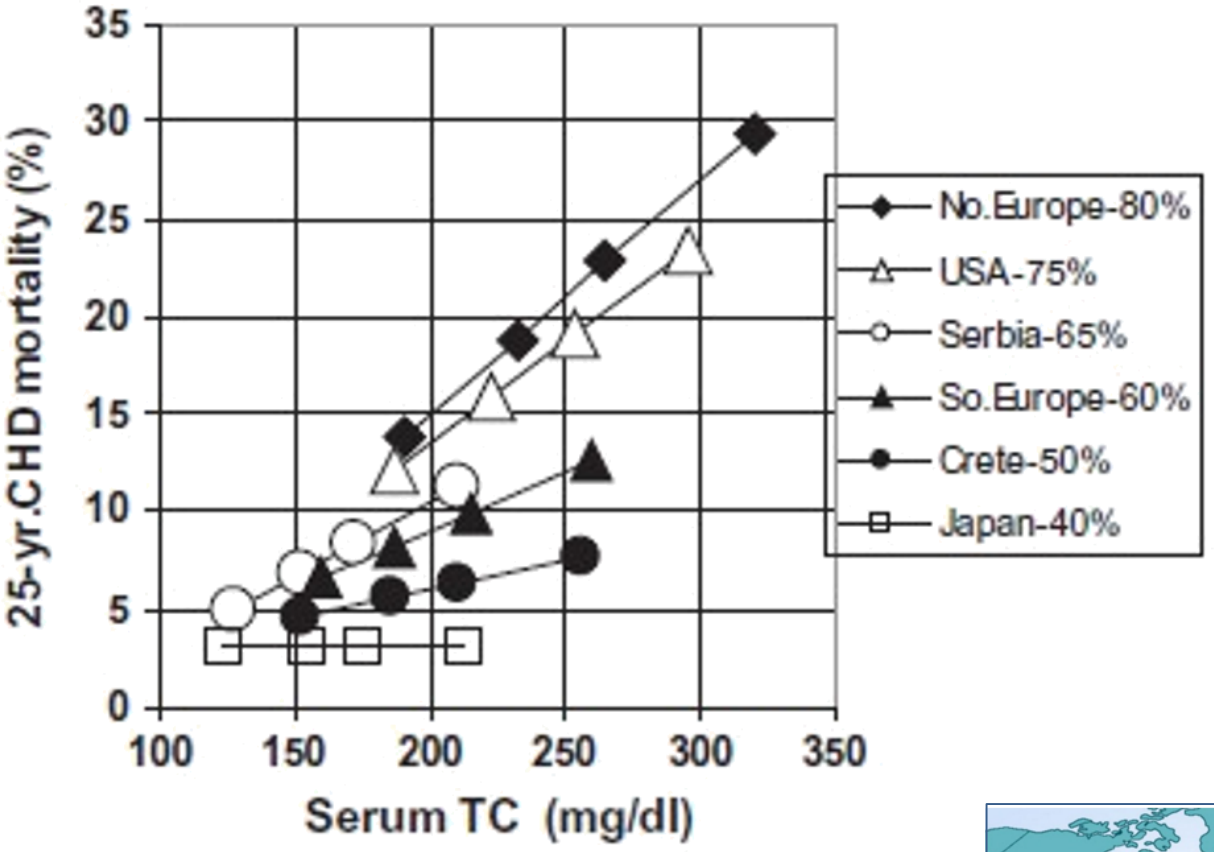


Figure: Lands, *Fish and Human Health*, Academic Press, 1986

Fish Oils and Epidemiology



Fish Oils and Epidemiology



The Seven Countries Study

ω-3 *vs* ω-6 Fatty Acids

- Fish oils
  - Hi ω-3/ω-6 ratio
- Few other good sources of ω-3
  - all have lots of ω-6
  - Low ω-3/ω-6 ratio

Fatty acid composition by source.

SOURCE	CONTENT (%)	
	ω-3	ω-6
Fish	13-35	1-4
Linseed Oil	26-58	5-23
Soybean	2-10	49-52
Sunflower	-	44-68
Olive	-	4-15
Coconut	-	1-3
Butter	-	3
Margarine	-	11-48

Seven Countries Study: French paradox

The French paradox refers to the observation that despite a **diet relatively high in saturated fats, particularly from cheese and other dairy products, the French population historically had lower rates of cardiovascular diseases compared to some other countries**.

Wine intake and other factors may explain the French paradox

Seven Countries Study

"[Ancel Keys] did not include, for instance, places like Germany, Switzerland, and France, where people ate a great deal of saturated fat yet experienced rates of heart disease similarly low to those included in the SCS. **Keys' selection of nations has given rise to the critique that he 'cherry picked' countries to 'prove' his hypothesis.**"

...

"In 1989, a re-analysis of the SCS data by some of the original study researchers found that **coronary mortality best correlated not with saturated fats, as originally reported, but with 'sweets,'** defined as sugar products and pastries."

N. Teicholz, Curr Opin Endocrinol Diabetes Obes 2023, 30:65–71

Oxylipins:

Prostaglandins, leukotrienes, and other eicosanoids

Inflammation in Clinical Medicine

Classic Inflammatory Response

- Symptoms
  - Redness (*rubor*)
  - Swelling (*turgor*)
  - Heat/Fever (*calor*)
  - Pain (*dolor*)
- Rapid Innate Defense
  - immobilizes injuries
    - pain & swelling
  - accelerates immune responses
    - blood flow (redness & warmth)
    - fever

Inflammatory Diseases

- Inappropriate Inflammatory response
- Many Triggers:
  - Musculo-skeletal Injuries
  - Arthritis
    - Rheumatoid
    - Gouty (Uric Acid crystals)
  - Headaches & Colds
  - Asthma
  - Toxic Shock Antigens
  - Debated: Pre-eclampsia?
  - Other, rarer conditions

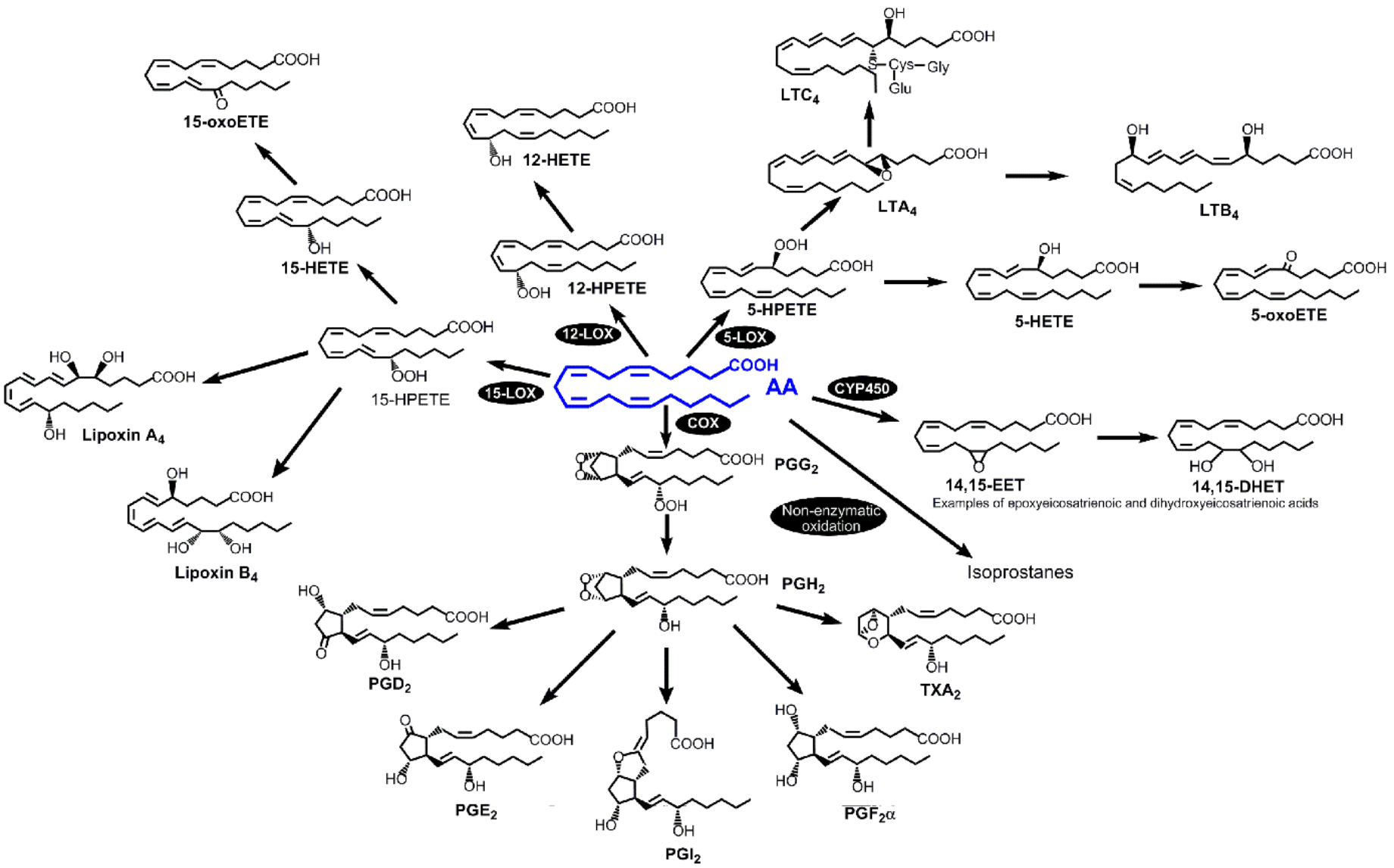
Mediators of Inflammation

Signal Molecules

- Histamine
- **Eicosanoids**
  - **Prostaglandins**
  - **Thromboxane**
  - **Leukotrienes**
- Bradykinins
- Cytokines
  - Interferons
  - Interleukins
  - Chemotaxins
- Other minor molecules…

- Made in almost all tissues
- Very short half-life
- Act locally on neighbors
- Not usually stored up
- 20-carbon backbones
- Made from arachidonic acid

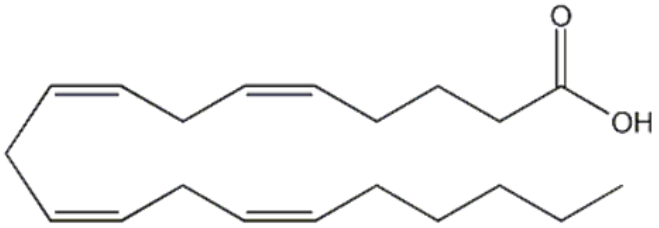
The Eicosanoids



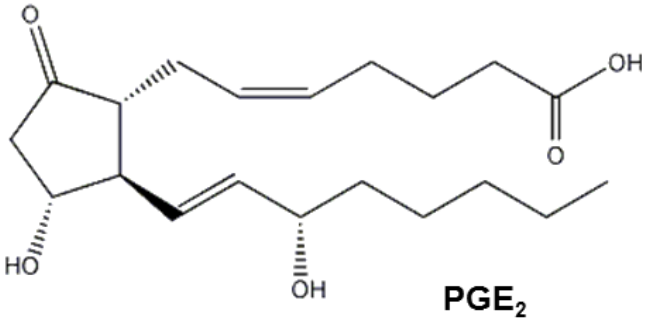
Key Definitions

Arachidonic Acid (AA) = the precursor fatty acid that is used to make most prostaglandins, thromboxanes and leukotrienes.

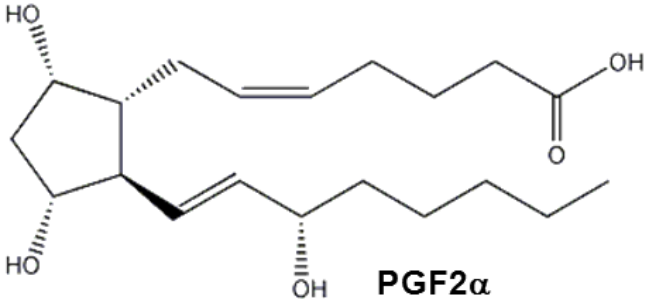
Prostaglandins (PG) = eicosanoids having a bridge making a 5-carbon ring, and either 1, 2 or 3 double bonds. Roughly a dozen different PG's have widely different effects (not all covered here).



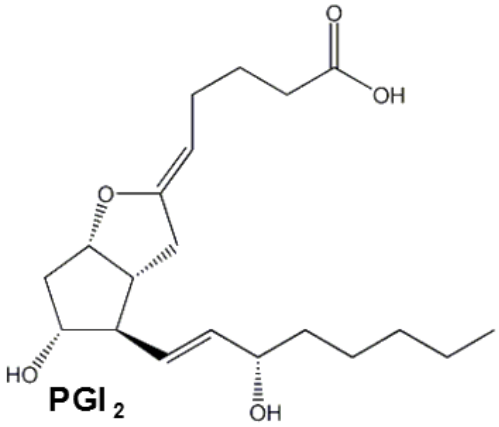
Arachidonic Acid



PGE_2



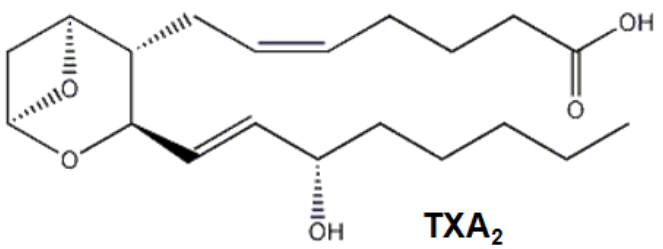
PGF2α



PGI_2

More Definitions

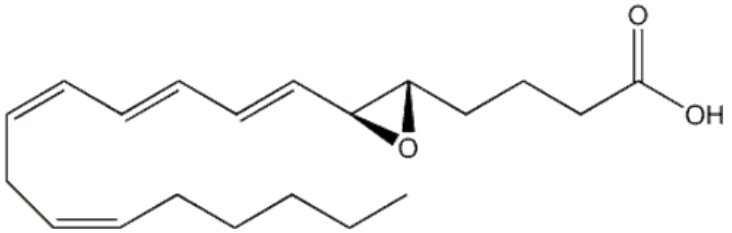
Thromboxanes (TX) = eicosanoids that have a 6-member oxygen-containing ring. TXA_2, a platelet activator, is the main one.



TXA_2

COX = cyclooxygenase, the enzyme that makes AA into PG's and TX's.

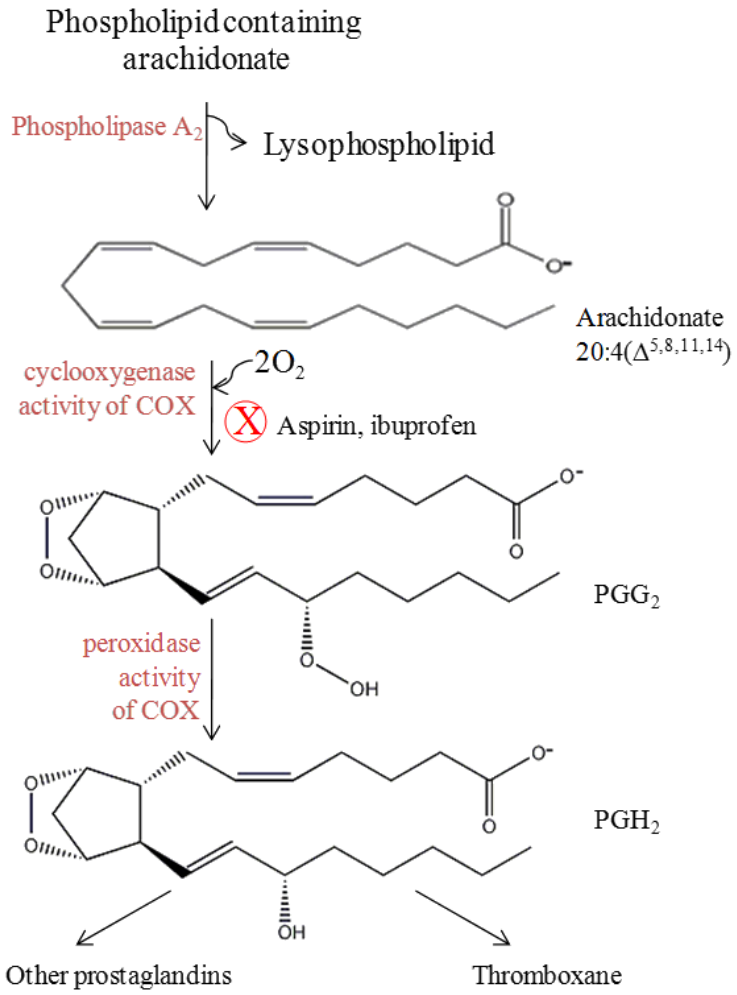
Leukotriene (LT) = eicosanoids that have an open backbone. LTA_4 is the intermediate. LTB_4 is a major chemotaxin and LTC_4, D_4 and E_4 are important in asthma.



LTA_4

5-LO= 5-lipoxygenase, the enzyme that makes AA into LT's.

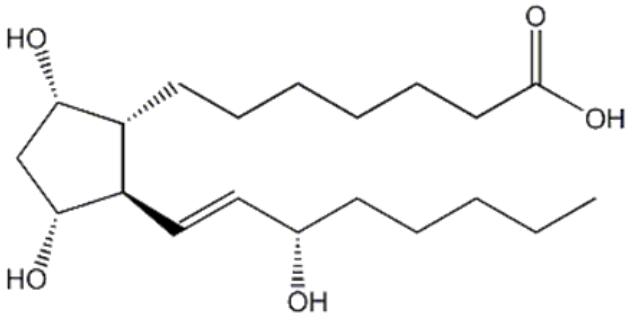
Synthesis of Prostaglandins



- Key enzyme is cyclooxygenase (COX)
- PGG_2 is a transition state
- PGH_2 is a stable intermediate
  - Rapidly made into specific PG and TX end products
- Various conversion enzymes make PGG_2 and PGH_2 into all the other PG's and TX's

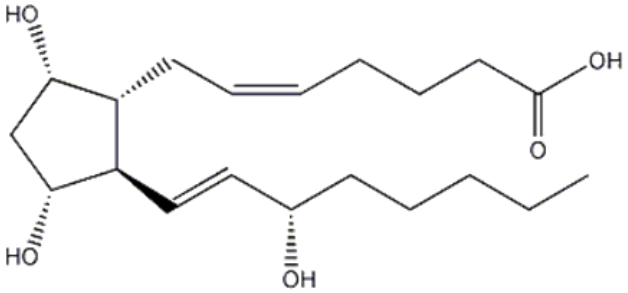
Prostaglandin Series

$PGF_{1\alpha}$



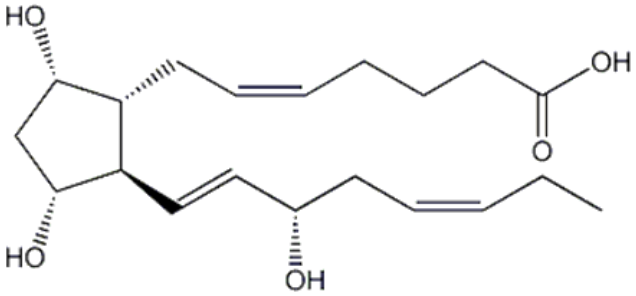
From dihomo-γ-linolenic acid

$PGF_{2\alpha}$



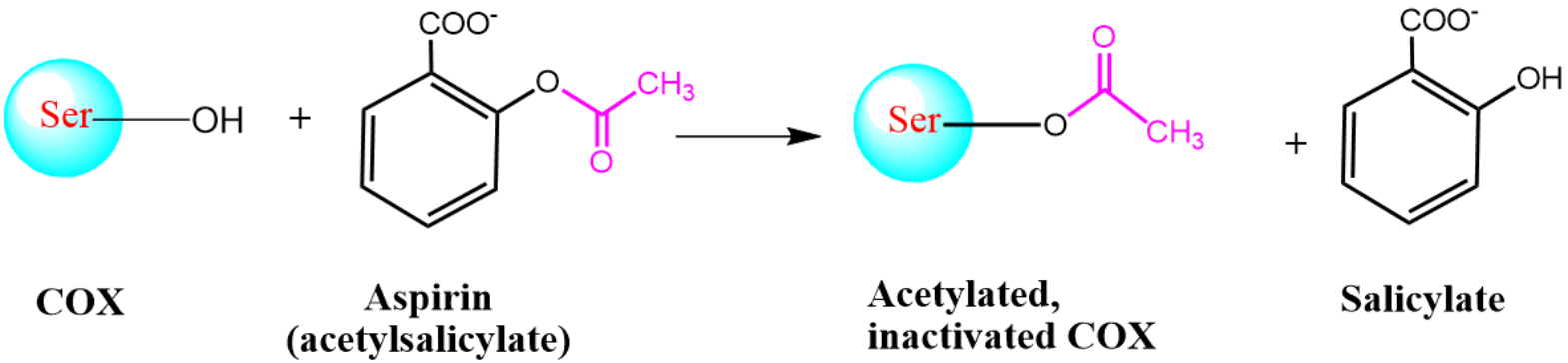
From arachidonic acid

$PGF_{3\alpha}$



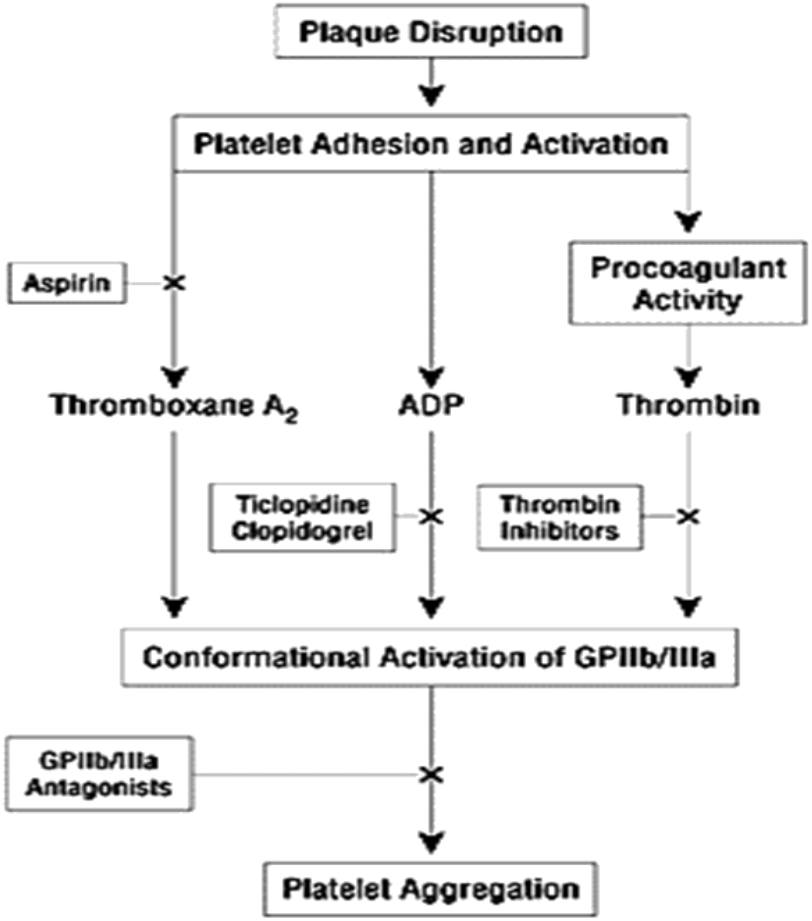
From eicosapentaenoic acid

Aspirin and Cyclooxygenase



- Aspirin donates an acetyl group
  - Covalent binding and inhibition
- Enzyme is permanently wrecked
  - Cell must translate more enzyme copies from scratch

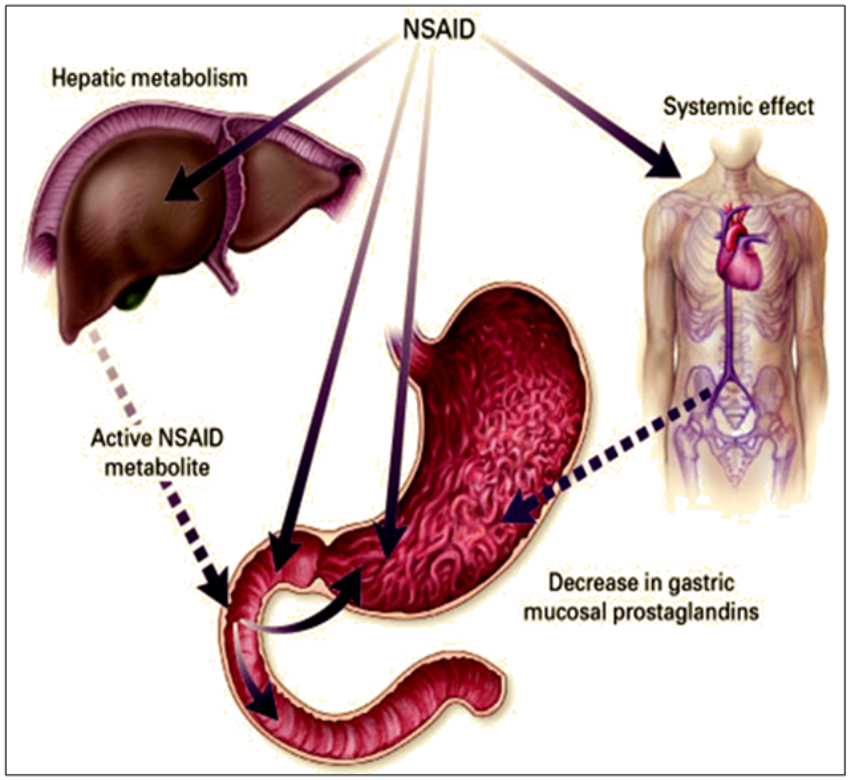
Aspirin vs Heart Disease & Stroke



Platelet thrombosis (clotting) biochemistry.

- **Incidence**: Very common, a daily event
- **Symptoms**: Tissue ischemia
  - Strokes: loss of neurological function
  - Heart attacks: chest pain & shock
- **Mechanism**: Platelet thrombosis
  - TXA_2 is a potent platelet activator
- **Treatments**: Block platelet aggregation
  - **Aspirin** prevents platelet TXA_2 production
    - Small daily dose safely cuts risks
    - Note, PGI_2 made in endothelial cells causes vasodilation-opposite of TXA_2
  - Anticoagulants (e.g. thrombin inhibitors)
    - Heparin, Coumadin, tPA
  - Other anti-platelet drugs
  - Fish oil (n-3) makes TXA_3 (inactive)

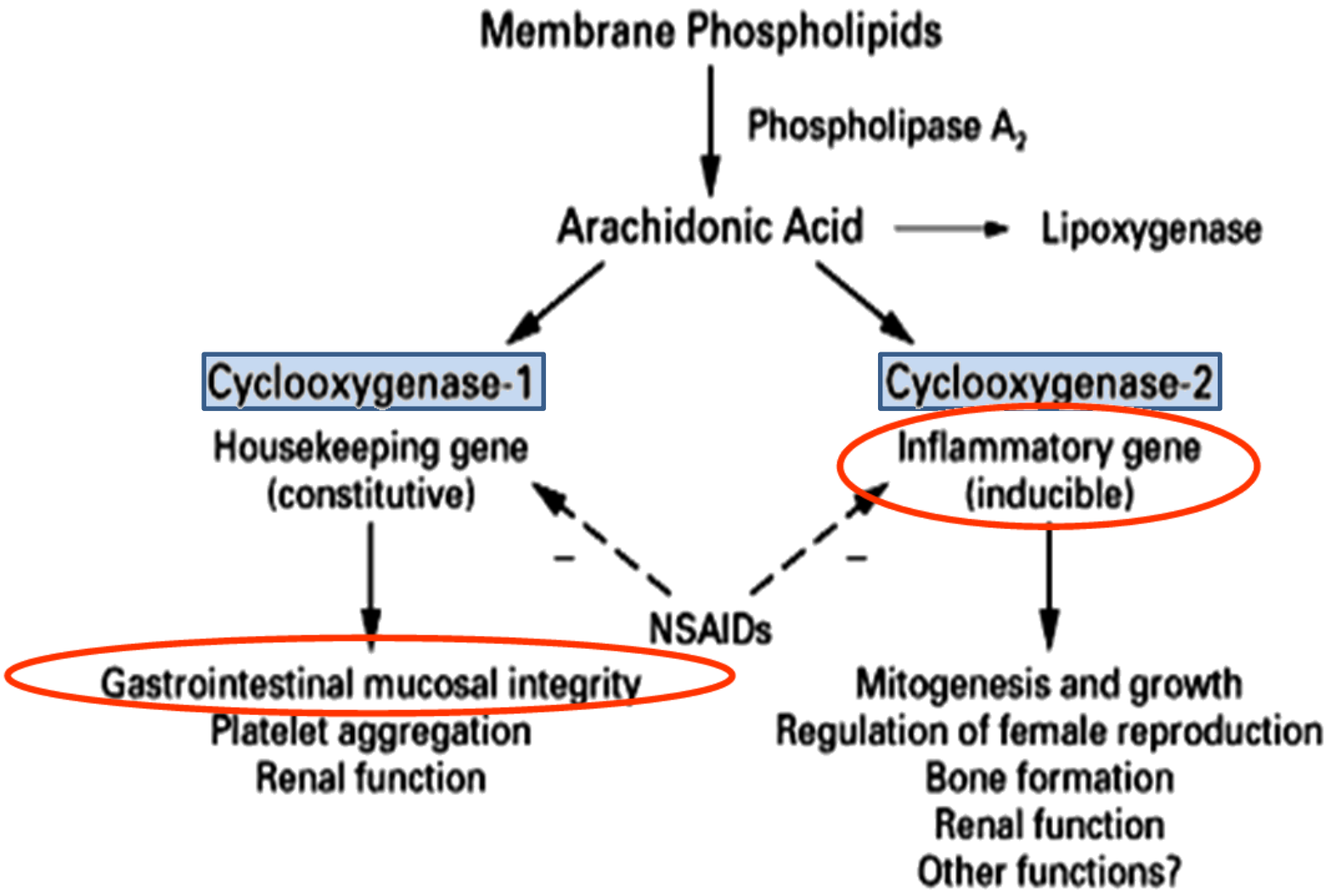
Peptic Ulcers and NSAIDs



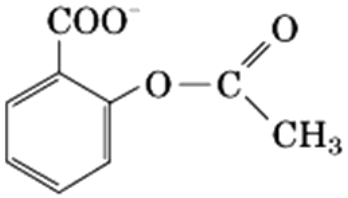
Direct and, in some cases, indirect (metabolite) effects of NSAIDs reduce mucosal protection and increase ulcer risk.

- **Incidence**: Common
- **Symptoms**: Stomach problems
  - Stomach pain
  - Vomiting, often with blood
  - Sometimes: anemia and death
- **Mechanism**: No mucosal layer
  - NSAIDs block production of protective layer of mucous
- **Treatments**: In patients requiring long term a/o high dose NSAID therapy:
  - Give acid-lowering drugs like the proton pump inhibitors (PPI).
  - Give **Misoprostol**, a synthetic prostaglandin E1 analog. It replaces the protective prostaglandins consumed with NSAID therapies
  - Consider *H. pylori* testing before beginning long term a/o high dose NSAID therapy. (*More during Micro.)*
  - In certain patients, a selective COX-2 inhibitors might still be considered.

Two COX Isoforms



COX-2-Selective NSAIDs



Aspirin
(acetylsalicylate)

- NSAID = "non-steroidal anti-inflammatory drug"
- All inhibit PG production
- Non-selective NSAIDs
- COX-2 selective NSAIDS
  - Only slightly inhibit COX-1
  - Fewer GI side effects

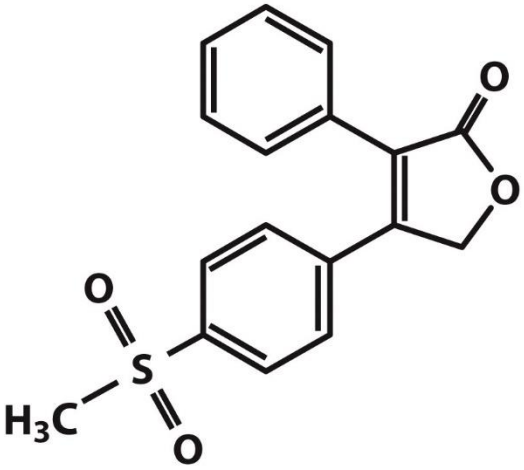
  The selective COX-2 inhibitors introduced a novel strategy for the prevention of NSAID-related gastroduodenal toxicity in high-risk patients. **However, cardiovascular toxicity has limited the use of these drugs,** and make it likely that they will have a diminishing clinical role. Currently, there is only one available.
  - **celecoxib (Celebrex) is approved by Food and Drug Administration (FDA) but carries a new boxed warning about GI and cardiovascular risk.**
  - valdecoxib (Bextra) was removed because of concerns of cardiovascular risk and reports of Stevens-Johnson Syndrome.
  - refocoxib (Vioxx) was removed by Merck due to an increased risk of stroke and myocardial infarctions with long-term use.

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

See full prescribing information for complete boxed warning.

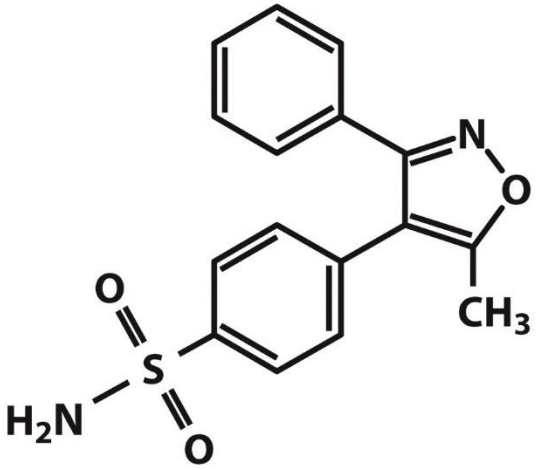
- Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in the treatment and may increase with duration of use. (5.1)
- CELEBREX is contraindicated in the setting of coronary artery bypass graft (CABG) surgery. (4, 5.1)
- NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events. (5.2)

COX-2-Selective NSAIDs



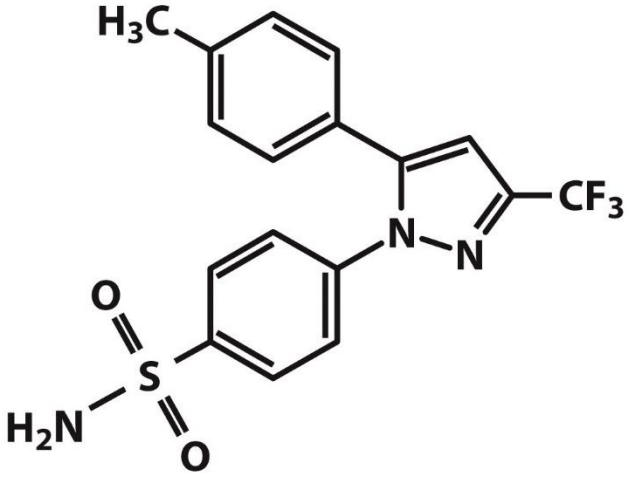
Rofecoxib
(Vioxx)

Merck
18 nM



Valdecoxib
(Bextra)

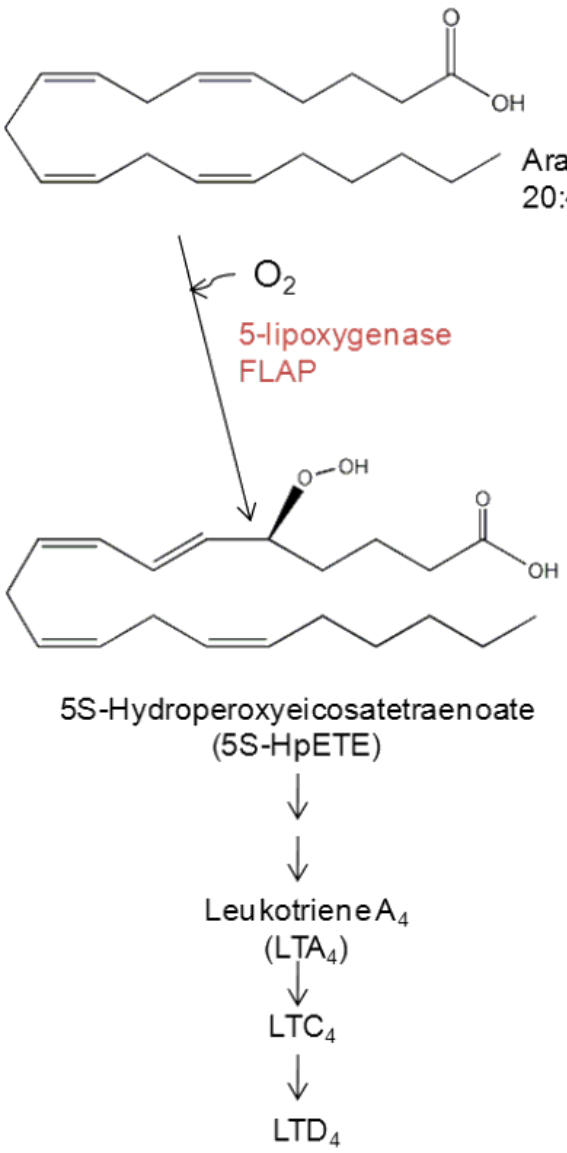
Searle
5 nM



Celecoxib
(Celebrex)

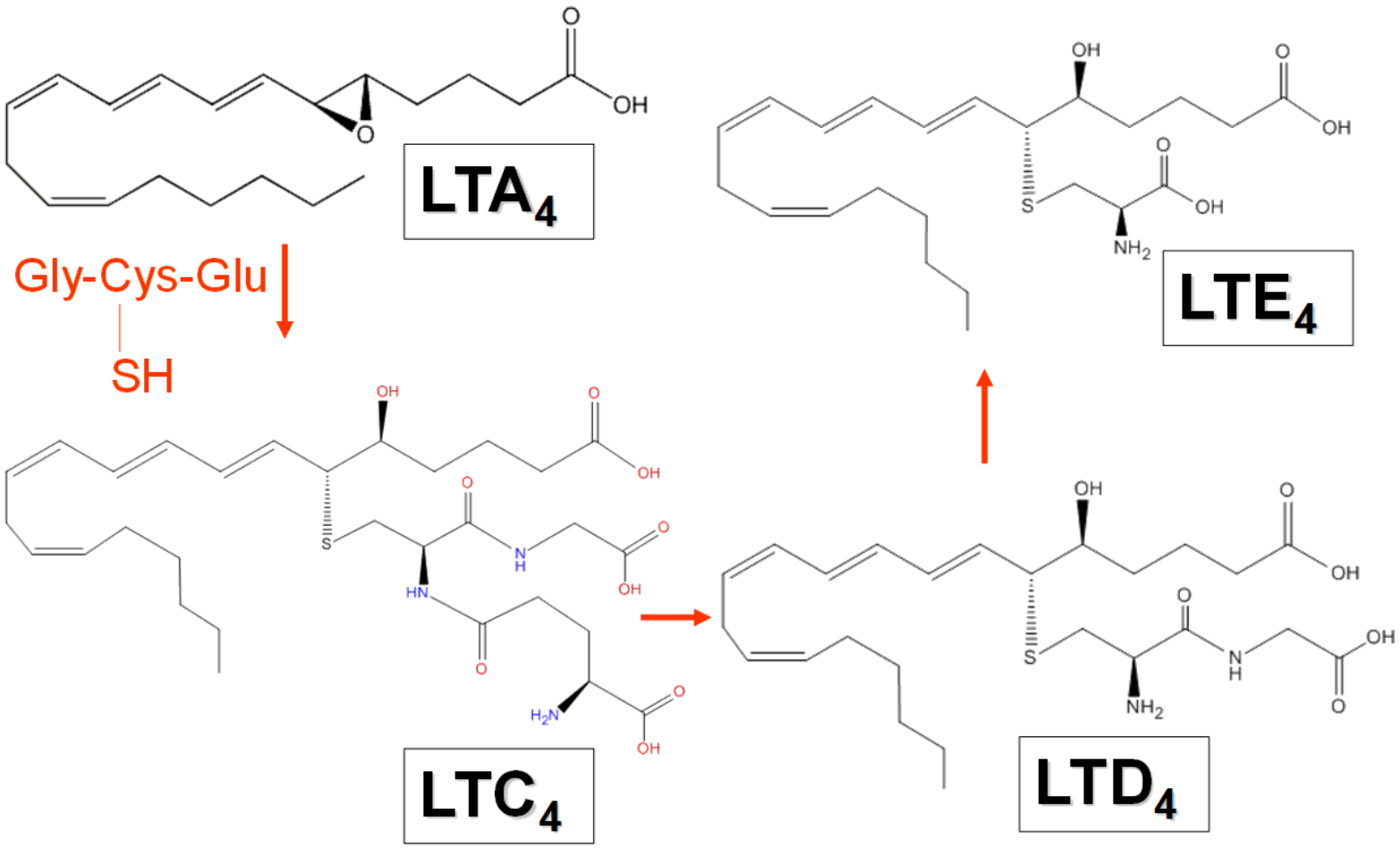
Pfizer
40 nM

Synthesis of Leukotrienes

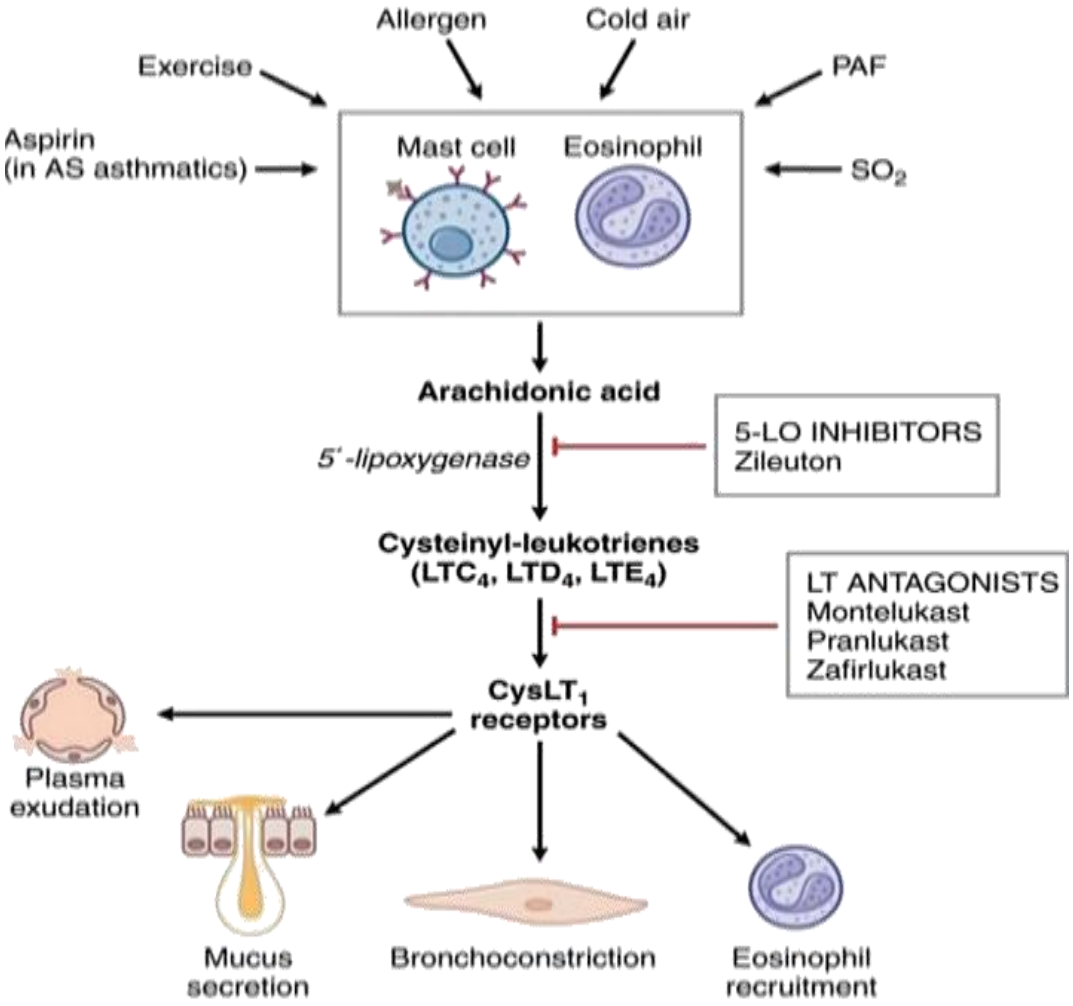


- 5-Lipoxygenase (5-LOX) is the key enzyme
- There may be competition with 12/15-LOX pathways

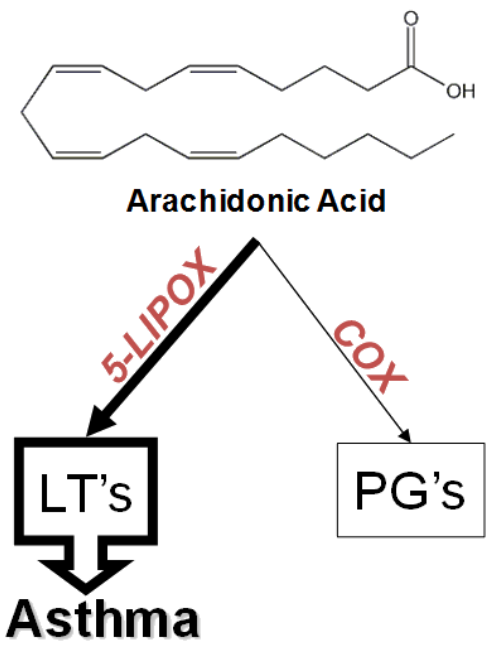
Structure of Core Leukotrienes



Leukotrienes and Asthma

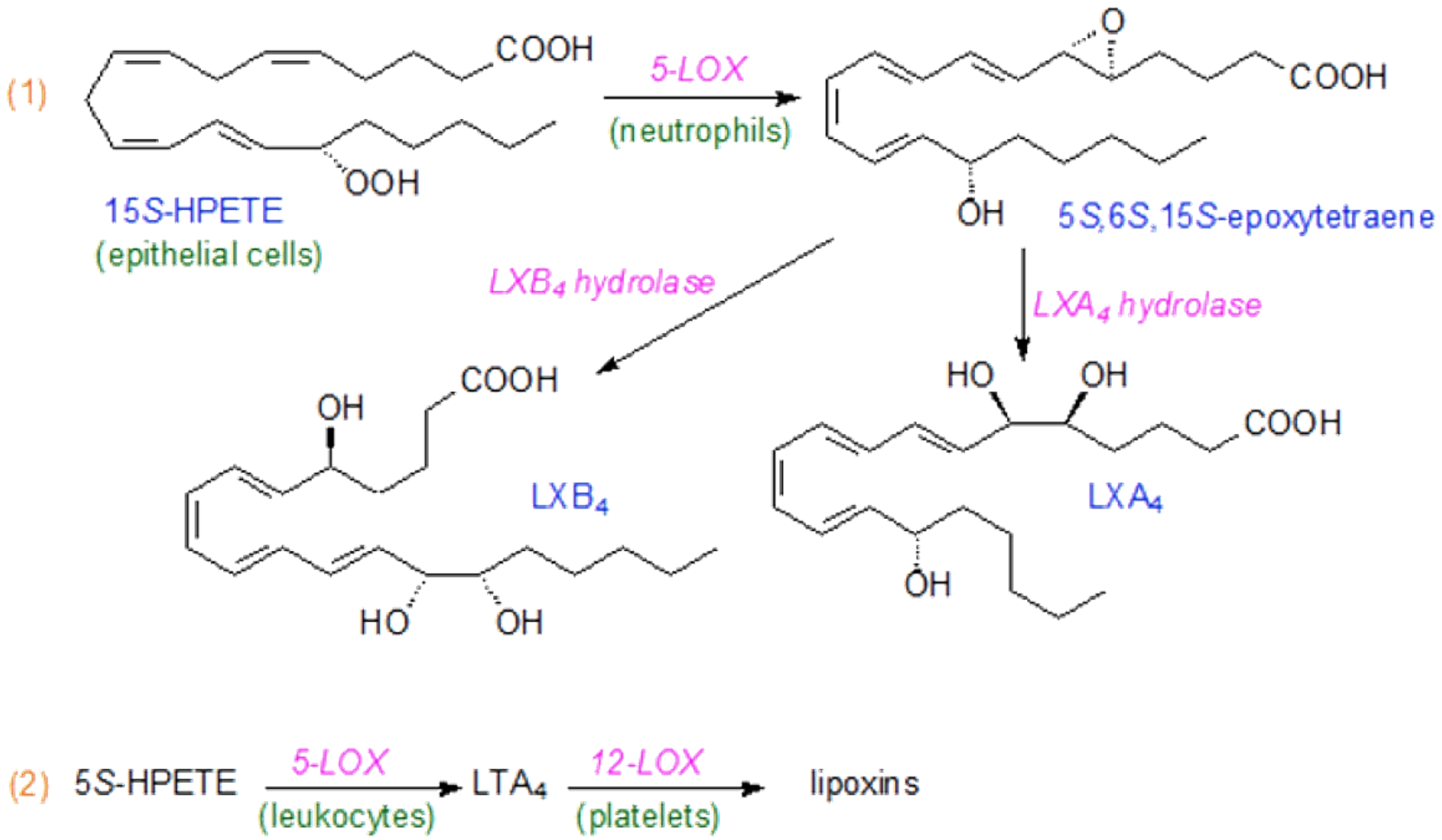


Aspirin-Triggered Asthma



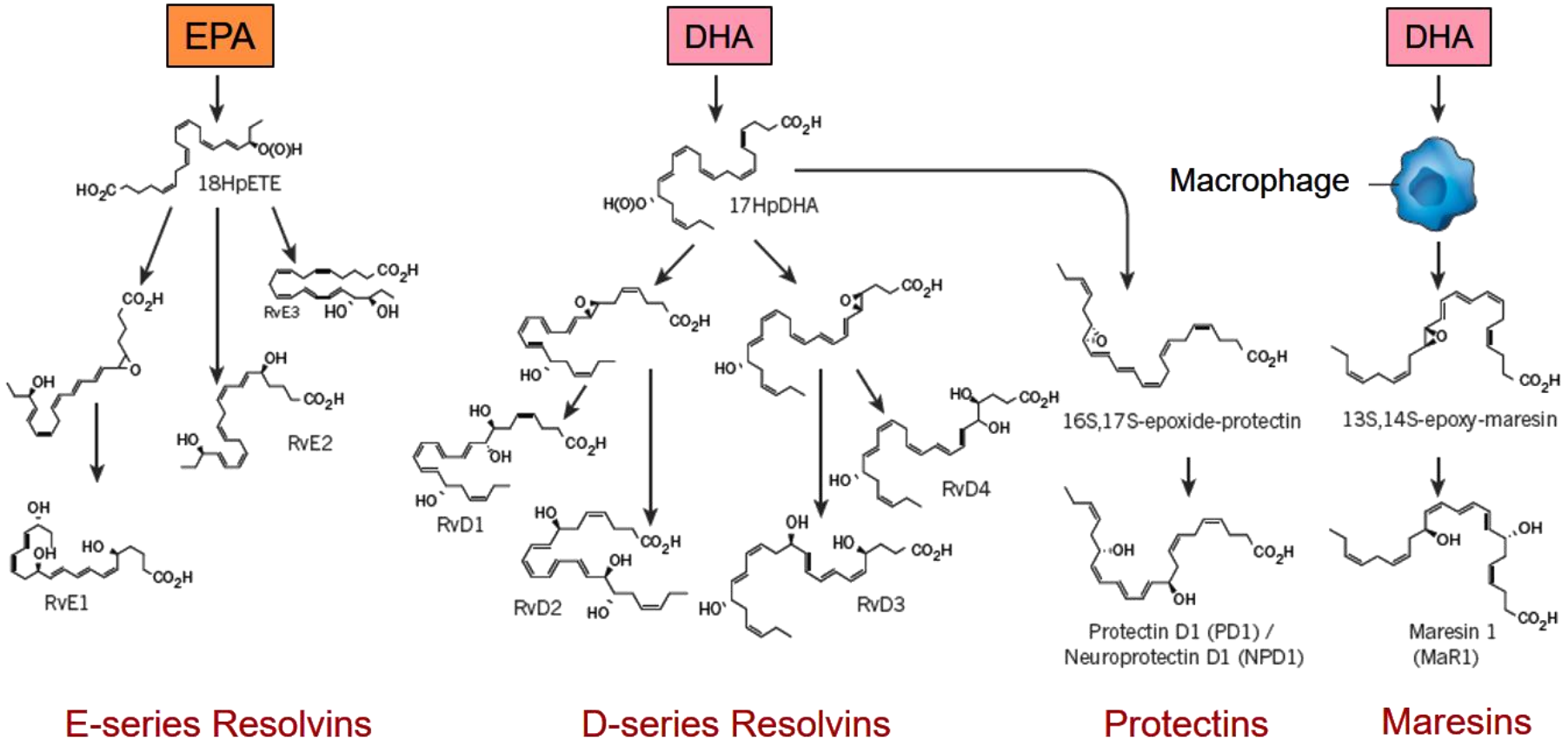
- **Incidence**: ~1 in 7 children have asthma
  - Triggers include allergens, exercise & aspirin
- **Symptoms**: Bronchoconstriction
- **Mechanism**: Surge in LT production
  - Aspirin blocks COX, leaving 5-LOX open
  - Arachidonic acid substrate becomes LT's
- **Treatments**: Reduce LT effects
  - **Discontinue Aspirin and other NSAIDs**
  - Give 5-LIPOX and LT receptor inhibitors
  - Use direct bronchodialators (e.g. albuterol)
  - Corticosteroids and anti-IgE antibodies

Synthesis of Lipoxins



ω-3-Derived Lipids: Specialized Pro-Resolving Mediators

Specialized Pro-resolving Mediators (SPMs)



Detection and roles under discussion