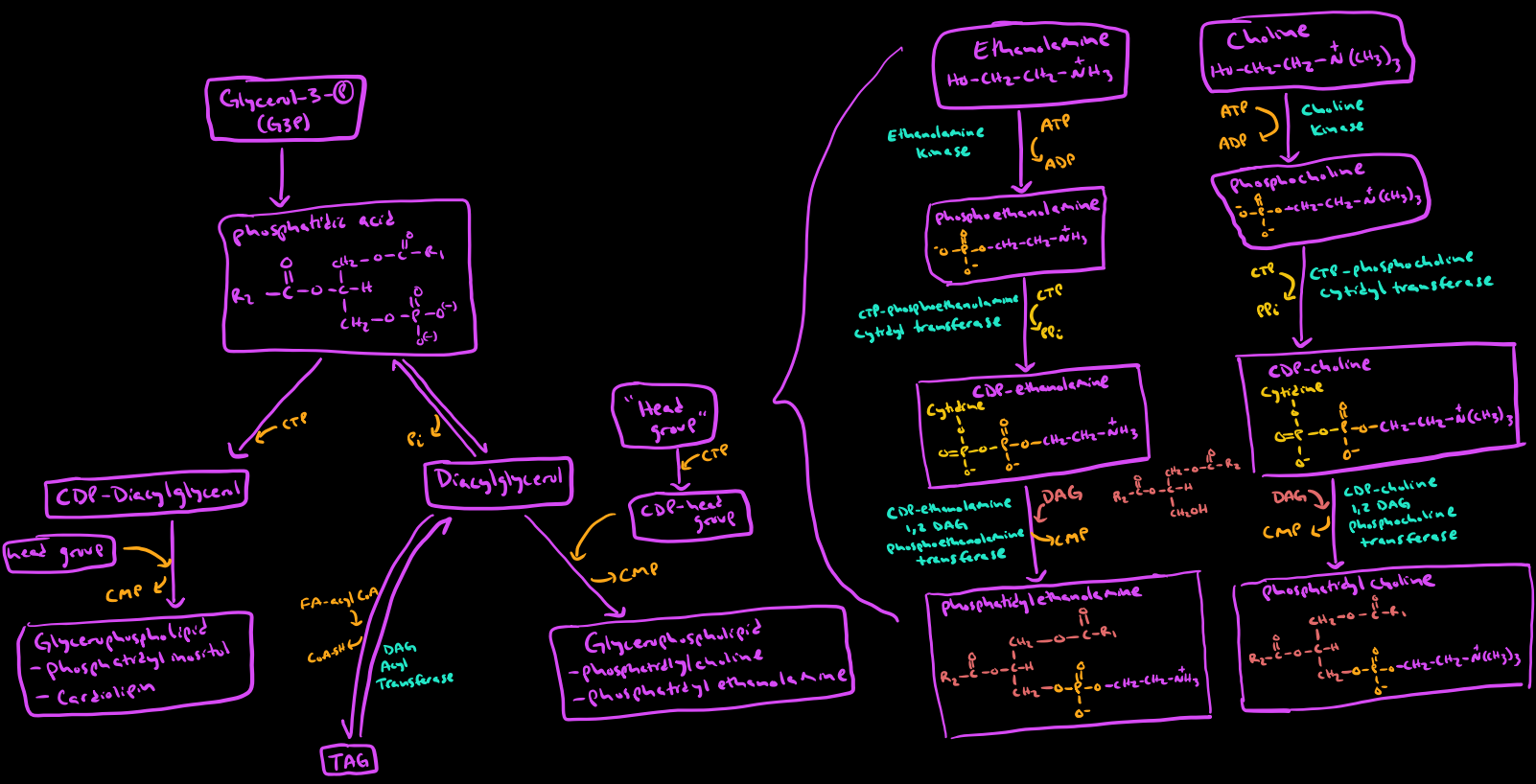
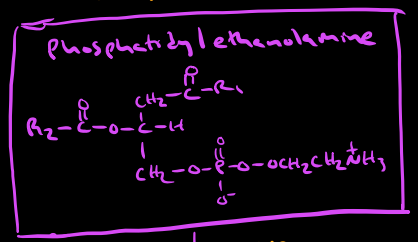
Phospholipid Synthesis - De novo



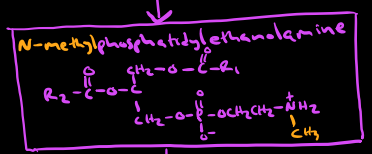
Phospholipid Conversions

Progressive Methylations

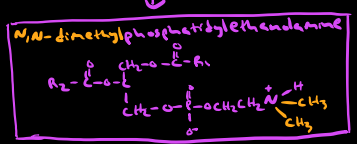
- S-adenosyl-methionine (SAM) = methyl donor
- S-adenosyl-homocysteine (SAH) = demethylated



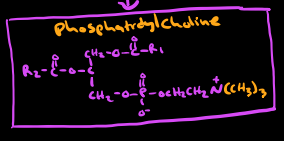
SAM → SAH



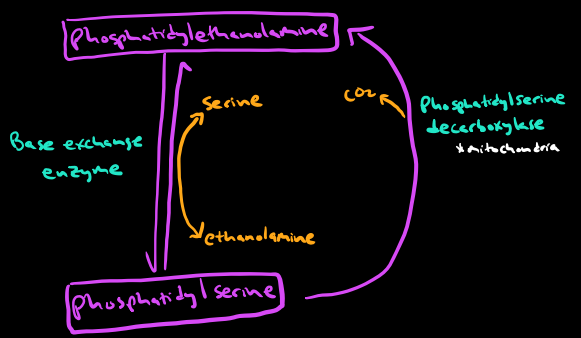
SAM → SAH



SAM → SAH

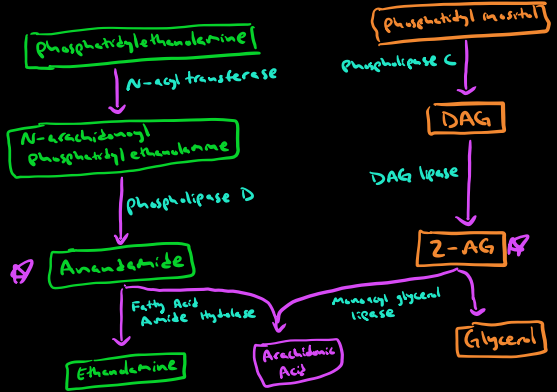


Base Change or Decarboxylation



Endocannabinoids

- major endogenous ligands for cannabinoid receptors (CB_1 & CB_2):
  - N-arachidonoyl-ethanolamide (anandamide)
  - 2-arachidonoyl-glycerol (2-AG)
- Act as retrograde signaling molecules → modulate transmission from pre-synaptic neurons



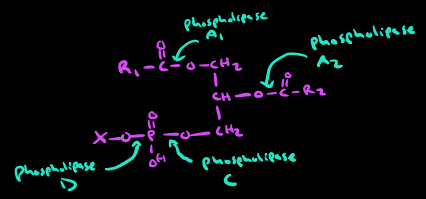
Eicosanoid Synthesis

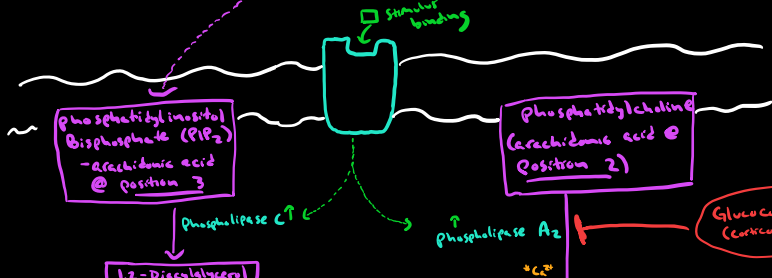
- Eicosanoids = 20 carbon derivatives of arachidonic acid (20:4Δ5,8,11,14) (Δ = double bonds)
- humans cannot create double bonds in FAs past position 9-10
  - ↳ must produce FAs like arachidonic acid from precursors obtained in diet

Essential FAs (dietary)
↓
Linoleic acid
↓ desaturase
↓ elongase
↓ desaturase
↓
Arachidonic acid
↓
membrane phospholipid

Phospholipid Cleavage

- different phospholipases cleave @ different positions in phosphoglyceride





Phospholipase C ↑ → 1,2-Diacylglycerol → DAG lipase → Monoacylglycerol → Monoacylglycerol lipase → Arachidonic Acid

Phospholipase A_2 ↑ (*Ca*) ← Glucocorticoids (Corticosteroids) → Arachidonic Acid

Arachidonic Acid + Arachidonic Acid + Arachidonic Acid → **Arachidonic Acid**

Arachidonic Acid →
- Cyt P450 → Epoxides → diHETE, EHETE
- Lipoxygenase (Zileuton) → HPETE → HETE, Lipoxins; HPETE → Leukotrienes
- COX-1 / COX-2

Leukotrienes → Montelukast, Zafirlukast (-receptor antagonists) → LTC_4 LTD_4 LTE_4 → bronchoconstriction; LTB_4 → neutrophil chemotaxis

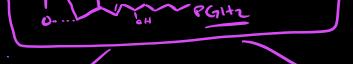
Cyclooxygenases (COX)

- aka PGH_2 Synthase b/c produces PGH_2 as intermediate
- COX-1 constitutively expressed in most cells @ low levels
- COX-II
  - highly regulated @ transcriptional level
  - stimulated by growth factors, cytokines, & endotoxins
- selective COX II inhibitors (e.g. Celebrex)
  - anti-inflammatory & block pain
  - less likely to cause gastric toxicity associated w/ NSAIDs (also block COX-1)
  - tendency to develop blood clots
    - ↓ PGI_2 production by endothelial cells
    - lack of inhibition of COX-1 mediated formation of pro-thrombotic thromboxanes in platelets

Aspirin
- Aspirin = irreversible b/c forms covalent bond by acetylating Serine hydroxyl group on COX near active site
  - ↳ Must be recycled/resynthesized
- other NSAIDs: -Ketorolac -Diclofenac -Ibuprofen -Naproxen -Indomethacin
  - Most NSAIDs = reversible ionic/hydrophobic interactions to block hydrophobic channel through which arachidonic acid enters active site of COX-1 and/or COX-2

Celecoxib

Cyclic Endoperoxides - PGH2 Intermediate



Prostaglandins

- PGI_2 (Prostacyclin)
  - ↓ platelet aggregation
  - ↓ vascular tone (vasodilation)
- PGE_1
  - ↓ vascular tone
- PGE_2
  - -↑ uterine tone
- $PGF_{2\alpha}$
  - -↑ uterine tone

Thromboxanes (TXA_2)

- ↑ platelet aggregation
- ↑ vascular tone (vasoconstriction)

*Aspirin effect on platelets is permanent b/c do not have nucleus → cannot resynthesize COX enzyme