FUND WEEK 3

metabolism + cell bio

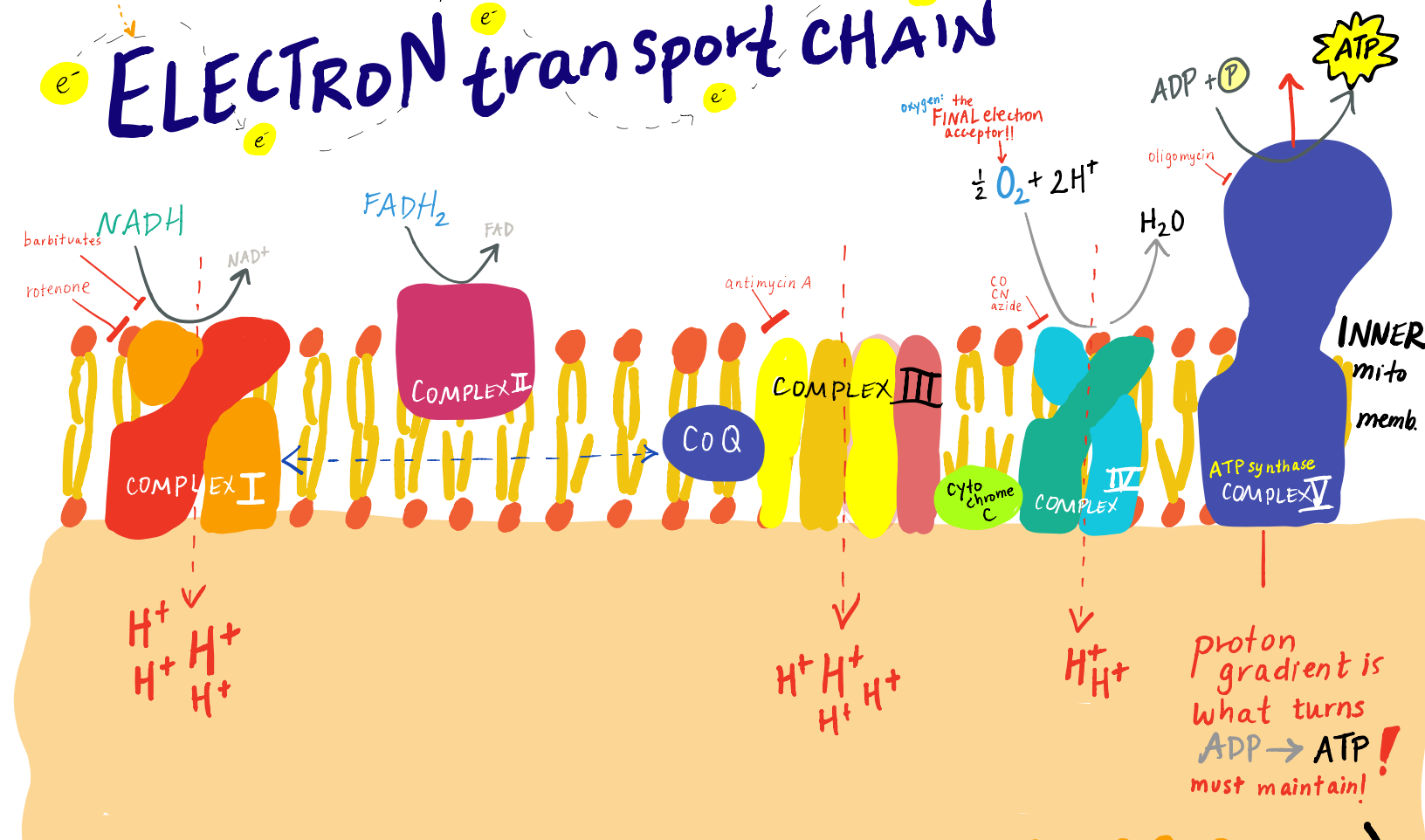
Last week: TCA Cycle/Krebs

YOUTUBE RESOURCES
- Armando Hasudnagan — cell biology
- AK Lectures — biochem

THIS WEEK:
- AT: Vesicular transport, endocytosis, barriers/transport, ion channels
- TV TV: neuro exam, patient-centered care
- AT AT AT TV: Fatty acid metabolism, membrane potential, action potential, Diabetic Ketoacidosis
- TV TV TV: embryology, histology: membrane + glandular epithelium, intro to anatomy
- TV TV TV: glycogen metabolism, health disparities & social determinants, macro nutrients

ELECTRON transport CHAIN

e^- e^- e^- e^- e^-



proton gradient is what turns ADP → ATP ! must maintain!

OUTER mitochondrial membrane

Cardiac muscle, liver cells, kidneys
malate-aspartate shuttle
↳ NADH = ATP ATP A 2.5ATP

↗ $FADH_2$ = ATP A 1.5ATP

glycerol 3-P shuttle
skeletal muscle, adipose

Increased permeability of membrane
- H^+ leaky... decreased H^+ gradient
- ETC continues to run w/ no energy payout (NO ATP)
- energy released as HEAT
- ex: brown fat has thermogenin, an uncoupling protein
  - also: valinomycin

disrupted ETC
- decreased H^+ gradient
- INHIBITED ATP synthesis

BARRIERS / TRANSPORT PROTEINS

in response, many mechanisms of barrier transport through membrane proteins:

Lipid Bilayers = impermeable to ions $^{+}_{-}$. (ESSENTIALLY) (CHARGE)

LEAKS (facilitated diffusion)

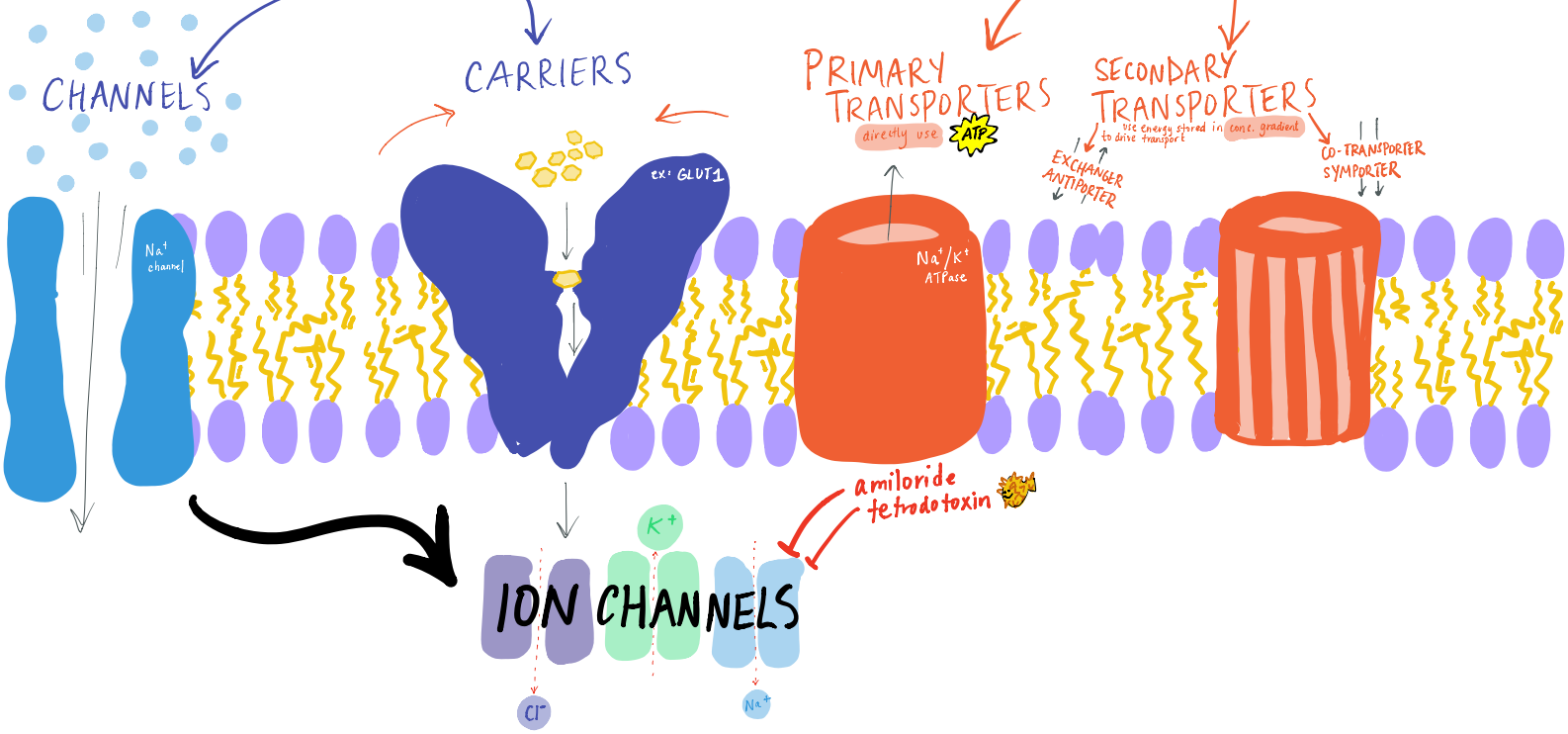
movement along concentration gradient

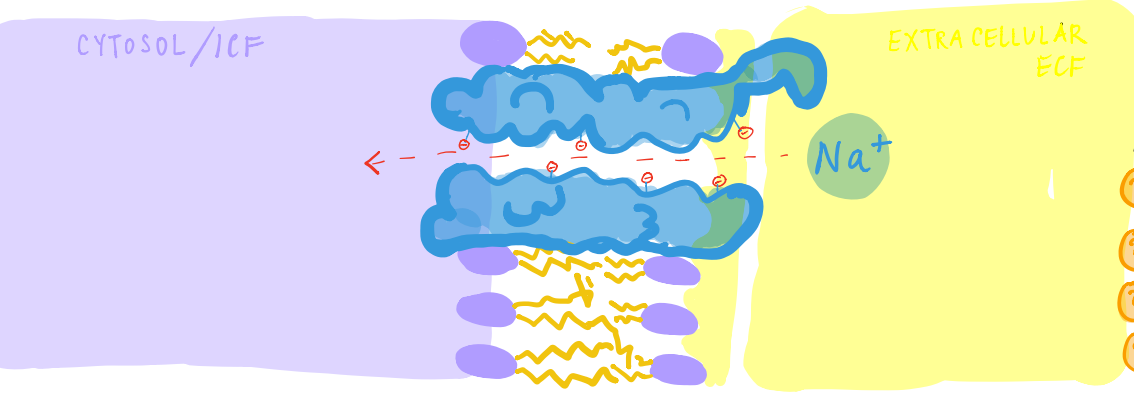
drive system toward equilibrium

PUMPS! (active transport)

often against concentration gradient

drive system away from equilibrium





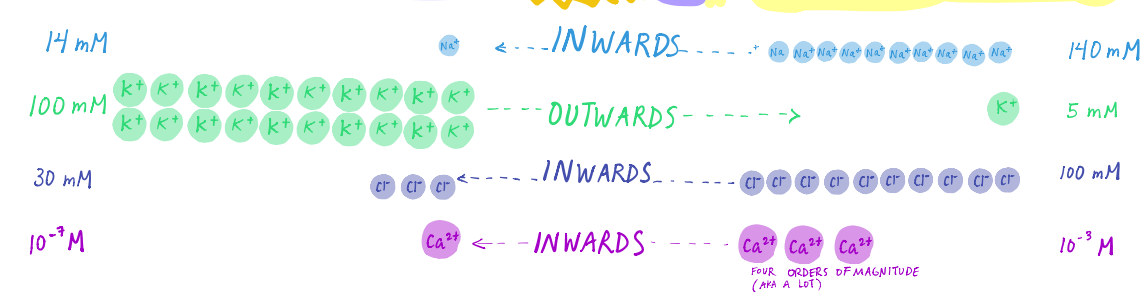
SOLUTION DIFFUSION PERMEABILITY

$$P = \frac{B \times D}{\Delta x}$$

B = partition coefficient
D = diffusion coefficient
Δx = thickness

ION CHANNEL TERMINOLOGY

- voltage gated: ion channel opened by ____
- ligand gated: ion channel opened by ____
- K^+ - selective: only allow ____ to go thru
- non-selective: only allow ____ to go thru



flow of ions = electric current

direction of current flow = direction of the flow of + + + POSITIVE charge

? if K^+ leaves the cell, is current inward or outward?

? if Cl^- leaves the cell, is current inward or outward?

HOW TO CALCULATE & PREDICT

passive ion flow

aka

ELECTROCHEMICAL gradient

passive ion flow

depends on two things:

1) CHEMICAL CONCENTRATION GRADIENT

FORCE DUE TO distribution of atoms based on gradient / differential / amount

[ion] = X mM

2) Membrane Potential

FORCE DUE TO movement of atoms based on charge

V_m = X mV

-70 mV

REMEMBER: V_m sign (−/+) is relative inside the cell

Calculate the magnitude of both forces to determine direction of flow of ion of interest (e.g. Na^+ K^+ Cl^-)

(OFTEN TIMES, THE FORCES ARE OPPOSING)

USING

Nernst Equation

$$E = 2.3 \left(\frac{RT}{zF}\right) \log \left(\frac{C_{out}}{C_{in}}\right)$$

ion VALENCE, e.g. +1, -1, -2...

Faraday constant

ion concentration out / in is std. convention

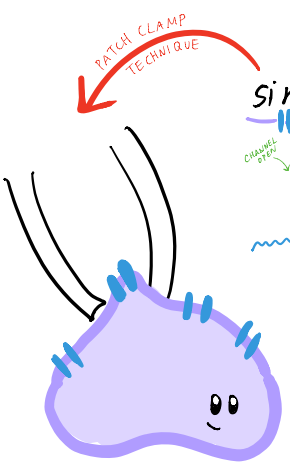
if z = +1 (like as in Na^+) since these are all constants, can often simplify to

$$E = 60$$ under standard conditions 37°C

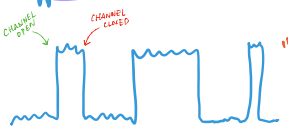
? Using Nernst equation: What is the direction of of flow of Cl^-?

V_m = -70mV

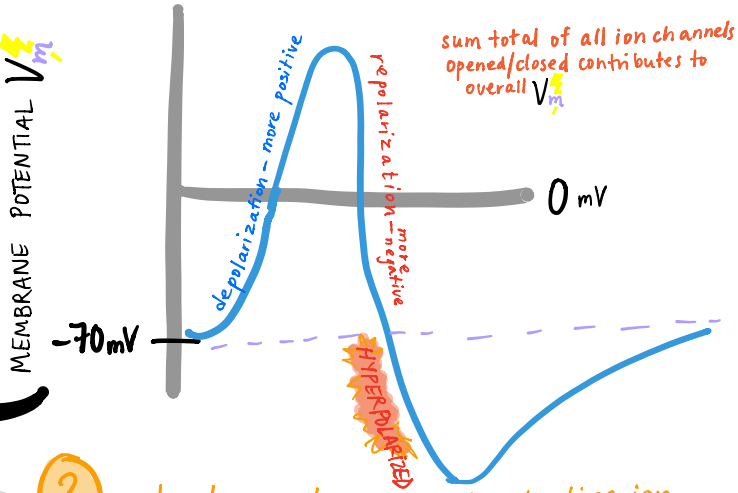
Cl^- 90 mM = Cl^- 4.5mM



single channel current VS macroscopic, whole cell current



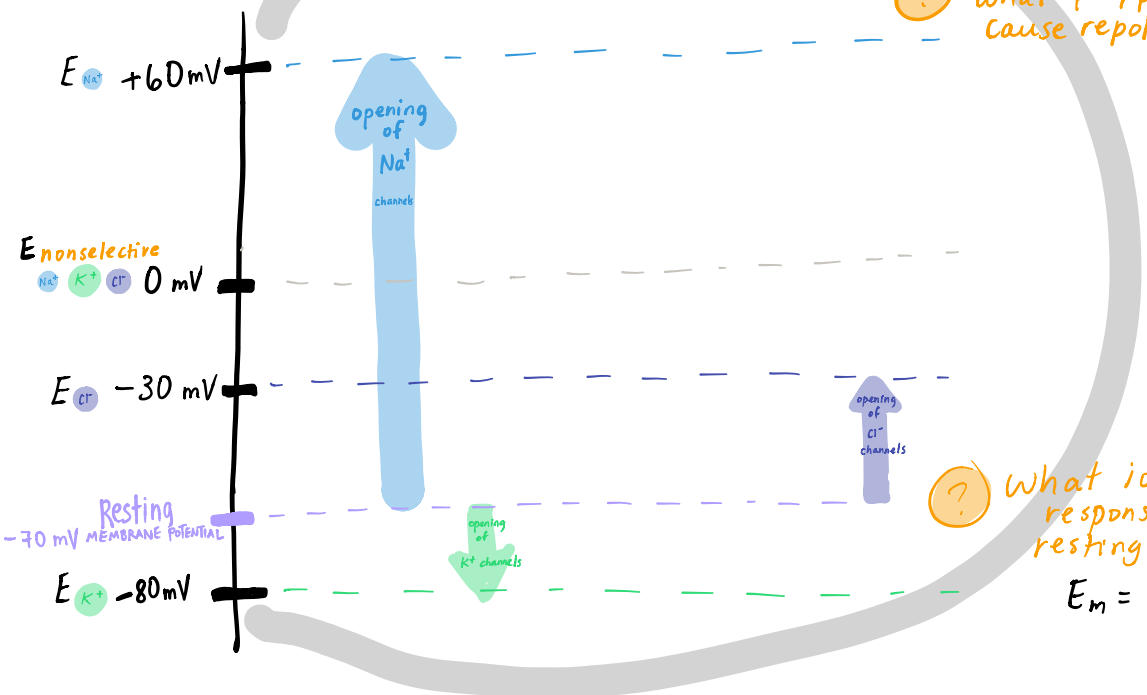
"ALL OR NOTHING" = ON/OFF



MEMBRANE POTENTIAL & interpreting graphs

? what open/permeable/conducting ion channels cause depolarization?

? what open/permeable/conducting ion channels cause repolarization? hyperpolarization

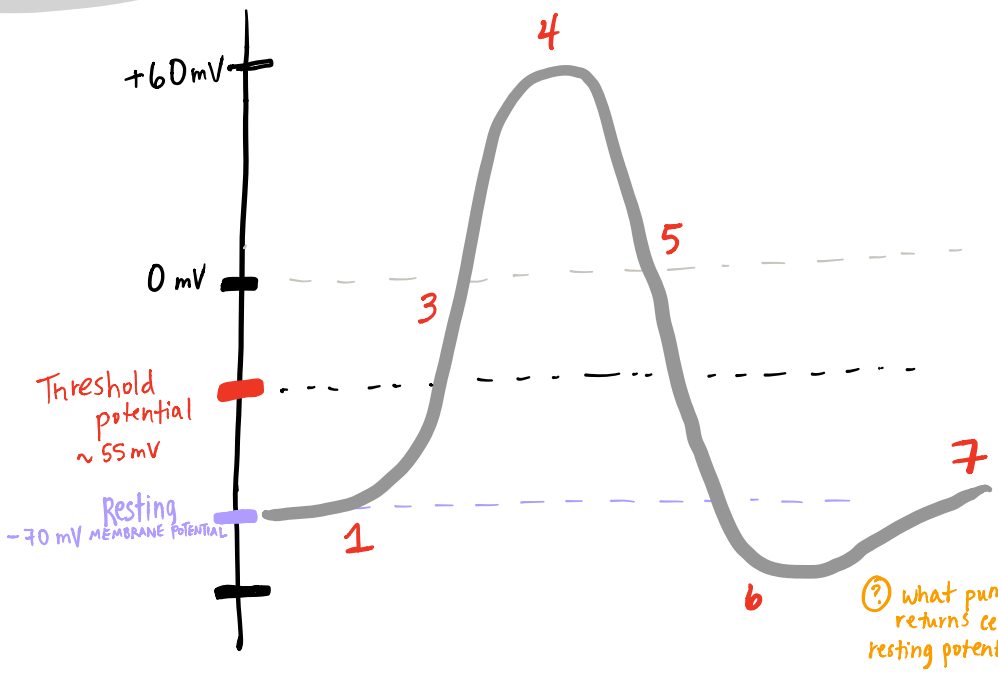


? what ion is most "dominant"/most responsible for the resting membrane potential?

$$E_m = \left(\frac{g_{Na}}{g_m}\right) E_{Na} + \left(\frac{g_K}{g_m}\right) E_K + \left(\frac{g_{Cl}}{g_m}\right) E_{Cl}$$

STEPS of the Action Potential

1. resting potential
2.
3.
4.
5.
6.
7



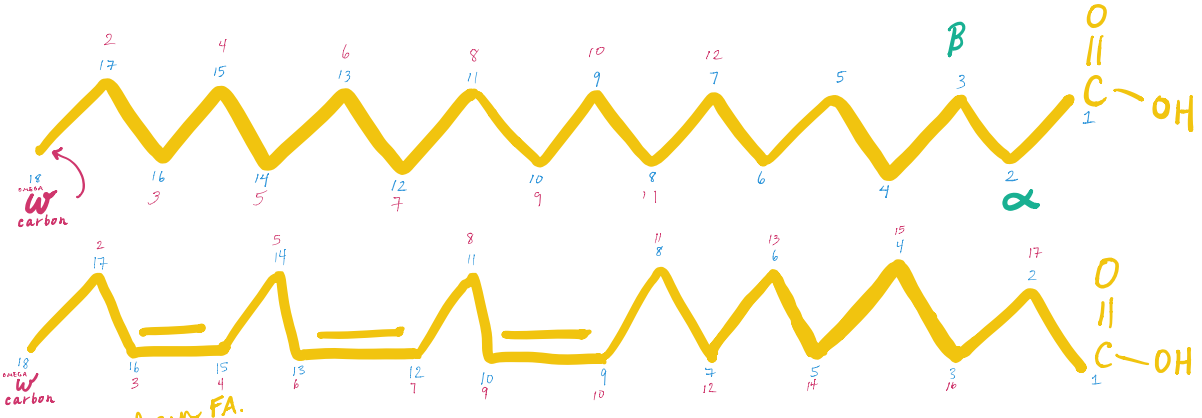
? what pump returns cell to resting potential?

Fatty Acids

- hydrocarbon tail + carboxylic acid
- hydrophobic – repelled by water
- higher energy yield than carbohydrates – great for storing energy

COUSINS of Fatty Acids (largely hydrophobic molecules)

- **phospholipids** — Phosphate + glycerol + 2 F.A
- **triacylglycerols** or **triglycerides** — E, glycerol backbone + 3 F.A.
- **sphingolipids** — serine + F.A (palmitate C16)
- **VLCFAs** — very long chain FA → brain/CNS
  - dx: X-linked adrenoleukodystrophy; VLCFA in beta-oxidation



FATTY ACID NOMENCLATURE

18:0 saturated

18:3 (9,12,15) polyunsaturated

Long chain FA. biosynthesis

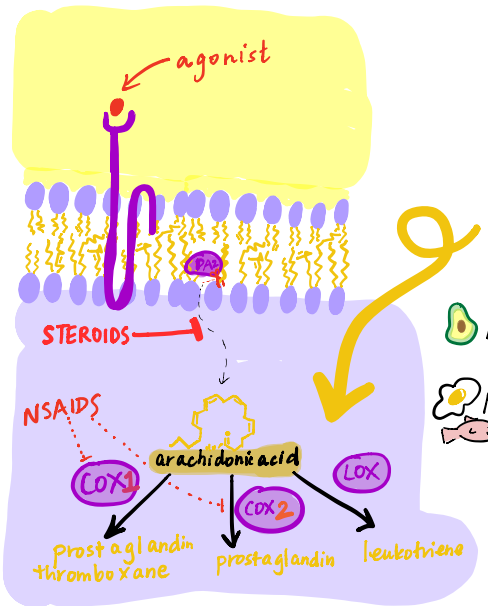
- **elongase** – carbon chain extension
- **desaturase** – inserts double bonds
  - Δ4
  - Δ5
  - Δ6
  - Δ9

Random but important: VITAMIN B12

needed for:

- → β oxidation of odd chain FA (L methyl malonyl coA mutase)
- → to make methionine, am. acid (methionine synthase)

↓def. in... long term vegan diet, GI surgery/malabsorption



FATTY ACIDS of note

palmitate
C16 aka 16:0
product of fatty acid synthase — lipogenesis

arachidonic acid
C20 aka 20:4 (5,8,11,14)
precursor to prostaglandins + eiconasoids

linoleic acid
C18:2(n-6)
* essential fatty acid ω6

linolenic acid
C18:3(n-3)
* essential fatty acid ω3

* essential because... humans cannot insert new double bonds past position Δ9 on F.A.
  - @ Δ9, Δ12
  - ? where do we get essential F.A?

Fatty Acid METABOLISM

LIPOGENESIS

OVERALL PURPOSE store excess energy

STARTING COMPOUNDS glucose

END COMPOUNDS palmitate C16 → sphingosine, triacylglycerol

? is ACC activated or inhibited when it is phosphorylated? what hormone is responsible for phosph. of ACC?

REGULATORY ENZYMES (Rate limiting step! = R.L.S.)

- ⊕ ↑↑ acetyl CoA
- ⊕ insulin (fed state)
- ⊖ glucagon – FIGHT or FLIGHT!
- ⊖ epinephrine

ACC = Acetyl CoA carboxylase: acetyl-CoA → malonyl-CoA

COFACTORS!

Biotin (B7), HCO_3^- (carbon source), NADPH, ATP

(Biotin: for carboxylation rxn)

FATTY ACID β OXIDATION

OVERALL PURPOSE generate energy in a pinch

STARTING COMPOUNDS triglycerides

END COMPOUNDS ketone bodies → β-hydroxybutyrate, acetoacetate, acetone

carnitine palmitoyl transferase I (CPTI) — part of the carnitine shuttle – LIMITED ENTRY!

Fatty acyl coA synthase makes fatty acyl CoA

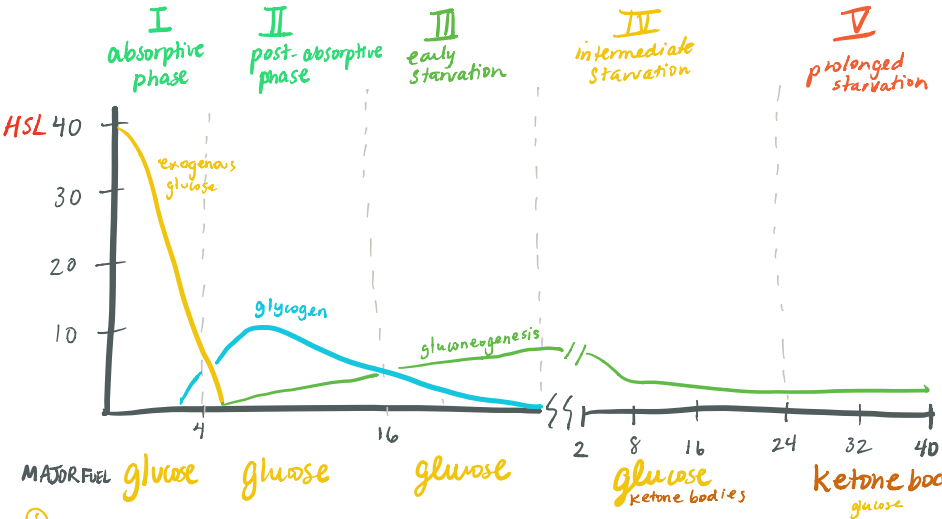
?

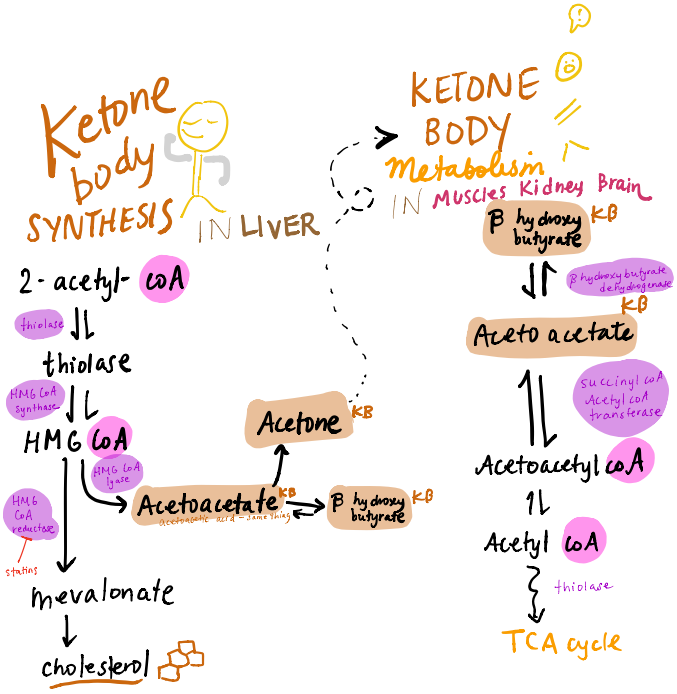
BRANCH POINT	TCA Cycle sphingolipid / surfactant eicosanoid production	TCA cycle Ketone body synthesis
CELL LOCATION	cytosol	mitochondrial matrix
TISSUE LOCATION	liver, kidney, brain, lung, adipose	
SHUTTLE	citrate shuttle	Carnitine shuttle

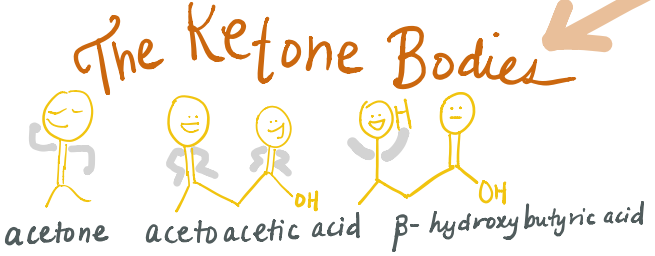
keep adding to this list...

insulin
- ↑ uptake & storage of glucose + FA
- ↑ glycogenesis
- ↑ ACC
- inhibits HSL
- ↑ fatty synthesis

glucagon
epinephrine
- ↑ gluconeogenesis
- ↑ hormone sensitive lipase HSL
- ↓ ACC



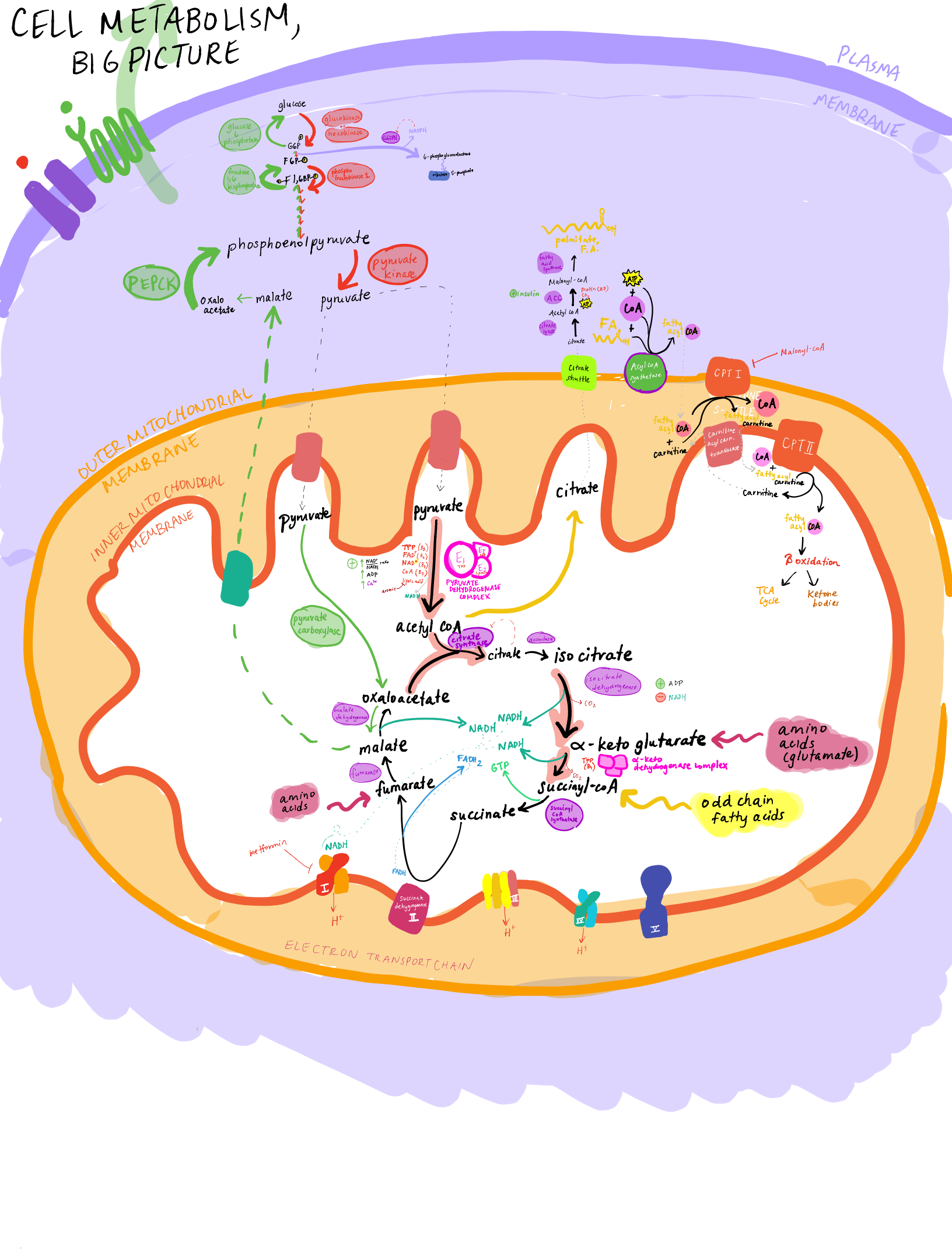




K.B synthesis in LIVER mitochondria
sent to peripheral tissues, where it's metabolized for energy
(muscle, kidney, brain)

Why can't liver metabolize the K.B it makes?
RBCs lack MITO CHONDRIA cannot use KB as energy

acetoacetate → acetoacetyl coA


CELL METABOLISM, BIG PICTURE
PLASMA MEMBRANE
glucose
glucose 6 phosphatase
glucokinase or hexokinase
G6PDH
NADPH
6-phosphogluconolactone
ribulose 5-phosphate
G6P
F6P
fructose 1,6 bisphosphatase
phospho fructokinase 1
F 1,6BP
phosphoenolpyruvate
PEPCK
pyruvate kinase
oxalo acetate
malate
pyruvate
palmitate, F.A.
fatty acid synthase
Malonyl-coA
insulin
ACC
Biotin (CO2)
Acetyl coA
citrate lyase
citrate
ATP
CoA
FA
fatty acyl CoA
Citrate shuttle
Acyl CoA synthetase
CPT I
Malonyl-coA
carnitine
carnitine acyl carn. translocase
CPT II
fatty acyl carnitine
β oxidation
TCA Cycle
Ketone bodies
OUTER MITOCHONDRIAL MEMBRANE
INNER MITOCHONDRIAL MEMBRANE
pyruvate
pyruvate carboxylase
PYRUVATE DEHYDROGENASE COMPLEX
acetyl coA
citrate synthase
citrate
aconitase
iso citrate
isocitrate dehydrogenase
ADP
NADH
oxaloacetate
malate dehydrogenase
malate
α-keto glutarate
amino acids (glutamate)
α-keto dehydrogenase complex
fumarase
fumarate
FADH2
GTP
succinyl-coA
amino acids
succinate
succinyl coA synthetase
odd chain fatty acids
metformin
FADH
Succinate dehydrogenase
ELECTRON TRANSPORT CHAIN