FUND

WEEK 2
genes + proteins

THIS WEEK:

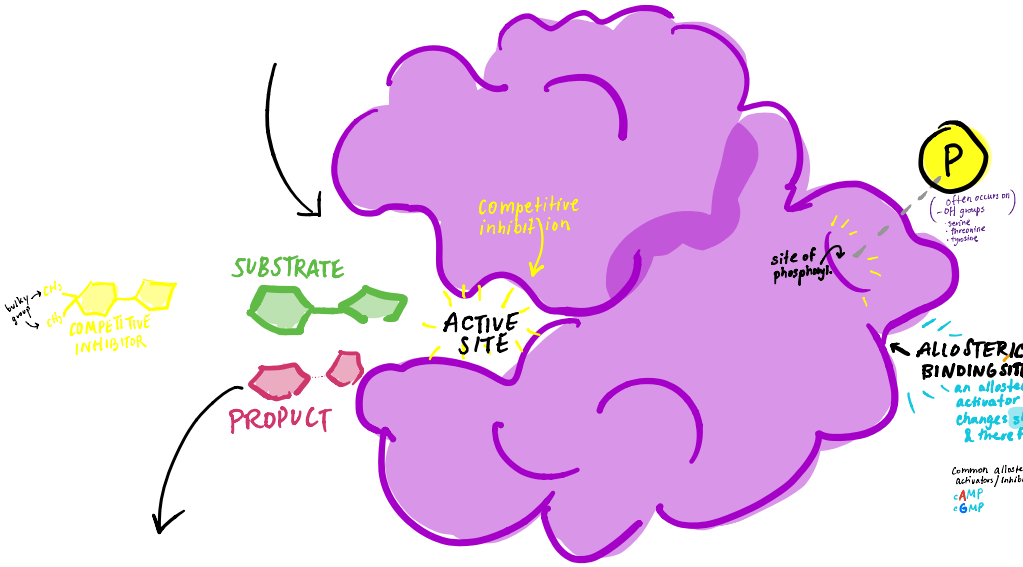
- Epidemiology
- Hemoglobin + Myoglobin
- Membranes
- Misfolding
- Enzymes I
- Vitals, Patient History, Hand Hygiene
- Medical Professionalism

- Glycolysis
- Pentophosphate Pathway
- Enzymes II
- Imatinib
- Sickle Cells

- Embryology
- Histology Basics

- Pyruvate, TCA Cycle
- Galactosemia Workshop
- Protein Translation

ENZYMES

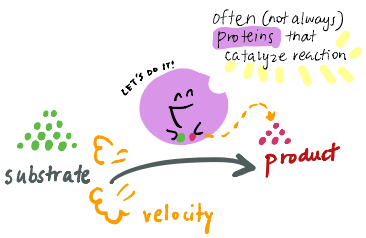


WHAT ARE OTHER THINGS THAT CAN ALTER protein structure → fxn → K_m → rate of rxn?

1. H^+
2. ~
3. ⁘
4. ⁘

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} E + P$$

WHAT IS LE CHATELIER'S principle? why do we care



- $[S]$ = substrate concentration
- V_0 = initial velocity (rate) of rxn
- V_{max} = maximum velocity of rxn
- K_m = substrate concentration needed to reach $\frac{1}{2} V_{max}$

HIGH K_m = enzyme has ? affinity for substrate

low K_m = enzyme has ? affinity for substrate

k_{cat} = turnover number
# of times each enzyme site converts S to P per unit time

CLASSES of ENZYMES

- oxidoreductase — transfer of electrons (e^-) (LEO GER goes)
- transferase — moeity ($-CH_3$) group transfer
- hydrolase — uses H_2O as substrate to break down molecule
- isomerase — rearranges bonds to make isomer
- ligase — formation of bonds, joins together
- lyase — elimination reaction, breaks down but uses other mech. besides hydrolysis

EQUATIONS

$$V_0 = \frac{V_{max} * [S]}{(K_m + [S])}$$

$$K_m = \frac{1}{2} V_{max}$$

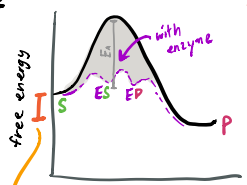
$$V_{max} = k_2 [E_T]$$

$$\text{catalytic efficiency} = \frac{k_{cat}}{K_m}$$

HOW DO ENZYMES WORK?

they lower activation energy of reaction (kinetics) w/o changing equilibrium constant (K_{eq}).

THERMODYNAMICS - not affected

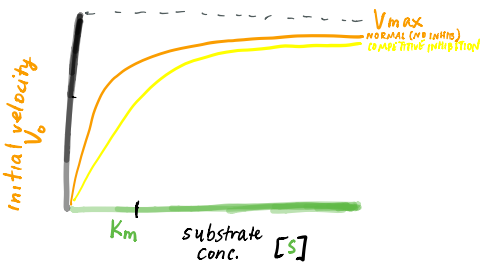


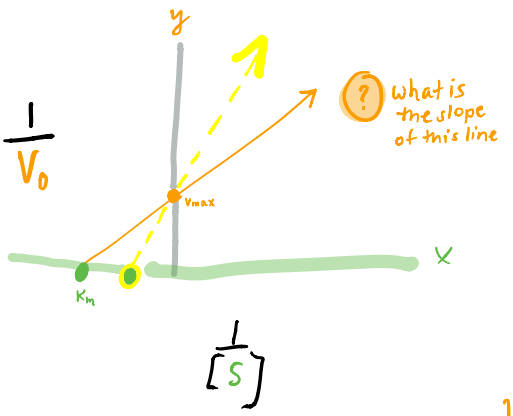
? what is this difference?

COMPETITIVE inhibition

$E + S \rightleftharpoons ES \rightarrow E + P$

$+ \; I \rightleftharpoons EI$





$V_{max} \rightarrow$

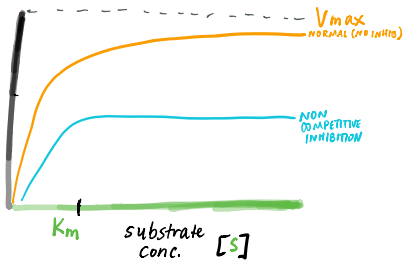
$K_m \rightarrow$

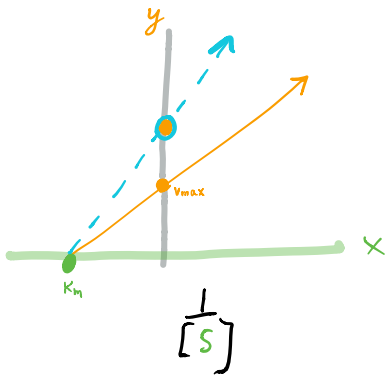
NONCOMPETITIVE inhibition

$E + S \rightleftharpoons ES \rightarrow E + P$

$+ \; I \qquad + \; I$

$EI + S \rightleftharpoons ESI$

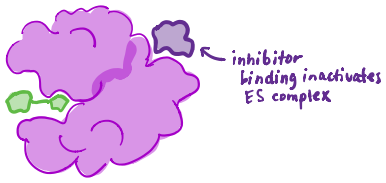




$V_{max} \rightarrow$

$K_m \rightarrow$

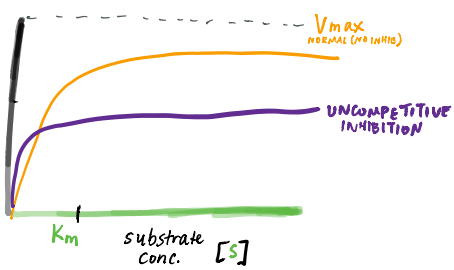
UNCOMPETITIVE inhibition

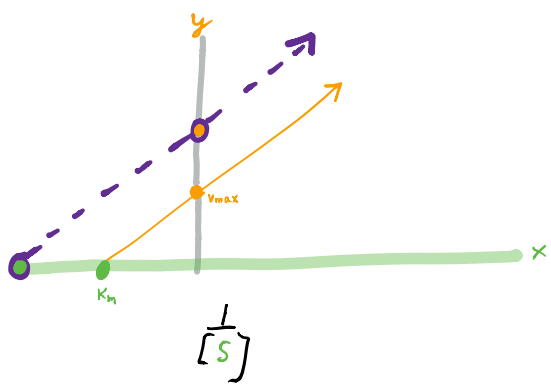


$E + S \rightleftharpoons ES \rightarrow E + P$

$+ \; I$

ESI





$V_{max} \rightarrow$

$K_m \rightarrow$

GLYCOLYSIS

is this a catabolic or anabolic process?

where in cell is this taking place?

OVERALL PURPOSE: generates energy

STARTING COMPOUNDS: glucose

END COMPOUNDS: pyruvate + 2 ATP + 2 NADH

lactate produced in O_2 depleted environm.

REGULATORY ENZYMES: F6P → F 1,6BP (PFK-1)

what enzyme catalyzes lact → pyruvate?

(#) what step of glycolysis is regulated by PFK?

⊕ insulin

BRANCH POINT: pentose phosphate pathway

GENETIC DISEASES: dx: pyruvate kinase deficiency (AR)

↓

HEMOLYTIC ANEMIA

PENTOSE PHOSPHATE SHUNT

aka Hexose Monophosph. shunt

neg. feedback

generates: ribose (for DNA & RNA) + 2 NADPH + CO_2

glucose-6-phosphate

ribose-5-phosphate

G6PDH

glucose 6-P → D-glucono 1,5-lactone

glycolysis branch pt

dx: G6PDH deficiency (XLR)

↳ protective against MALARIA

DON'T EAT FAVA BEANS!

what is the link between fava beans & G6PDH deficiency?

glucose 6-P → (G6PDH; oxidized NADP+ → reduced NADPH) → 6 phosphogluconate → ribose 5 phosph.

NADPH → (glutathione reductase) 2 GSH; GSSG (disulfide form)

RBC STRESS → HEMOLYSIS

GLUCONEOGENESIS

occurs in liver

OVERALL PURPOSE: generates blood glucose when in FASTING STATE

STARTING COMPOUNDS: pyruvate

END COMPOUNDS: glucose

lactate produced in O_2 depleted environm.

REGULATORY ENZYMES: ⊕ glucagon

① pyruvate carboxylase: pyruvate → oxaloacetate

where can this branch?

② F-1,6 bisphosphatase (RLS): F1,6BP → F6P

BRANCH POINT: TCA cycle, fatty acid, amino acid catabolism

GENETIC DISEASES: dx: glucose-6-phosphatase deficiency (AR)

↓ fasting

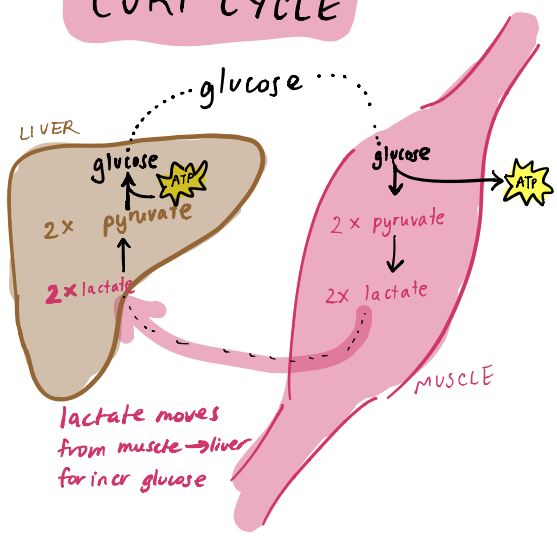
sx: HYPOGLYCEMIA

tremors

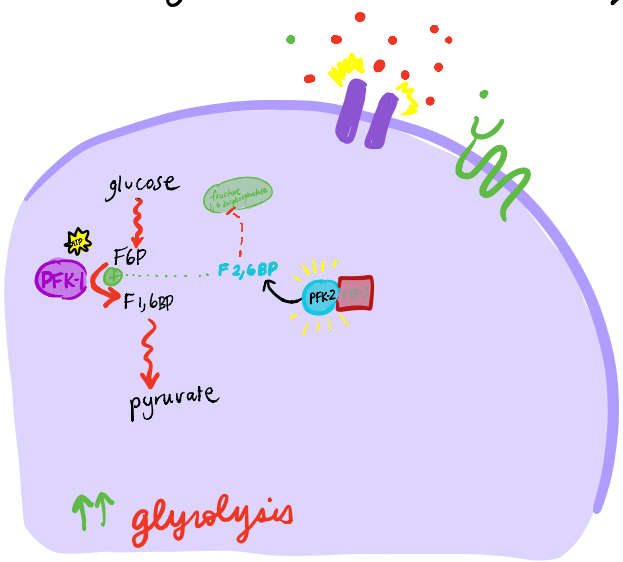
seizures

cyanosis/apnea

CORI CYCLE



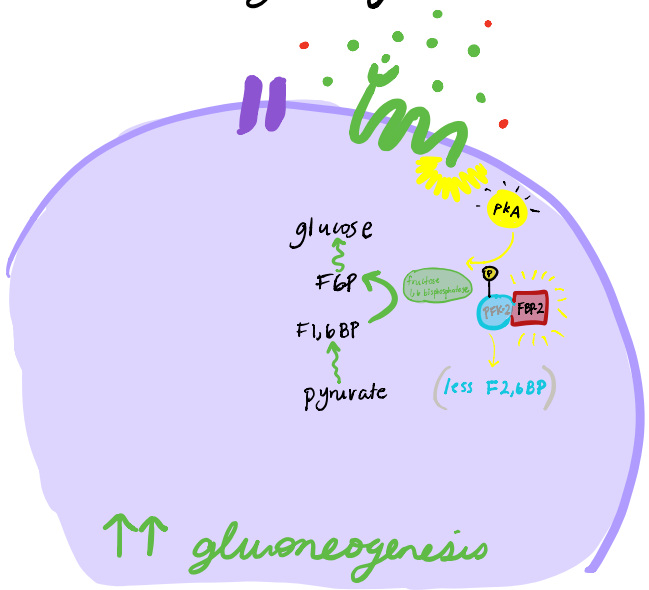
high insulin levels ⇒ ?



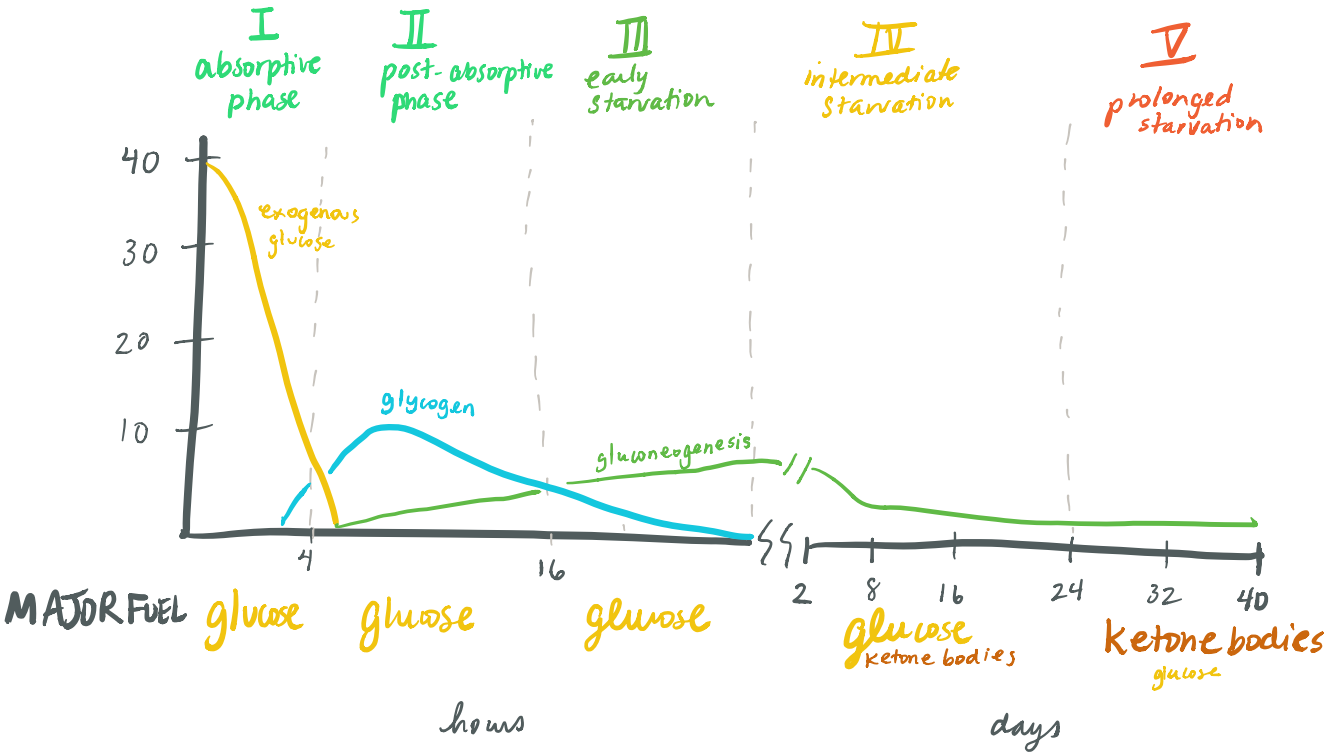
↑↑ glycolysis

VS

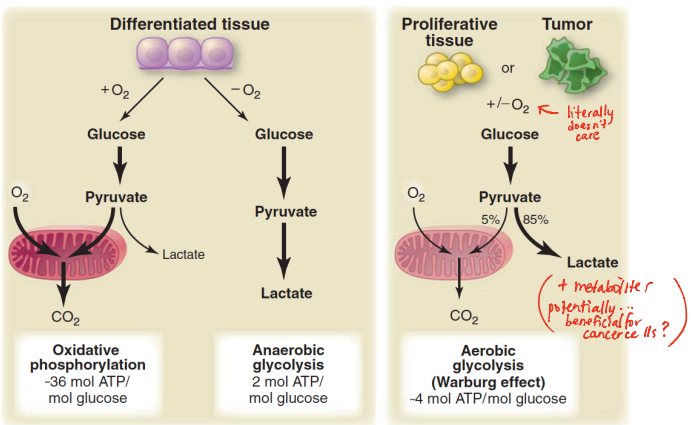
high glucagon levels ⇒ ?



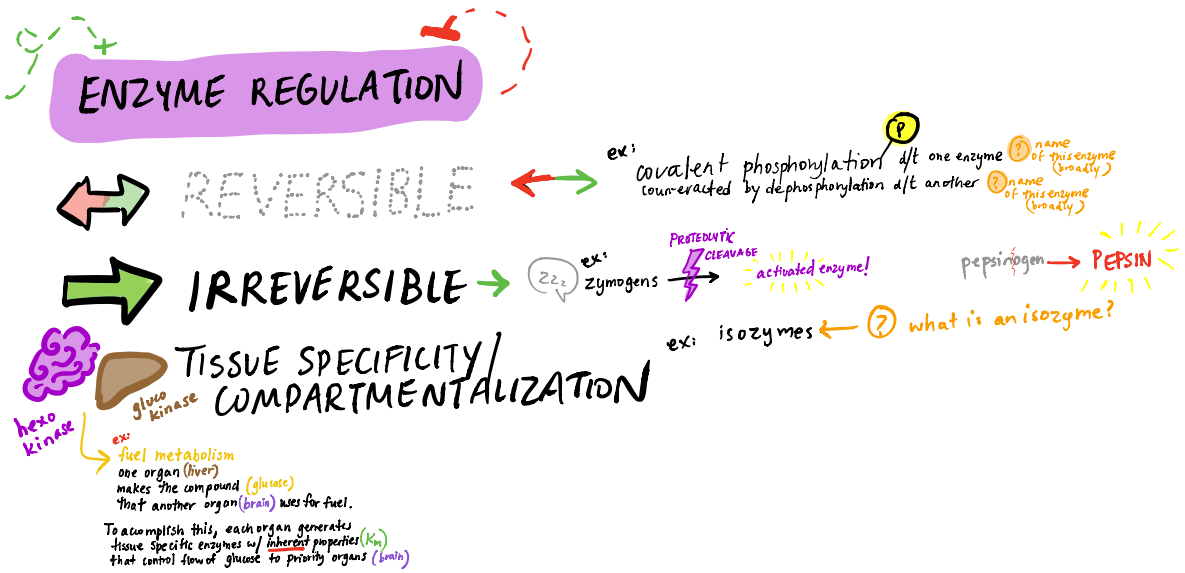
↑↑ gluconeogenesis

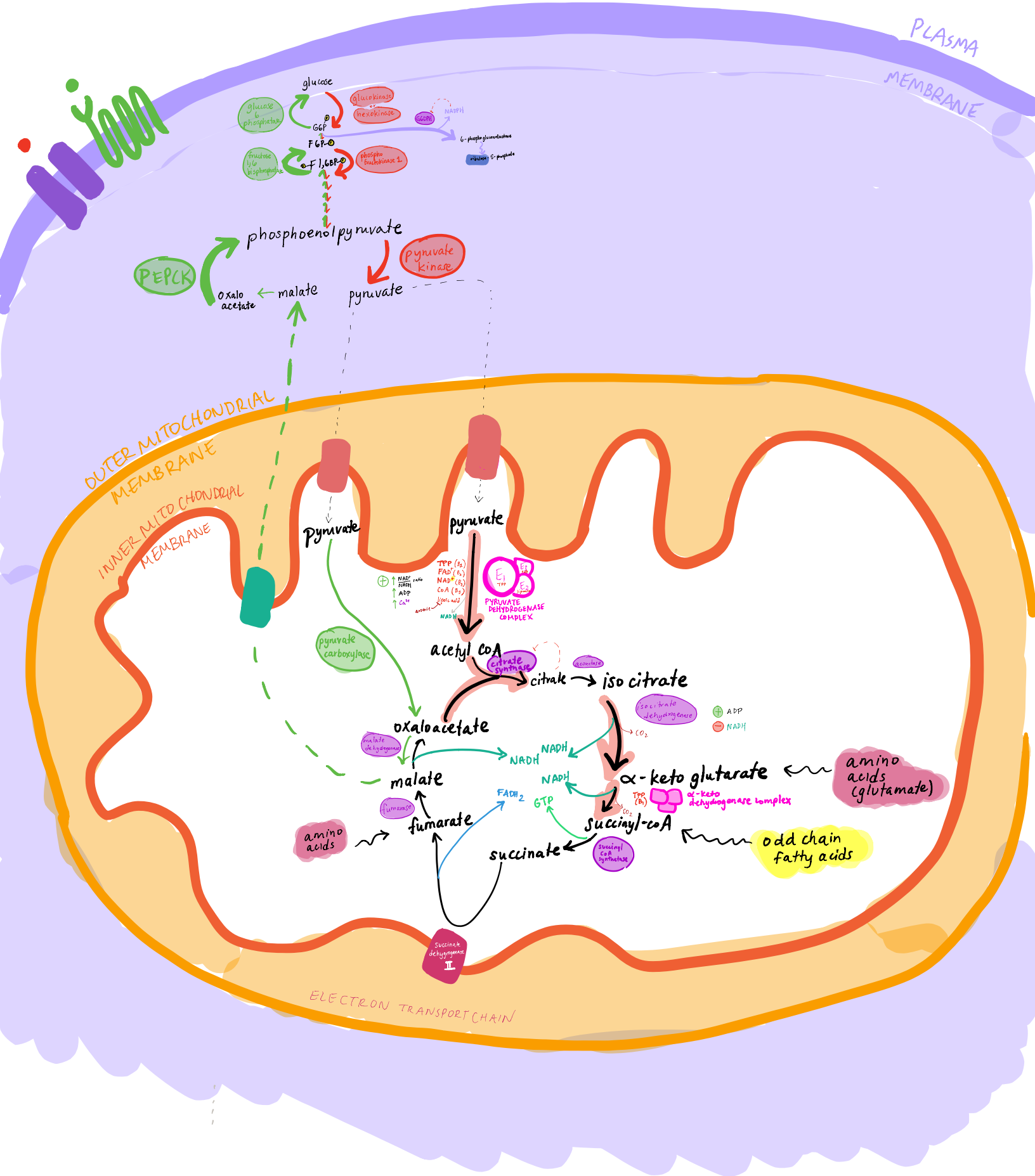


WARBURG EFFECT - aka "aerobic glycolysis"



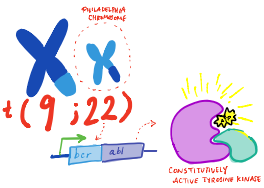
PET scans can detect altered metabolic activity d/t cancer




PLASMA MEMBRANE
glucose
glucose 6 phosphatase
glucokinase or hexokinase
G6P
G6PDH
NADPH
6-phosphogluconolactone
ribulose 5-phosphate
F6P
fructose 1,6 bisphosphatase
F 1,6BP
phospho fructokinase 1
phosphoenolpyruvate
PEPCK
pyruvate kinase
oxalo acetate
malate
pyruvate
OUTER MITOCHONDRIAL MEMBRANE
INNER MITOCHONDRIAL MEMBRANE
pyruvate
pyruvate
NAD+/NADH ratio
ADP
Ca++
TPP (B1)
FAD+ (B2)
NAD+ (B3)
CoA (B5)
lipoic acid
arsenic
NADH
PYRUVATE DEHYDROGENASE COMPLEX
pyruvate carboxylase
acetyl CoA
citrate synthase
citrate
aconitase
iso citrate
isocitrate dehydrogenase
ADP
NADH
CO2
oxaloacetate
malate dehydrogenase
NADH
NADH
α-keto glutarate
amino acids (glutamate)
malate
NADH
TPP (B1)
α-keto dehydrogenase complex
CO2
fumarase
FADH2
GTP
fumarate
succinyl-coA
amino acids
succinate
succinyl coA synthetase
odd chain fatty acids
succinate dehydrogenase II
ELECTRON TRANSPORT CHAIN

IMATINIB

aka Gleevec, a TKI.



? What is the target substrate for a tyrosine kinase?

cancer: CHRONIC MYELOID LEUKEMIA

tx: tyrosine kinase inhibitors

Competitively inhibit ATP for binding site on fusion BCR/abl protein

? what would lineweaver burk plot look like? DRAW HERE →

POPULATION GENETICS

	A	a
A	AA	Aa
a	Aa	aa

in HWE:

p = frequency of allele A

q = frequency of allele a

$$p^2 + 2pq + a^2 = 1$$

p^2: HOMOZYGOUS DOMINANT

$2pq$: HETEROZYGOUS

a^2: HOMOZYGOUS RECESSIVE

$$p + q = 1$$

? what is the freq of an X-linked recessive disease in males? in females?

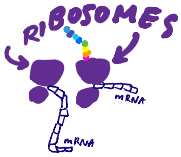
HW equilibrium

"the genetic variation of a population will [redacted] from one generation to the next in the absence of disturbing factors."

Hardy Weinberg law assumes:

1) NO mutation occurring @ locus
2) natural selection is not occurring
3) Completely [redacted] mating
4) no net migration
5) [redacted] population

PROTEIN TRANSLATION



watch the videos Dr. Mayinger posted ☺