Chapter 16: Glycolysis and Gluconeogenesis

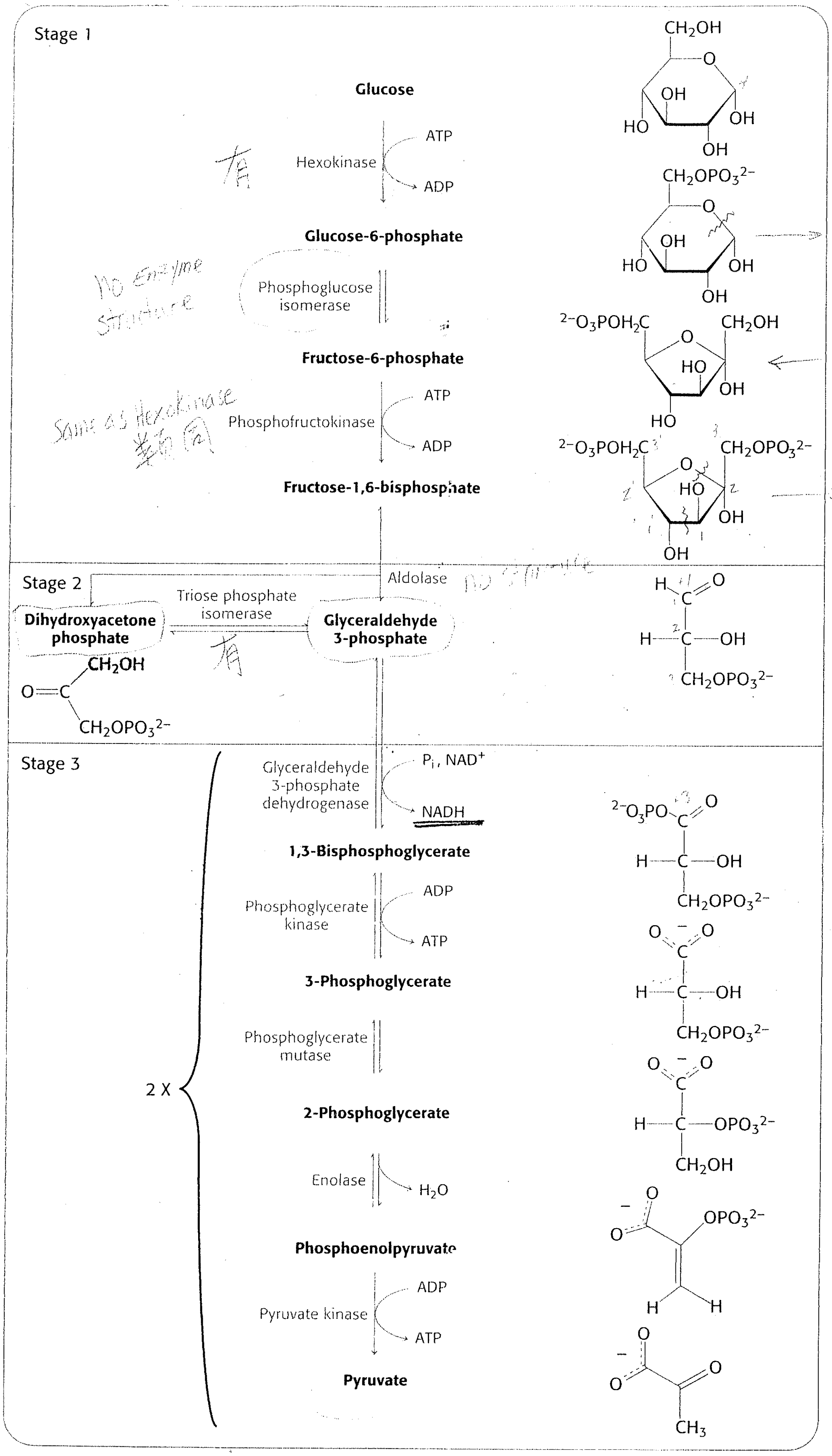

FIGURE 16.3 Stages of glycolysis. The glycolytic pathway can be divided into three stages: (1) glucose is trapped and destabilized; (2) two interconvertible three-carbon molecules are generated by cleavage of six-carbon fructose; and (3) ATP is generated.

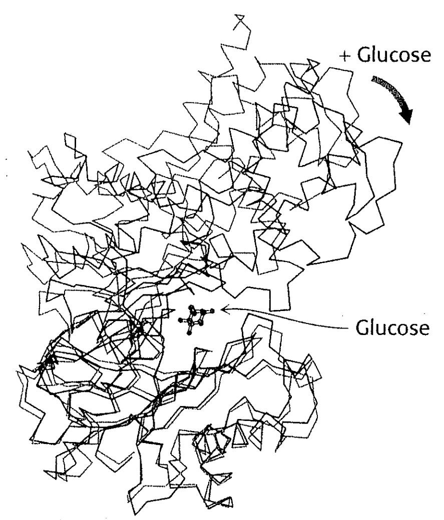

FIGURE 16.4 Induced fit in hexokinase. As shown in blue, the two lobes of hexokinase are separated in the absence of glucose. The conformation of hexokinase changes markedly on binding glucose, as shown in red. The two lobes of the enzyme come together and surround the substrate. [Courtesy of Dr. Thomas Steitz.]

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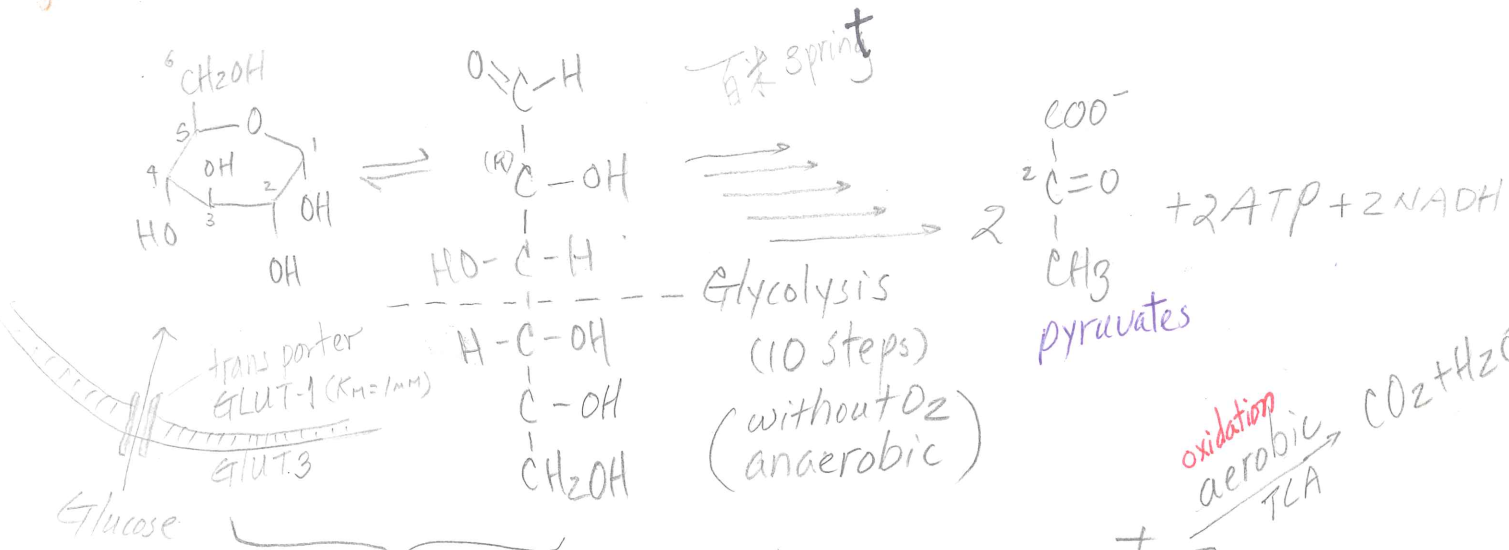
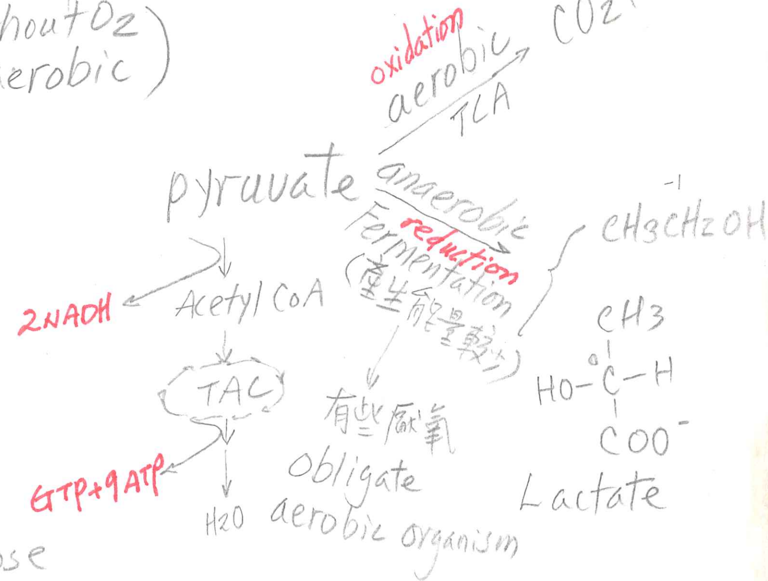


Glucose

Insulin ⟶ Fed state ⟶ convert glucose to fat
Insulin promote Glucose uptake



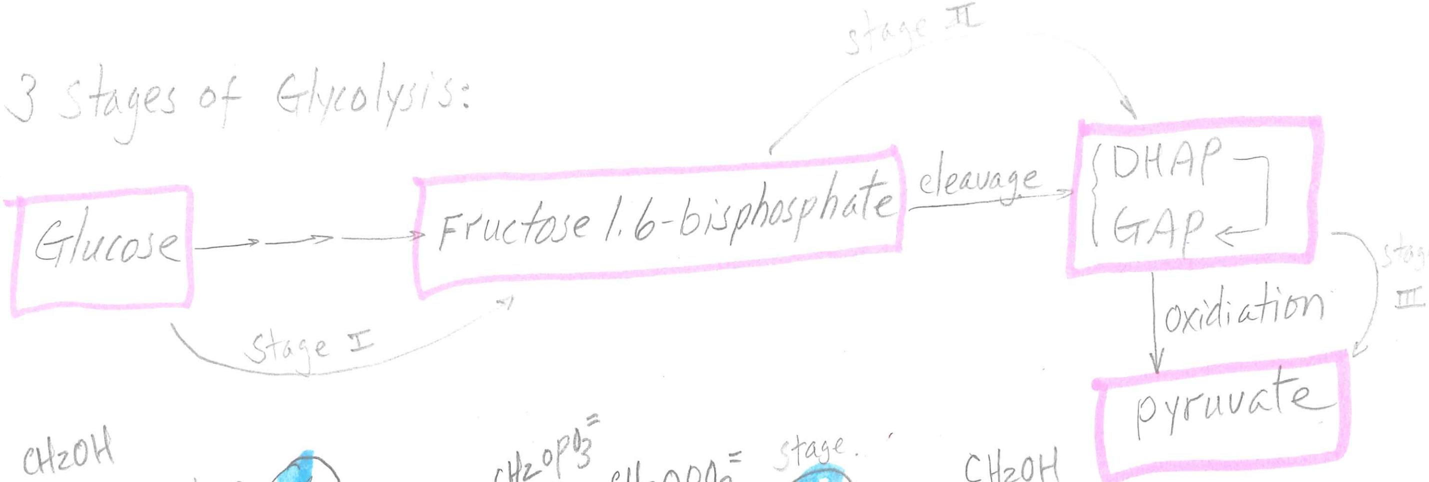
pyruvate ⇌ Glucose
Gluconeogenesis

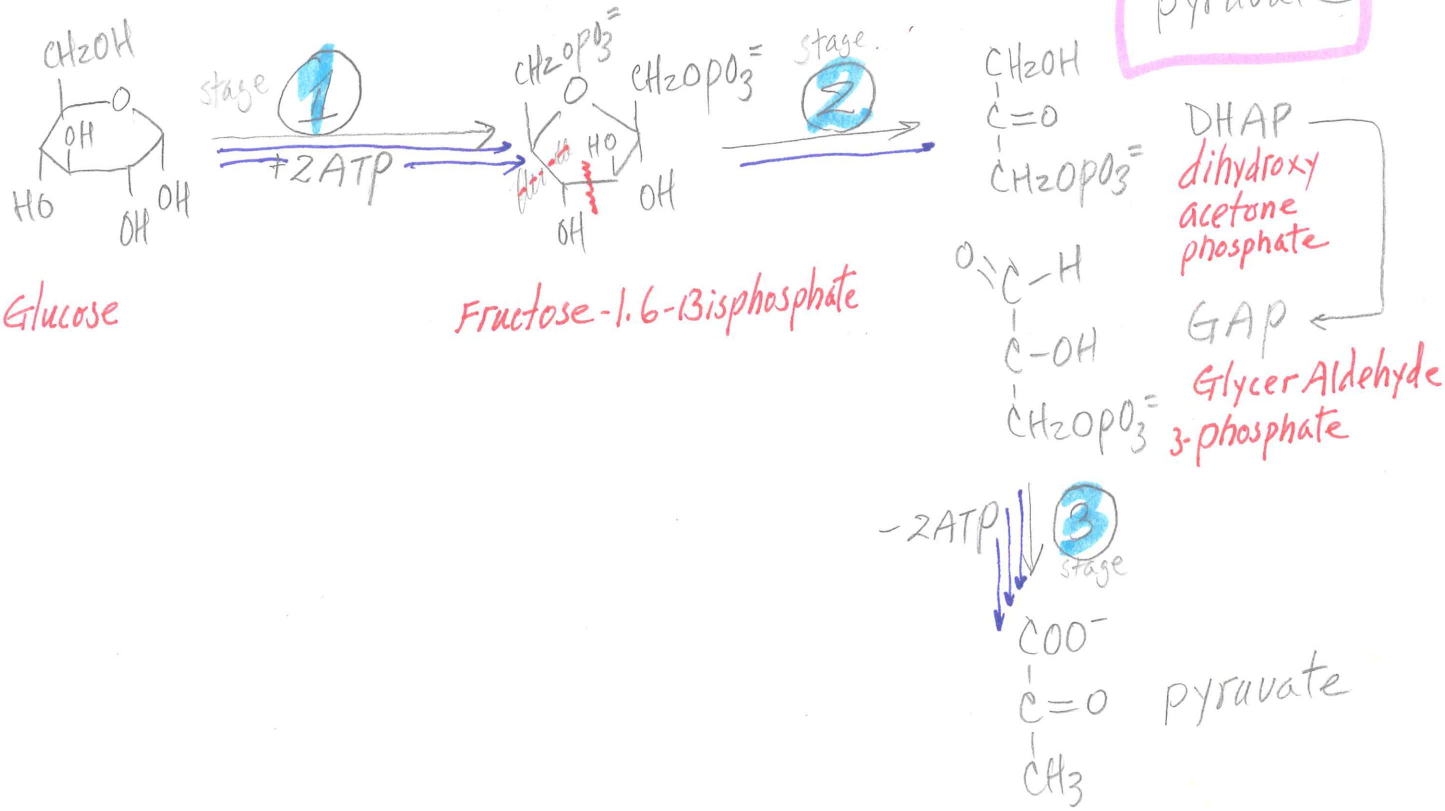
Gluconeogenesis: bypath highly exergonic irreversible steps in glycolysis

In mamals, Glucose 在腦及 red blood cell 中為唯一的 fuel.
因為 Glucose 有很強的 tendency 以 ring form 存在(無 aldehye group), 可免將 protein modify 成 schiff base

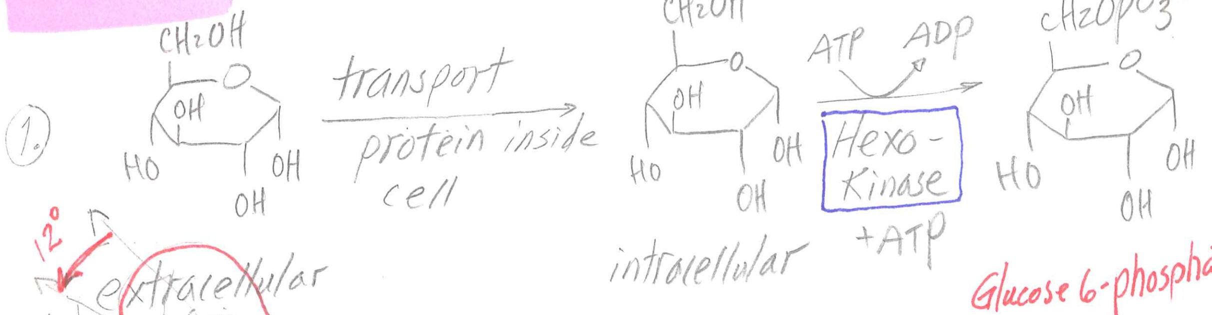
citric acid cycle 為 aerobic? yes!

3 Stages of Glycolysis:

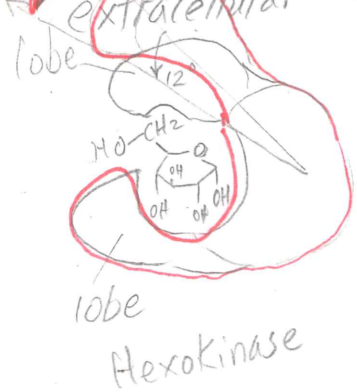




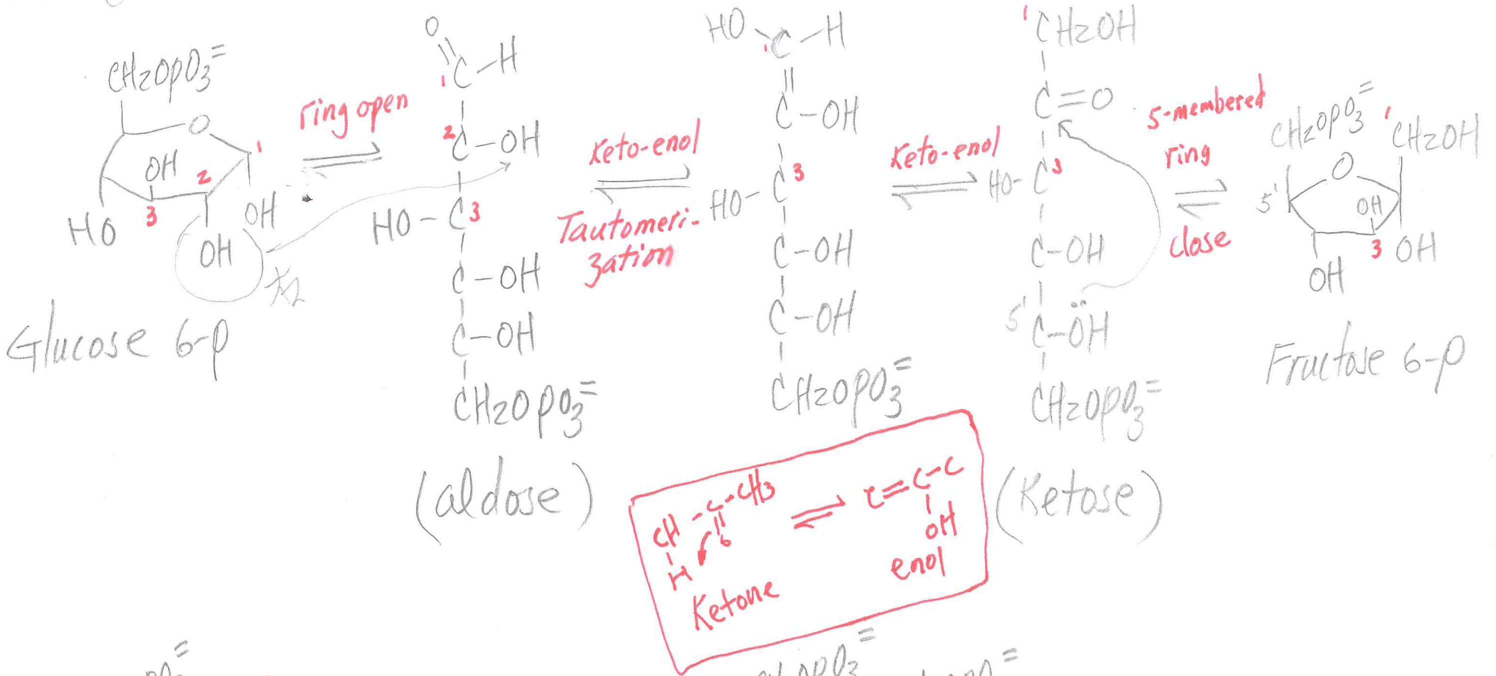
Stage ①

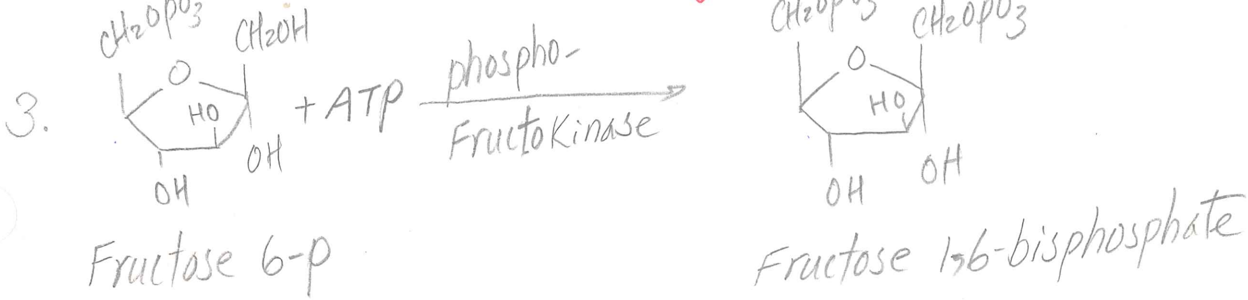


① 含有 -2價
不易走回
extracellular
② destabilized
而走下一反應

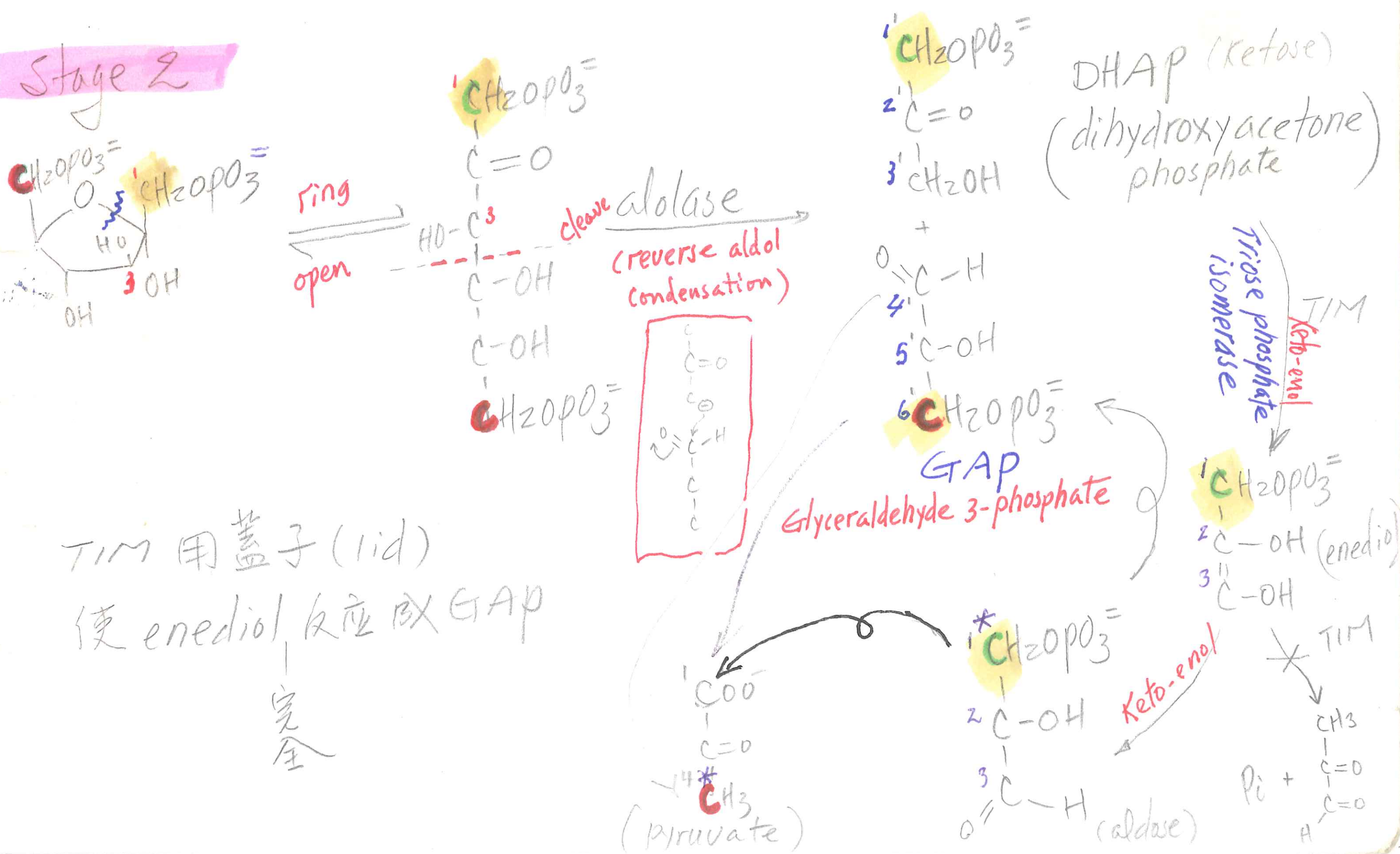


2. glucose 6-phosphate ⇌ (isomerize) Fructose 6-phosphate



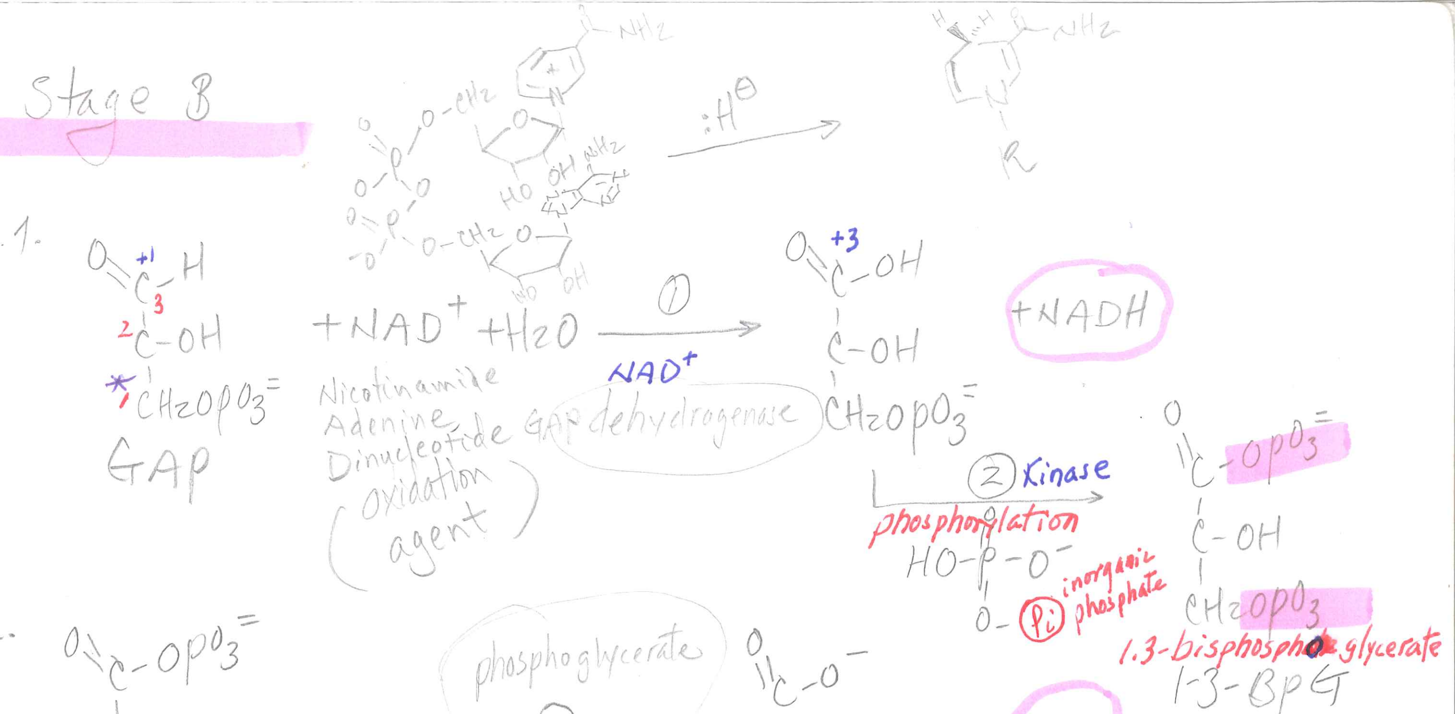


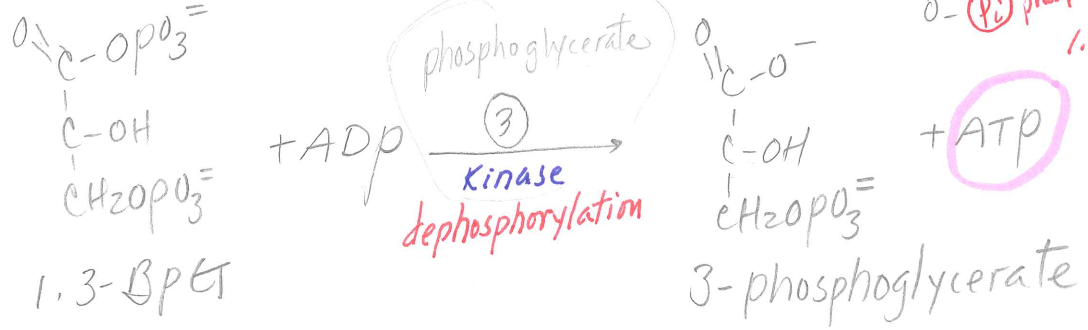
Stage 2

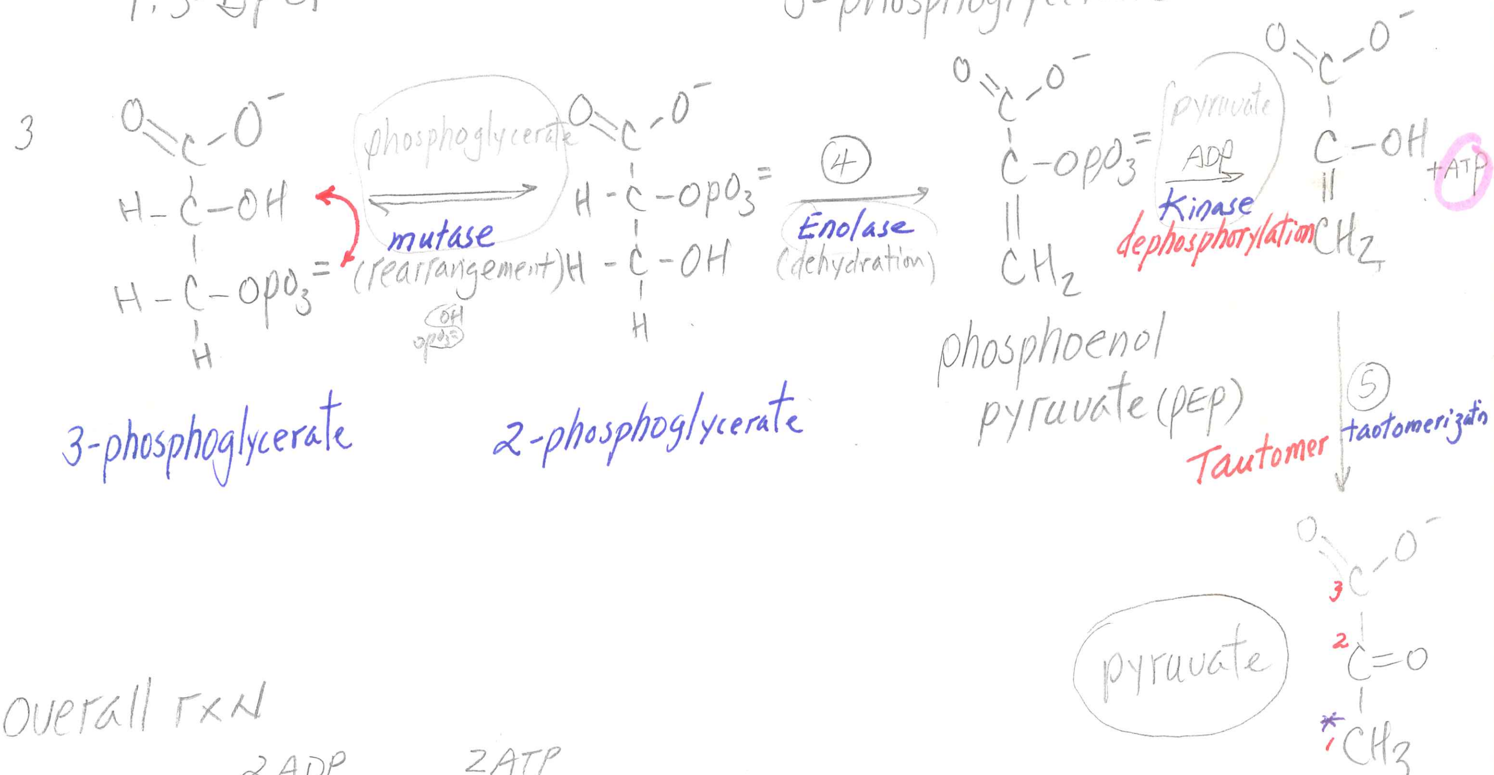


TIM 用蓋子(lid)
使 enediol 反应成 GAP
完全

Stage 3

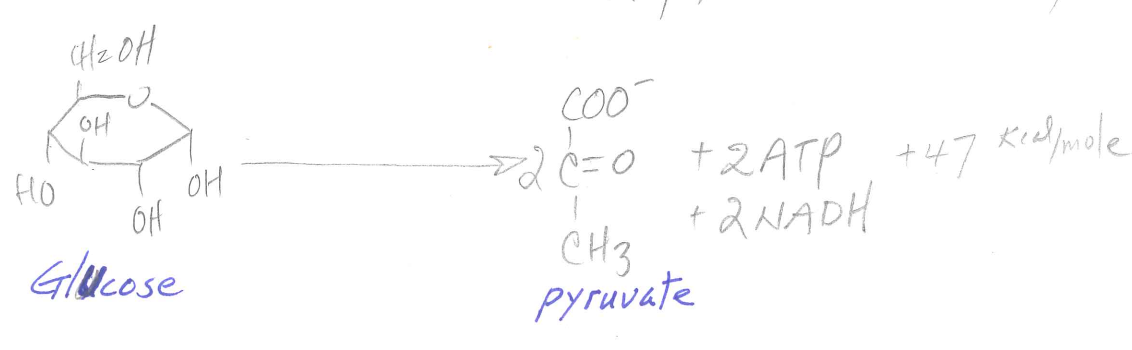




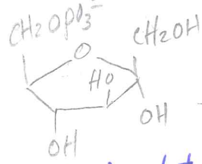


Overall rxn

Glucose $\xrightarrow[\text{NAD}^+ \quad 2\text{NADH}]{2\text{ADP} \quad 2\text{ATP}}$ 2 pyruvate + 47 Kcal/mole

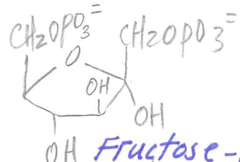


phosphofructoKinase : The control of glycolysis

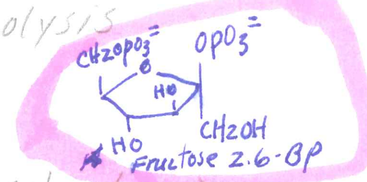


Fructose-6-phosphate

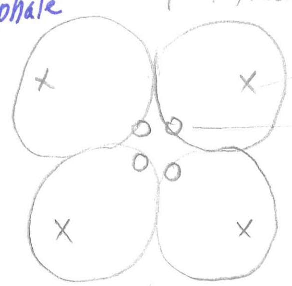
phosphofructoKinase →
1. ATP 3. citrate
2. AMP 4. Fructose 2.6-Bp



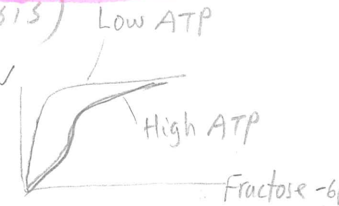
Fructose-1.6-Bisphosphate

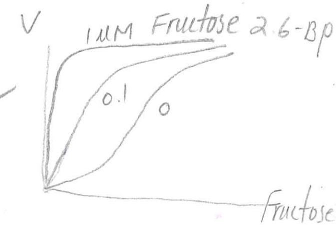


(Glycolysis)



catalytic site
→ ATP : Allosteric inhibitor
AMP : " activator
Fructose 2,6-Bp activator





Fructose 6-P ⇄ Fructose 2.6-BP (activate phosphofructoKinase)
PFK 2 → phosphorylation
FBpase 2 → dephosphorylation
speed up glycolysis

phosphofructoKinase 2

F6P → PFK2 → F26BP

F26BP → FBpase 2 → F6P

[ ] [phosphofructoKinase 2 (Kinase domain) | Fructose bisphosphatase 2 phosphatase domain]

regulatory domain

liver cell
[blood Glucose] ↑
↓
[fructose-6p] ↑ — activate PFK2 →
[fructose-2,6-Bp] ↑
↓
activate phophofructoKinase
↓
stimulate glycolysis

Glucose is scarce ⟹ Glucagon binds to 7TM receptor ⇒ slow down Glycolysis
↓
G protein dissociates : Gα + Gβγ
↓
Gα binds to Andenylate cyclase
↓
ATP ⟶ cAMP
↓
cAMP activate pKA (for phosphorylation)
↓
(PFK2)—(FBpase2), ser—(P) ← phosphorylate bifunctional enzyme (phosphofructoKinase 2) on PFK2 site
↓
inactive pFK2 and FBpase activated (make)
↓
make F26BP —dephosporylate (FBpase)→ F6P (no PFK stimulation, Glycolysis inactive)

Glucose is abundant ⟹ speed up Glycolysis
↓ no activation of pKA
(PFK2)—(FBpase2) ser
↓
activate pFK2
↓
make F6P —PFK2→ F26BP (Stimulate PFK Glycolysis active)

Control points (irrevesible rxn) for Glycolysis

Glycolysis regulation (control point)

Glucose —hexokinase→ Glucose-6p → → Fructose-6p

↓ phosphofructokinase

Fructose-1,6-Bp

↓

↓

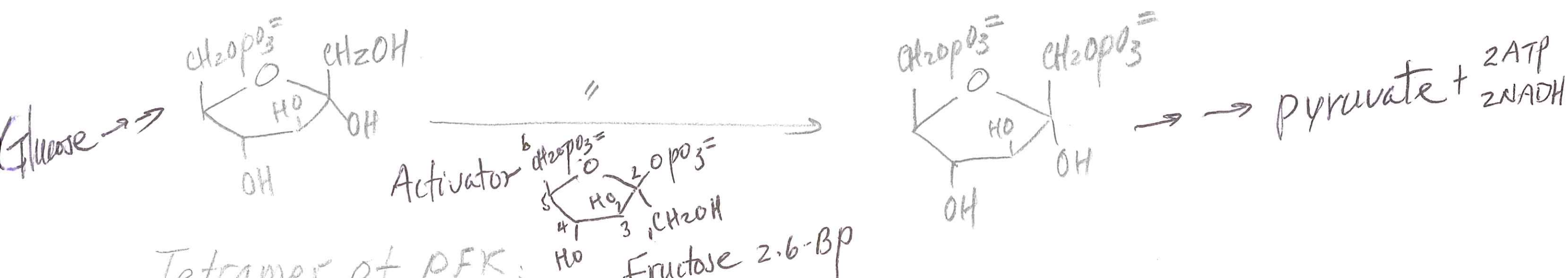
phosphoenopyruvate

↓ pyruvate kinase

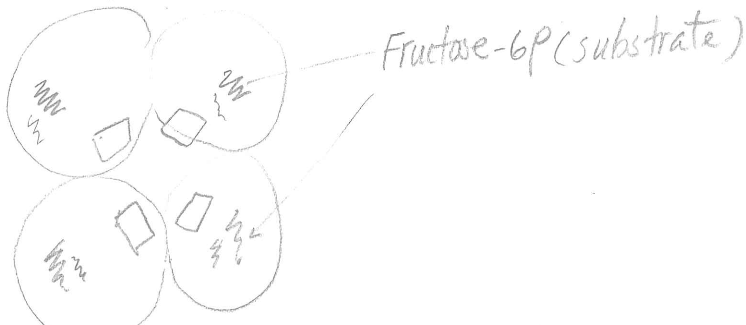
pyruvate

1. primary control point: phosphofructokinase

Fructose-6p —phosphofructokinase→ Fructose-1,6-Bp



Tetramer of PFK:

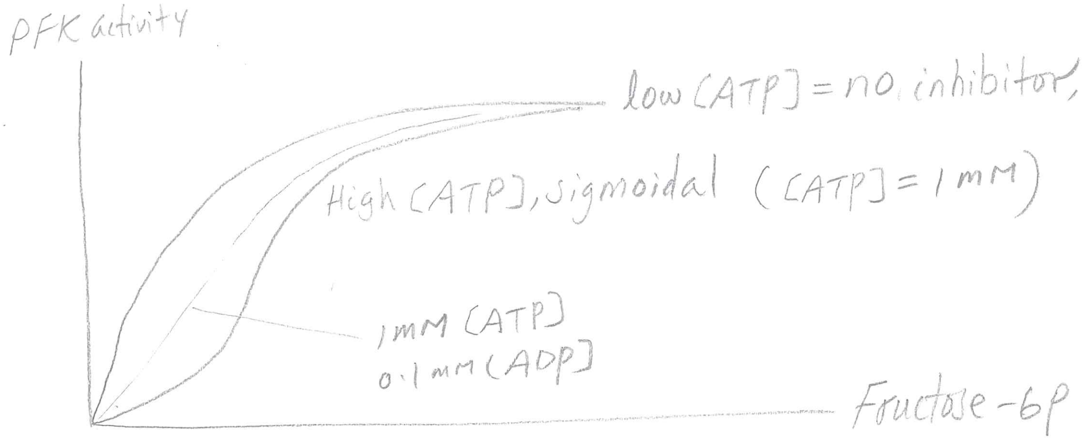


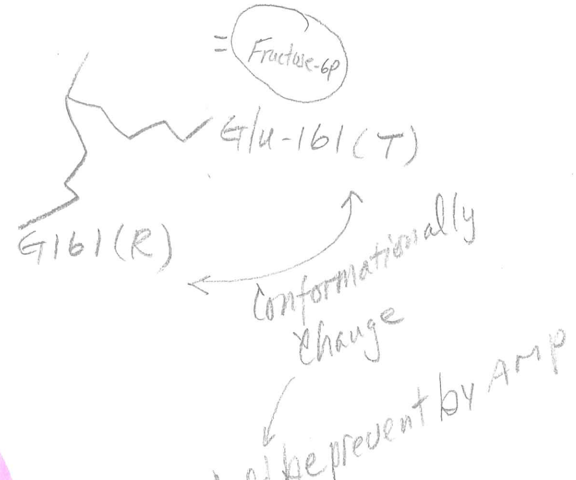
① pFK is tetramer, and have R state (active) and T state (inactive) in equilibrium

~~② Each pFK binds 2 ATP and Fructose-6p~~

② Each pFK has substrate binding site (bind 1^{st} ATP and Fructose-6p) and Inhibitor binding site (2^{nd} ATP)

③ when 2^{nd} ATP binds to pFK, a switch of R ⟶ T state

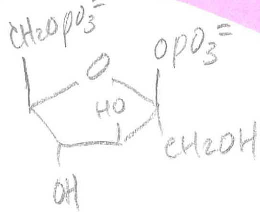




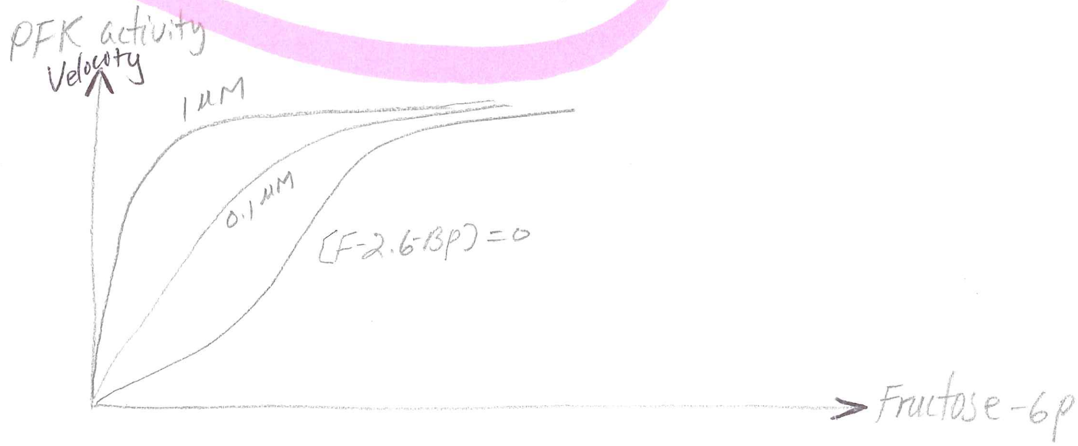
allosteric inhibitor: ATP
" activator: AMP

$\frac{[ATP]}{[AMP]}$

Another activator:



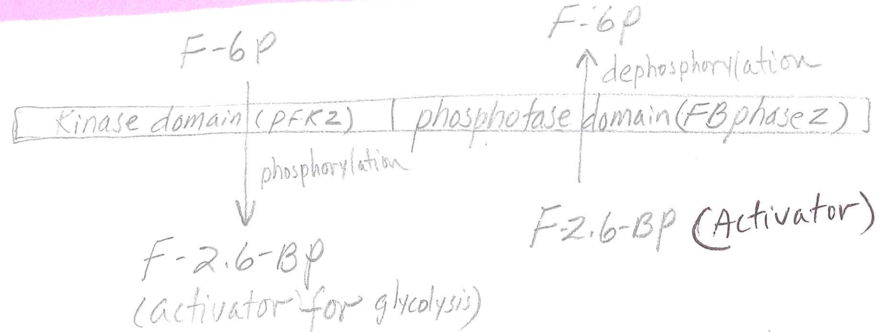
Fructose-2,6-BP



Glycolysi's process

Glucose → → Fructose-6p —phosphofructose kinase→ Fructose-1,6-Bp → → pyruvate
Inhibitor: ATP, citrate
Activator: AMP, F2-6BP
+2ATP
+2NADH

phosphofructosekinase 2: bifunctional enzyme



(Activator) F6P $\underset{\text{FBphase2}}{\overset{\text{PFK2}}{\rightleftharpoons}}$ F-2,6-BP

Summary (Maintenance of blood glucose level)

1. when glucose is scarce in cell enviroment (blood [glucose] is too low)

⇓

hungry signal, Glucagon will bind to 7TM receptor

⇓

Gαβγ dissociate to Gα(GDP)

⇓

Gα(GTP)

⇓

bind to Adenylate cyclase

⇓

cAMP

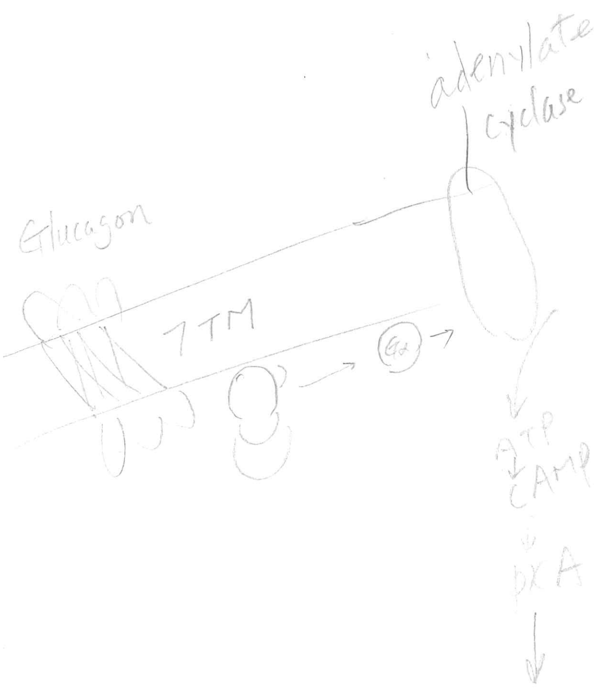
⇓

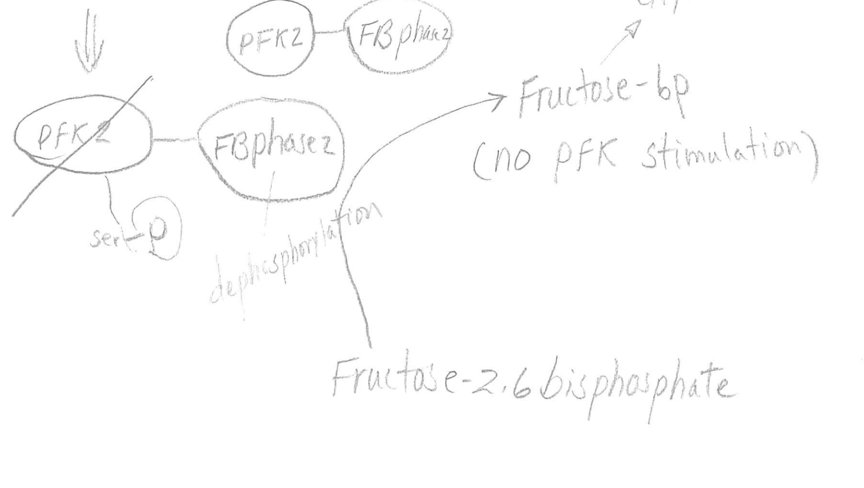
pKA

⇓

phosphorylate phosphofructosekinase 2

⇓





2. **When Glucose is abundant in cell** (blood [Glucose] is too high)

↓

PFK2 — ~~FBphase~~

activate

↓ phosphorylation

Fructose-6p ⟶ Fructose-2.6-Bp
(stimulate pFK)

↓

speed up Glycolysis

↓

[Glucose] ↓

Other tightly control

phosphofructoKinase unactive

↓

[Fructose-6p] ↑

↓

[Glucose-6p] ↑

↓

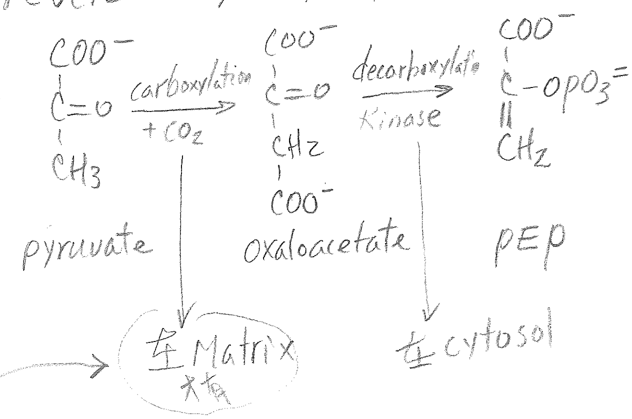
Inhibit hexoKinase

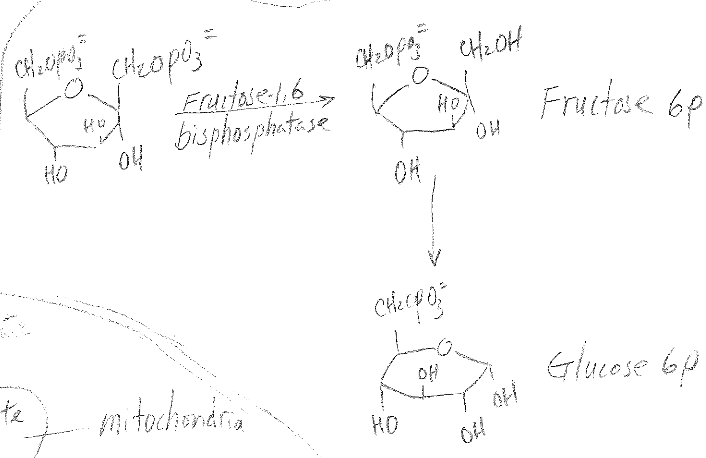
Gluconeogenesis (pyruvate → Glucose)

1. Brain and red blood cell use glucose as the only fuel
2. 每天消耗 160 gram of glucose. 其中 120 gram 用在 brain 上
3. 体液中含有 20 gram 的 glucose
   另有 190 gram 可用 glycogen 提供
4. liver (Kidney) 為主要進行 gluconeogenesis 的器官, 供给 brain 使用

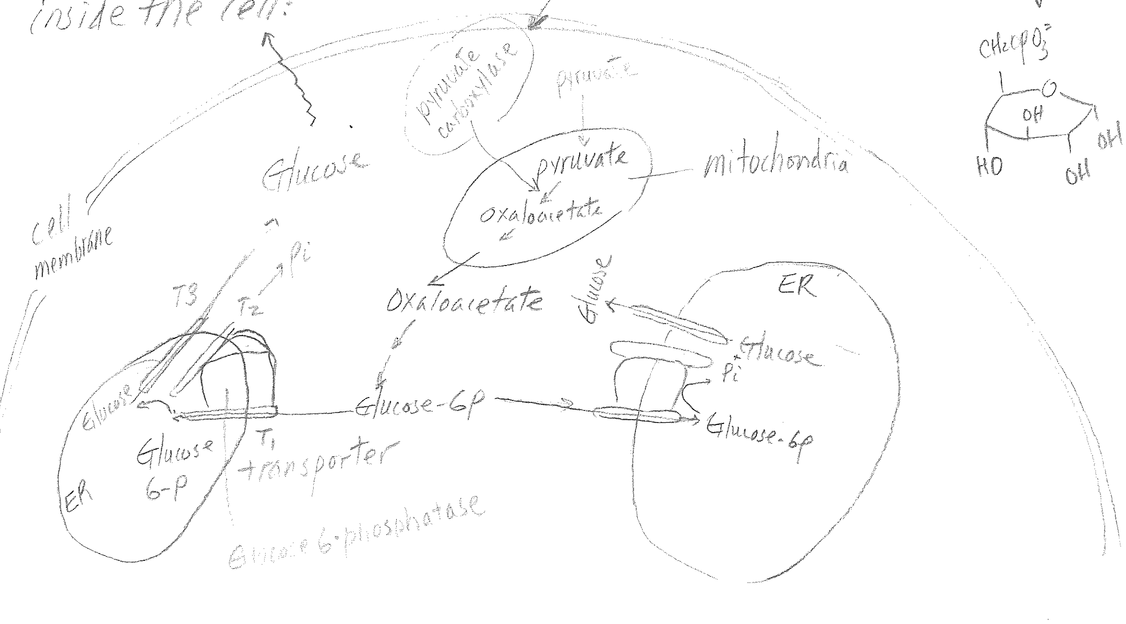
Gluconeogenesis is not a reversal of Glycolysis in 3 steps:

1. pyruvate Kinase →
2. phosphofructoKinase
3. hexoKinase

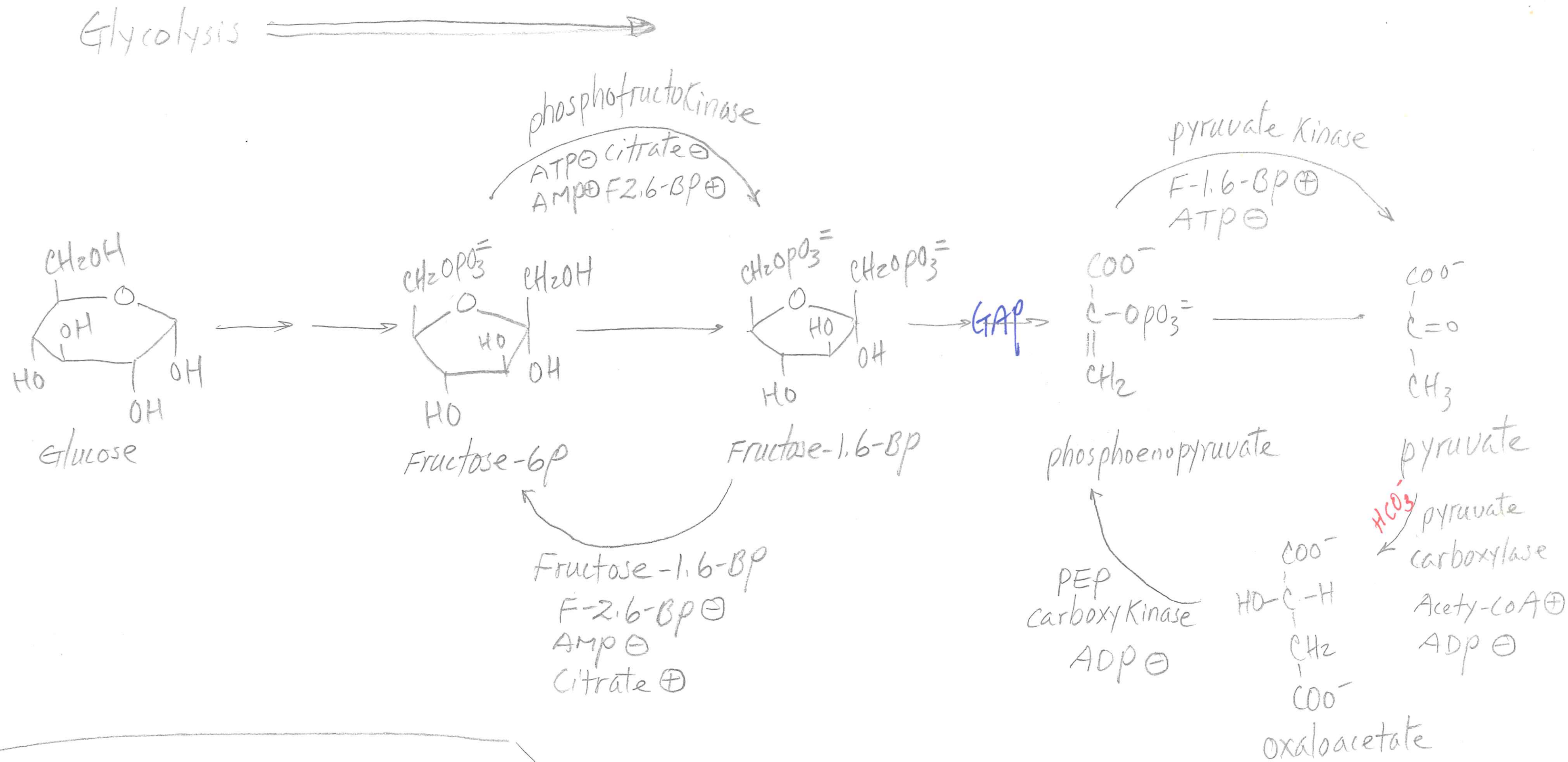




Generation of free Glucose is controled: To Keep Glucose inside the cell:



Reciprocally regulation of Interconversion



Hormon effect

Fed state
⇓
[Insuline]↑
⇓
[phosphofructoseKinase]↑
[pyruvate Kinase]↑
[F-2,6-BP]↑
⇓
Glycolysis

Starvation
⇓
[Glucagen]↑
⇓
[phosphoenopyruvate carboxylase]↑
[Fructose-1,6-BP]↑
⇓
Gluconeogenesis

Lactate form by contracting muscle

1. skeletal muscle —vigorous exercing→ Glucose —(2ADP → 2ATP; NAD^+ → NADH)→ pyruvate accumulated → TCA (mitochondria)

① 生產太快，來不及 TCA
② erythrocyte 沒 mitochondria
③ NAD^+ 耗盡

pyruvate —(NADH → NAD^+)→ Lactate

COO
|
HO-C-H
|
CH_3
Lactate

Lactate —blood→ Well-oxygenated cell (cardiac muscle) → pyruvate → TCA

Lactate —blood→ liver cell for gluconeogenesis → pyruvate → Glucose

Cori cycle