Session 21 - Regulation of Metabolism

A

-- To now, 5.07 has been at the molecule to cell level

-- Now we consider cell to organ and organ to organism levels

Pathways (and sites of regulation)

B

1.) Glycolysis
(GK / HK, PFK-1 / F16BPase, PK)

2.) TCA
(PDH; all steps that make NADH)

3.) GNG
(PC, F16BPase via F2,6BP, GS / GP)

4.) FA Catabolism
(MalCoA ⊣ CAT-I)

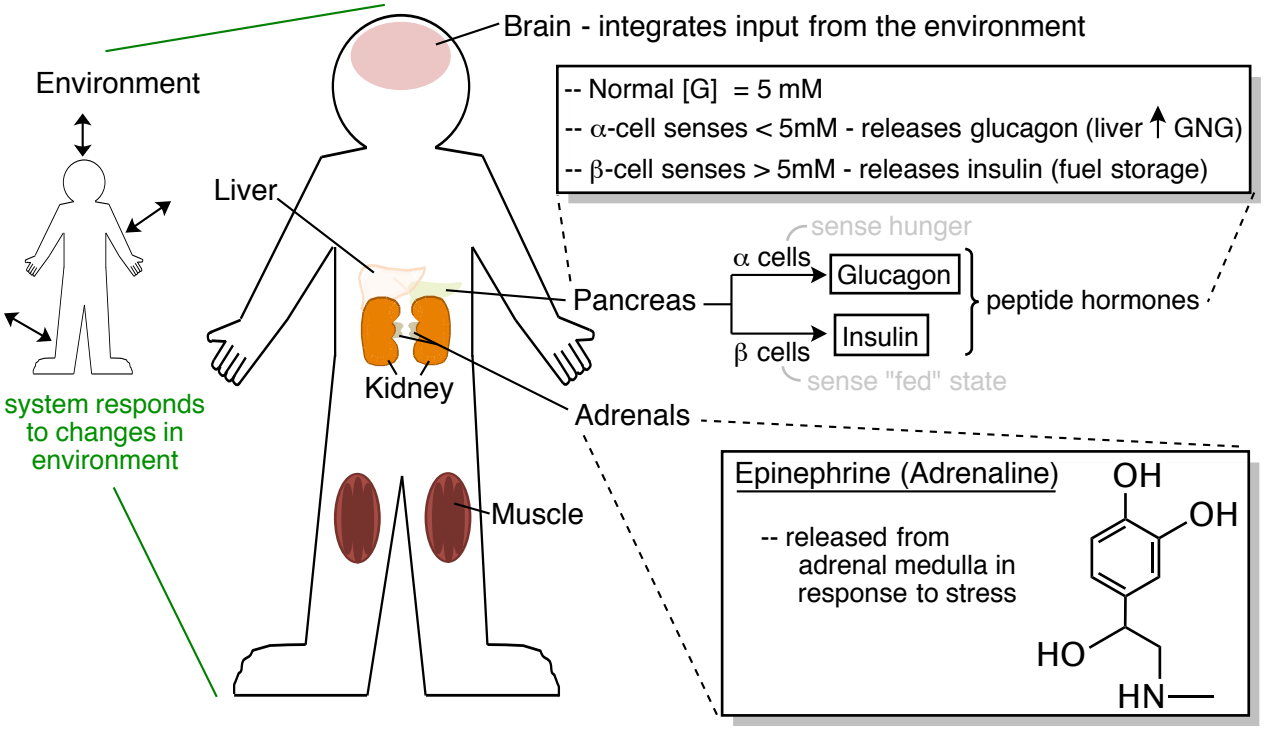
5.) FA Biosynthesis
(ACC activated by Insulin)

6.) PPP
(G6PDH stimulated by $NADP^{\oplus}$)

7.) ET/Oxidative Phosphorylation
(ADP [↑] needed for $H^{\oplus}$ flow; NADH or $FADH_2$ needed for $e^{\ominus}$ flow to oxygen)

Key organ systems and hormones

C



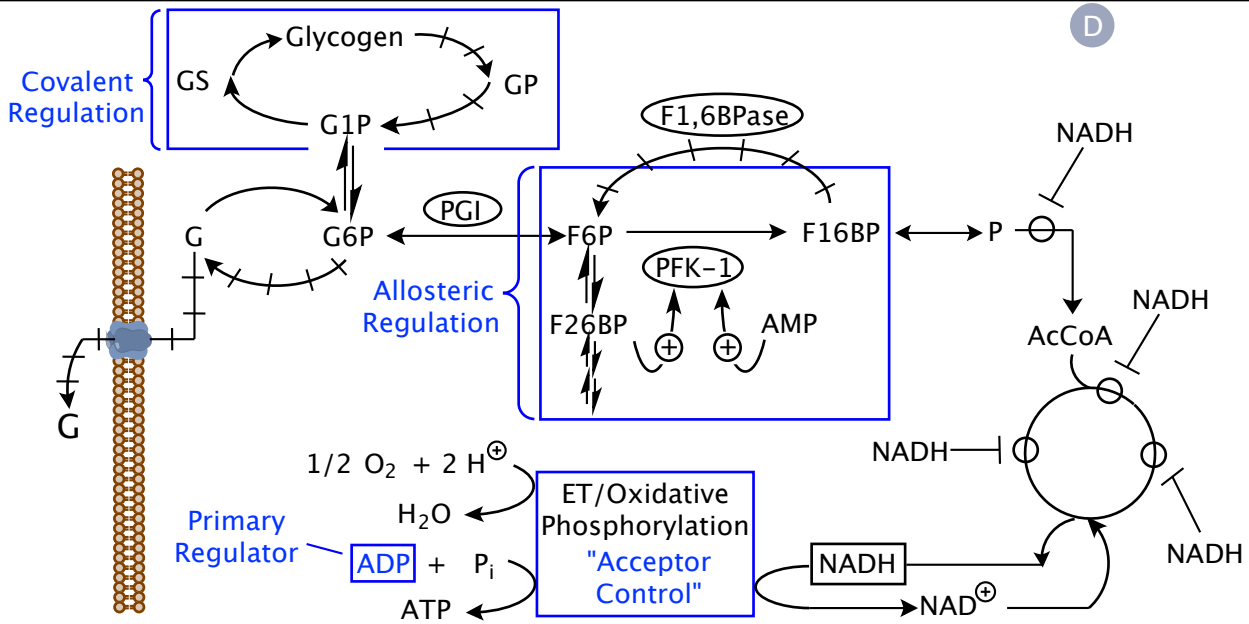
General Paradigms of Pathway Control

1.) Covalent ("Hormonal") Control
- covalent modification of enzyme affects activity
- e.g., as we saw with GP in session 8

2.) Allosteric Control
- model = Hemoglobin
- others: PFK-1 very sensitive to [AMP] (AMP ↑ activity) as well as F26BP

3.) "Acceptor Control"
- ADP = "Acceptor" of P_i in ET/Oxidative Phosphorylation
- we already covered this in detail

D



Paradigm I: Covalent Control

(A)

GS / GP Regulation = Primarily by covalent post-translational modification of the enzymes

GS—OP	inactive	Prevents "futile cycling"
GP—OP	active	

Scenario = Stress

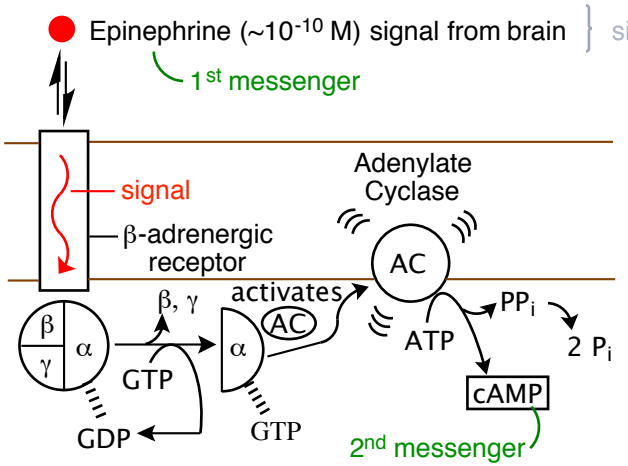
-- Liver (makes and stores fuel)
- instructed to liberate G from glycogen (G → other organs)

-- Muscle (run away or otherwise deal with stress)
- instructed to absorb glucose and liberate G from glycogen for local (in-muscle) use by glycolysis

Muscle or Liver Cell - Top part of pathway is similar

(B)

A.) Primary messenger (Epinephrine) to secondary messender (cAMP) ✻



1.) Hormone ⇌ β-adrenergic receptor
- signal transduced to G-protein

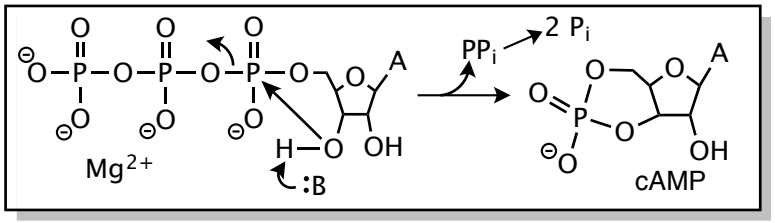
2.) α subunit released
- It is replaced by GTP
- It is now "active"

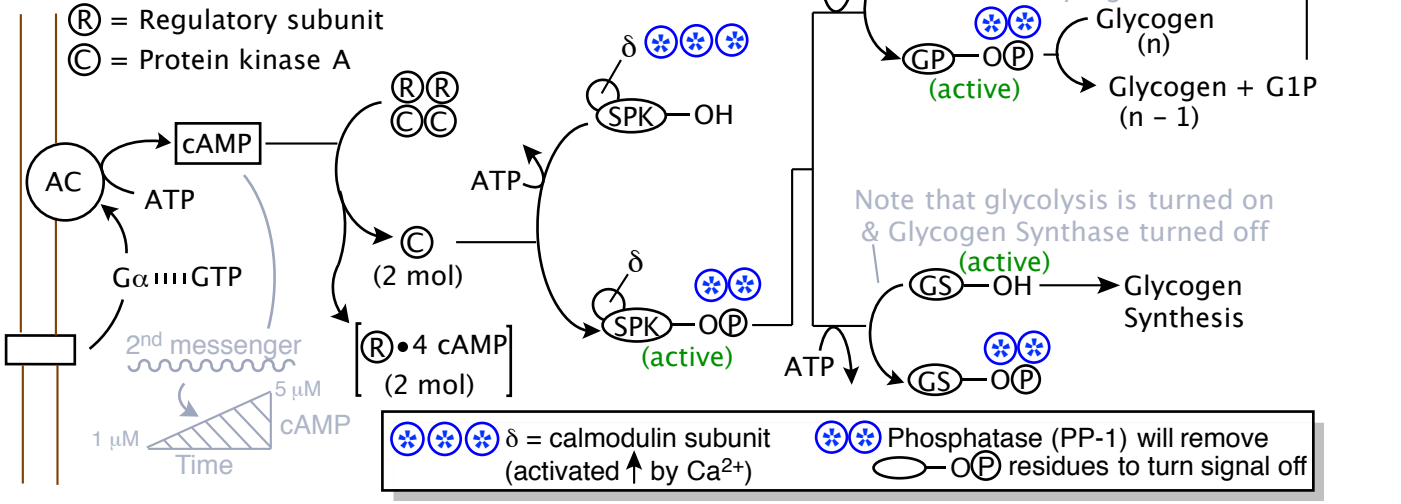
3.) α-GTP activates AC

4.) AC makes cAMP (second messenger)

✻ Glycogen (senses hunger) will do pretty much the same thing

B.) Second messenger initiates a "Kinase Cascade"





(C)

1.) Ⓒ ≡ cAMP dependent protein kinase ≡ PK-A
- It is inhibited by Ⓡ (its regulatory protein)

2.) PK-A phosphorylates SPK
SPK ≡ Synthase-phosphorylase kinase
(Synthase = GS; Phosphorylase = GP)

3.) SPK—OP = active kinase

4.) In liver - glycogen → G → other organs

5.) In muscle - use G for energy (run away from stressor)

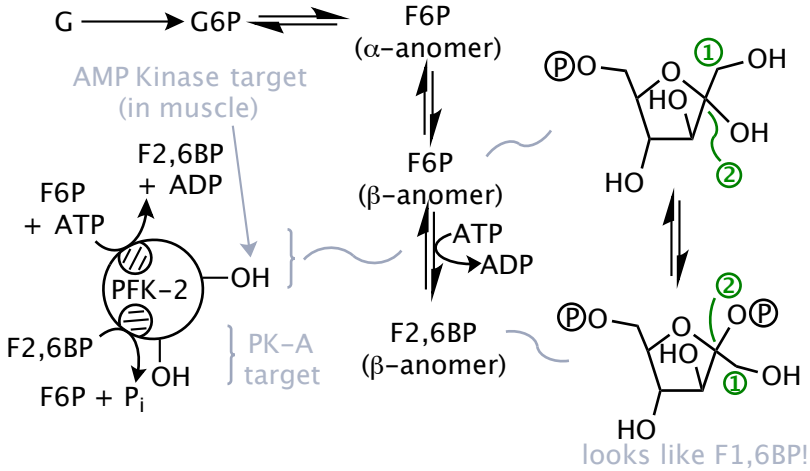
Paradigm II: Allostery (mostly)

A

PFK-1 / F16BPase Regulation = Primarily by small molecule allosteric effector (or competitive inhibitor)

-- F2,6BP = primary effector of glycolysis/GNG (AMP also has an effect)

-- Made by PFK-2 ≡ Complicated enzyme

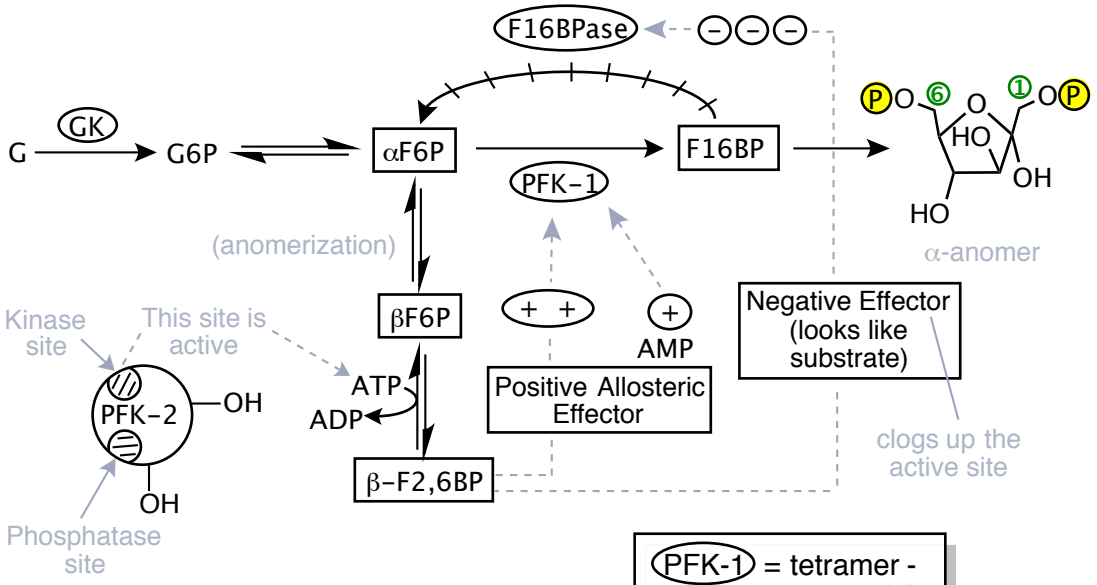


Scenario 1 (Liver, pre-stress state)

B

-- Net flux favors Glycolysis

Glycolysis ~ Net Flux



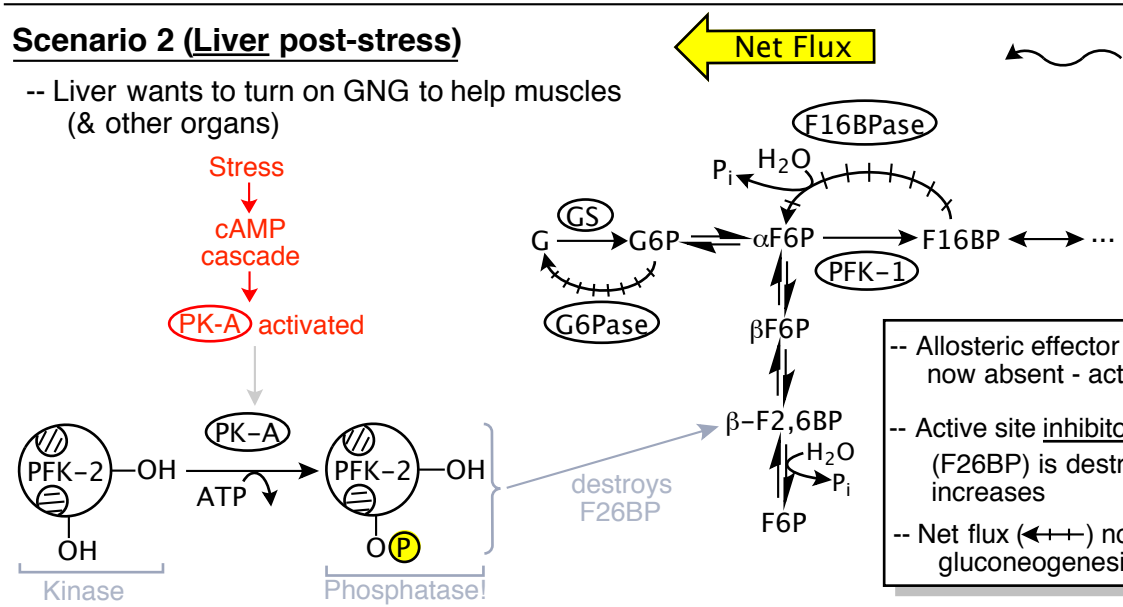
PFK-1 = tetramer - suggests cooperativity

Scenario 2 (Liver post-stress)

C

-- Liver wants to turn on GNG to help muscles (& other organs)

Net Flux ~ GNG



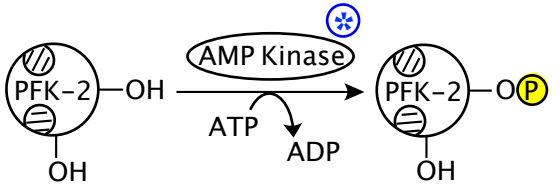
-- Allosteric effector of PFK-1 is now absent - activity drops

-- Active site inhibitor of F16BPase (F26BP) is destroyed - activity increases

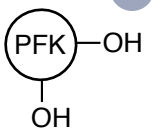
-- Net flux (←+→) now favors gluconeogenesis

Scenario 3 (Muscle post-stress)

D



This PFK does the same thing as in Panel A



but it is more active.

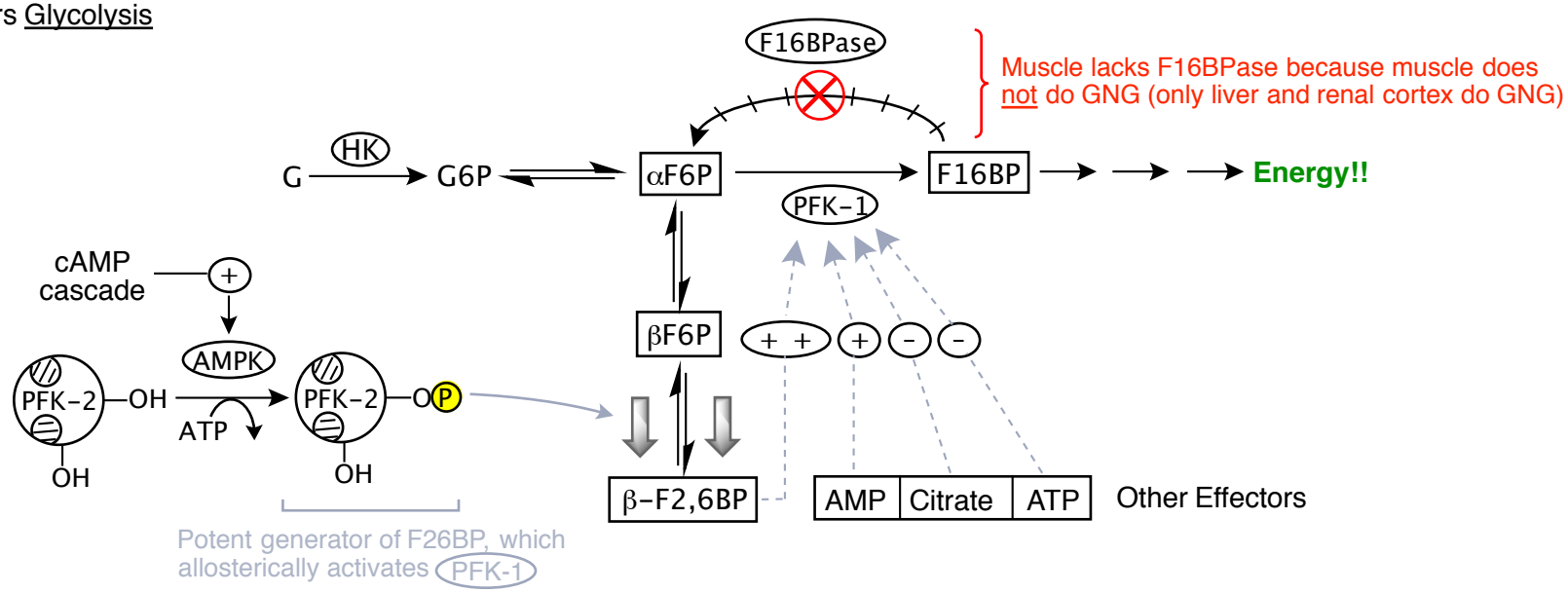
AMPK = energy sensing kinase

Scenario 3 (Muscle post-stress) - continued

Glycolysis ~~> Net Flux

A

-- favors Glycolysis



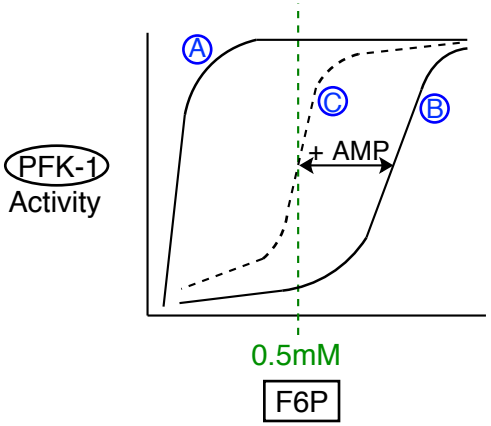
B

PFK-1

-- PFK-1 is a tetramer, is subject to allosteric regulation, as well as covalent regulation

-- PFK-1 = tetramer ⟹ cooperativity

-- A lot is known about its activity in presence of AMP (senses energy need) and ATP (energy surplus).

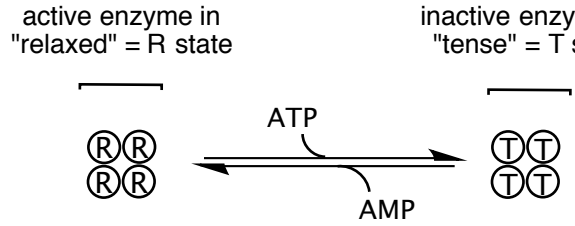


Ⓐ low or no ATP (not realistic)

Ⓑ 1mM ATP (typical = 1-10 mM)

Ⓒ condition Ⓑ plus 0.1mM AMP

C



-- AMP (allosteric activator) binds better to Ⓡ than to Ⓣ

-- Shifts ⇌ to more active protein

-- ATP binds better to T state

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