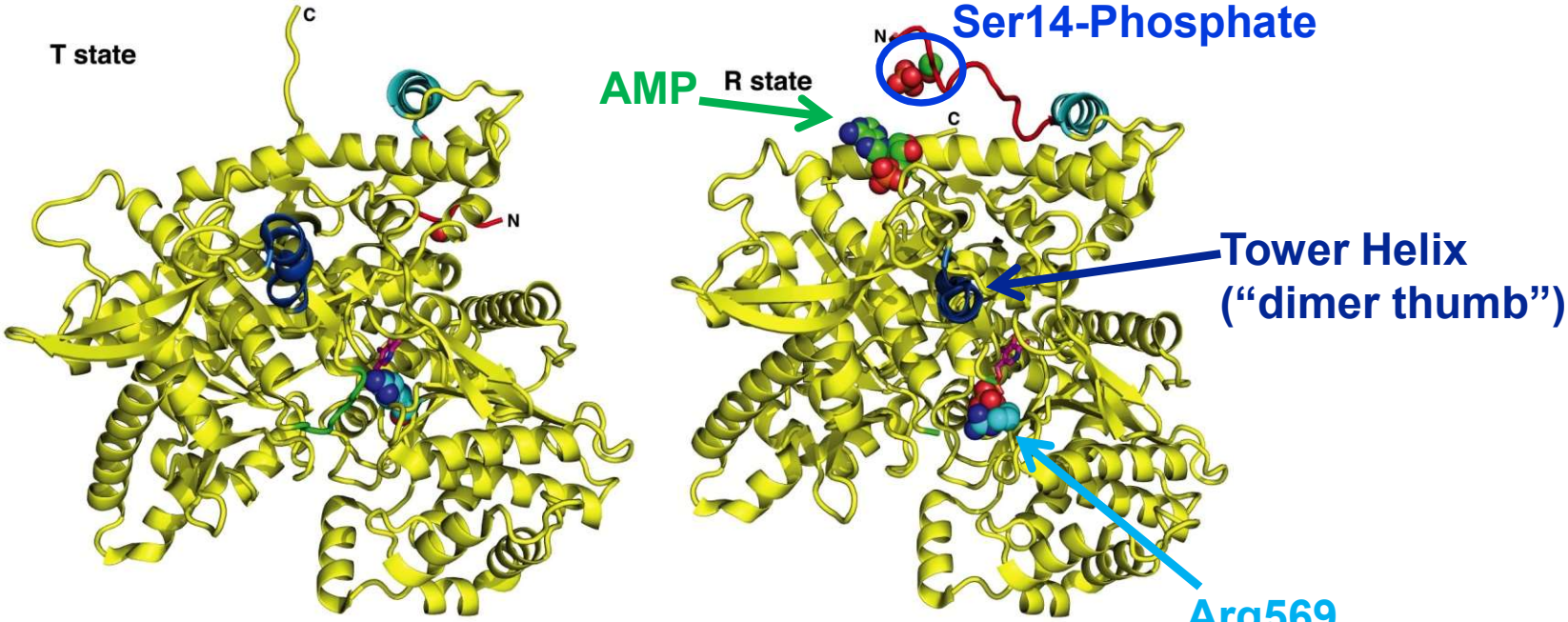
Control of Glycogen Metabolism is Tight



1.) Control by covalent modification (higher-level regulation)

2.) Direct allosteric control

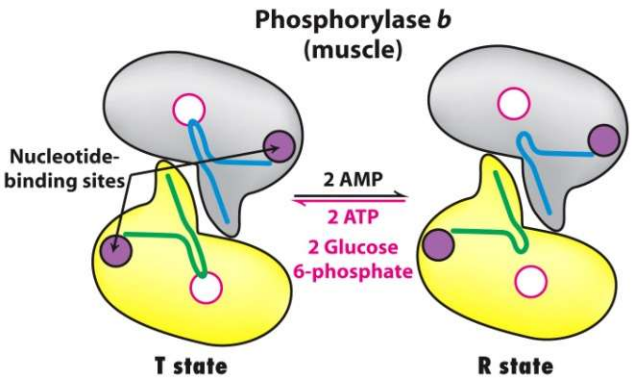


Figure 21.12
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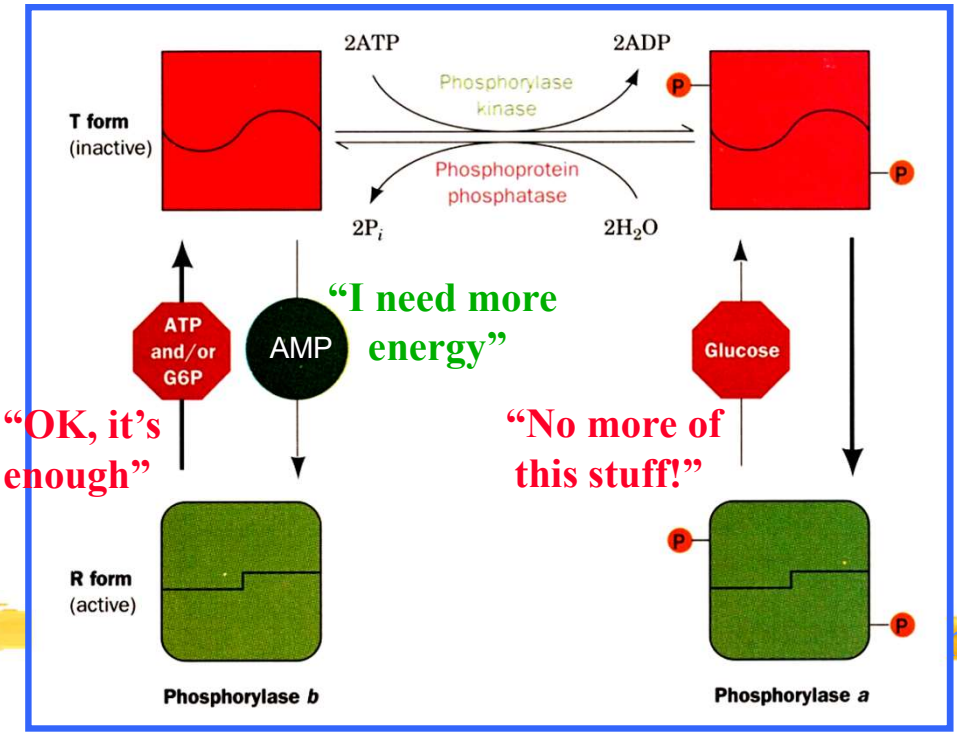
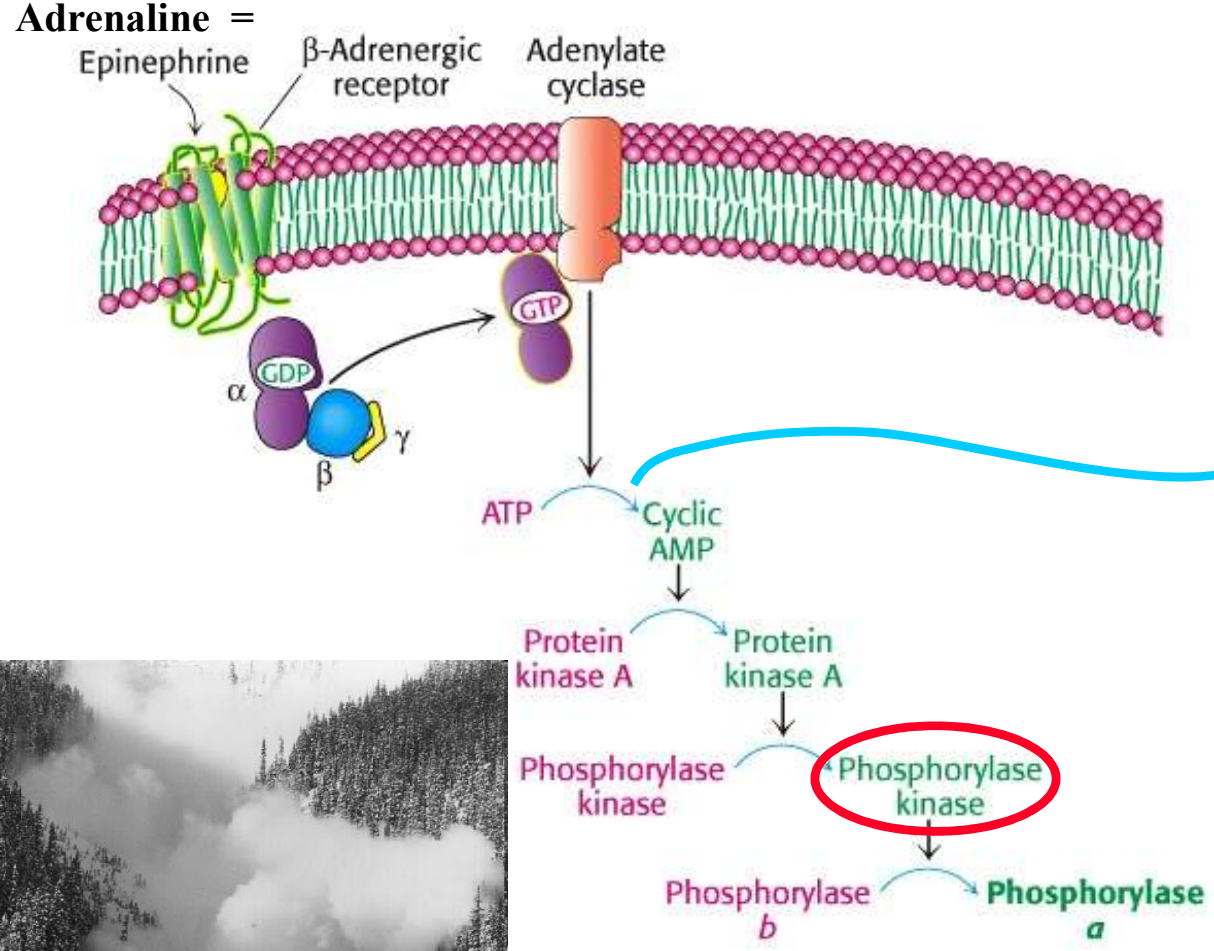
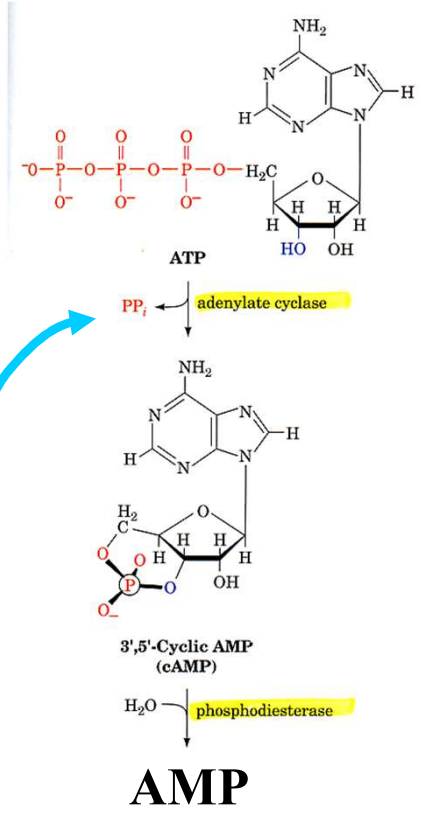


Glycogen Phosphorylase is the Target of a Cyclic Signaling Cascade

Adrenaline =



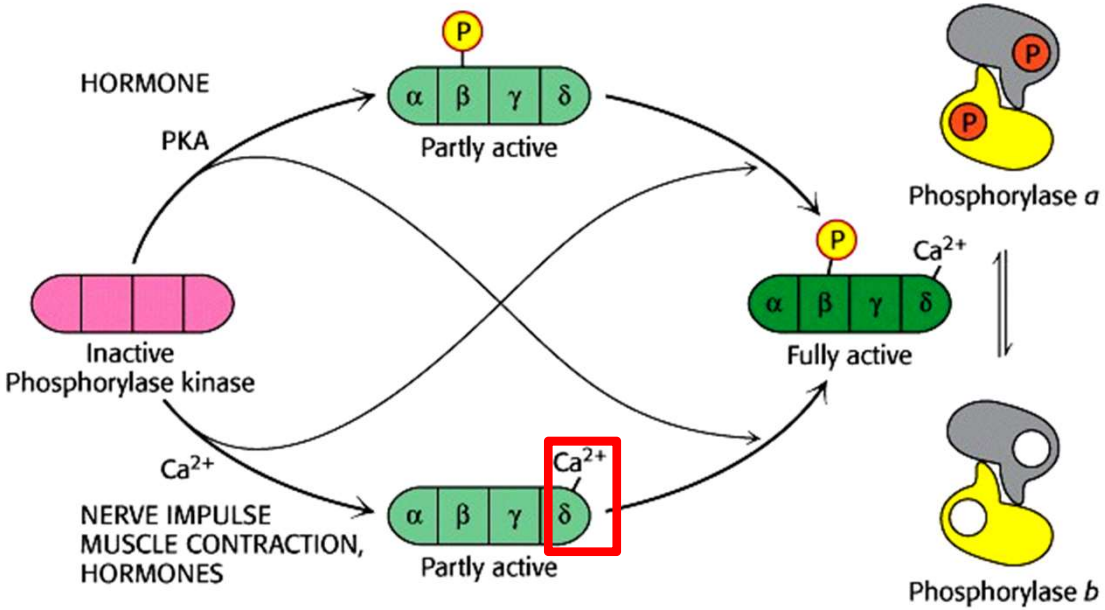


Advantages:

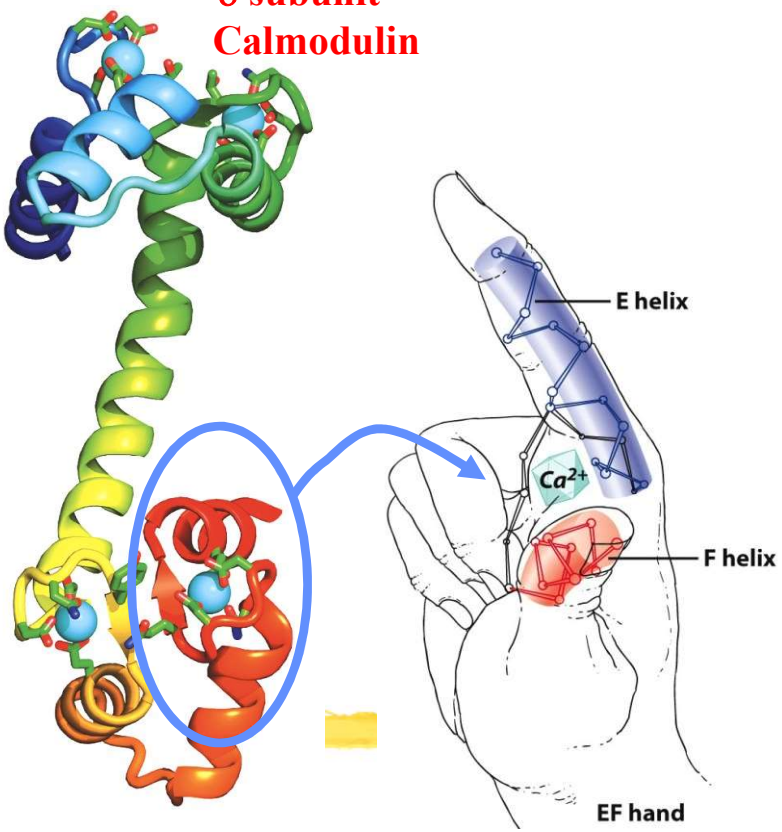
- Amplification
- More flexible control
- More allosteric stimuli possible

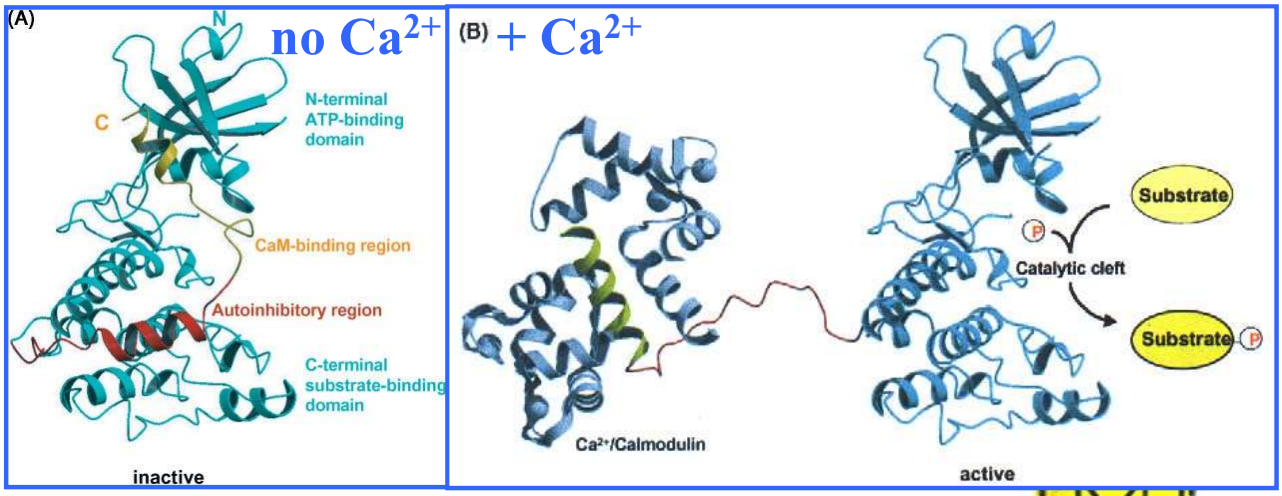
Phosphorylase Kinase is Controlled by Hormones and Ca^{2+}

- $(\alpha\beta\gamma\delta)_4$; 1,200 kD
- γ unit alone is fully active
- α, β, δ subunits regulate activity
- β subunit can be phosphorylated
- δ subunit binds Ca^{2+} at 0.1 μM

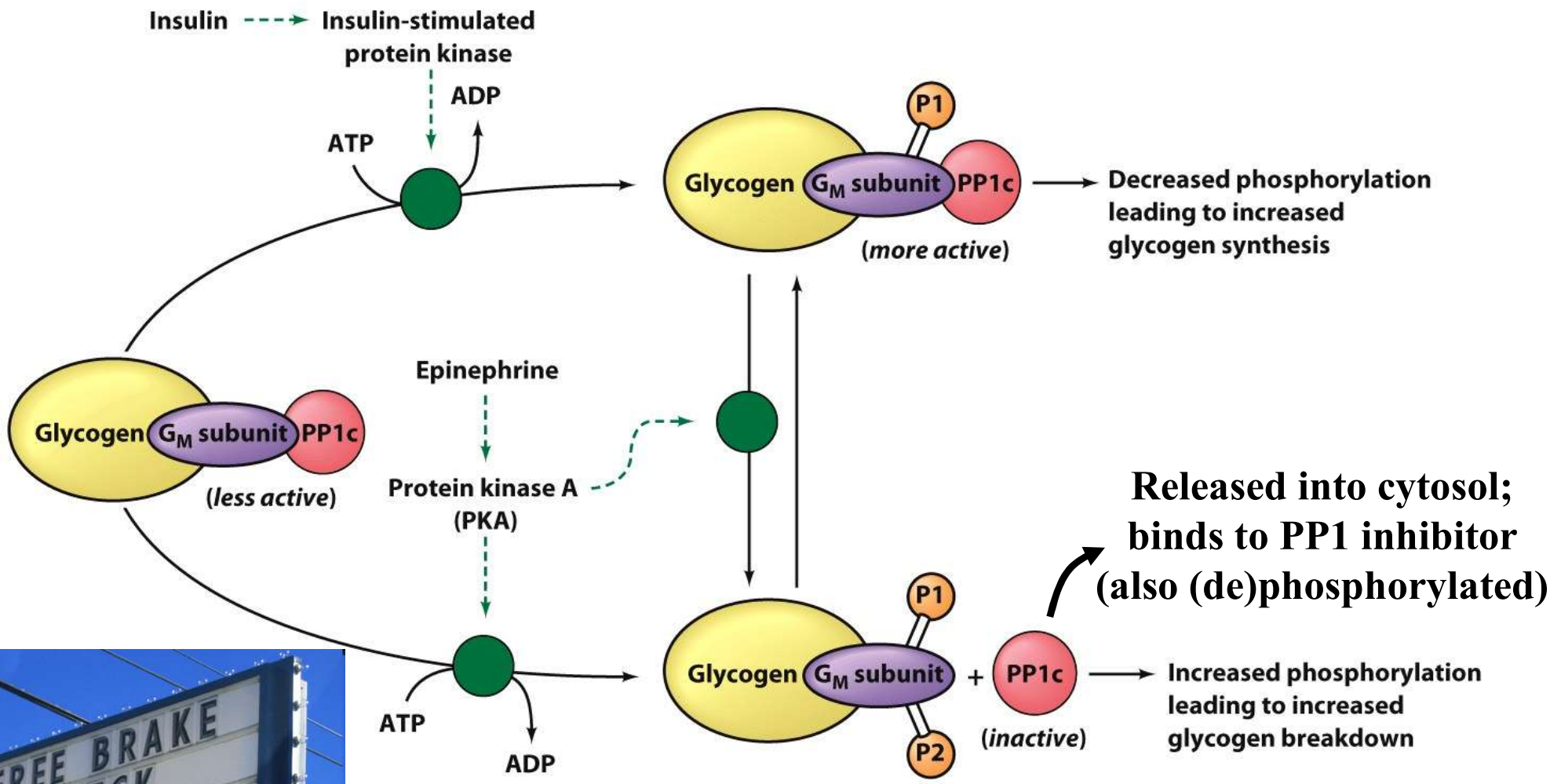


δ subunit = Calmodulin



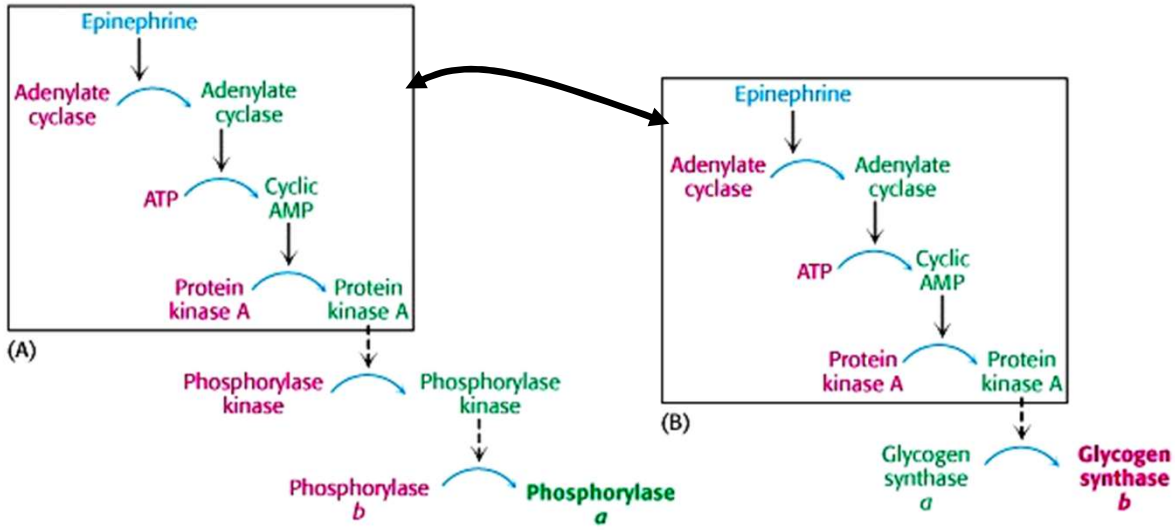


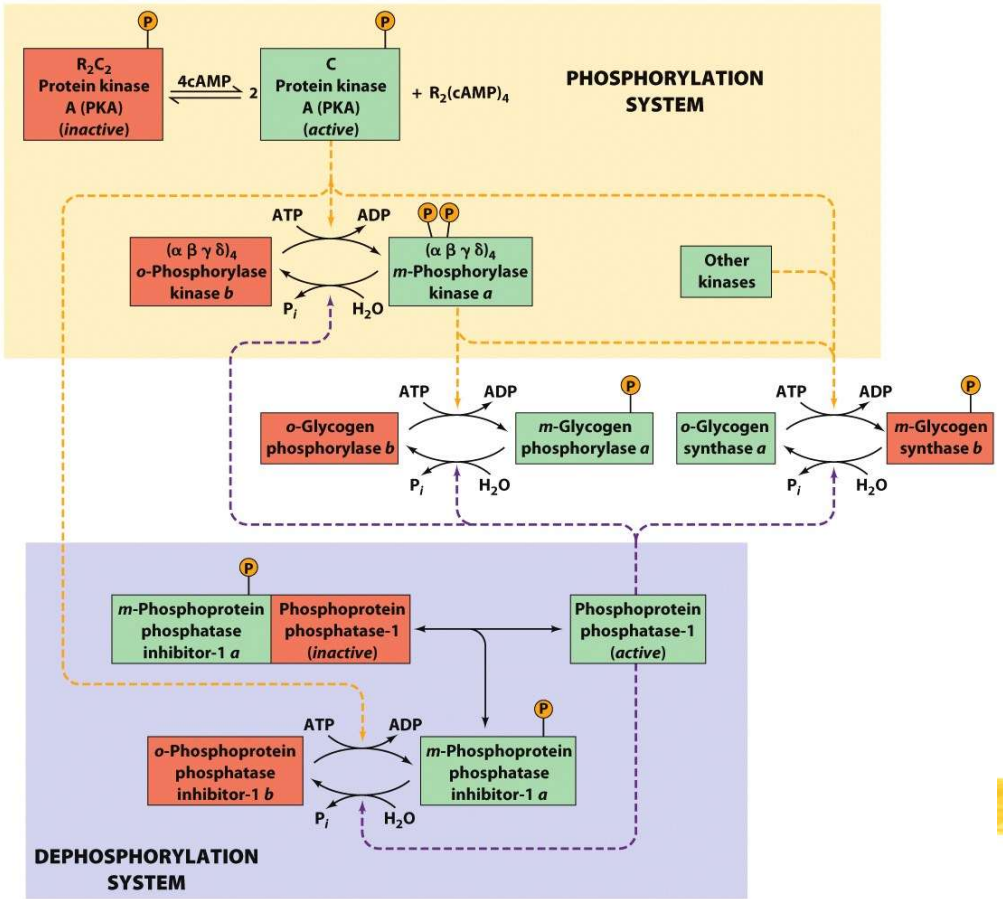
How Can the Cascade be Stopped? With Phosphoprotein Phosphatase 1 (PP1)!



And Glycogen Breakdown and Synthesis are Reciprocally Regulated!

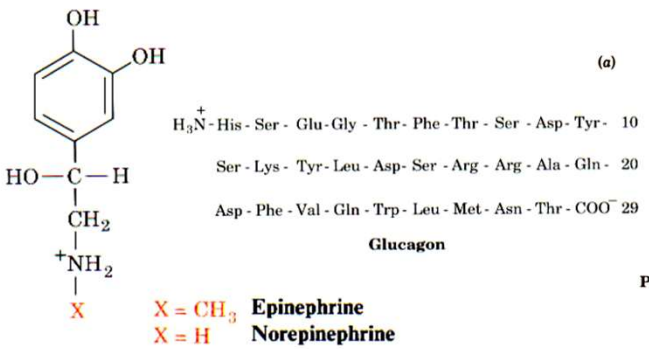
red = inactive
green = active





⇒ **Whether there is net synthesis or degradation of glycogen depends on the relative balance between the active forms of glycogen synthase and phosphorylase and, therefore, on the rates of (de)phosphorylation in the cyclic cascades**

Liver: Guardian of Blood Glucose



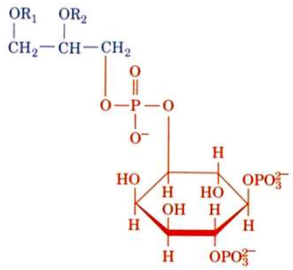
(a)

$H_3\overset{+}{N}$-His-Ser-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Tyr- 10

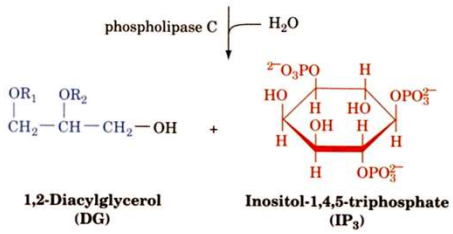
Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln- 20

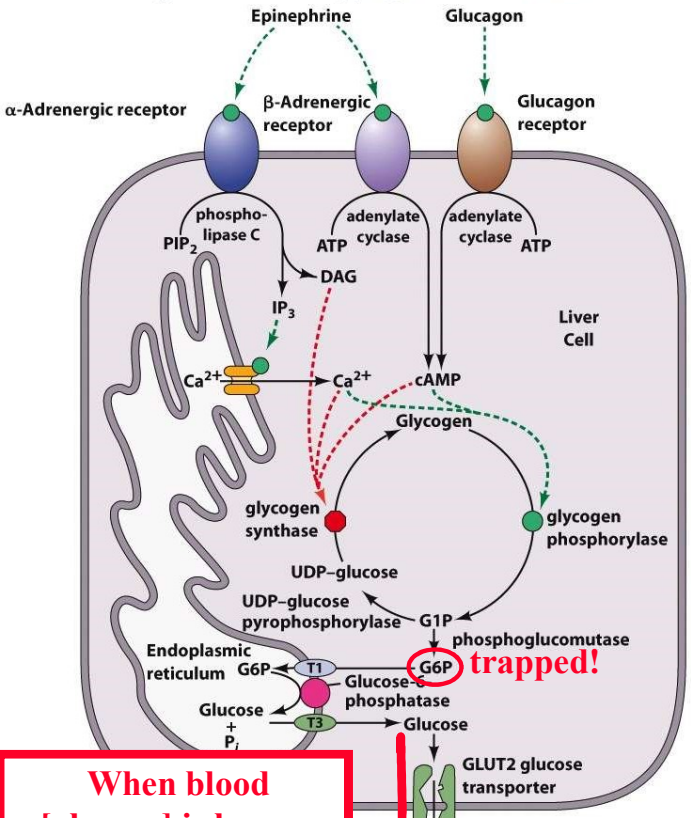
Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr-COO^- 29

Glucagon



Phosphatidylinositol-4,5-bisphosphate (PIP_2)

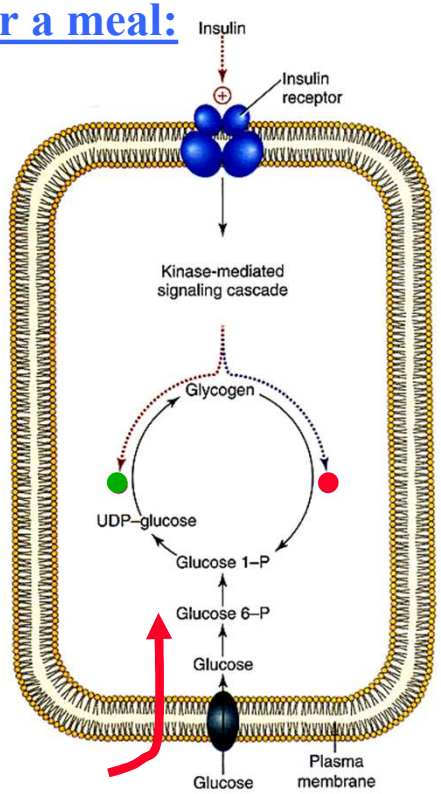


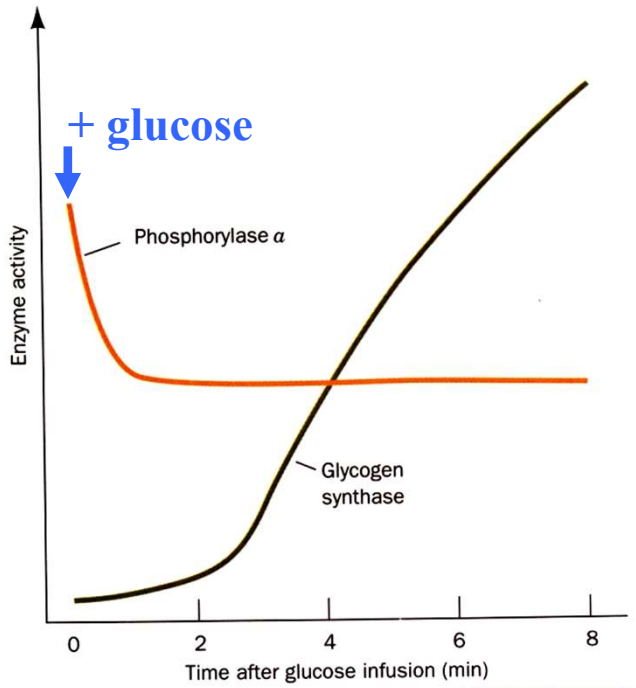


When blood [glucose] is low or under stress ("fight or flight") ⇒ more glucose exported

These hormone-induced enzyme cascades allow fast adjustments and a fine regulation! Important to keep brain happy!

After a meal:



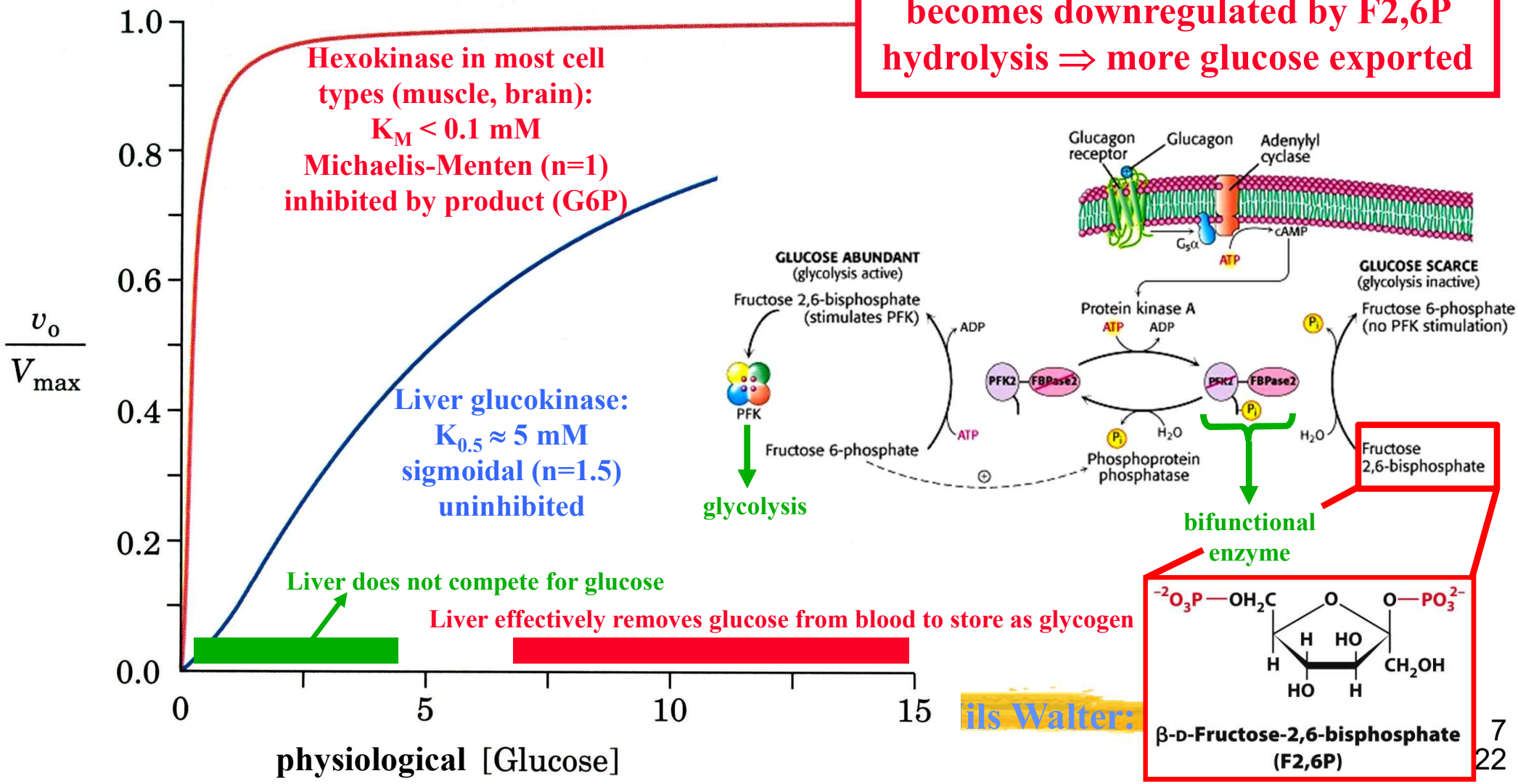


⇒ Fast removal of glucose from blood after a meal

But Wait: How Does This Work so that the Liver Does Not Gobble Up all Glucose?

Trick 1: Liver traps glucose for glycogen synthesis and glycolysis only when abundant

Trick 2: When blood [glucose] low (glucagon!), glycolysis in the liver becomes downregulated by F2,6P hydrolysis ⇒ more glucose exported



ils Walter: