16

Sheet Slides

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ALL THE FIGUERS IN THIS SHEET ARE VERY IMPORTANT AND USEFUL , PLEASE DON'T SKIP THEM.

Glycogen phosphorylase kinase = GPK // glycogen phosphorylase=GP // glycogen synthase = GS

We will talk about regulations of glycogenesis and glycogenolysis .

We have two ways in order to regulate :

1- covalent regulation " adding phosphate group and remove it " page : 1-3

2- allosteric regulation " glucose-6-phosphate/ATP/glucose/AMP/Ca " page : 4-6

-Glycogen is fond in both : liver and muscles

-Glycogen in liver is used to maintain blood sugar concentration

-Glycogen in muscle is used to provide the muscle with energy if needed

1- The covalent regulation " phosphate is the KEY " ((((IN LIVER)))

Fasting state

-In the fasting state :Low concentration sugar in the blood → glucose conc. Is low → glycogenolysis must start in order to produce glucose from the glycogen , HOW ?

1-when blood sugar concentration is low , glucagon "from ALPHA-cells of pancreas " and epinephrine "from renal " will be secreted

2-both glucagon and epinephrine work on G-protein coupled receptor (GPCR) , so when glucagon/epinephrine bind to the receptor the ALFA subunit will be released , which will activate the adenylyl cyclase .

3- adenylyl cyclase will convert ATP to cAMP , binding of 4 cAMP to the regulatory subunit of protein kinase A (PKA) ,will cause releasing of the two catalytic subunit of the PKA .

4-Now the PKA is activated

++LETS BUILD THE BASE ++

	Enzyme +phosphate	Enzyme - phosphate
Glycogen Phosphorylase kinase "GPK"	active	Inactive
Glycogen phosphorylase "GP"	active	inactive
Glycogen synthase "GS"	inactive	Active

Q1 : when does PKA get activated ? in the fasting state → low concentration of glucose → release glucagon

Q2 : what is the function of PKA ? add phosphate group to :

A- GPK and make it active.

B- GS and make it inactive

Q3 : what is the function of GPK ? add phosphate group to GP and make it active

Q4 : what is the function of GP ? glycogenolysis "produce glucose from glycogen"

-When 4 cAMP bind to the regulatory subunit of PKA , the 2 catalytic subunit will be released , The 2 catalytic subunit will add phosphate group to GPK therefore activate it .

GPK will add phosphate group to GP therefore activate it . GP will start the glycogenolysis

-Recall :

1- phosphodiesterase convert cAMP to 5-AMP , so when this conversion happen , PKA wont stay active → GP will not stay active → glycogenolysis will stop . (Insulin activates phosphodiesterase)

2-caffeine which is found in coffee inhibit phosphodiesterase therefore cAMP will remain for longer duration → → → glycogenolysis will remain active too.

-Why the activations on GP happens in two steps , why GP isn't activated directly via the PKA ?

To amplify the effect of the hormonal signal ; a few hormone molecule binding to their GPCR result in a number of PKA molecules being activated that can each activate many GPK→many GP will be activated

Well-fed state

Well-fed state →high glucose conc.→pancreas will secrete insulin

Q1 : what is the function of protein phosphatase 1 (pp1) ? remove the phosphate group from GPK , GP, GS

Q2 : when does PP1 get activated ? well-fed state " insulin will activate it "

Q3 : what inactivate PP1 ? "Inhibitor proteins"

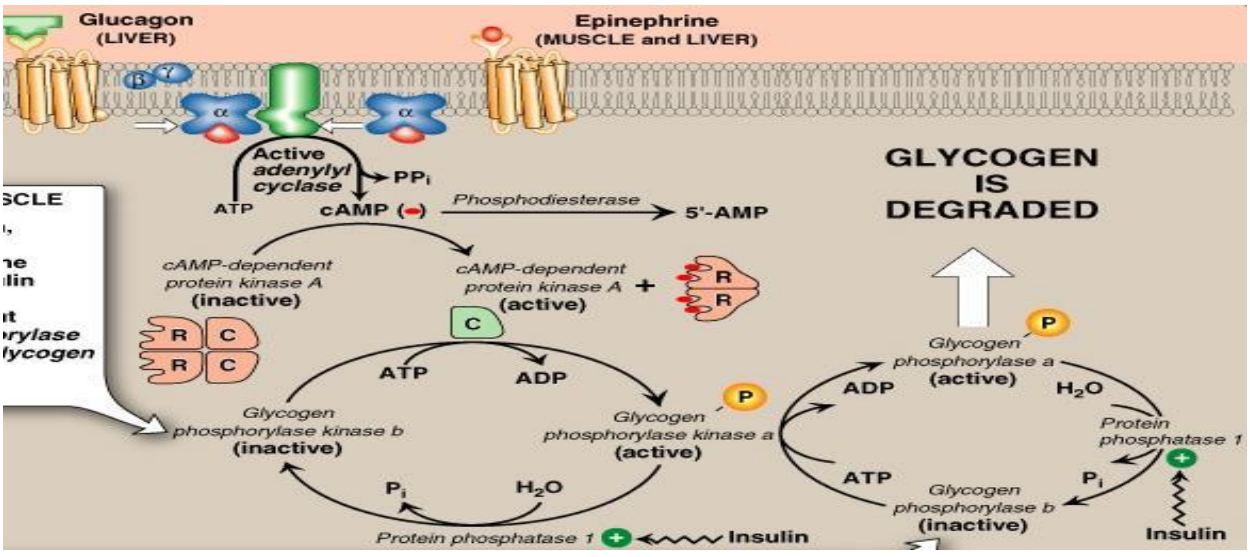
Q4 : when does inhibitor protein get activated in order to inhibit the pp1 ? when PKA is activated "fasting state ", PKA will add phosphate group to the inhibitor protein and make it active

PP1 in the fasting state will not be active , in the well-fed state will be active

Whats the function of PP1 ?

A- PP1 will remove the phosphate group from GPK and GP and make them inactive

B-PP1 will remove the phosphate group from GS and make it active , therefore , glycogenesis will start



2-allosteric regulation " glucose-6-phosphate/ATP/glucose/AMP/Ca "

A- Glucose-6-phosphate (((IN BOTH : LIVER AND MUSCLES)))

Recall : A state ---> ACTIVE STATE //// B state ---> inactive state

In the well-fed state , GS (B state) in both liver and muscles is allosterically activated(will be converted to the A state) by Glucose-6-phosphate , which is present in elevated concentrations

In contrast , GP (A state) is allosterically inhibited(will be converted to the B state) by glucose-6-phosphate

B- ATP(((IN BOTH : LIVER AND MUSCLES)))

SAME AS GLUCOSE-6-PHOSPHATE

C- Glucose (((IN LIVER)))

Free glucose is also an allosteric inhibitor of GP , HOW ?

Glucose will bind to GP , this binding will make GP more capable to bind to PP1 , and then PP1 will remove the phosphate group from GP and convert it to the inactive form "B state "

D-AMP (((IN MUSCLES)))

AMP concentrations that occur under extreme conditions of anoxia and ATP depletion will bind to GP (B state) , causing its activation (without phosphorylation)

Recall : AMP is strong activator of phosphofructokinase : This enzyme is used in the last step in this pathway (glycolysis) :

Glucose →glucose-6-phosphate→fructose-6-phospahte→fructose-1,6-bisphosphate

You can notice that glucose is needed in this pathway , so AMP will also activate GP which will produce the needed glucose from glycogen .

E – Ca (((IN MUSCLES)))

-Calmodulins are Ca binding family we will talk about 2 types :

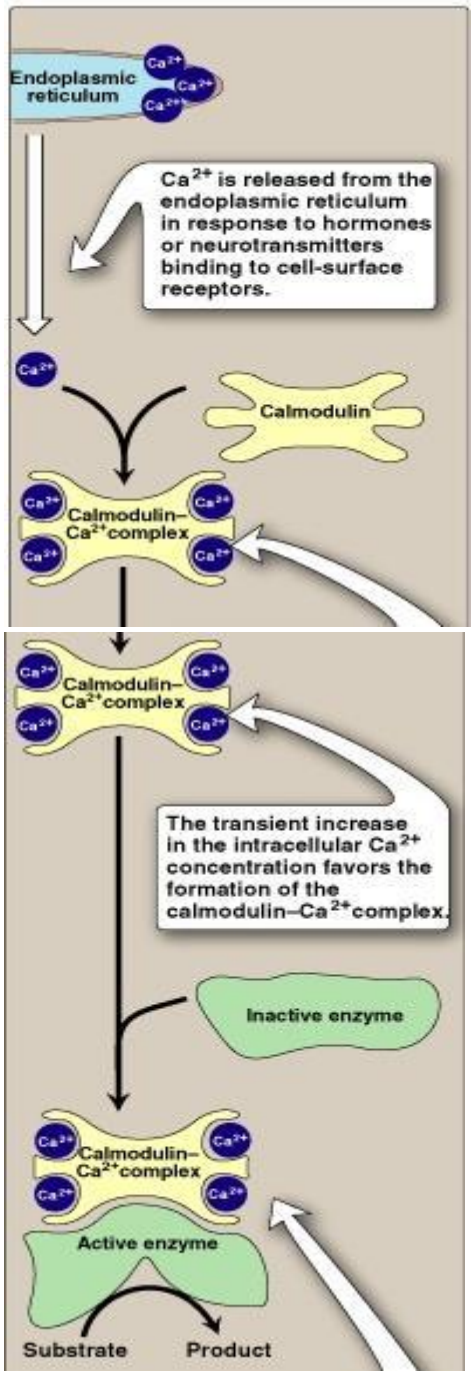
1- Calmodulin the BETA subunit of GPK (in muscles)

2- Ca^{+2}- Calmodulin complex (in liver) (discussed in page 6)

Note : you just have to know that ca^{+2}- calmodulin complex (in liver) is not a subunit of GPK , its just a complex simply ☺

-While HAMDAN is walking from AL-ENSANEYEH COMPLEX to AL-TEBBEYEH COMPLEX :

Ca ions will be released from the ER of HAMDAN'S myocytes , binding of 4 ca ions to the calmodulin (independent protein kinase) , will cause conformational change in the GPK therefore activation of the GPK
→ GP will be activated
→glycogenolysis will start



F – Ca (((IN Liver)))

1- epinephrine will bind to ALFA-agonist receptor , this receptor is also GPCR

2-The ALFA subunit of the GPCR will be released causing activation of phospholipase c

3- phospholipase c will hydrolyze a membrane lipid called PIP2

4- The PIP2 when is hydrolyzed will give : 1- DAG 2-IP3

-DAG :

A- DAG will activate protein kinase **C (PKC)**

2-PKC will add phosphate group to GS and inactivate it

-IP3 :

IP3 will bind to the ER causing release of Ca ions

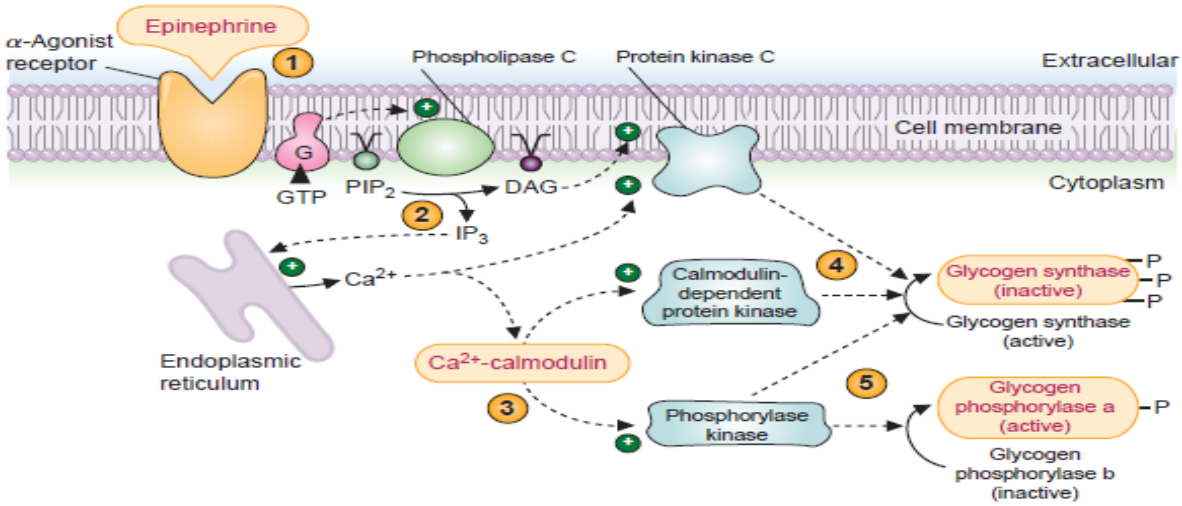
Ca will bind to :

1- Calmodulin : produce ca^{+2}- Calmodulin complex which activate :

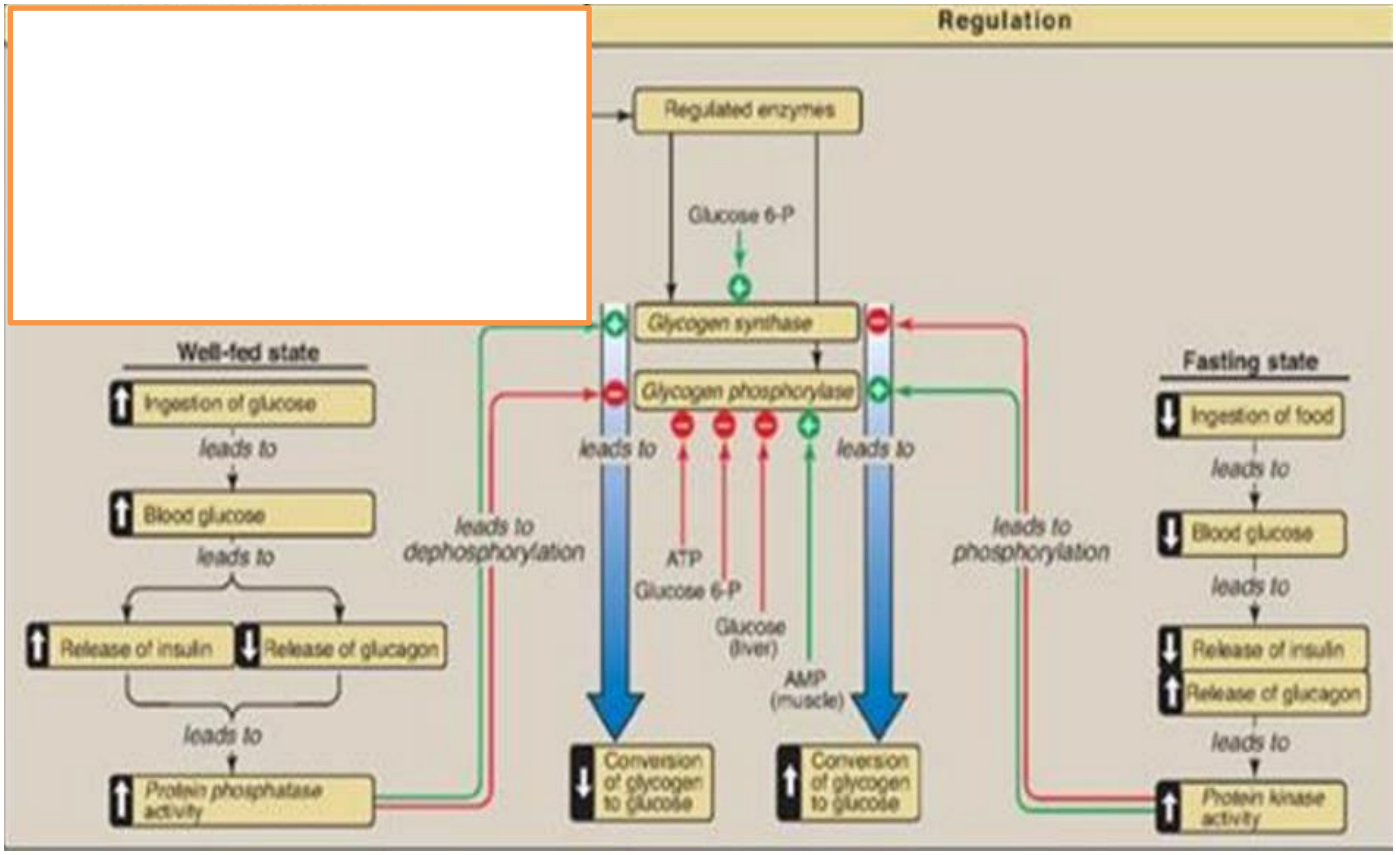
a. Calmodulin-dependent protein kinase which will add phosphate group to GS and inactivate it

B. Glycogen Phosphorylase Kinase which will add phosphate group to both : GP and GS . GP will be activated , GS will be inhibited

2- Protein kinase C : then PKC will add phosphate group to GS and inactivate it



VERY USEFUL SAMMARY



Alcohol metabolism

The doctor said that those 2 slides are enough , and they summarize what the doctor said in the lecture about Alcohol metabolism

(THOSE SLIDES ARE TAKEN FROM MARK'S BOOK)

Ethanol is a **dietary fuel** that is metabolized to acetate principally in the liver, with the generation of reduced nicotinamide adenine dinucleotide (NADH). The principal route for metabolism of ethanol is through hepatic **alcohol dehydrogenases**, which oxidize ethanol to **acetaldehyde** in the cytosol (Fig. 33.1). Acetaldehyde is further oxidized by **acetaldehyde dehydrogenases** to **acetate**, principally **in mitochondria**. Acetaldehyde, which is toxic, also may enter the blood. **NADH** produced by these reactions is used for adenosine triphosphate (ATP) generation through oxidative phosphorylation. Most of the acetate enters the blood and is taken up by skeletal muscles and other tissues, where it is activated to **acetyl coenzyme A** (**acetyl-CoA**) and is oxidized in the tricarboxylic acid (TCA) cycle.

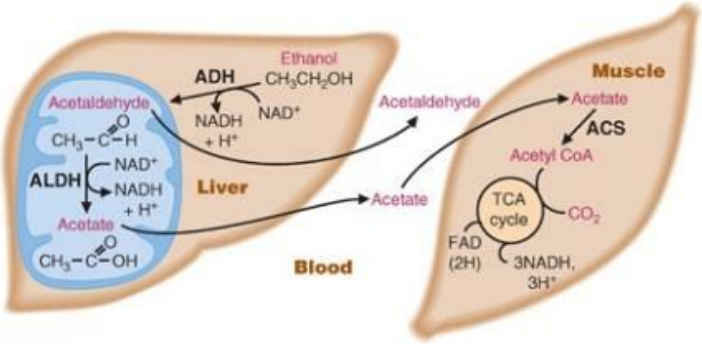


FIGURE 33.1 The major route for metabolism of ethanol and use of acetate by the muscle. *Acetyl CoA*, acetyl coenzyme A; *ADH*, alcohol dehydrogenase; *ALDH*, acetaldehyde dehydrogenase; *ACS*, acetyl coenzyme A synthetase; *NAD*, nicotinamide adenine dinucleotide; *FAD*, flavin adenine dinucleotide; *TCA*, tricarboxylic acid.

Approximately 10% to 20% of ingested ethanol is oxidized through a microsomal ethanol-oxidizing system (**MEOS**), comprising **cytochrome P450** enzymes in the endoplasmic reticulum (especially **CYP2E1**). CYP2E1 has a high K_m for ethanol and is inducible by ethanol. Therefore, the proportion of ethanol metabolized through this route is greater at high ethanol concentrations and greater after chronic consumption of ethanol.

Acute effects of alcohol ingestion arise principally from the generation of NADH, which greatly increases the **NADH/NAD**$^+$ ratio of the liver. As a consequence, **fatty acid oxidation is inhibited**, and **ketogenesis** may occur. The elevated **NADH/NAD**$^+$ ratio may also cause **lactic acidosis** and inhibit **gluconeogenesis**.

Ethanol metabolism may result in **alcohol-induced liver disease**, including **hepatic steatosis** (fatty liver), **alcohol-induced hepatitis**, and **cirrhosis**. The principal toxic products of ethanol metabolism include **acetaldehyde** and **free radicals**. Acetaldehyde forms **adducts** with proteins and other compounds. The **hydroxyethyl radical** produced by the MEOS and other radicals produced during inflammation cause irreversible damage to the liver. Many other tissues are adversely affected by ethanol, acetaldehyde, or by the consequences of **hepatic dysmetabolism** and injury. **Genetic polymorphisms** in the enzymes of ethanol metabolism may be responsible for individual variations in the development of alcoholism or the development of liver cirrhosis.