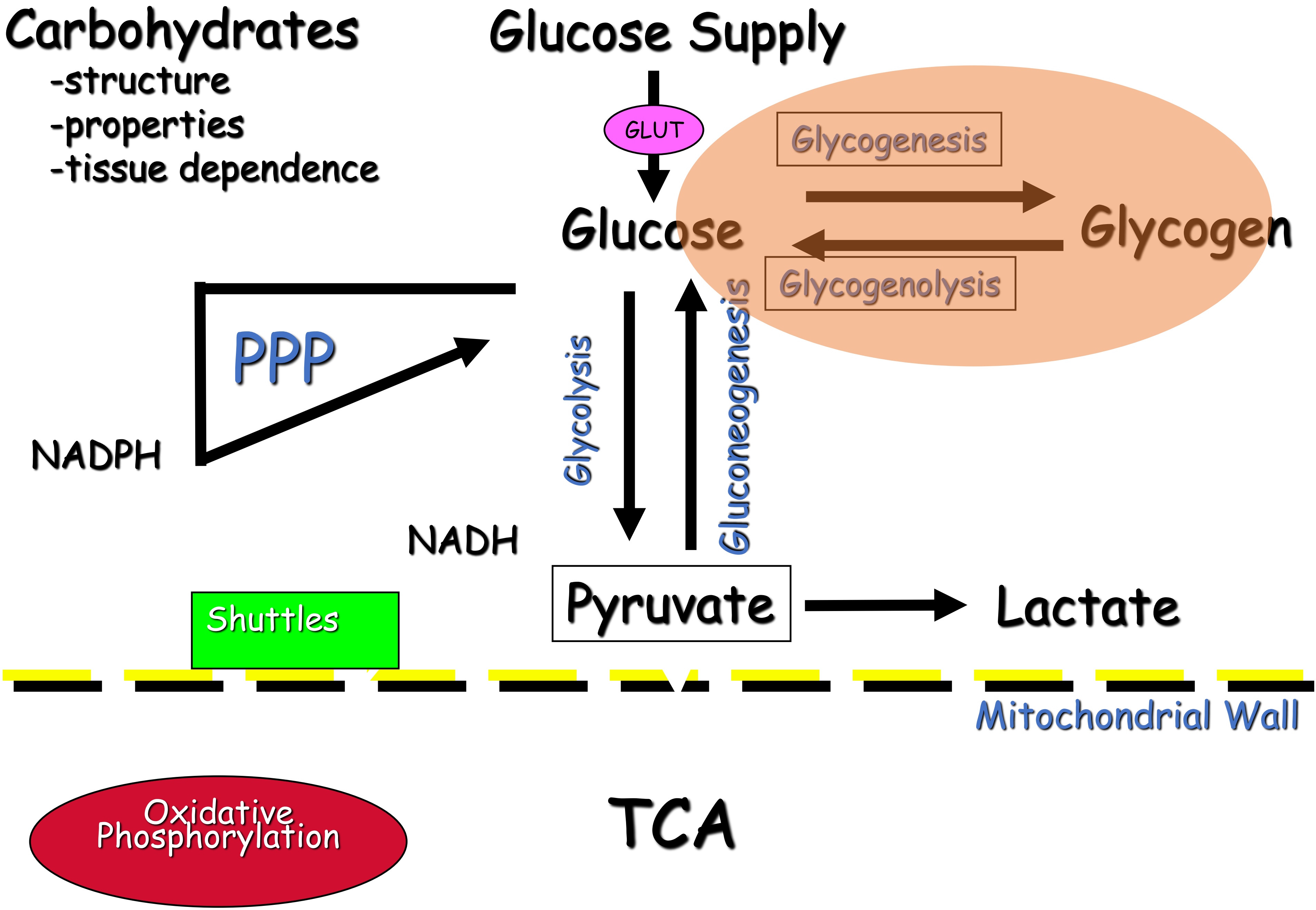
Glycogen Metabolism

Carbohydrates

- -structure
- -properties
- -tissue dependence



Glycogen

Structure:

- polysaccharide of α-D-glucose linked α1->4, and branched α 1->6
- major carbohydrate store in animals

Location:

cytosol of all tissues, mainly in liver (up to 6% of weight) & muscle (1-2% of weight)

Function of Glycogen Stores

Liver: storage & export of glucose; maintains blood [glucose].

Depleted after 12-18 hours fasting.

ESSENTIAL FOR GLUCOSE HOMEOSTASIS

Muscle: fuels glycolysis within muscle only. Depleted through prolonged vigorous exercise.

NOT ESSENTIAL FOR GLUCOSE HOMEOSTASIS

Used for high intensity exercise

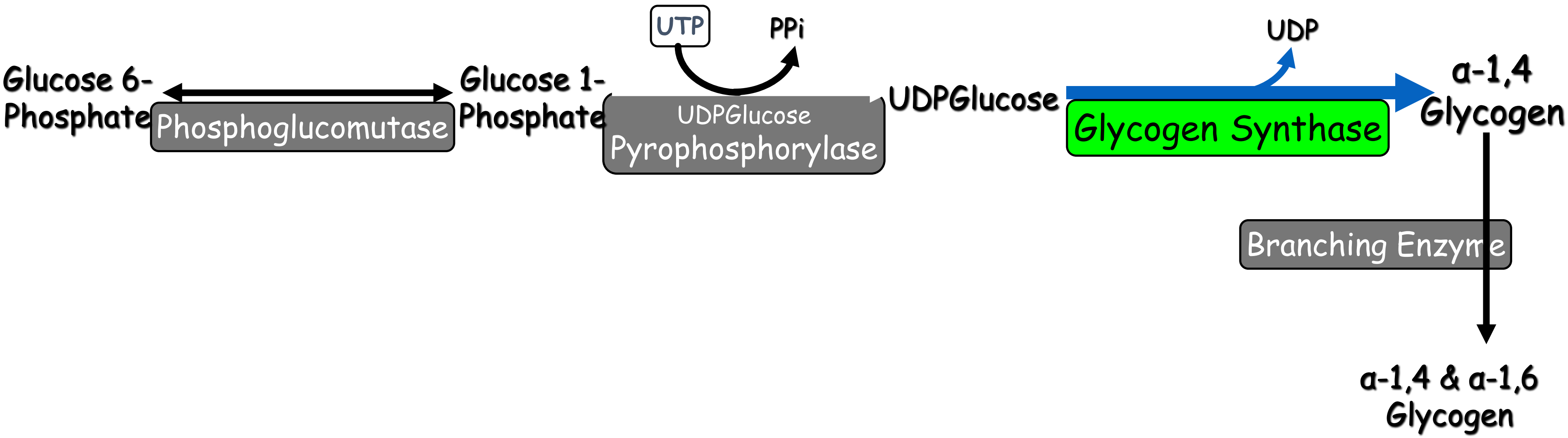
A time for storage & breakdown

- glycogen is synthesised and broken down by different pathways

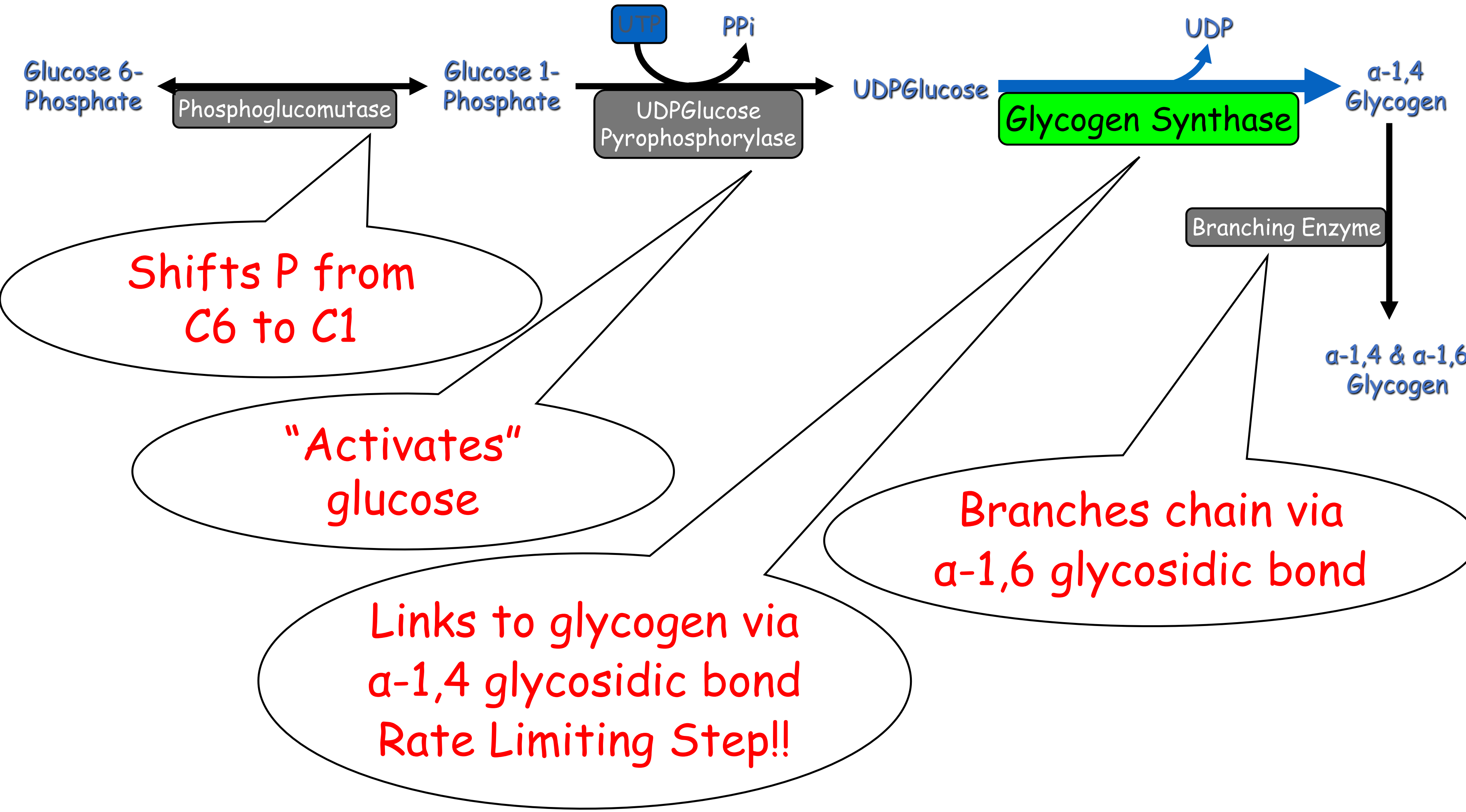
- **Glycogenesis** (synthesis of glycogen)
  - when glucose supply is in excess (after meal)

- **Glycogenolysis** (breakdown of glycogen)
  - in liver when blood glucose concentration is low (glucose homeostasis)
  - in muscle for ATP production during exercise

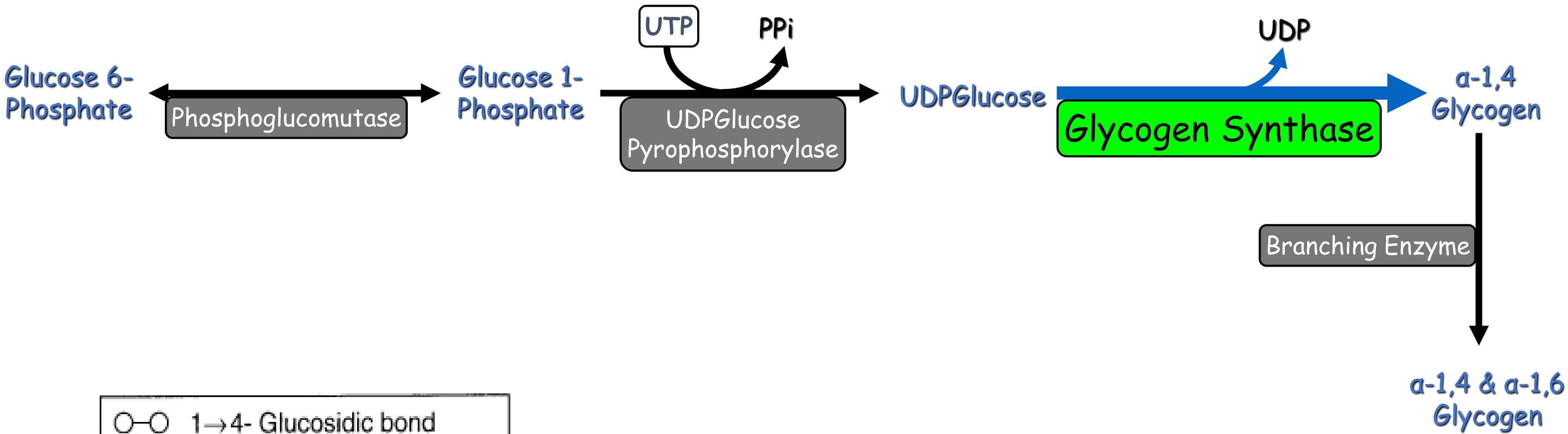
Glycogenesis (synthesis)

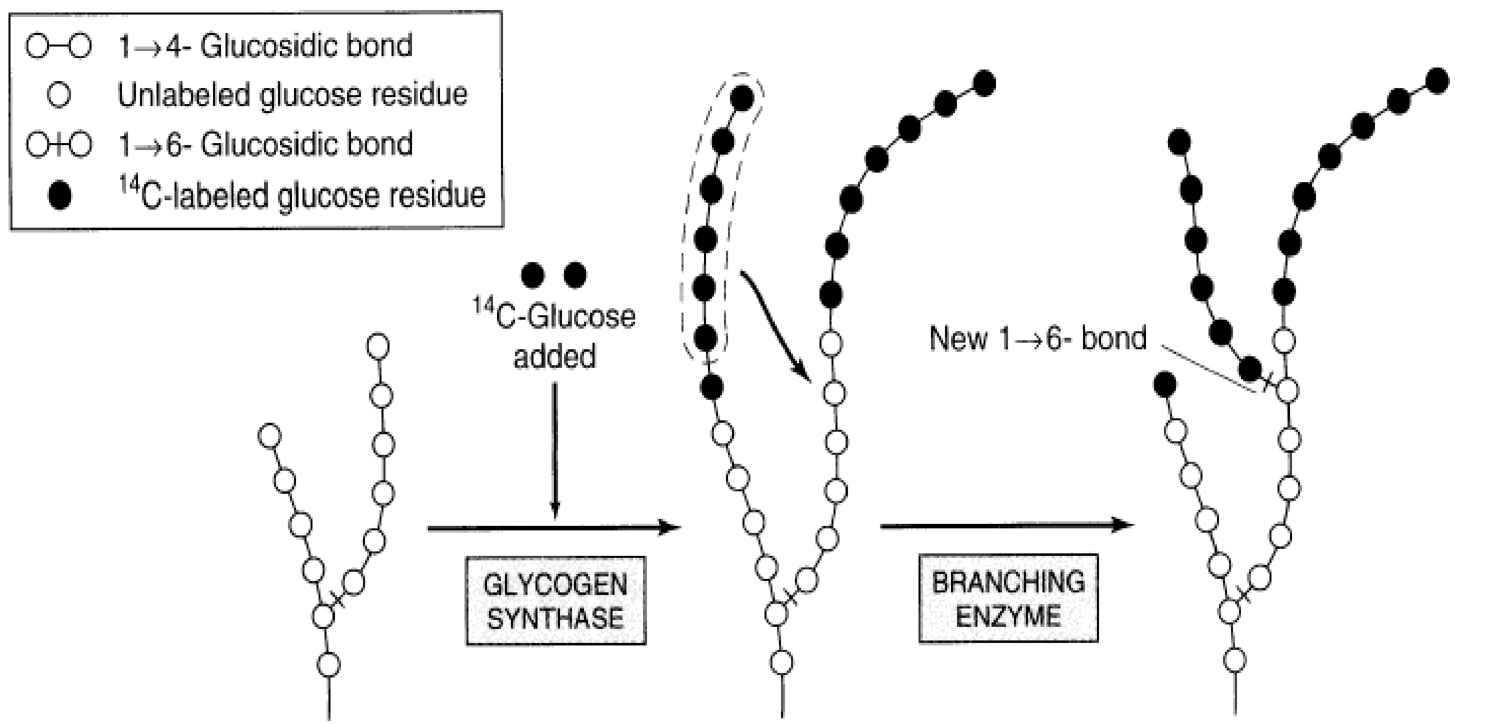


Glycogenesis (synthesis)

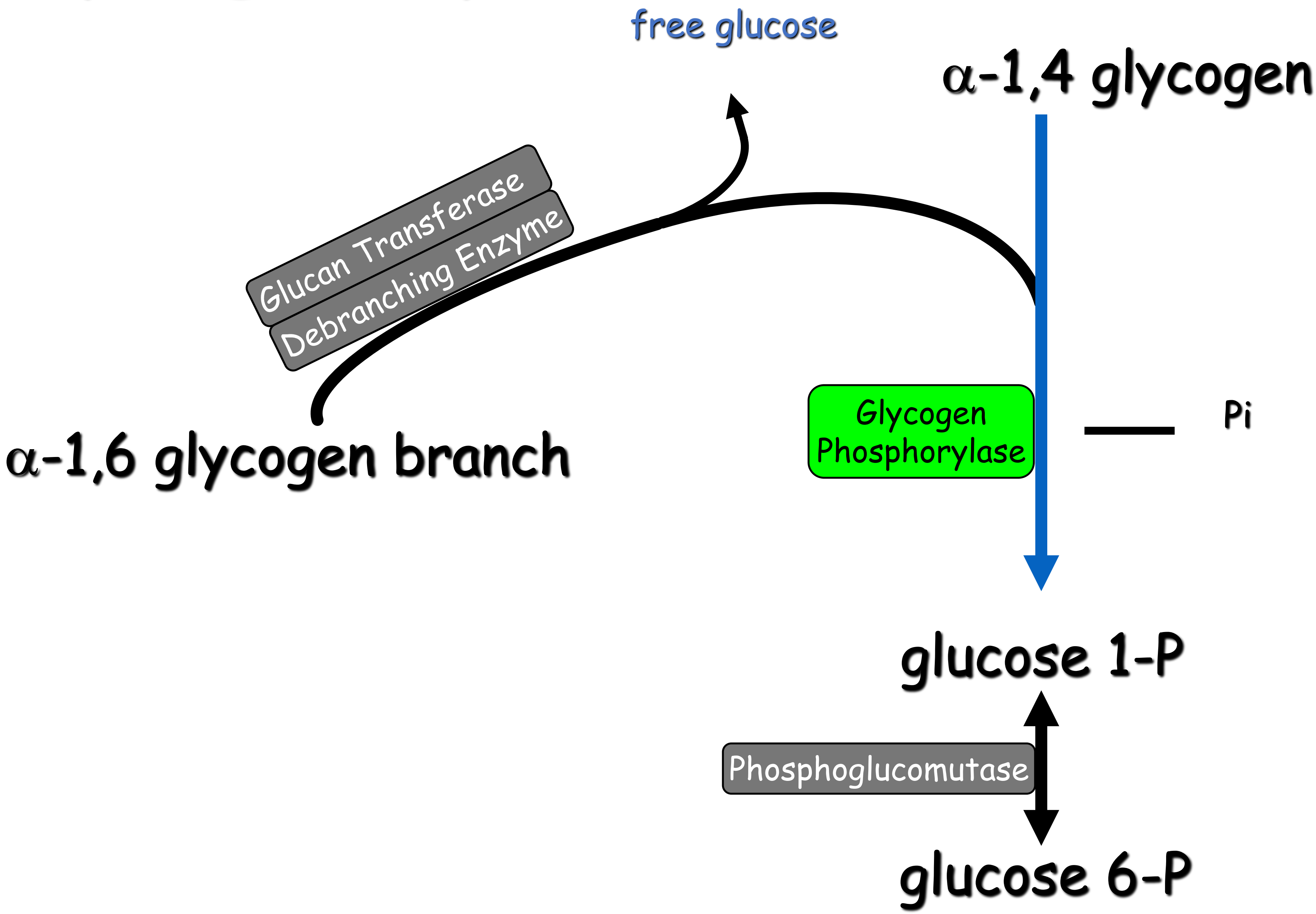


Glycogenesis (synthesis)

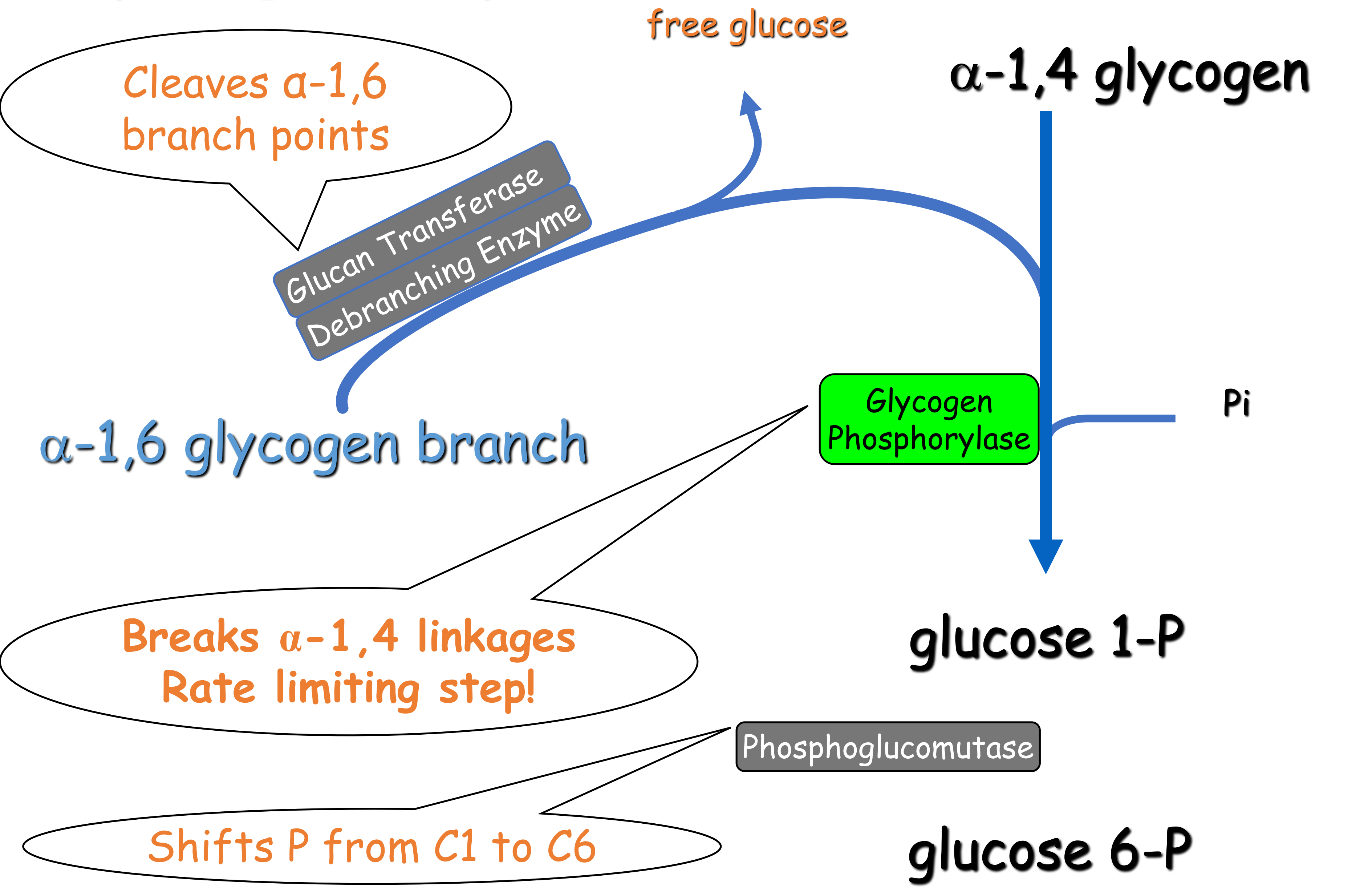




Glycogenolysis (breakdown)



Glycogenolysis (breakdown)



Glycogenolysis (breakdown)

free glucose

α-1,4 glycogen

Glucan Transferase

Debranching Enzyme

Glycogen Phosphorylase

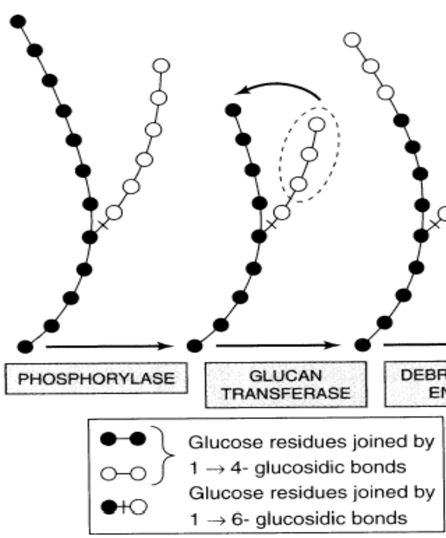
Pi

α-1,6 glycogen branch

glucose 1-P

Phosphoglucomutase

glucose 6-P



Glycogenolysis (breakdown)

Improved ATP efficiency!!

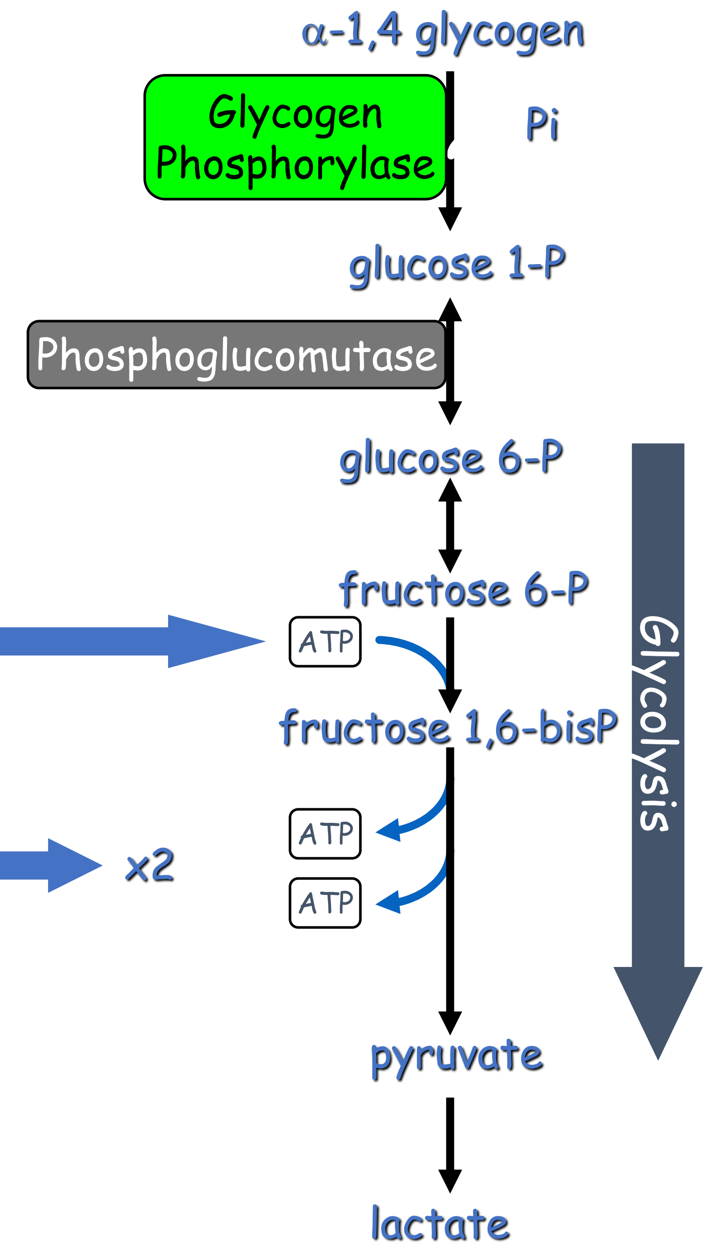
3 ATP per glucose 6-P

Hexokinase step not required!

-1 ATP

+4 ATP

x2



Net ATP = 4-1 = 3
(per glucose 6-P)

Glycogenolysis vs Glycogenesis

How do we regulate opposing pathways?

Rate Limiting Steps

Glycogen Phosphorylase

Glycogen Synthase

Glucose Homeostasis

- Short term - just fed (day 1)
  - emphasis on storage of excess glucose as glycogen and excess carbon as fat
  - driven by insulin
- Short term shortage
  - emphasis on mobilisation of glycogen stores
  - driven by glucagon
- Medium term - starvation (2 days on)
  - emphasis on glucose sparing
  - gluconeogenesis for glucose dependent tissues
  - driven by glucagon
- High demand - stress / exercise
  - emphasis on maximising glucose availability
  - driven by adrenalin

Major Hormones Controlling Fuel Metabolism

Hormone	Biochemical Actions	Physiological Actions
Insulin	↑Glut 4 in muscle & fat	signals fed state
	↑glycolysis	lowers blood glucose
	↑glycogen synthesis	increases fuel storage
	↓gluconeogenesis	↑cell growth & differentiation
	↑triacylglycerol synthesis	
	↑fat (lipid) synthesis	
	↑protein, DNA & RNA synthesis	
	↓protein degradation	
Glucagon	↑cAMP in liver & fat	
	↓ glycolysis	
	↓glycogen synthesis	↑glucose release from liver
	↑glycogenolysis	increases blood glucose
	↑ gluconeogenesis	increases fuel supply
	↑triacylglycerol hydrolysis	
	↑protein degradation	

Major Hormones Controlling Fuel Metabolism

Hormone	*Biochemical Actions*	*Physiological Actions*
Adrenalin	↑ *cAMP in liver, muscle & fat*	
[acute action]	↓ *glycogen synthesis*	↑ *glucose release from liver*
	↑ *glycogenolysis*	↑ *blood glucose*
	↑ *TAG hydrolysis*	↓ *glucose use by muscle*

Summary: Glycogen Metabolism

- Glycogenesis
  - Glycogen synthase (regulating enzyme)
  - Insulin stimulates
- Glycogenolysis
  - Glycogen phosphorylase (regulating enzyme)
  - Glucagon & adrenalin stimulate
- Coordinated regulation
  - cAMP and cAMP-dependent protein kinase

Glycogen metabolism

- Rate limiting step for glycogenesis
  - glycogen synthase
- Rate limiting step for glycogenolysis
  - glycogen phosphorylase

Control of glycogenesis & glycogenolysis:

coordinated regulation of glycogen synthase

& glycogen phosphorylase.

cAMP: Coordinates regulation

- futile to have synthesis/breakdown at same time
- activity coordinated by cAMP (2nd messenger)

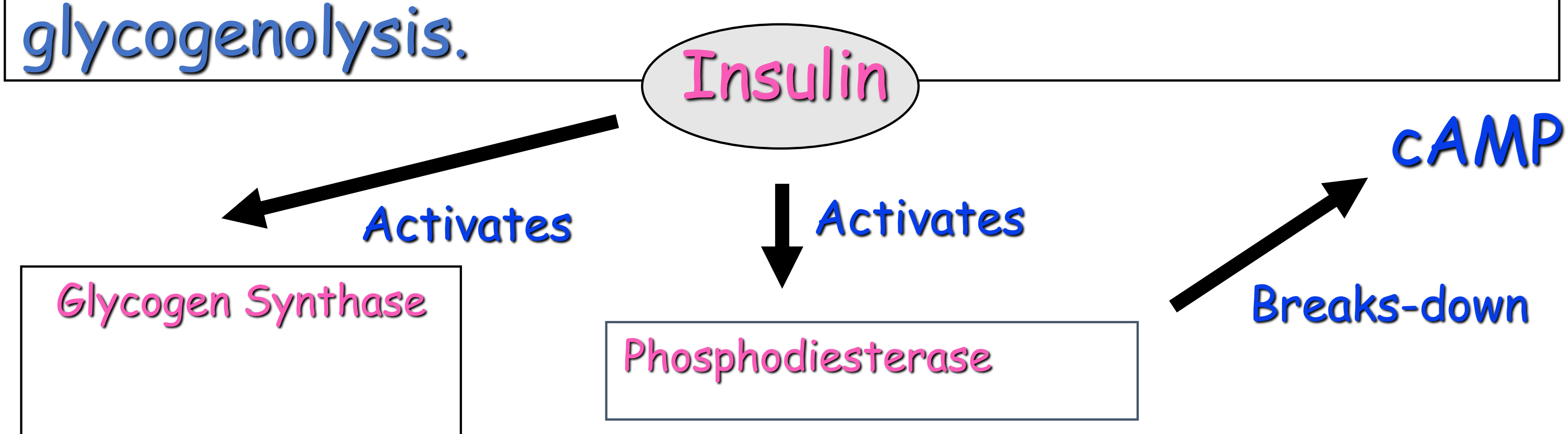
- cAMP formed by adenylate cyclase in response to hormone message (1st message)
  - enzyme on inner surface of cell membranes
  - activated by adrenalin/noradrenalin
    (β receptors) on liver or muscle
  - glucagon (glucagon receptor) LIVER ONLY
- cAMP destroyed by phosphodiesterase
  - phosphodiesterase activity increased by insulin

Regulators of glycogen metabolism

1. Adrenalin/noradrenalin (muscle/liver) and glucagon (liver only) stimulate glycogenolysis and inhibit glycogenesis via cAMP.

2. Muscle contraction stimulates glycogenolysis.

3. Insulin stimulates glycogenesis and inhibits glycogenolysis.



Regulating glycogen metabolism: a balancing act

Due to mediation through cAMP-dependent

protein kinase:

*Inhibition of glycogenolysis enhances net glycogenesis.

*Inhibition of glycogenesis enhances net glycogenolysis.