Integration of metabolism

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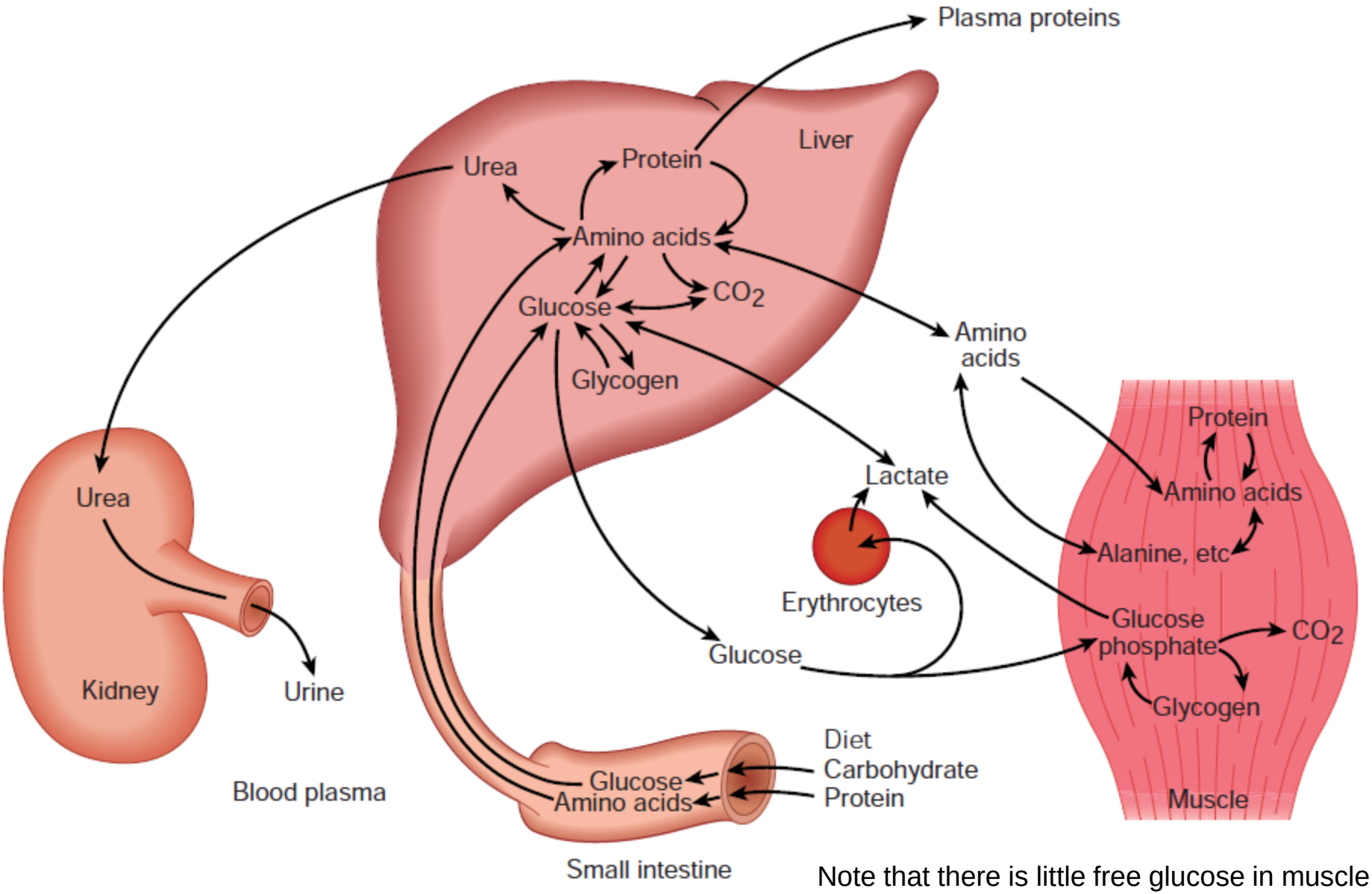
Transport and fate of major carbohydrate and amino acid substrates and metabolites



Note that there is little free glucose in muscle, since it is rapidly phosphorylated upon entry.

Starve-feed cycle

1. The fed (absorptive) state

- ✓ during a meal (~ 2 h)

  glucose represents the major fuel

2. The fasting (postabsorptive) state

- ✓ between meals (2 h after a meal)

  fatty acids represent the major fuel

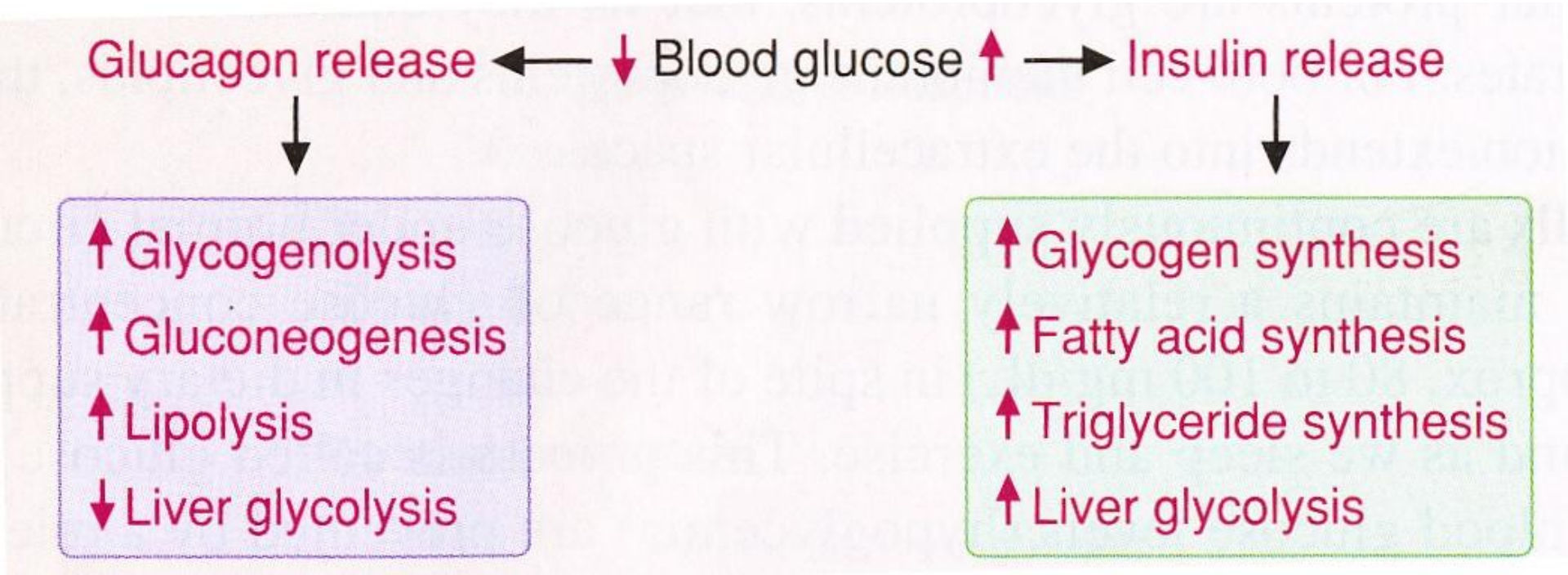
3. The starved state

- ✓ more than 3 days fasting

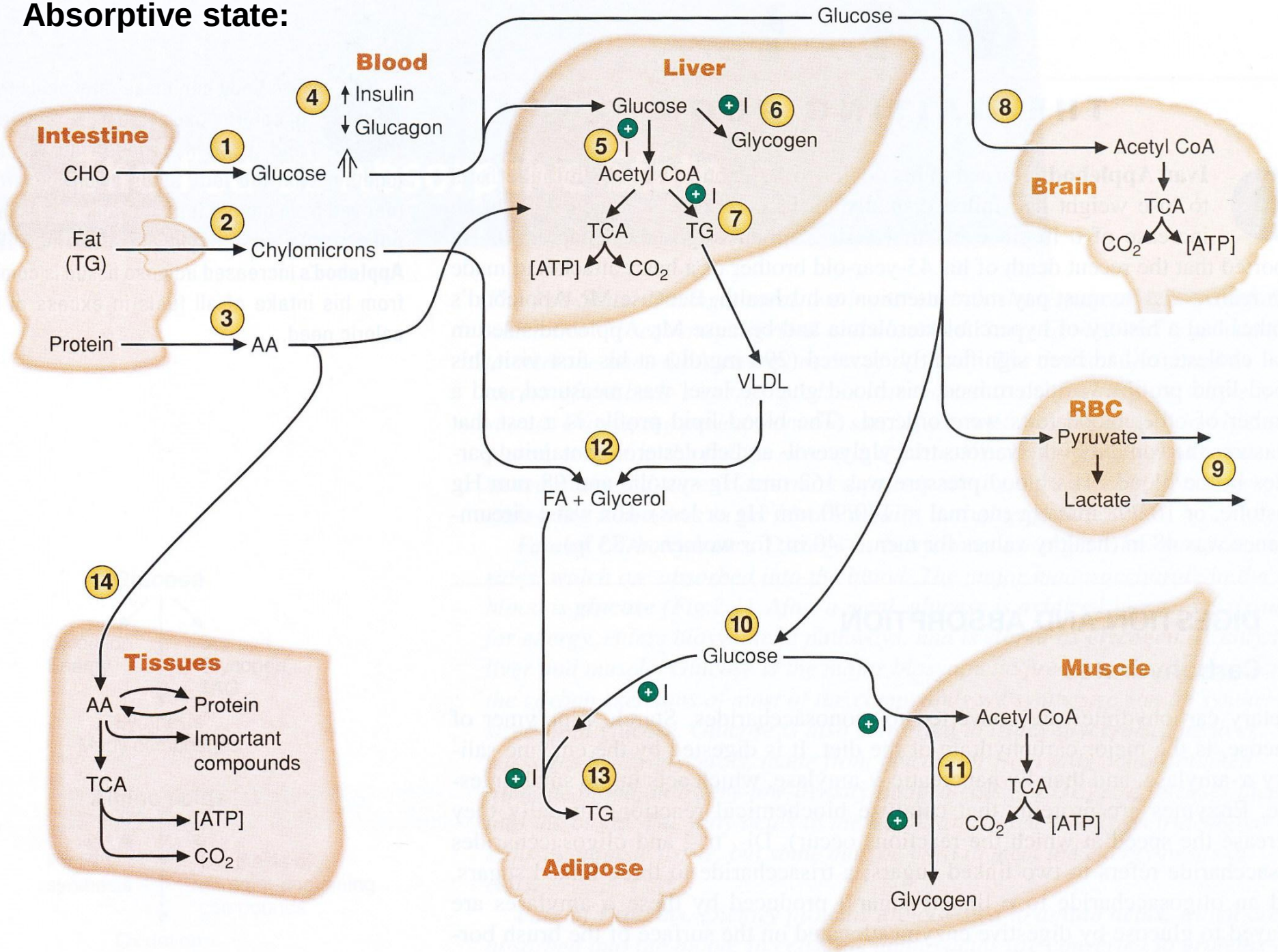
  brain begins to oxidize ketone bodies

  gluconeogenesis decreases

Hormonal regulation of metabolism:



Absorptive state:



Absorptive state:

- ✓ glucose and aminoacids are absorbed to the portal blood
- ✓ triacylglycerols are absorbed in chylomicrons by the way of the lymph into the blood
- ✓ increased concentration of glucose in the portal blood

⇩

pancreas: increased secretion of insulin, decreased secretion of glucagonu

liver:
- synthesis of glycogen
- synthesis of triacylglycerols
- synthesis of proteins

muscle:
- synthesis of glycogen
- synthesis of proteins

adipose tissue:
- synthesis of triacylglycerols
- storage of triacylglycerols

Absorptive state:

1 oxidation of fuels from the diet:

- ✓ oxidation of glucose, fatty acids, aminoacids

⇩

energy

- ✓ end-products of metabolism: CO_2, H_2O, ATP, urea

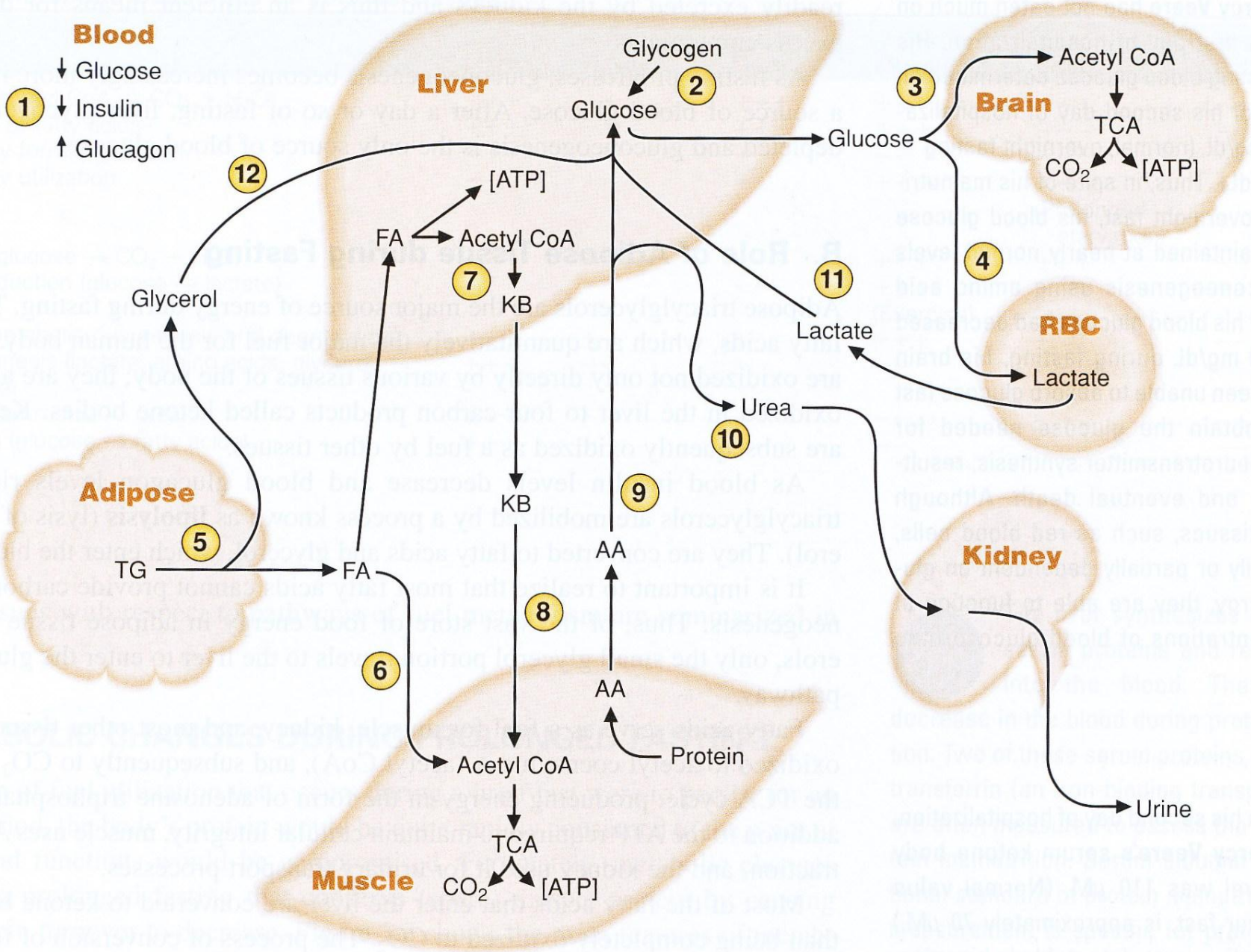
2 fuel storage:

- ✓ synthesis of glycogen (liver, muscles)
- ✓ synthesis of triacylglycerols (adipose tissue)
- ✓ synthesis of proteins (liver, muscles)

Oxidation of substrates after a meal:

Tissue	**Glucose**	**FA**	**KB**	**AA**
Nervous	++	-	-	-
Muscle	+	++	-	++
Heart	++	++	-	-
Liver	++	-	-	+
GIT	+	-	-	++
Kidney	++	++	-	++

Postabsorptive state:



Postabsorptive state:

pancreas: decreased secretion of insulin, increased secretion of glucagonu

A) activation of lipolysis in adipose tissue

- ✓ fatty acids and glycerol release
- ✓ increased levels of fatty acids in plasm
- ✓ oxidation of fatty acids in various tissues ⇨ glucose sparing

  (heart, muscles)
- ✓ increased levels of fatty acids in liver ⇨ synthesis of ketone bodies

  (oxidized in heart, muscles, kidney)

B) activation of gluconeogenesis

- ✓ synthesis of glucose *de novo* (liver, kidney)
- ✓ glucose for the brain

Postabsorptive state:

1 oxidation of substrates from the body storage:

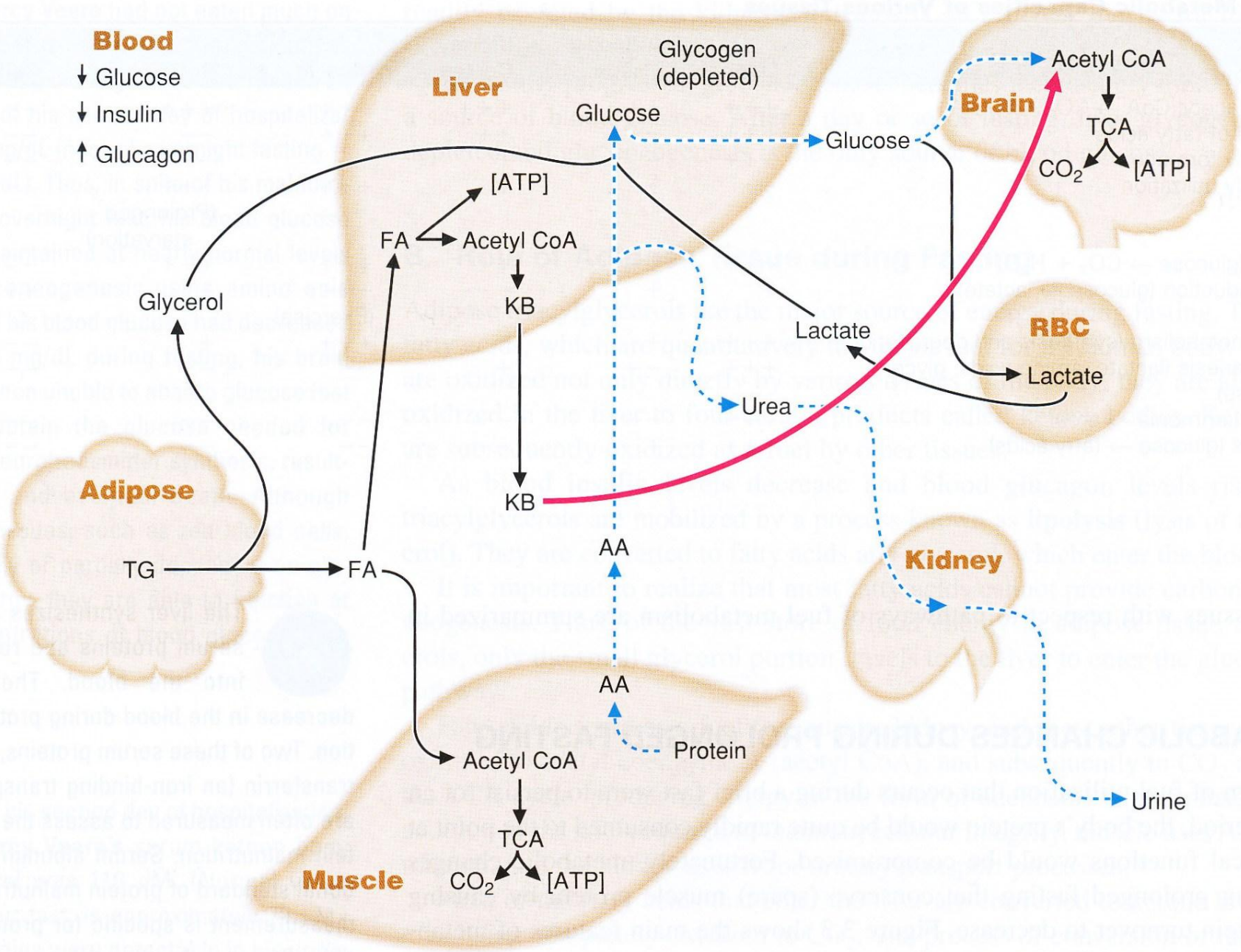
- ✓ of glucose (by glucose dependent tissues)
- ✓ of fatty acids (by muscle, liver)
- ✓ of ketone bodies (by muscle, kidney): production of ketone bodies from fatty acids released from triacylglycerols

2 glucose homeostasis:

- ✓ degradation of the liver glycogen
- ✓ gluconeogenesis

3 protein degradation and urea synthesis

Starvation:


Blood
Glucose
Insulin
Glucagon
Liver
Glycogen
(depleted)
Glucose
[ATP]
FA
Acetyl CoA
KB
Glycerol
Lactate
Urea
KB
Brain
Acetyl CoA
TCA
CO_2
[ATP]
Glucose
RBC
Lactate
Adipose
TG
FA
AA
Kidney
AA
Protein
Urine
Acetyl CoA
TCA
Muscle
CO_2
[ATP]

Starvation:

pancreas: decreased secretion of insulin, increased secretion of glucagonu

A) oxidation of ketone bodies in muscles decreases

- ✓ increased concentration of ketone bodies in blood
- ✓ brain begins to oxidize ketone bodies ⇨ glucose sparing

B) reduced gluconeogenesis ⇨ protein sparing

- ✓ reduced production of urea

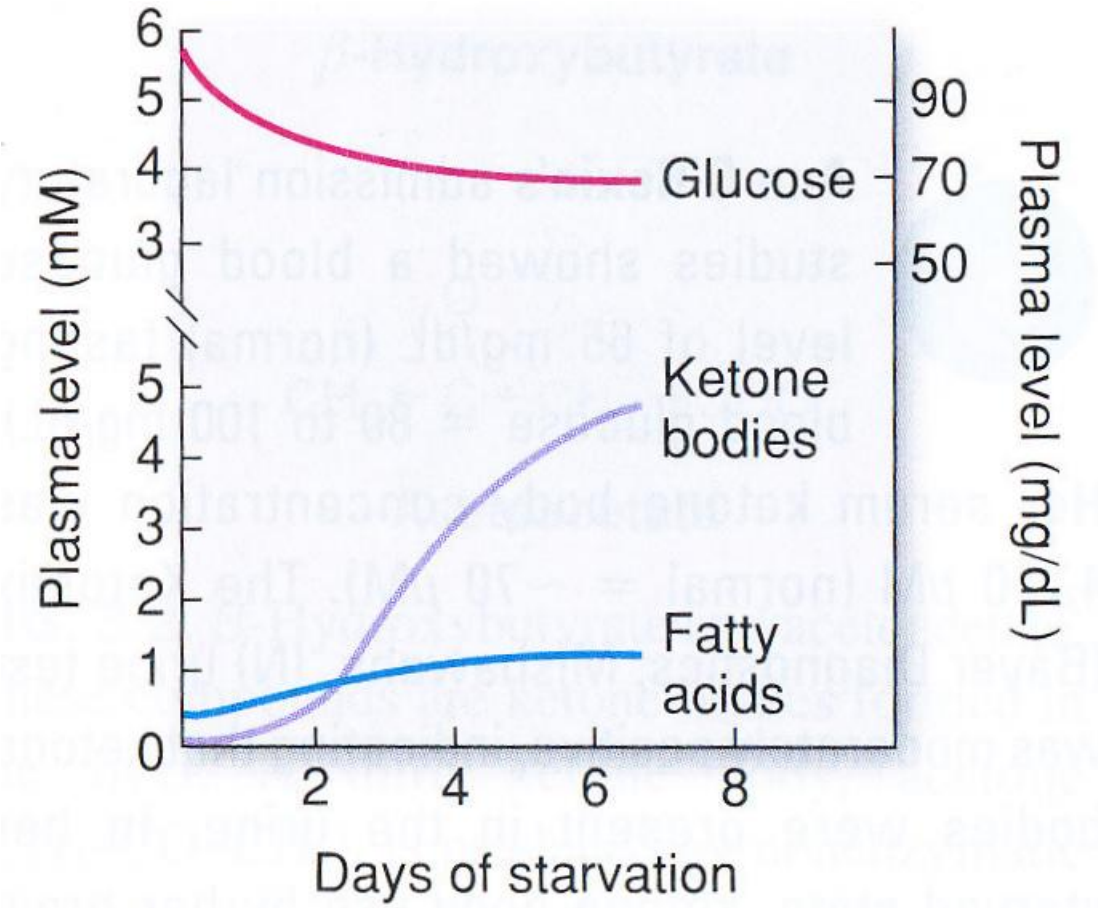
Metabolic capacities of various tissues:

Process	Liver	Adipose tissue	Kidney	Muscle	Brain	Erythrocytes
TCA cycle	+ + +	+ +	+ + +	+ + +	+ + +	- -
β-Oxidation of fatty acids	+ + +	- -	+ +	+ + +	- -	- -
Ketone body formation	+ + +	- -	+	- -	- -	- -
Ketone body utilization	- -	+	+	+ + +	+ + + starvation	- -
Glycolysis (aerobic)	+ + +	+ +	+ +	+ + +	+ + +	- -
Glycolysis (anaerobic)	+	+	- - -	+ + + exercise	+	+ + +
Glycogen metabolism	+ + +	+	+	+ + +	+	- -
Gluconeogenesis	+ + +	- -	+	- -	- -	- -
Urea cycle	+ + +	- -	- -	- -	- -	- -
Lipogenesis	+ + +	+	- -	- -	- -	- -

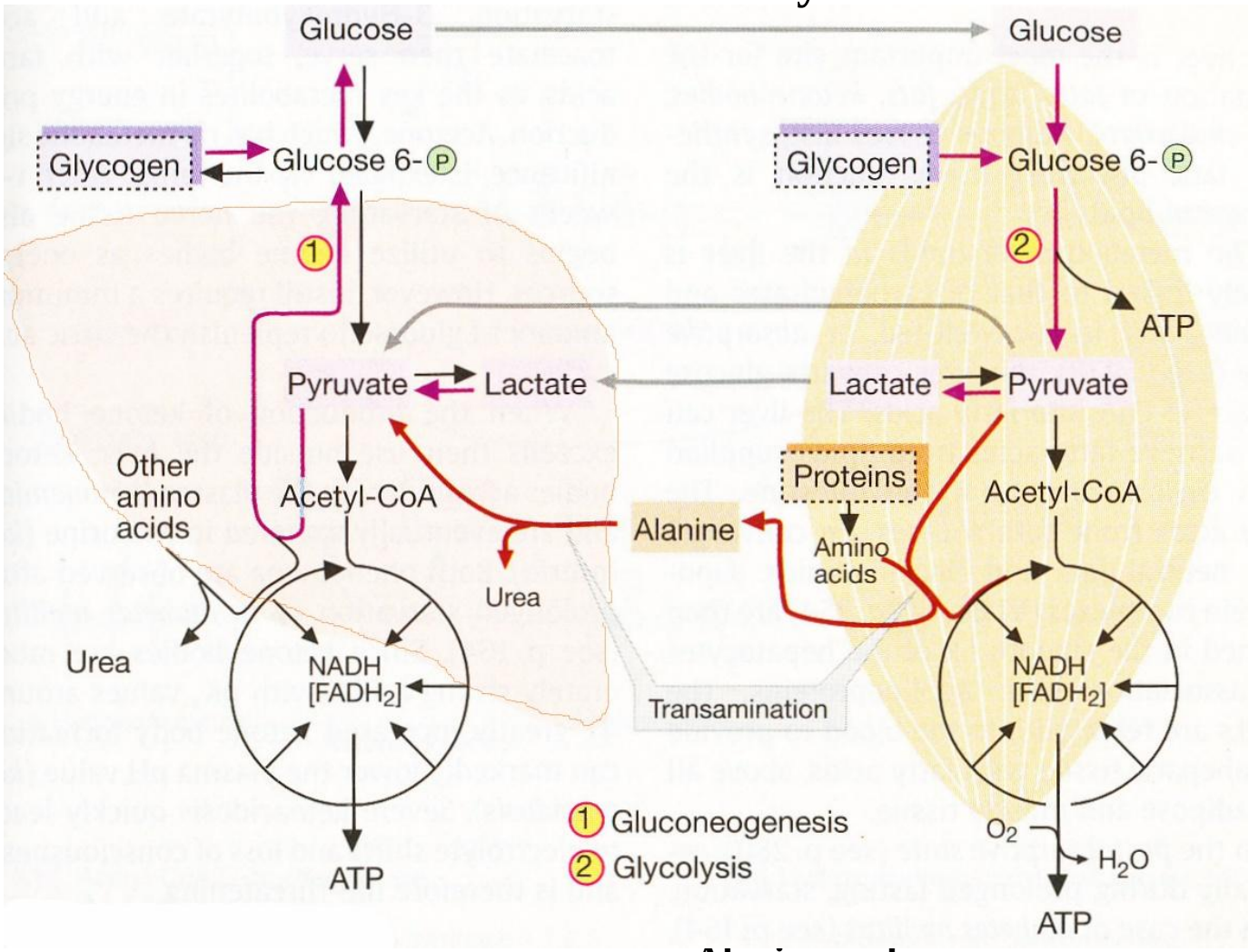
Oxidation of substrates during fasting:

Tissue	**Glucose**	**FA**	**KB**	**AA**
Nervous	++	-	++	+
Muscle	-	++	++	++
Heart	-	++	+	-
Liver	-	++	-	+
GIT	-	-	++	++
Kidney	-	+	+	++

Changes in the concentrations of fuels in the body during prolonged fasting



Cori and alanine cycles



Cori cycle:

Lactate (anaerobic glycolysis)

-transported to the liver

-converted back into glucose via gluconeogenesis

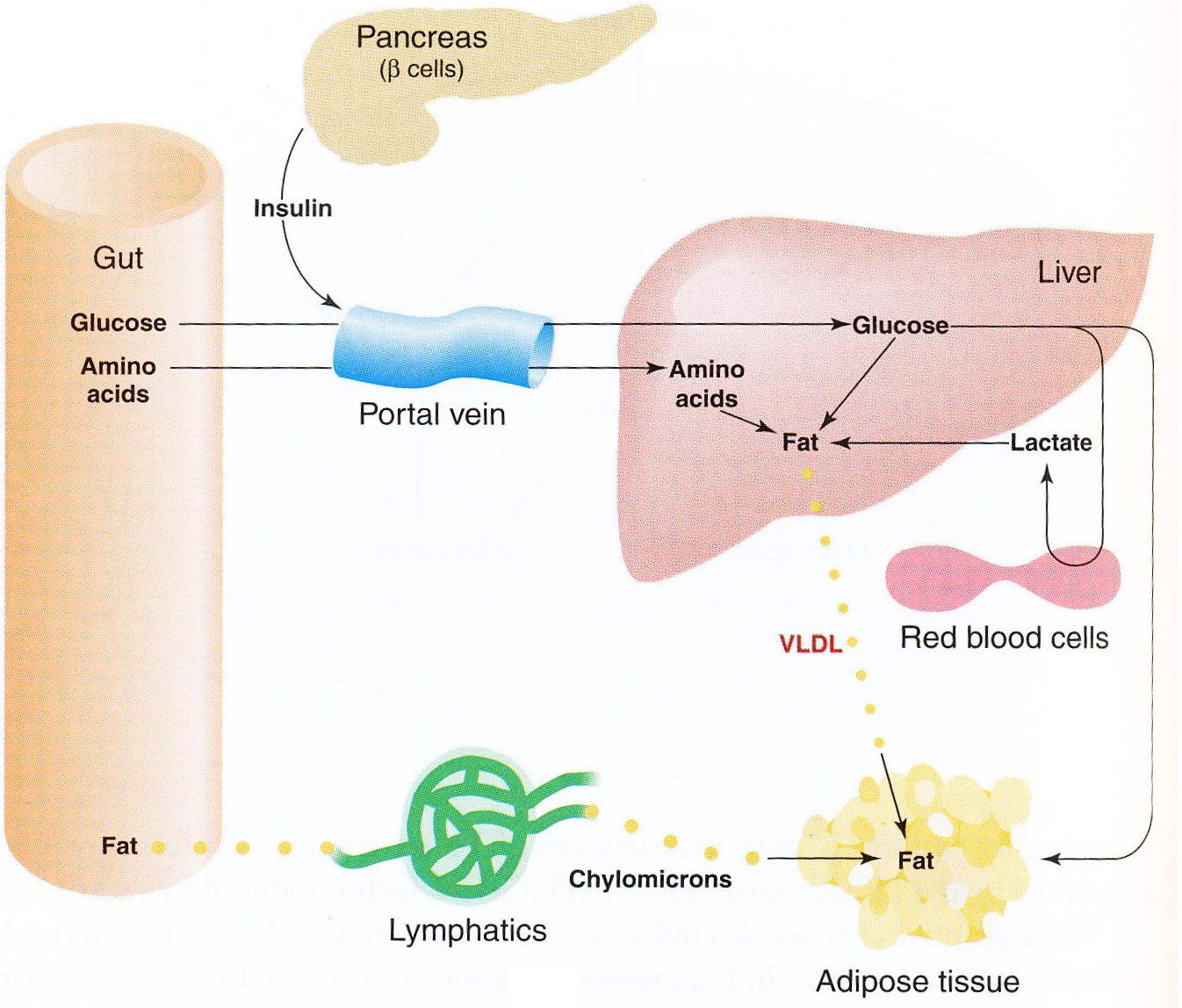
Glucose- is sent back to its site of utilization

Alanine cycle:

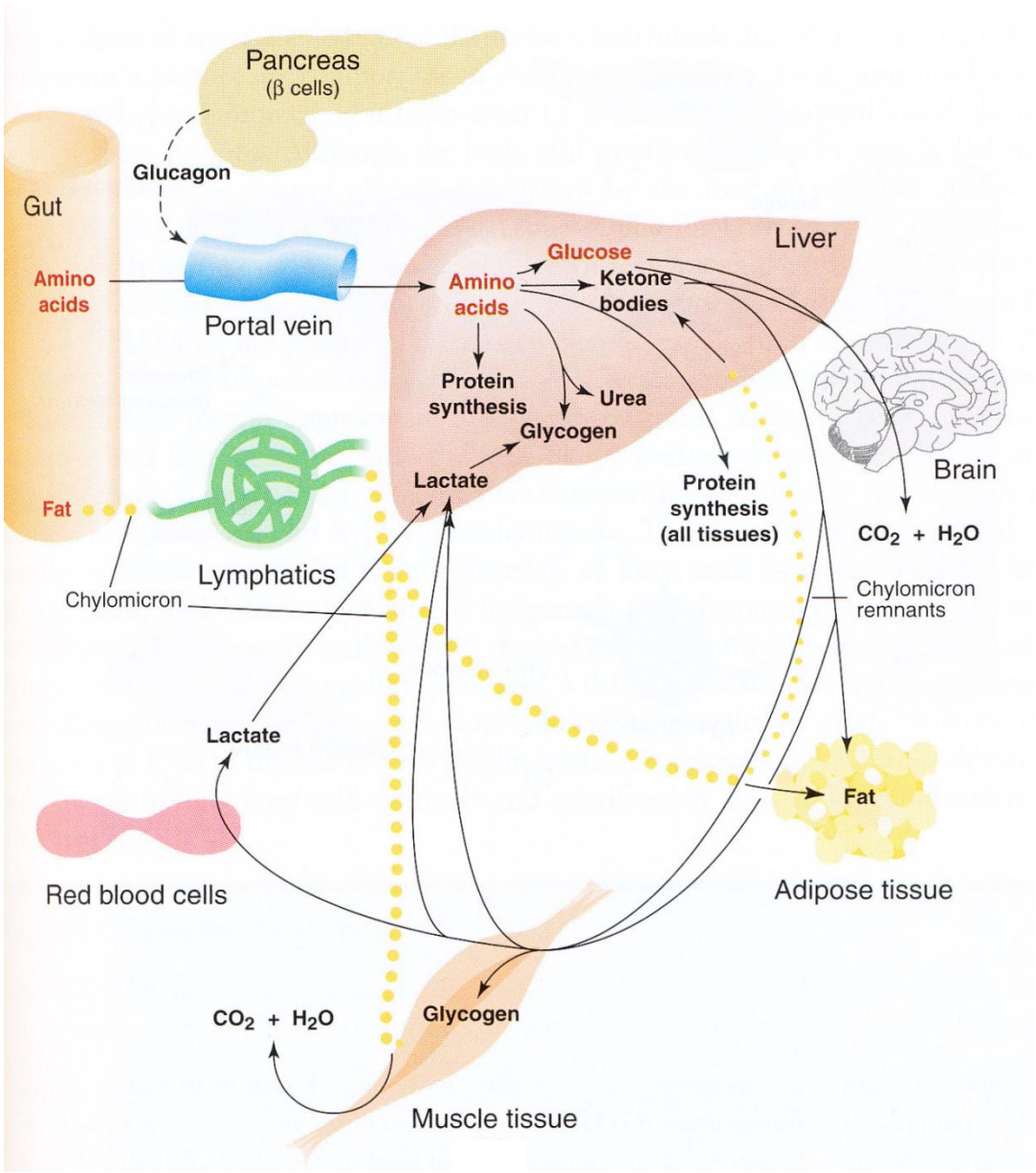
Degradation of proteins: -the amino groups are transferred to pyruvate, giving rise to alanine

Alanine is transported to the liver: -the carbon skeleton is converted into glucose, -nitrogen is converted into urea

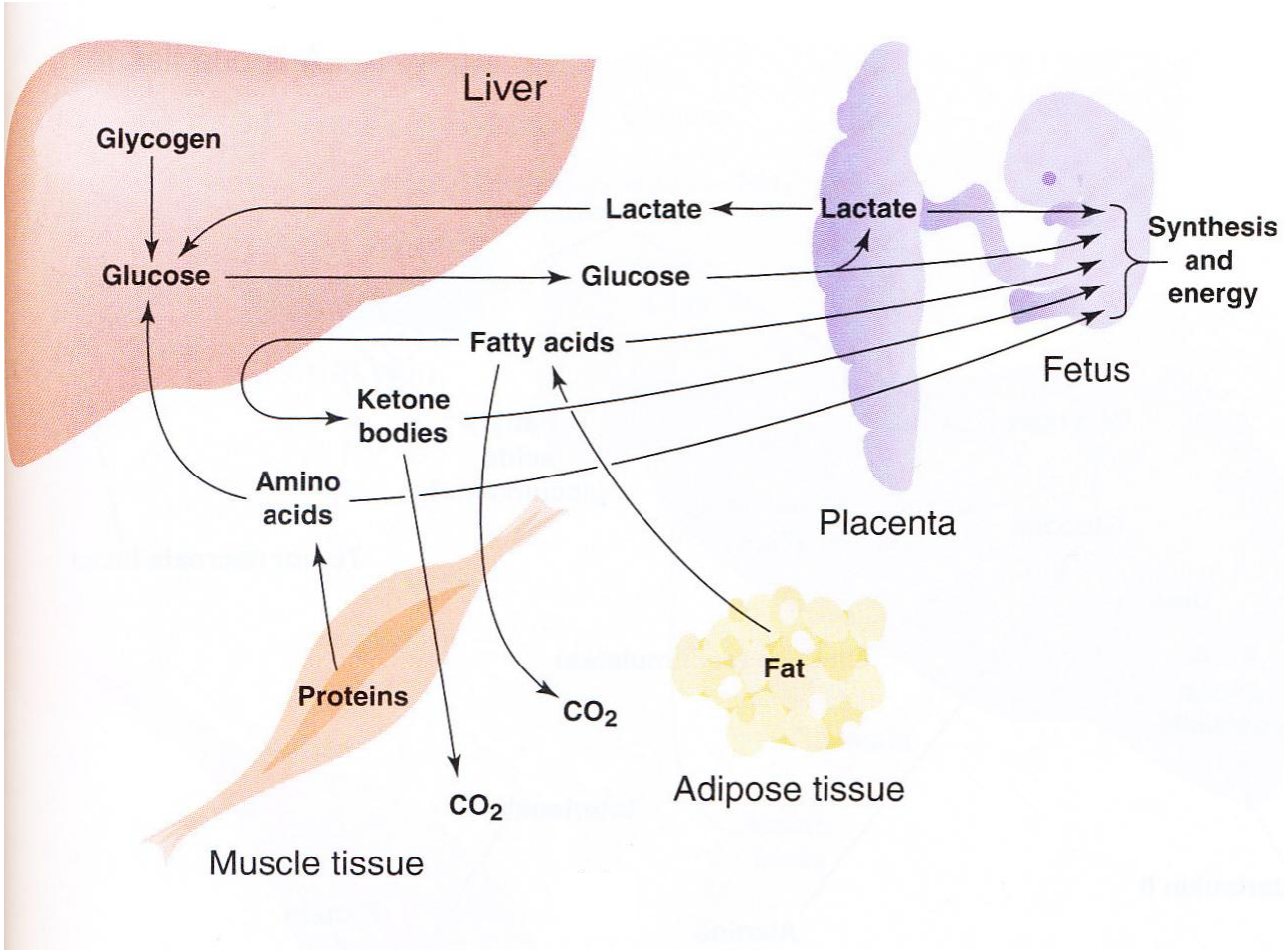
Interrrelationship of tissues in obesity



Interrrelationship of tissues in dieting



Interrrelationship of tissues in pregnancy



Mechanisms involved in switching liver metabolism between the well-fed and starved states:

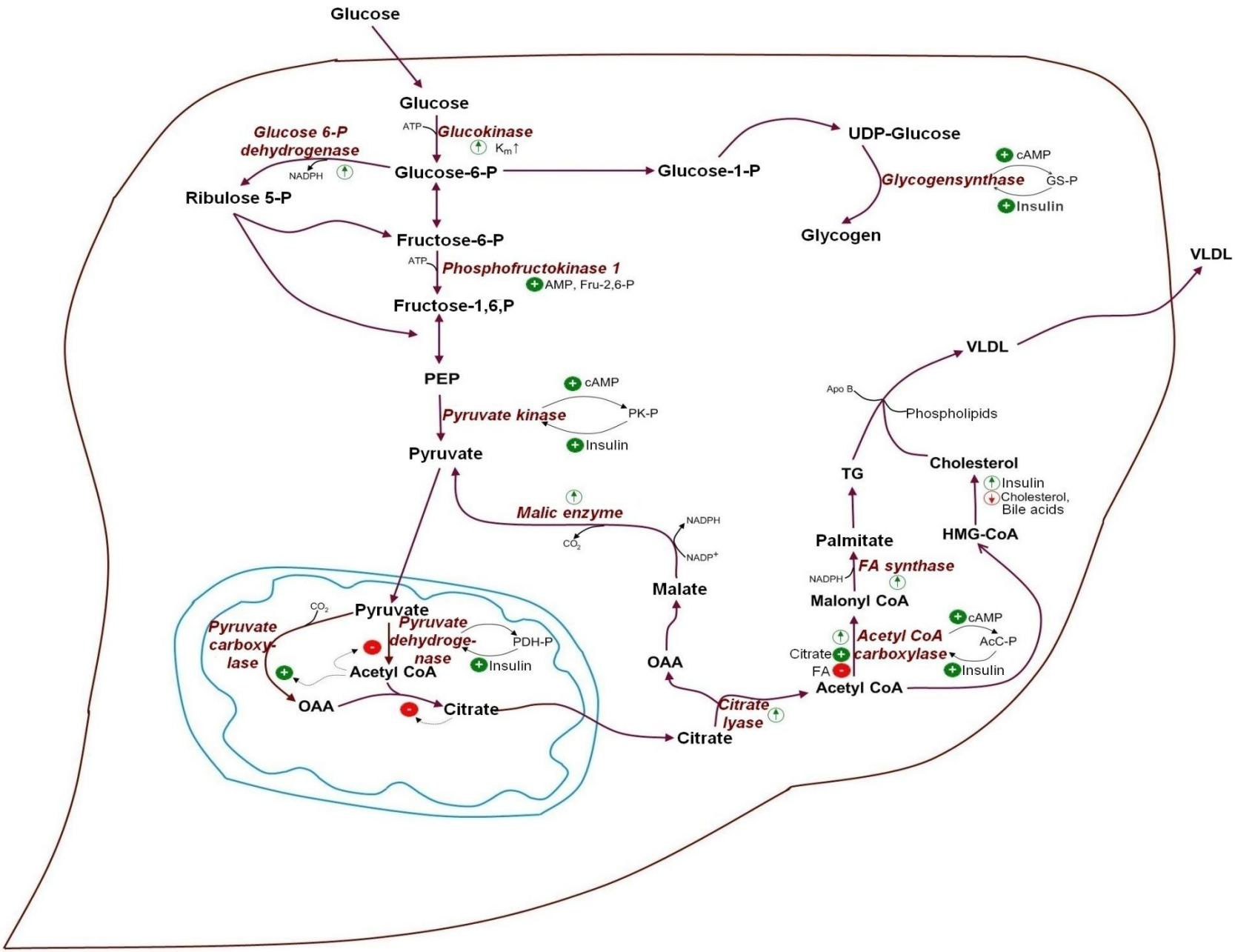
- Substrate availability
- Allosteric efectors
- Covalent modifications

short-term regulations

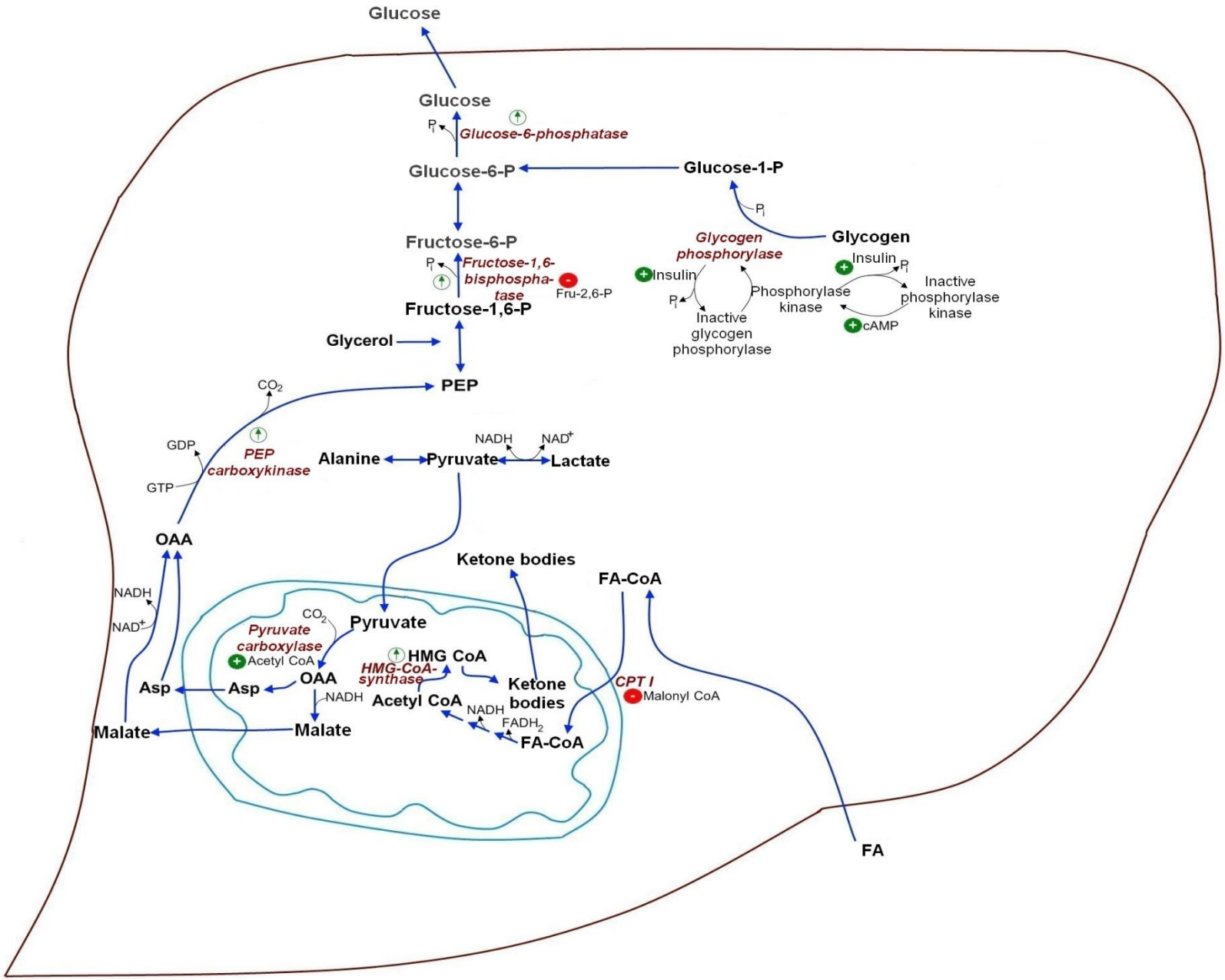
- Induction/represion of enzymes

long-term regulations

Regulations after a meal:

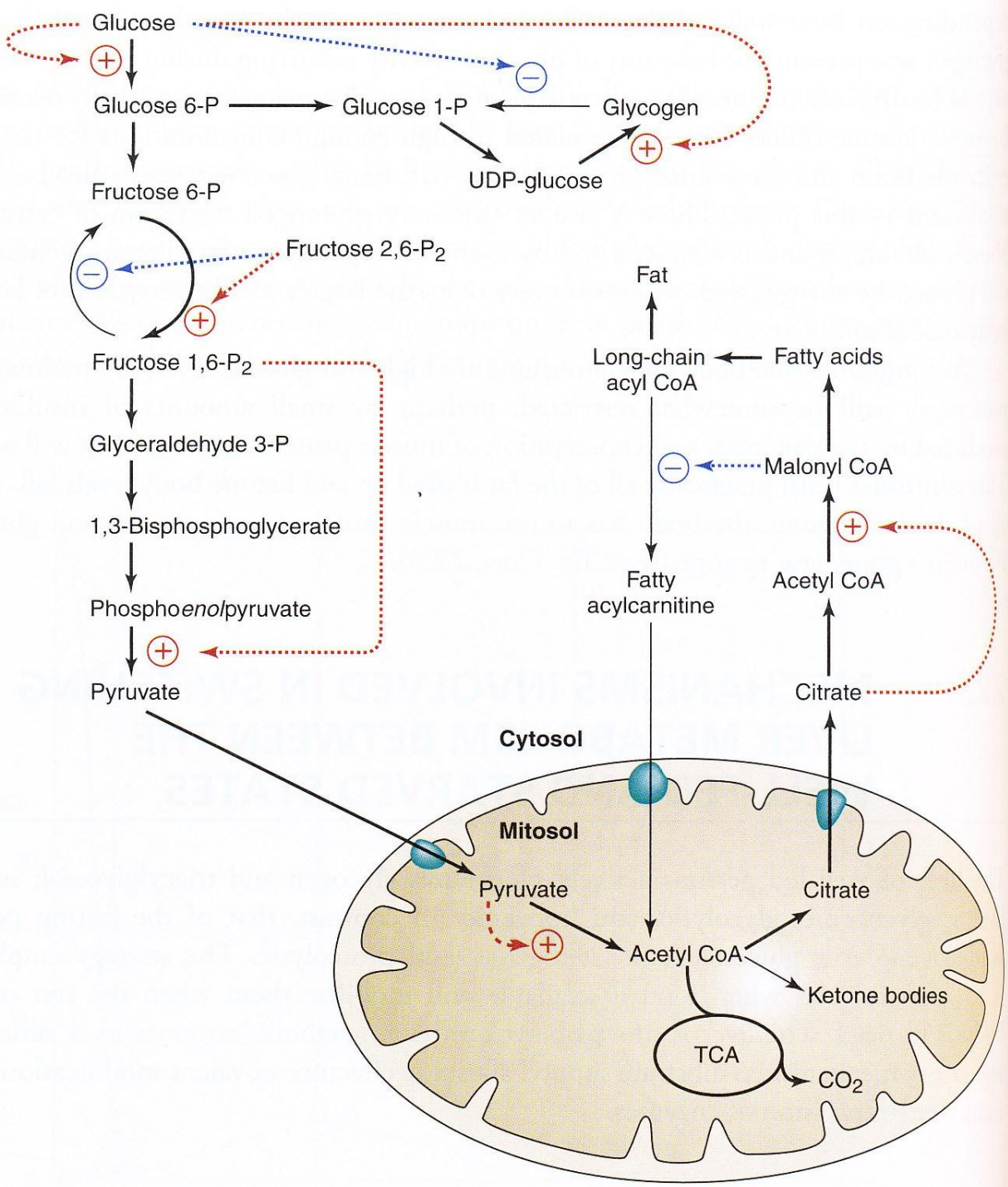


Regulations in the postabsorptive state:



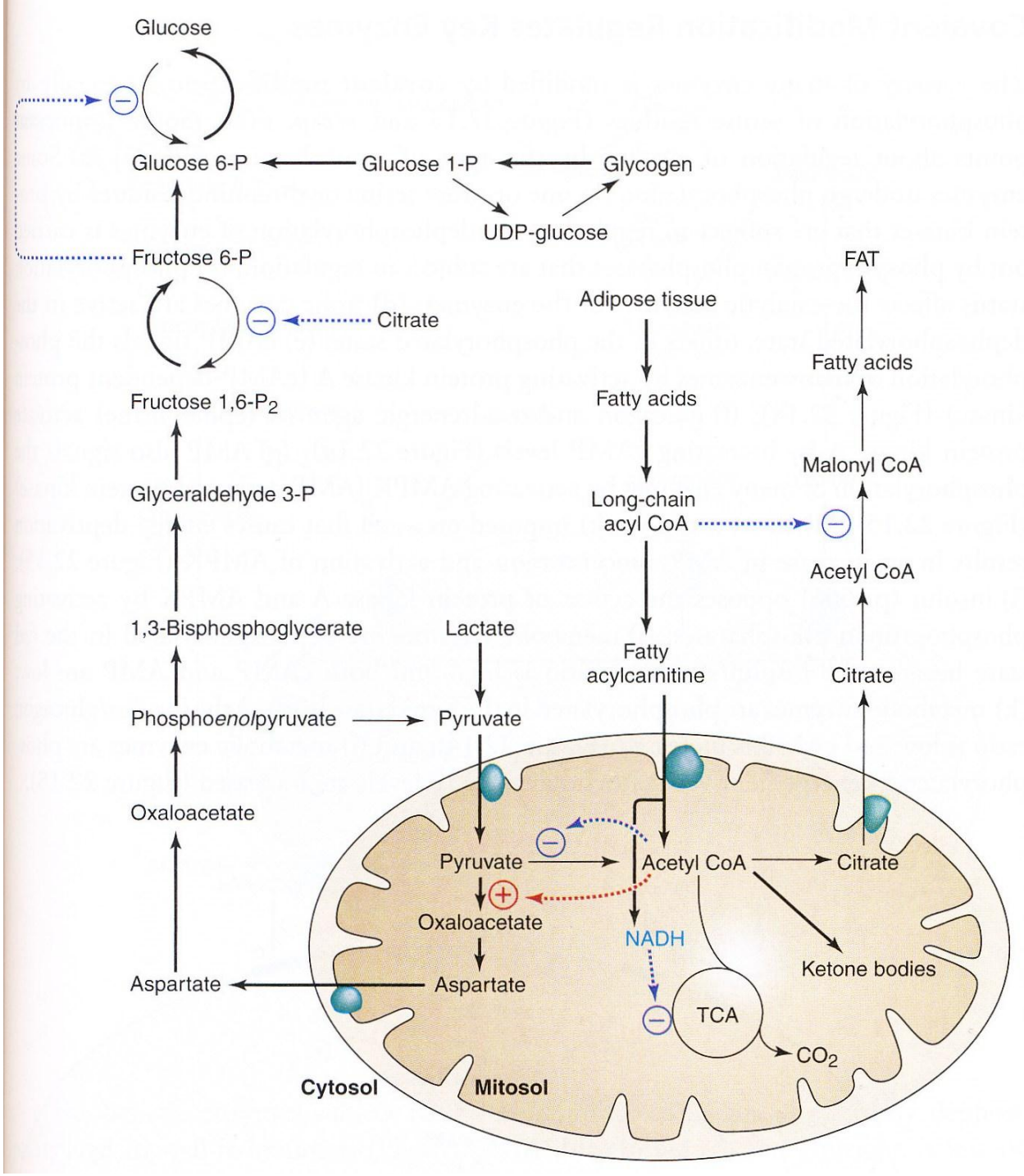
Allosteric regulations

- ✓ after a meal



Allosteric regulations

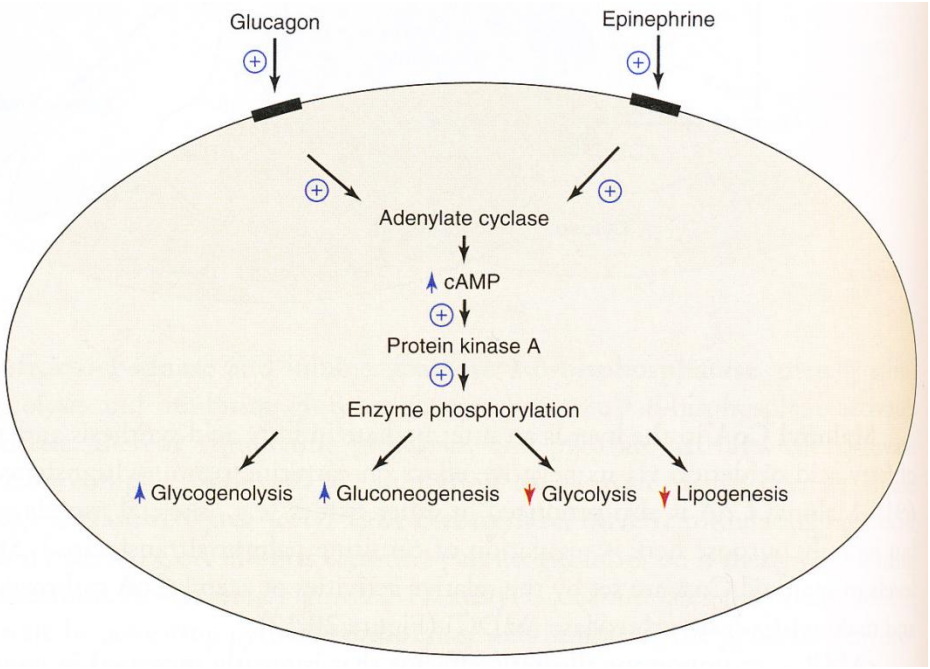
- ✓ **fasting**



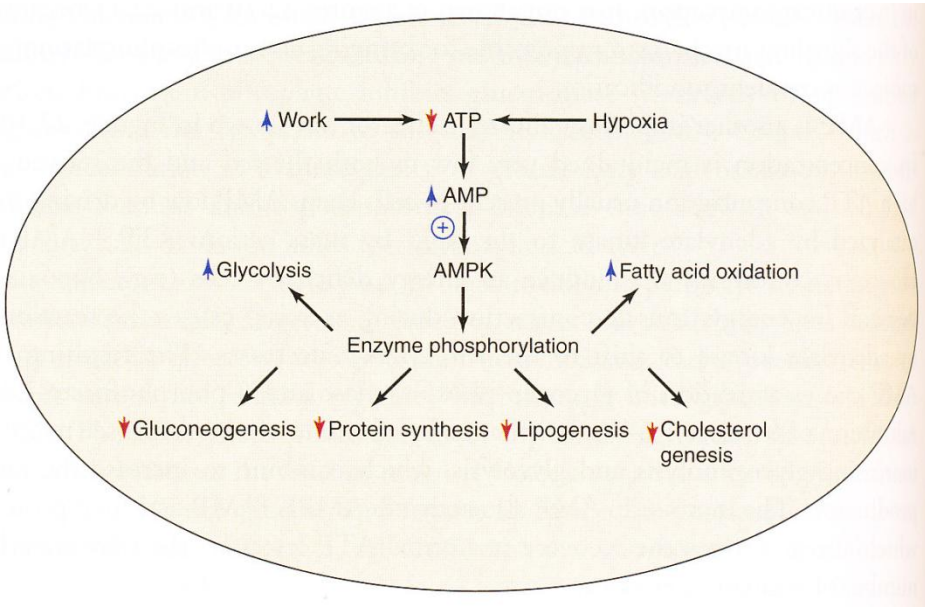
Other allosteric effectors: **cAMP, AMP**

Covalent modifications

Hormones (fasting x meal)



AMP-activated protein kinase (during energy deprivation)



After a meal

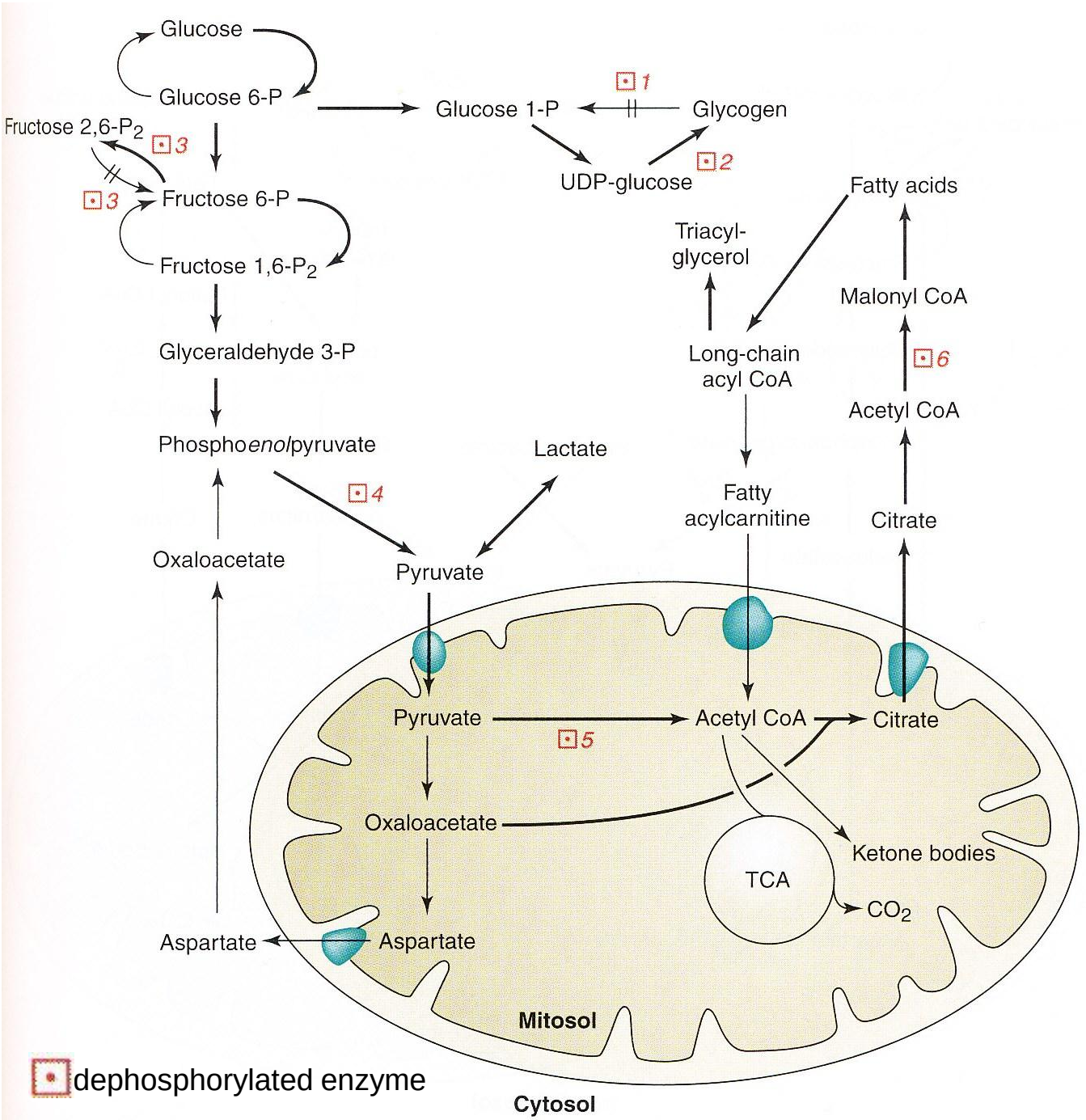
- insulin → dephosphorylation

Covalent modifications

✓ **after a meal**

⇩

enzyme dephosphorylations



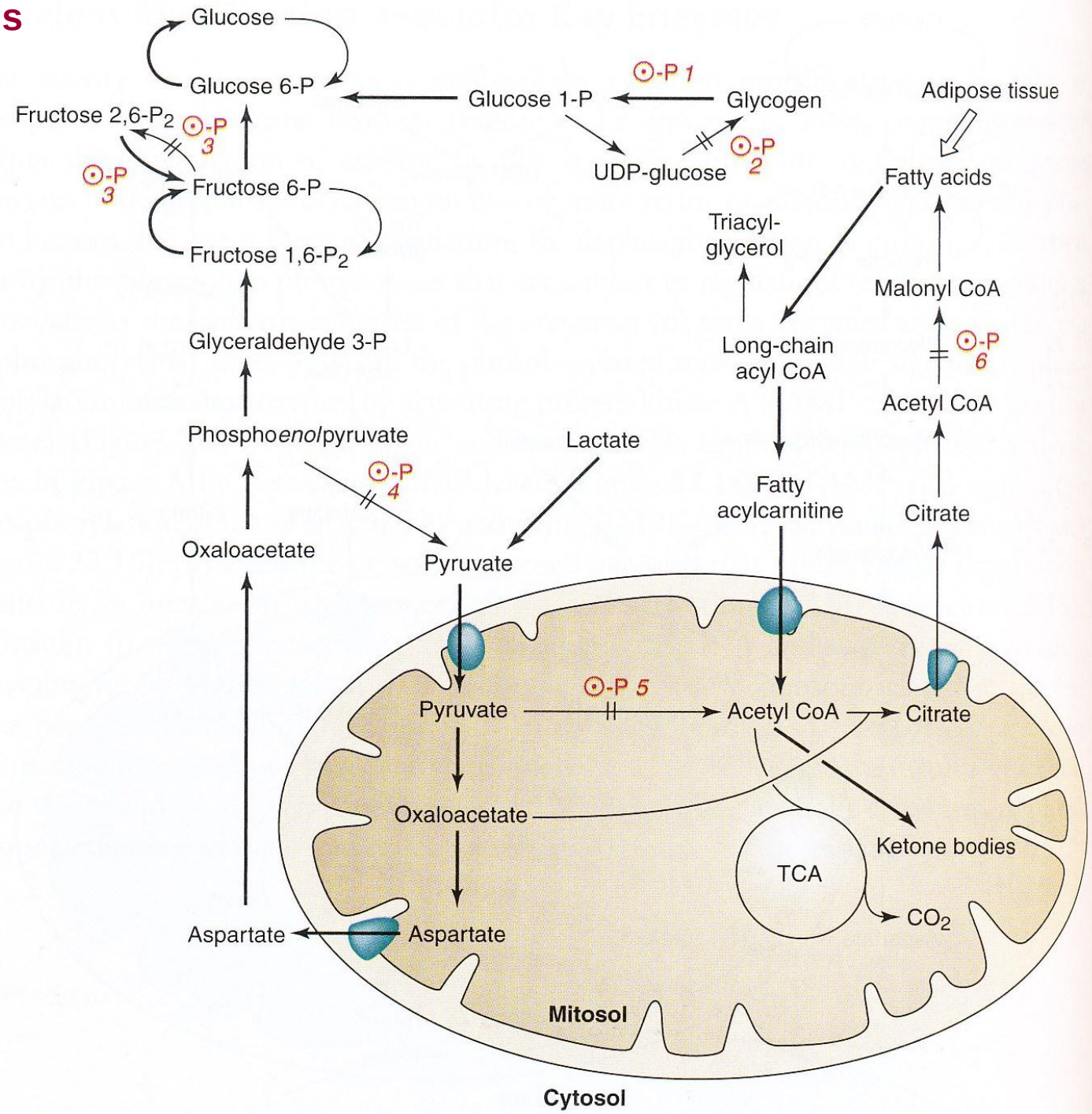
dephosphorylated enzyme

Covalent modifications

✓ **fasting**

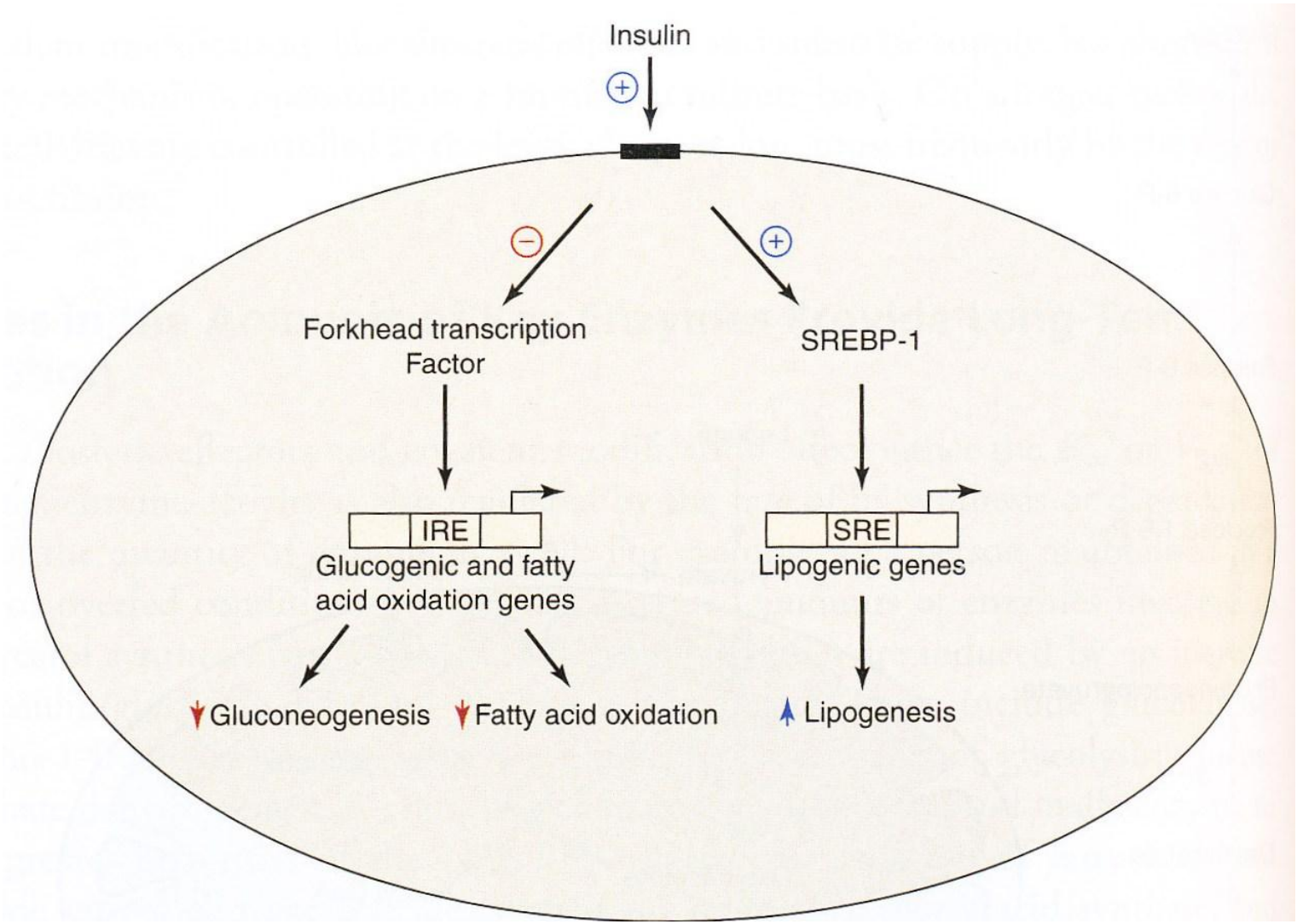
⇩

enzyme phosphorylations



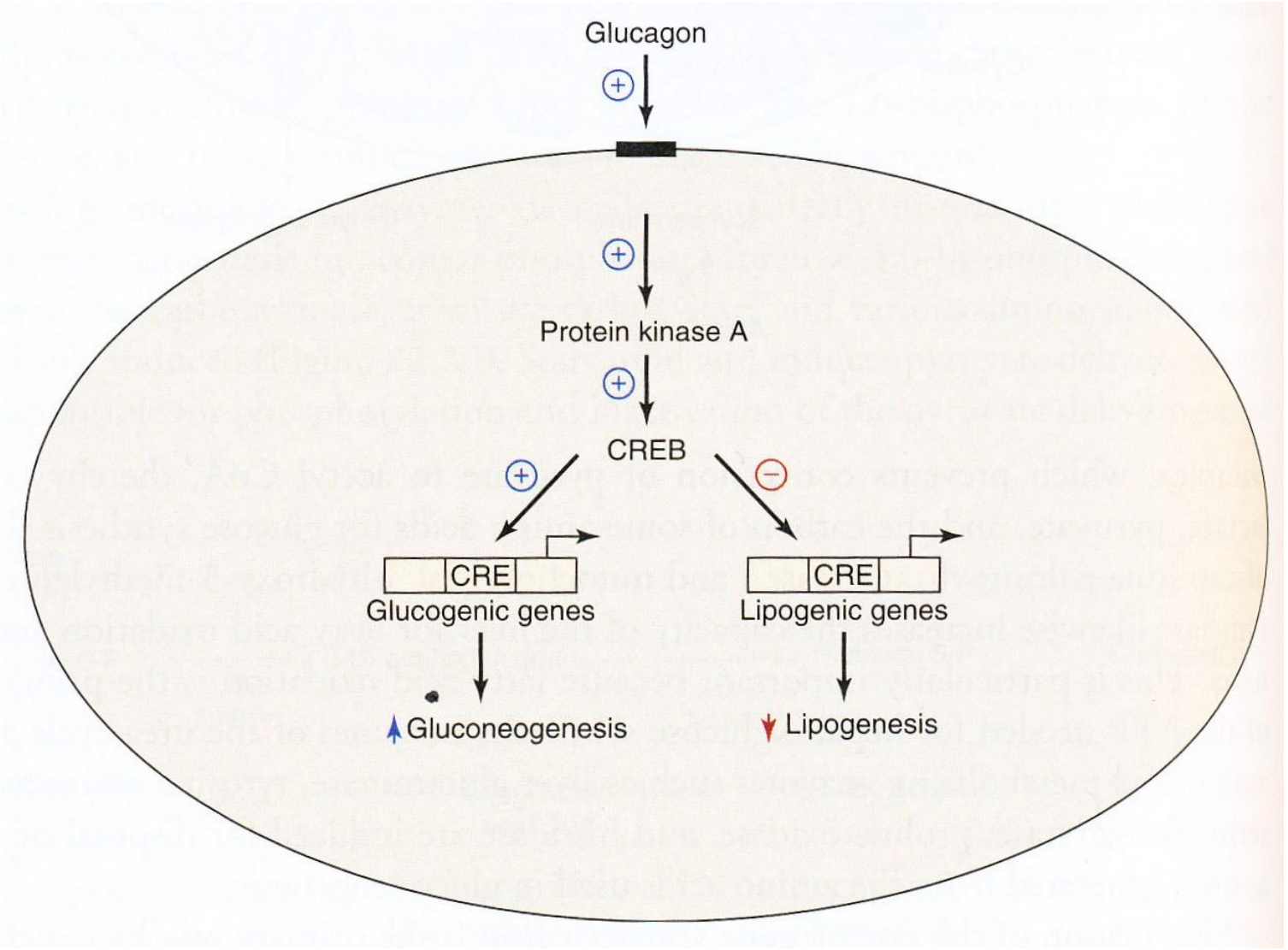
Induction/represion of enzymes

- **after a meal**



Induction/represion of enzymes

- **fasting**



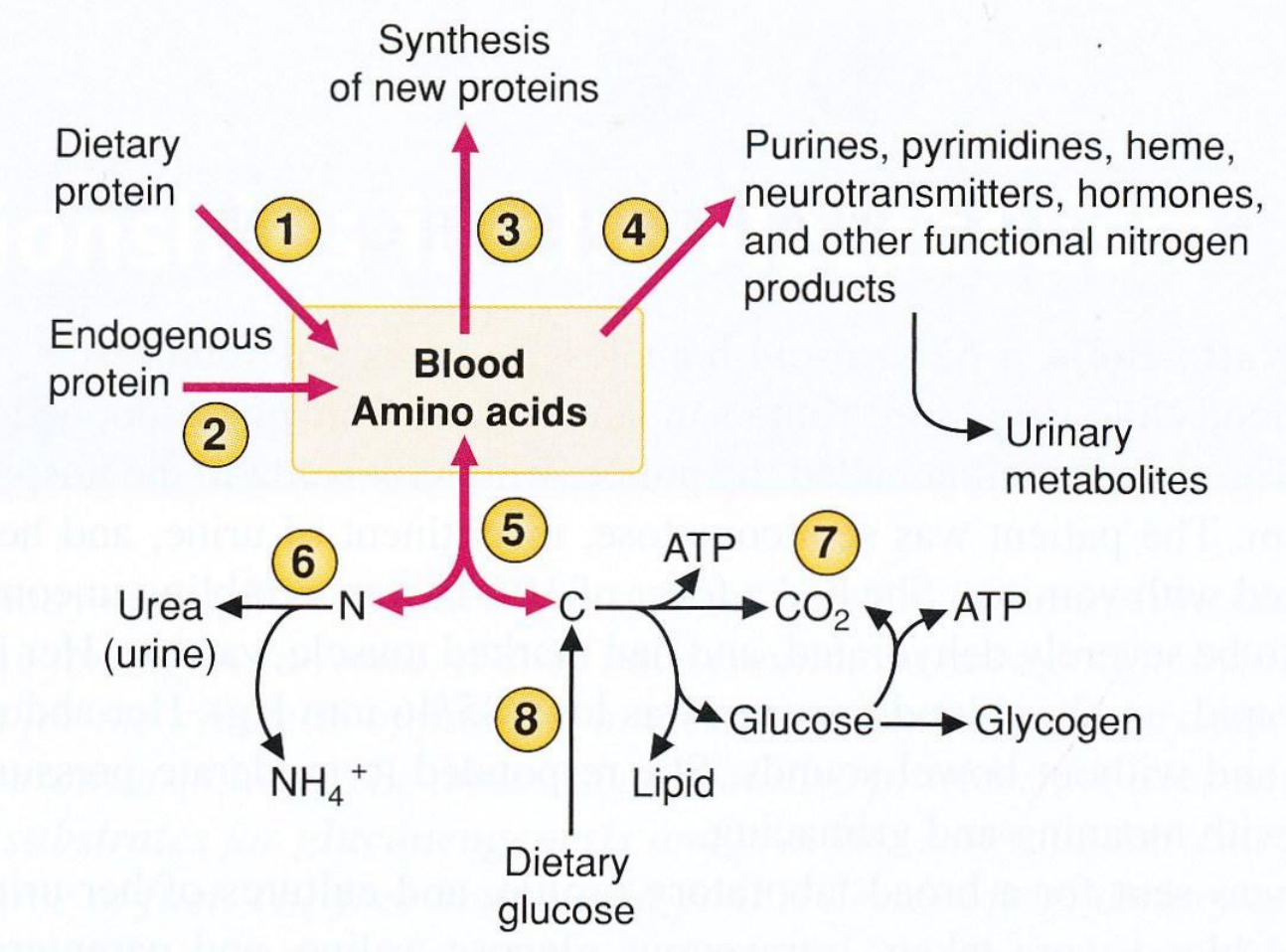
Induction/represion of enzymes

Liver enzymes regulated by induction/repression:

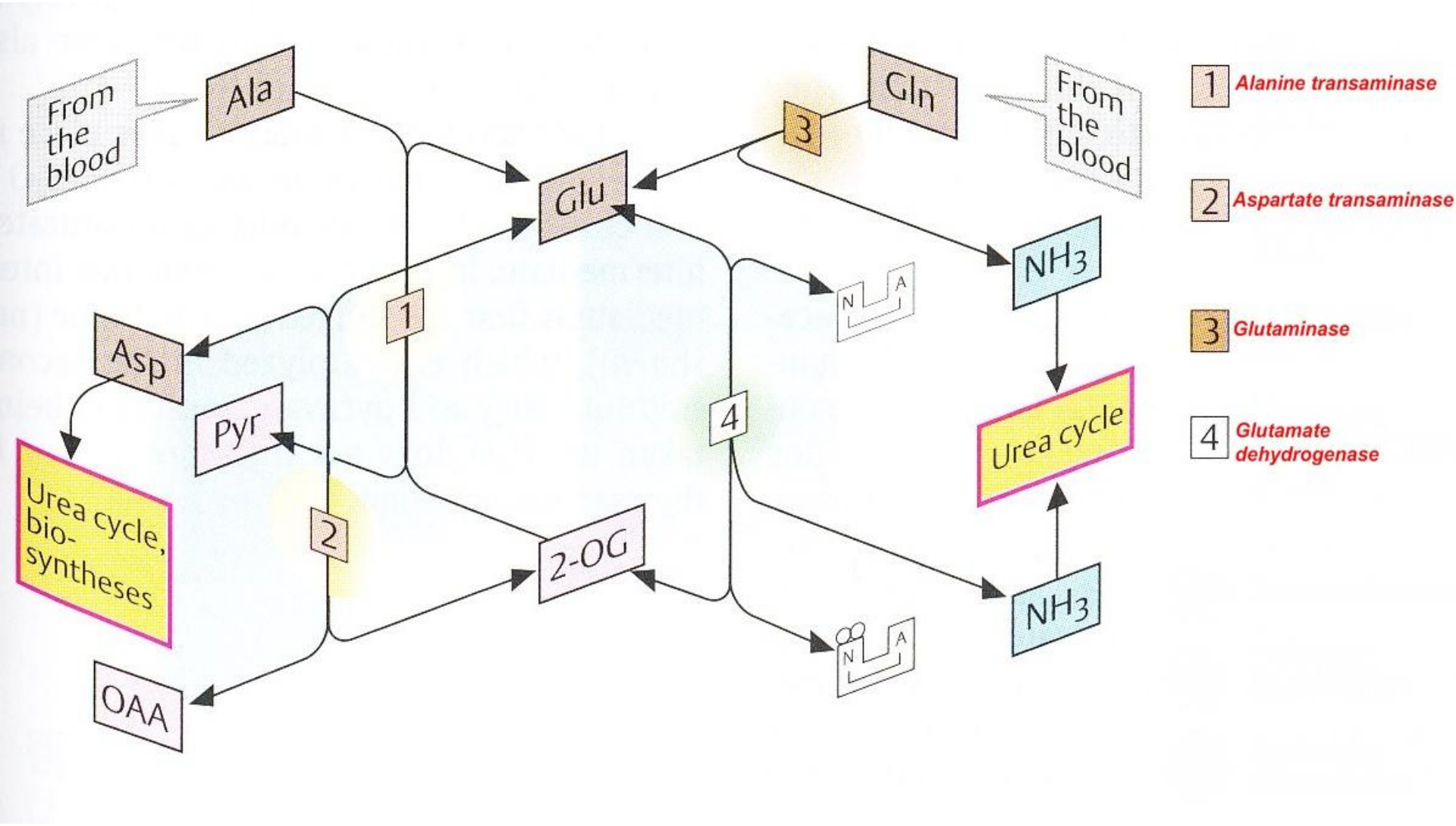
Enzym	State in which induced	Process affected
Glucokinase	Fed	Glu → TG
Citrate lyase	Fed	Glu → TG
Acetyl CoA carboxylase	Fed	Glu → TG
Fatty acid synthase	Fed	Glu → TG
Malic enzyme	Fed	Production of NADPH
Glucose-6-P dehydrogenase	Fed	Production of NADPH
Glucose 6-phosphatase	Fasted	Production of blood glucose
Fructose 1,6-bisphosphatase	Fasted	Production of blood glucose
Phosphoenolpyruvate carboxykinase	Fasted	Production of blood glucose

Interorgan amino acid exchange

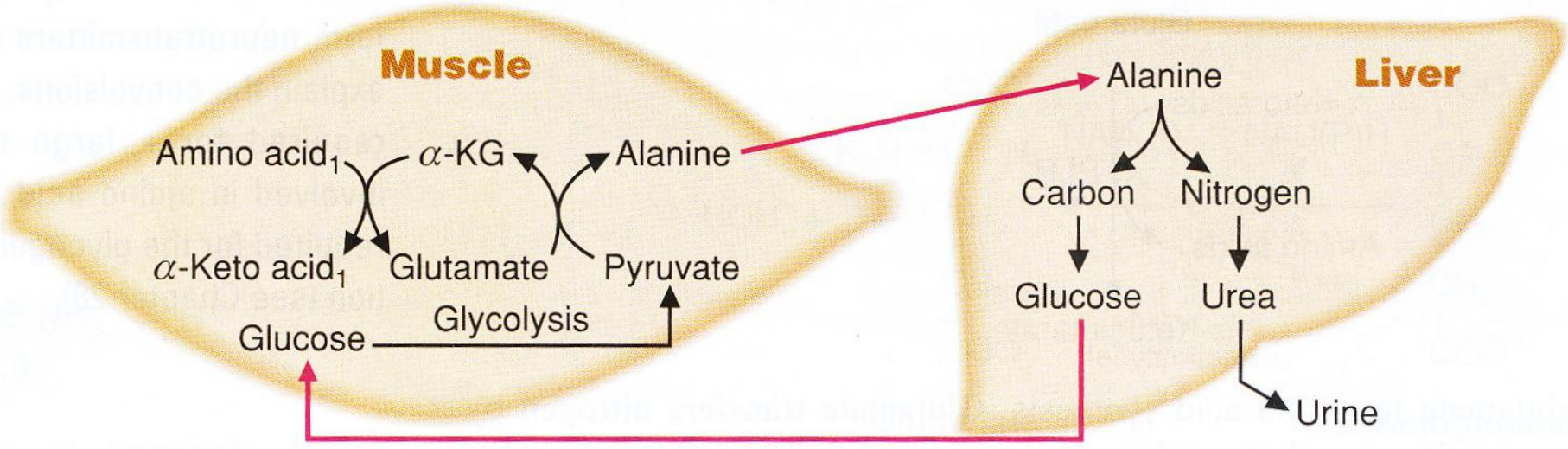
Maintance of the blood amino acid pool:



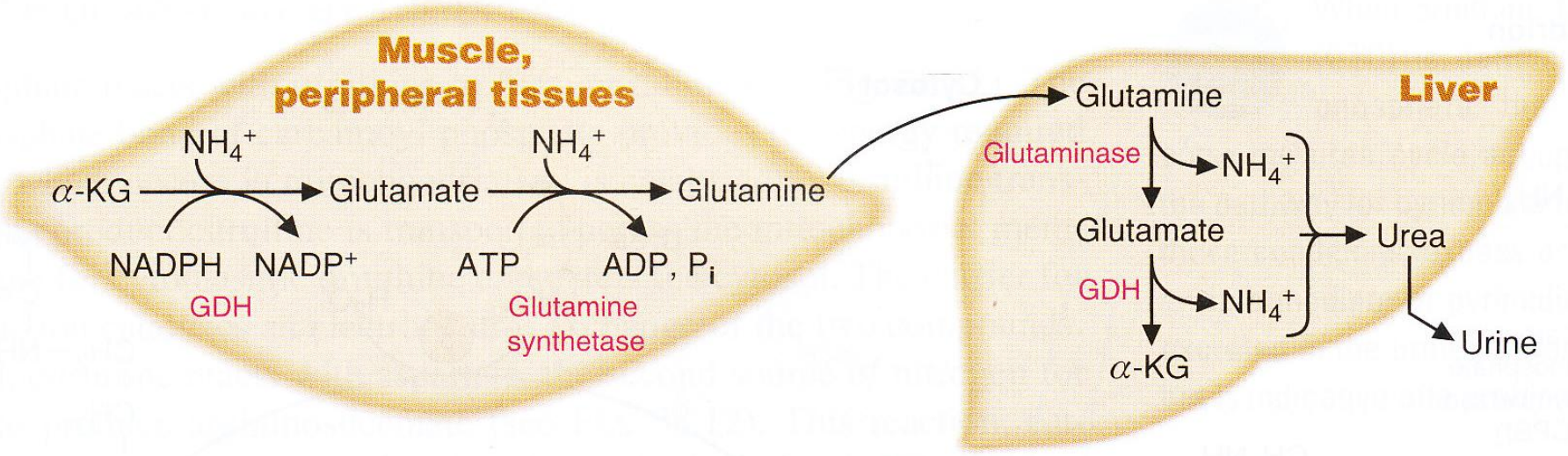
NH_3 metabolism in the liver:



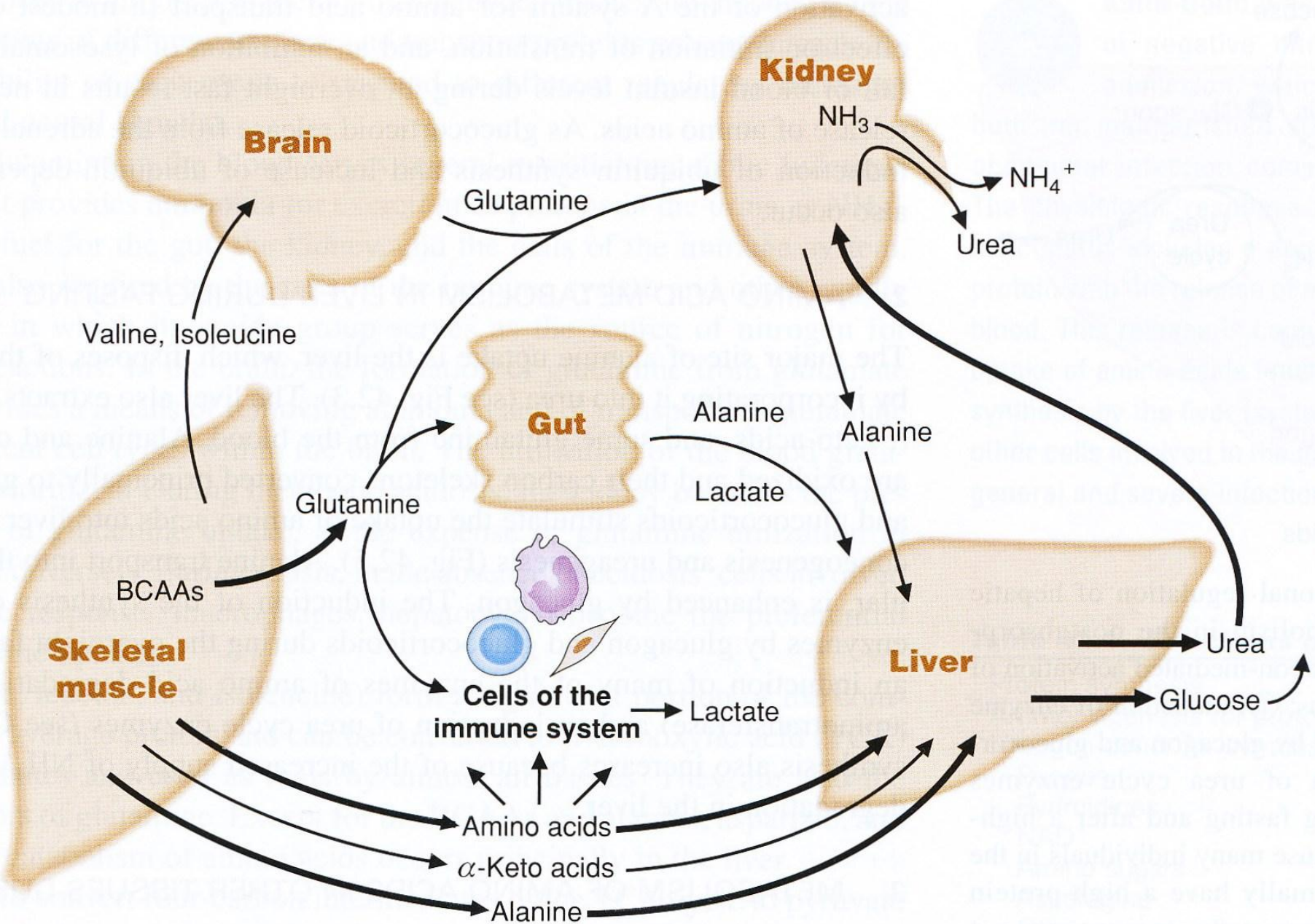
The glucose/alanine cycle:



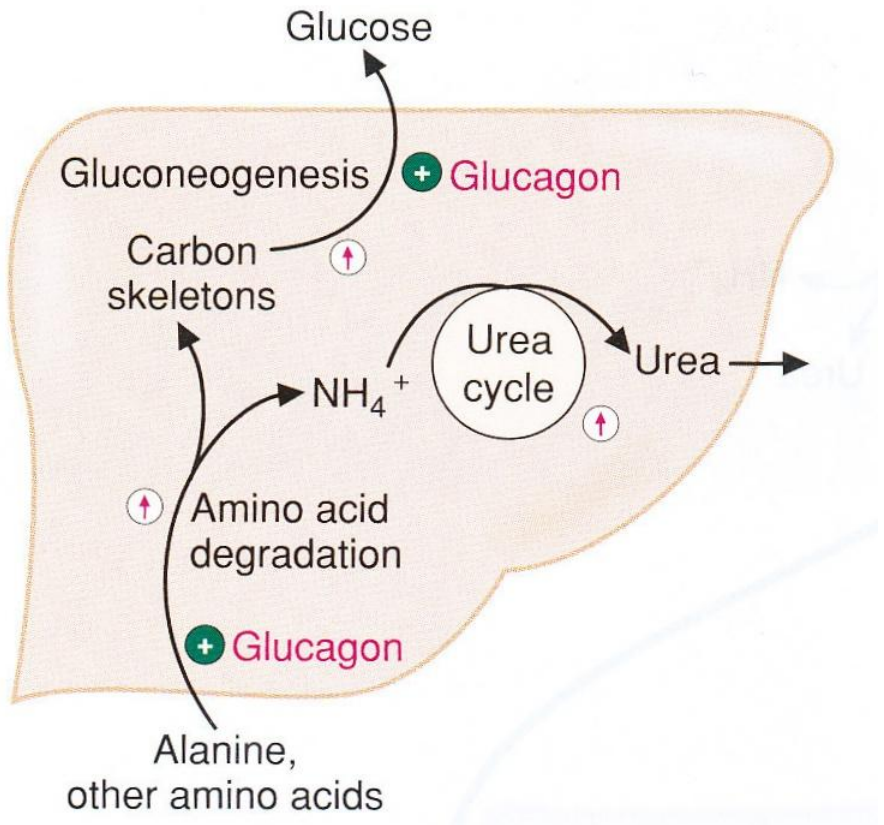
The metabolism of glutamin:



Interorgan amino acid exchange after an overnight fast:



Hormonal regulation of hepatic amino acid metabolism in the postabsorptive state



Principles governing amino acid flux between tissues:

- ✓ NH_3 is toxic → alanine, glutamine
- ✓ The pool of glutamine
  - excretion of protons (NH_4^+)
  - a fuel (gut, kidney, immune system cells)
  - the source of nitrogen for biosynthetic reactions (immune system cells)
  - glutamate transport in the brain
- ✓ BCAAs (valine, leucine, isoleucine) → conversion to intermediates of the TCA (most tissues)
- ✓ Amino acids represent major substrates for gluconeogenesis
- ✓ The protein turnover determines the size of the free amino acid pools available for the synthesis of new proteins

Functions of glutamine:

A fuel (gut, kidney, immune system)
Proteosynthesis
Excretion of protons
Nitrogen donor for synthesis of purines, pyrimidines, NAD^+, amino sugars, asparagine
Glutamate donor for synthesis of glutathione, GABA, ornithine, arginine, proline

Summary:

✓ The metabolism switches between different nutritional states

- regulated by hormones
- storage, mobilization and utilization of fuels

✓ Mechanisms involved in switching liver metabolism between the fed and starved states

✓ Changes in different nutritional and hormonal states are variations on the starve-feed cycle (obesity, pregnancy)

✓ Different organs cooperate in amino acids metabolism

Pictures used in the presentation:

Marks´ Basic Medical Biochemistry, A Clinical Approach, third edition, 2009 (M. Lieberman, A.D. Marks)

Textbook of Biochemistry with Clinical Correlations, sixth edition, 2006 (T.M. Devlin)