ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

METABOLIC INTEGRATION

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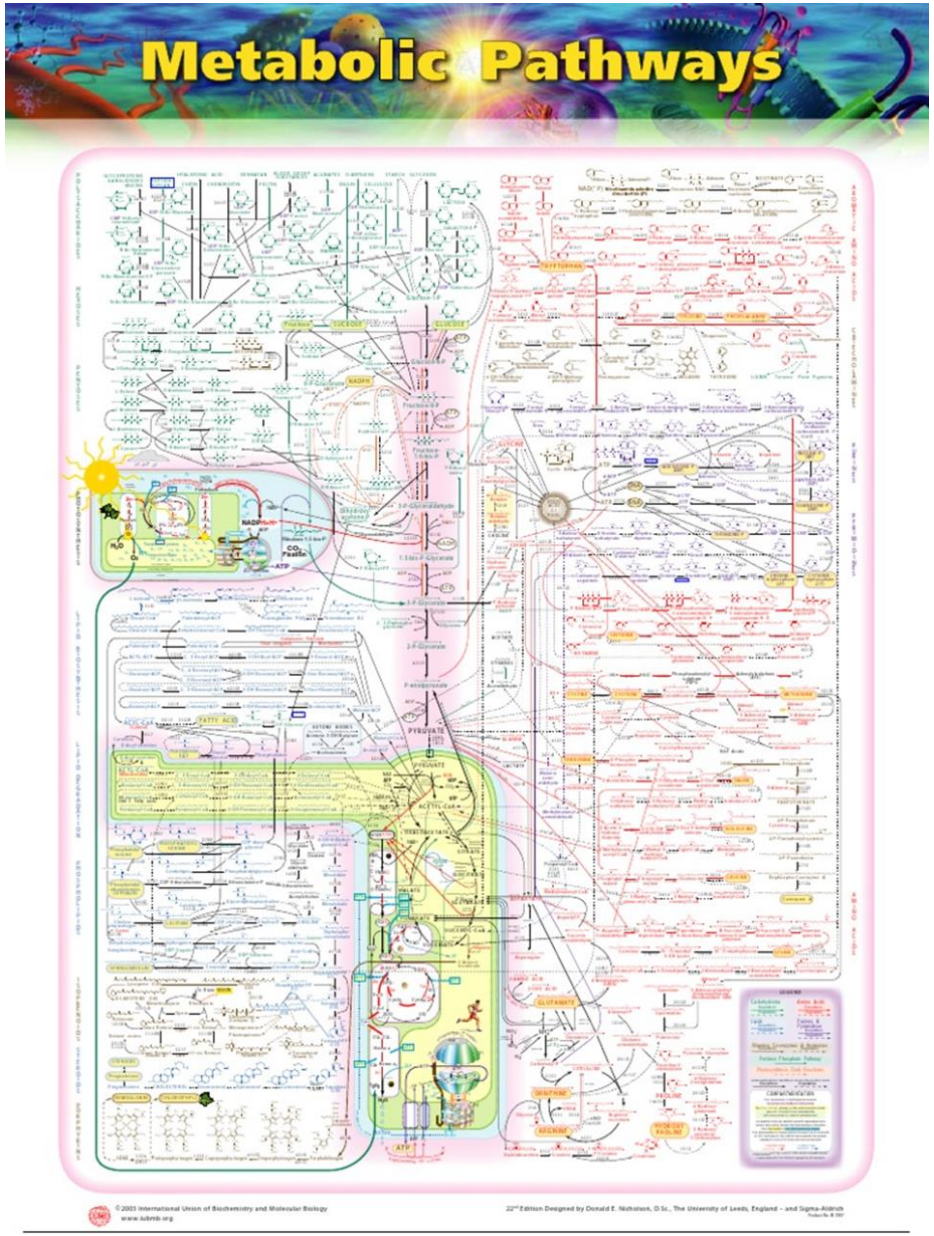
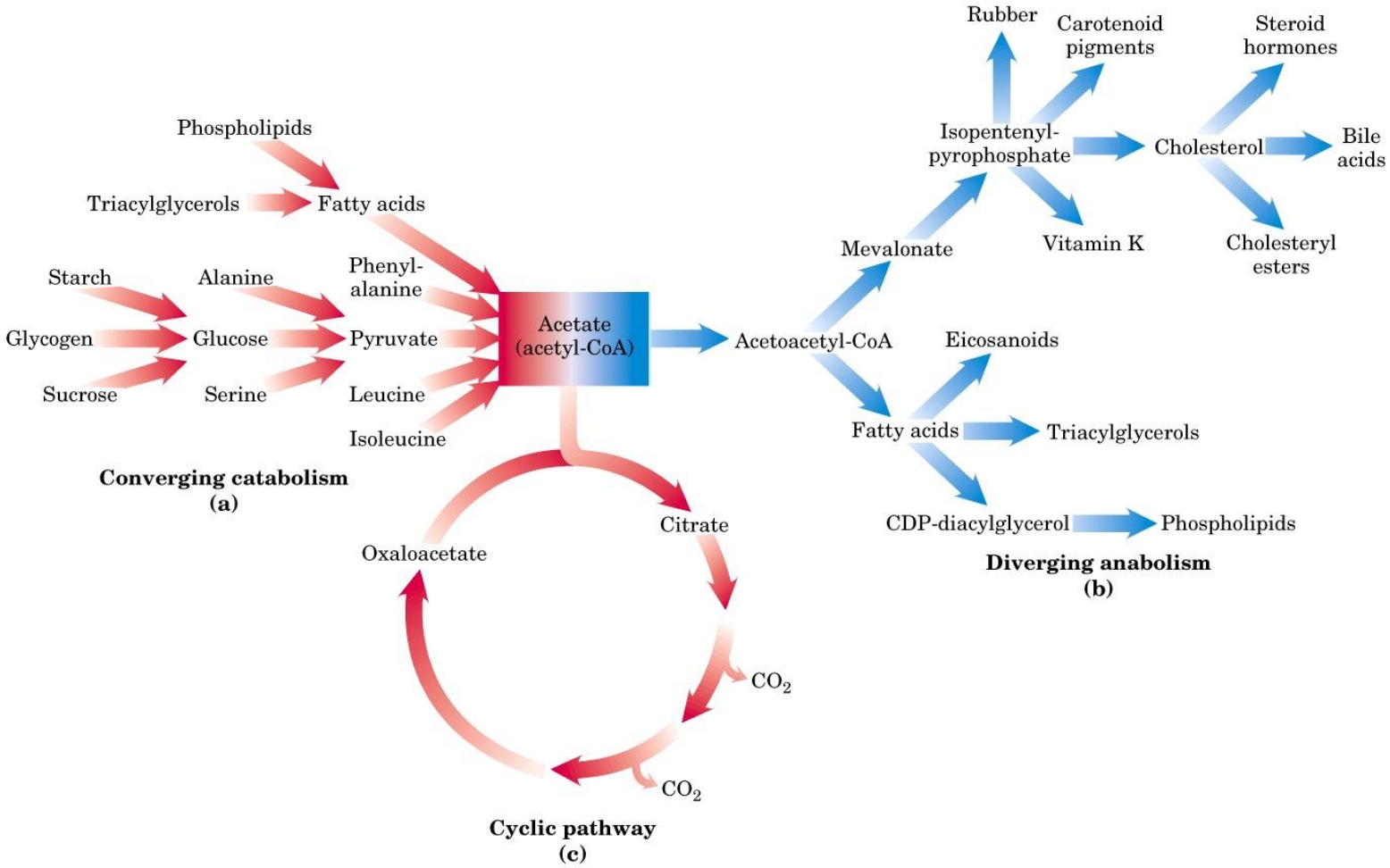
METABOLIC INTEGRATION



METABOLIC INTEGRATION



METABOLIC INTEGRATION

Thousands of chemical reactions, often contrasting, can co-occur.

How is metabolic traffic disciplined and controlled?

- Connecting metabolites
- Ratio [NADH]/[NAD^+] and [NADPH]/[$NADP^+$]
- Energy charge by concentration of ATP, ADP, AMP
- Steady-state concentrations of intermediates
- Allosteric regulation of key enzymes
- Enzyme protein expression
- Compartmentalisation
- Hormonal regulation

METABOLIC INTEGRATION

How is metabolic traffic disciplined and controlled?

- **Connecting metabolites**

- Main metabolites at the *intersection* of different pathways:

  Pyruvate

  Oxaloacetate

  Malate

  Acetyl-CoA

  α-ketoglutarate

  Aspartate

  Serine

METABOLIC INTEGRATION

How is metabolic traffic disciplined and controlled?

- **Ratio [NADH]/[NAD^+] and [NADPH]/[$NADP^+$]**

- [NADH]/[NAD^+]: low, NADH used in respiration (mitochondria);
- [NADPH]/[$NADP^+$]: high, NADPH used in *biosynthesis* (fatty acids, cholesterol, nucleotides) and *cellular protection* from oxidation.

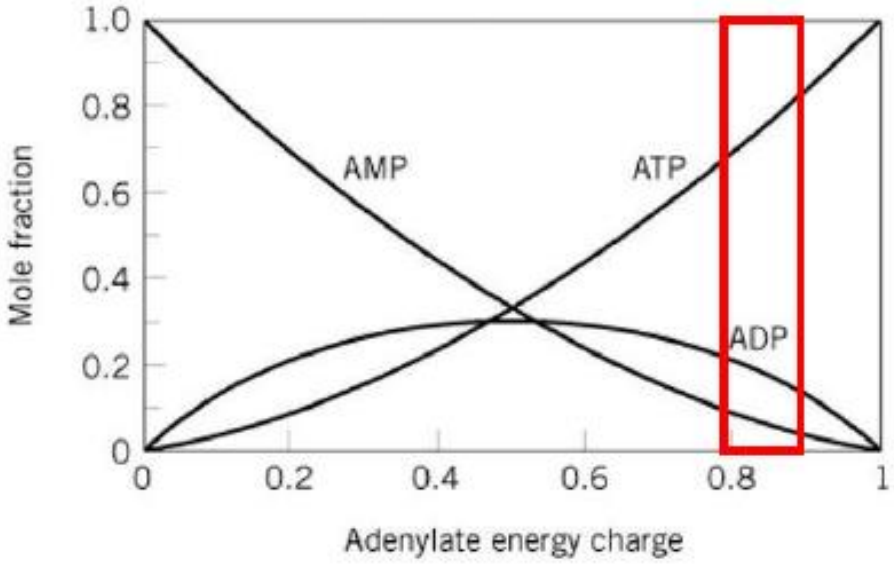
METABOLIC INTEGRATION

How is metabolic traffic disciplined and controlled?

- **Energy charge** by concentration of ATP, ADP, and AMP

$$\mathrm{EC} = \frac{[\mathrm{ATP}] + 0.5\,[\mathrm{ADP}]}{[\mathrm{ATP}] + [\mathrm{ADP}] + [\mathrm{AMP}]}$$

This value ranges from 0 (all AMP) to 1 (all ATP), with most cells maintaining an EC of **0.85–0.9** under normal conditions (11.4 mM ATP, 3.7 mM ADP, and 0.6 mM AMP).



METABOLIC INTEGRATION

How is metabolic traffic disciplined and controlled?

- **Energy charge** by concentration of ATP, ADP, and AMP

$$\mathrm{EC} = \frac{[\mathrm{ATP}] + 0.5\,[\mathrm{ADP}]}{[\mathrm{ATP}] + [\mathrm{ADP}] + [\mathrm{AMP}]}$$

- *High EC* stimulates *anabolism* and inhibits catabolism:

ATP (also UTP, CTP, GTP) as a *substrate* of biosynthetic reactions

ATP as an *allosteric inhibitor* of catabolic reactions (glycogen phosphorylase, PFK, isocitrate DH)

- *Low EC* stimulates *catabolism* and inhibits anabolism

AMP (ADP) as an *allosteric activator* of catabolic reactions (glycogen phosphorylase, PFK, isocitrate DH)

Lack of ATP → lack of substrate for anabolic reactions

METABOLIC INTEGRATION

How is metabolic traffic disciplined and controlled?

- **Steady-state concentrations of intermediates**

- In a *non-inhibited pathway,* the formation and removal of products pull all uphill reactions by mass action toward chemical equilibrium, which is never reached. At the same time, the accumulation of precursors *pushes* downhill reactions. The entire system remains in a steady state.

- If the *pathway is blocked*, e.g. by an inhibitor, all the intermediates upstream of the block will accumulate. The accumulation of precursors necessitates the exploration of alternative options if available.

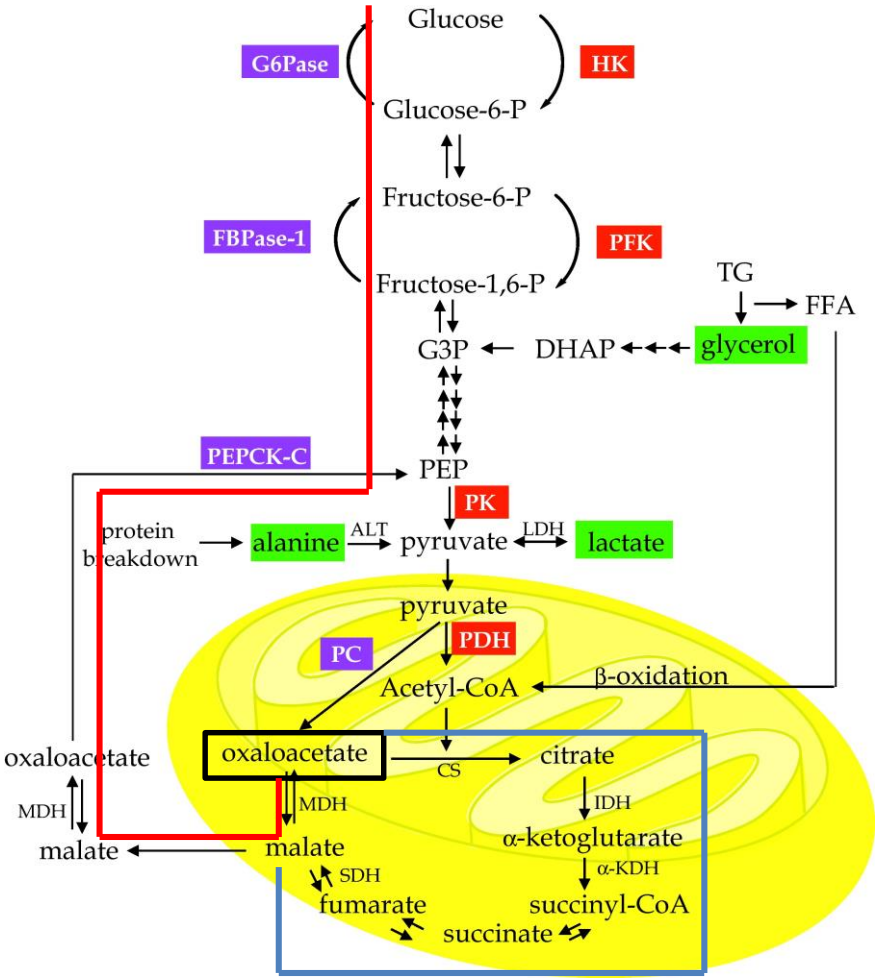
METABOLIC INTEGRATION

How is metabolic traffic disciplined and controlled?

- **Steady-state concentrations of intermediates**

Example:

- if *gluconeogenesis* is *operative*, *oxaloacetate* is removed from the TCA cycle because it is quickly reduced to malate to follow the gluconeogenic path;
- if *gluconeogenesis* is *inhibited*, oxaloacetate is available to activate the TCA cycle (citrate synthase).



METABOLIC INTEGRATION

How is metabolic traffic disciplined and controlled?

- **Steady-state concentrations of intermediates**

Accumulation of an intermediate will never reverse an irreversible reaction!

Example:

- Accumulation of acetyl-CoA cannot reverse PDH and get pyruvate! Consequence: It is impossible to synthesise glucose from fatty acids.

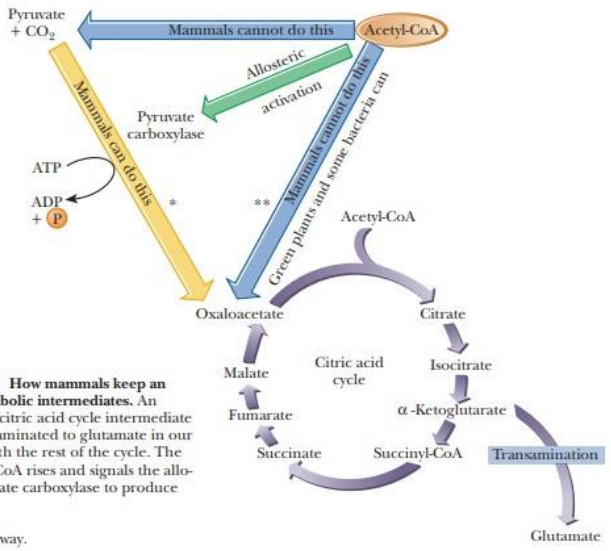


FIGURE 19.11 **How mammals keep an adequate supply of metabolic intermediates.** An anabolic reaction uses a citric acid cycle intermediate (α-ketoglutarate is transaminated to glutamate in our example), competing with the rest of the cycle. The concentration of acetyl-CoA rises and signals the allosteric activation of pyruvate carboxylase to produce more oxaloacetate.
*Anaplerotic reaction
**Part of glyocylate pathway.

METABOLIC INTEGRATION

How is metabolic traffic disciplined and controlled?

- **Expression of key proteins (enzymes, carriers, signalling..)**

- *Tissue specificity*

Lack of fatty acid oxidation in the brain: absence of long-chain thiolase

$CH_3(CH_2)_{12}$-CO-CH_2-CO-SCoA + CoA-SH → $CH_3(CH_2)_{12}$-CO-SCoA + CH_3-CO-SCoA

but presence of short-chain thiolase allows *ketone bodies oxidation*

CH_3-CO-CH_2-COOH + succinyl-CoA → CH_3-CO-CH_2-CO-SCoA + succinate

CH_3-CO-CH_2-CO-SCoA + CoASH → CH_3-CO-SCoA + CH_3-CO-SCoA

Lack of fatty acid oxidation in erythrocytes: no mitochondria

Lack of glycerol kinase in adipose tissue: glycerol cannot be used

Specific isozymes: liver glucokinase

METABOLIC INTEGRATION

How is metabolic traffic disciplined and controlled?

- **Expression of key proteins (enzymes, carriers, signaling..)**

- *Organelle specificity*

Unique localisation: e.g. Pyruvate carboxylase in mitochondria

Different isozymes in mitochondria and cytosol: malate DH, aspartate transaminase, isocitrate DH

- *Inducible proteins*

Short-lived

Expression by nutrition

Expression by hormones

METABOLIC INTEGRATION

How is metabolic traffic disciplined and controlled?

- **Cell compartimentalisation**

- Plasma membrane and internal membranes
- Membrane dynamics (fusion, fission, vesicular traffic, autophagy)
- Membrane diffusion (O_2, NH_3, small uncharged molecules*, hydrophobic molecules, some drugs…)
- Membrane transport: kinetics and thermodynamics
- Charged molecules and ions: membrane potentials

** For example NH_3, not NH_4^+; acetic acid, not acetate ion; H_2O, not H^+*

METABOLIC INTEGRATION

How is metabolic traffic disciplined and controlled?

- **Cell compartimentalisation**

- *Pathways having cytosolic and mitochondrial reactions*

Aerobic pyruvate oxidation, Glycolytic shuttles (NADH)

Gluconeogenesis (malate)

Fatty acid oxidation (carnitine)

Fatty acid biosynthesis (citrate)

Urea cycle (ornithine/citrulline)

Pyrimidine biosynthesis (dihydro-orotate DH)

Heme biosynthesis (δ-aminolevulinic, protoporphyrin)

METABOLIC INTEGRATION

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- **Cell compartimentalisation**

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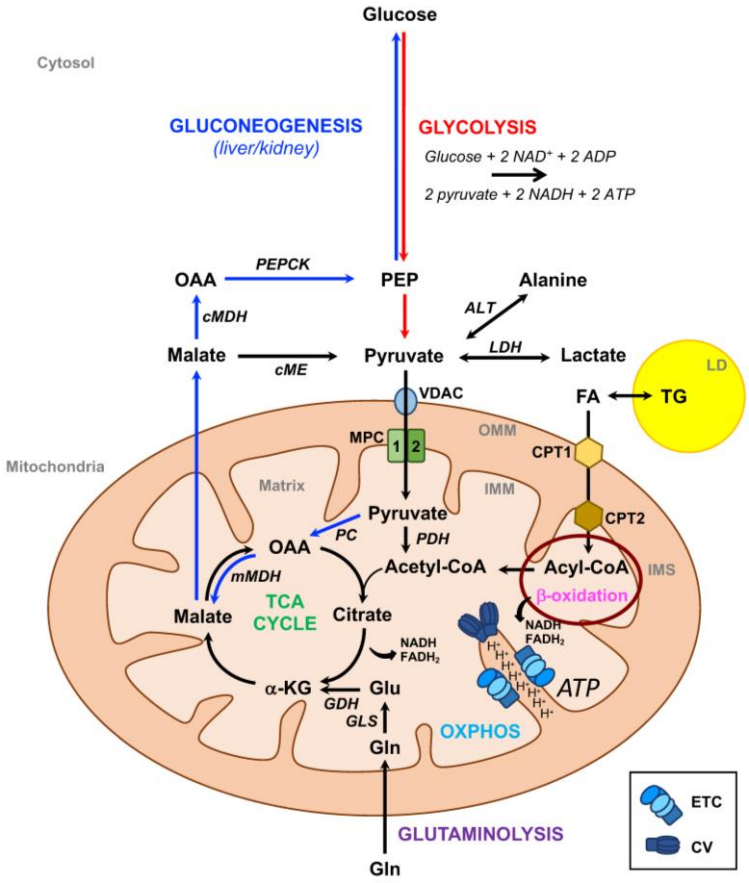

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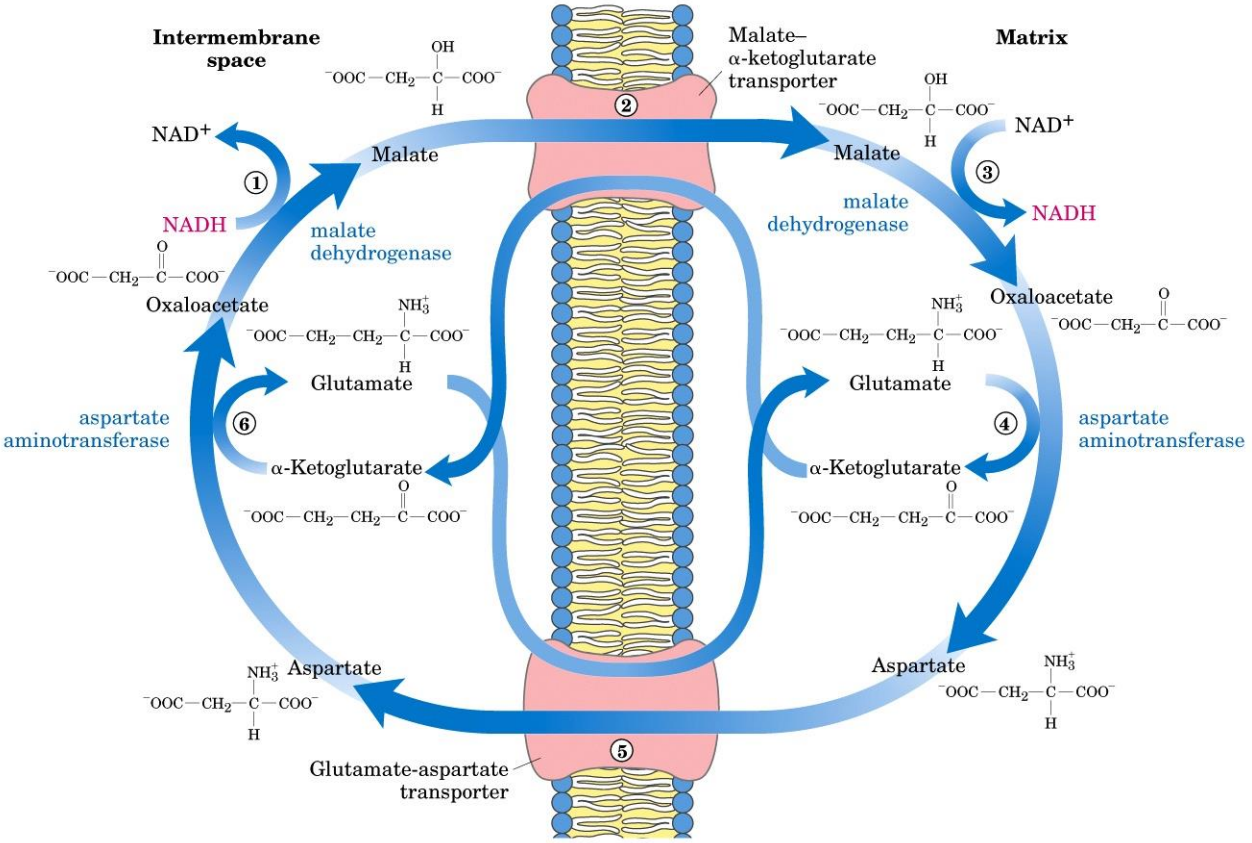

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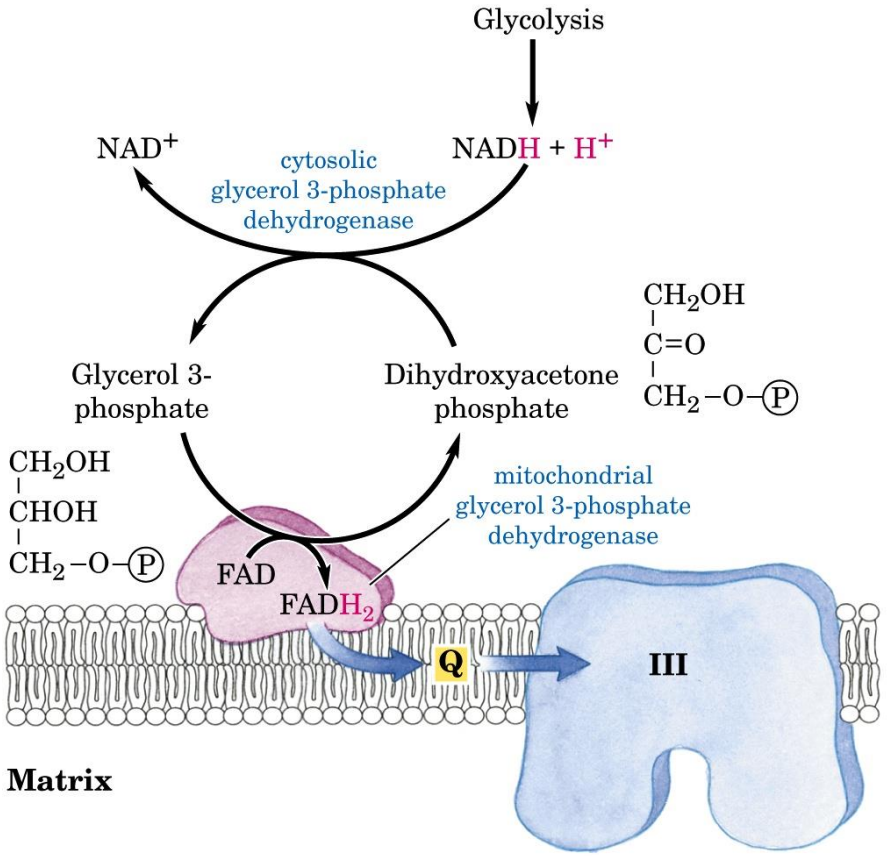

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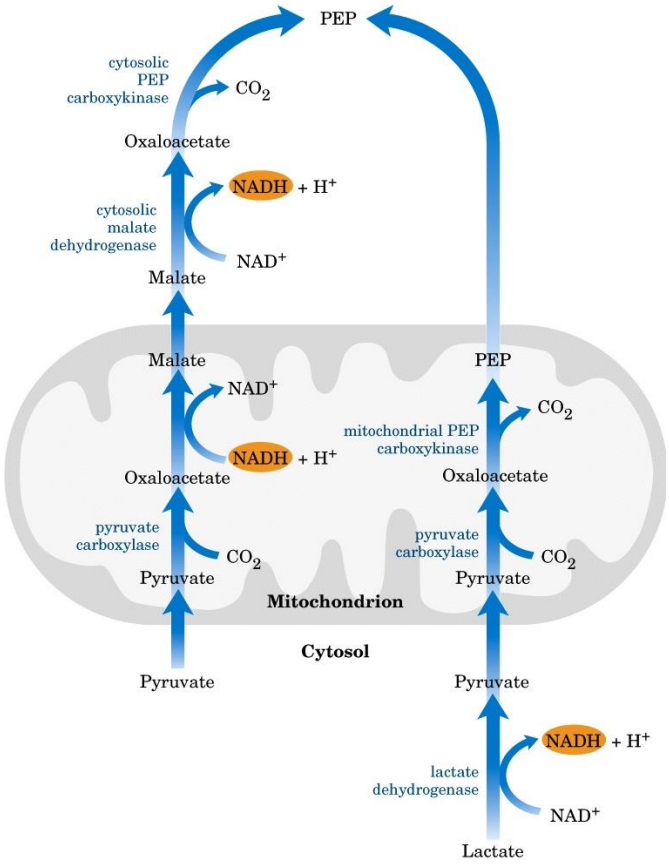


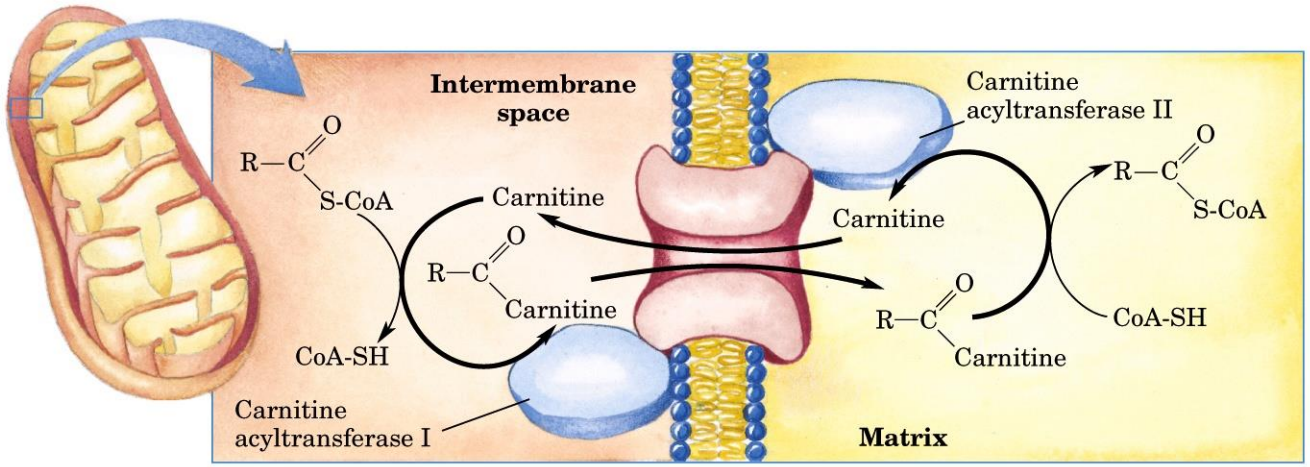
METABOLIC INTEGRATION

How is metabolic traffic disciplined and controlled?

- **Cell compartimentalisation**

- *Pathways having cytosolic and mitochondrial reactions*

The carnitine shuttle: CAT I is inhibited by malonyl-CoA, an intermediate of fatty acid biosynthesis; if fatty acid biosynthesis occurs, their oxidation is inhibited!



METABOLIC INTEGRATION

How is metabolic traffic disciplined and controlled?

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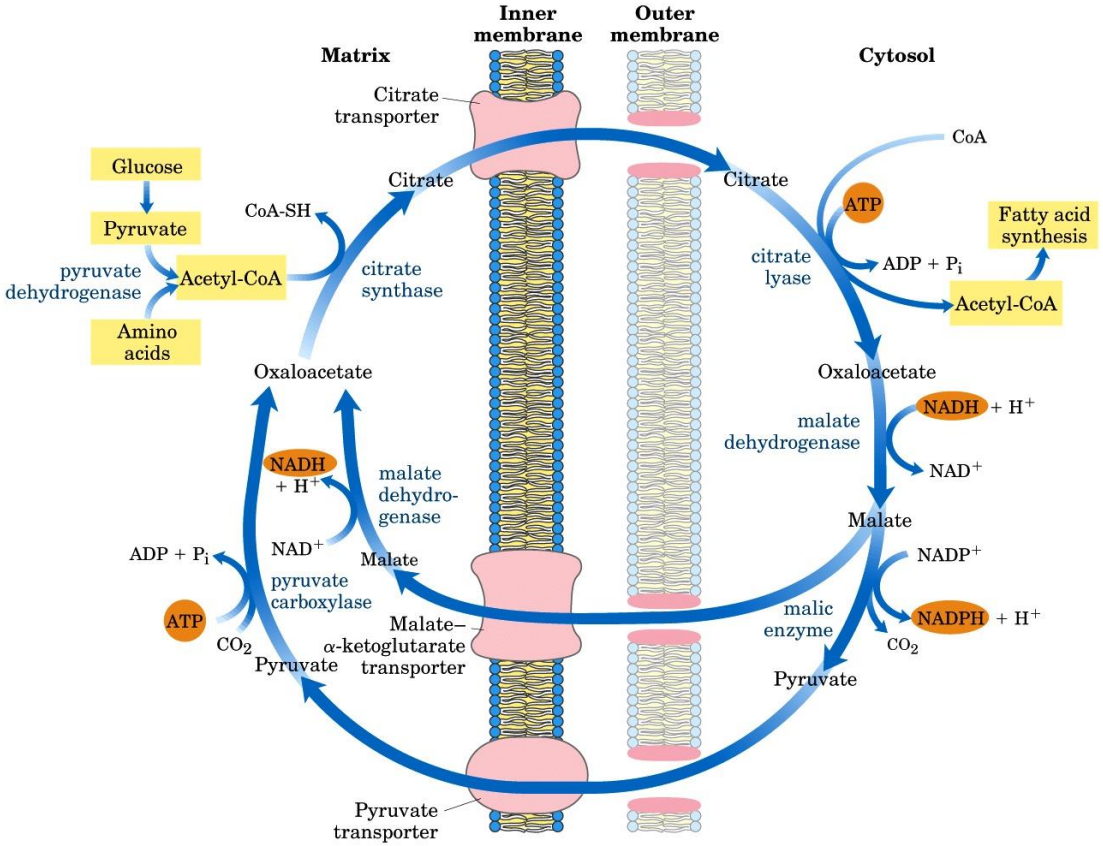
- *Pathways having cytosolic and mitochondrial reactions*



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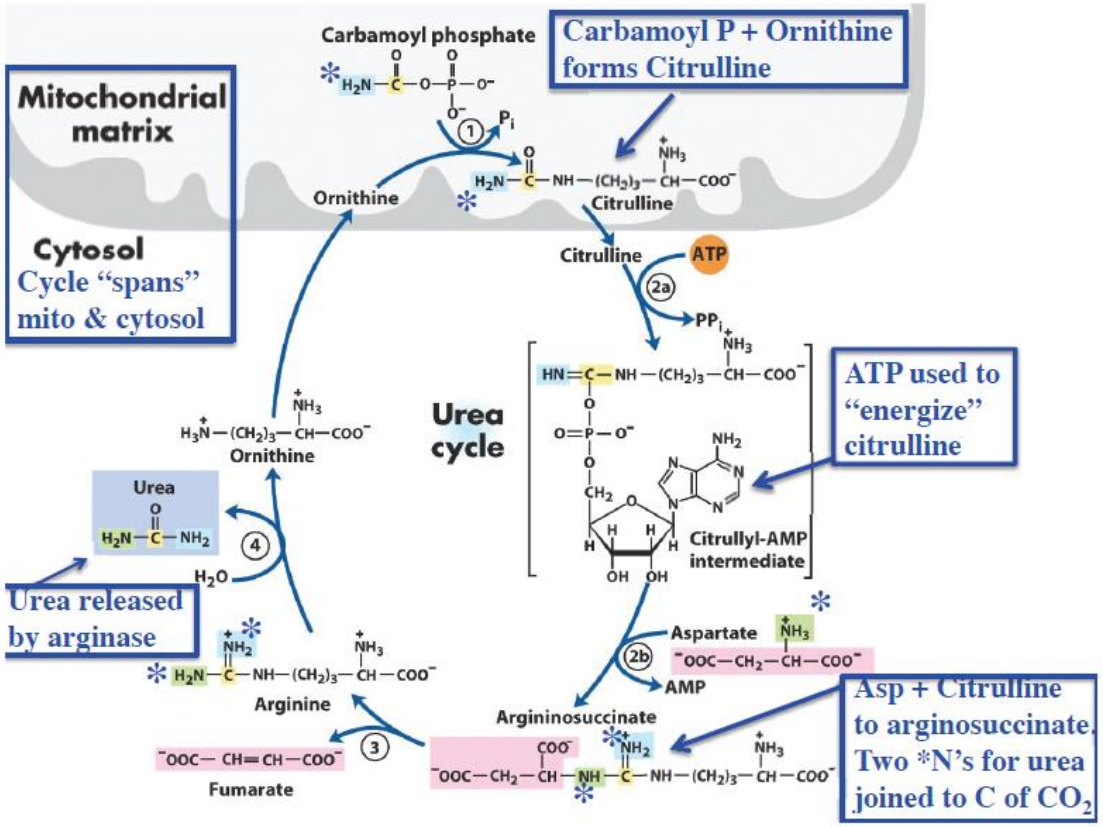


METABOLIC INTEGRATION

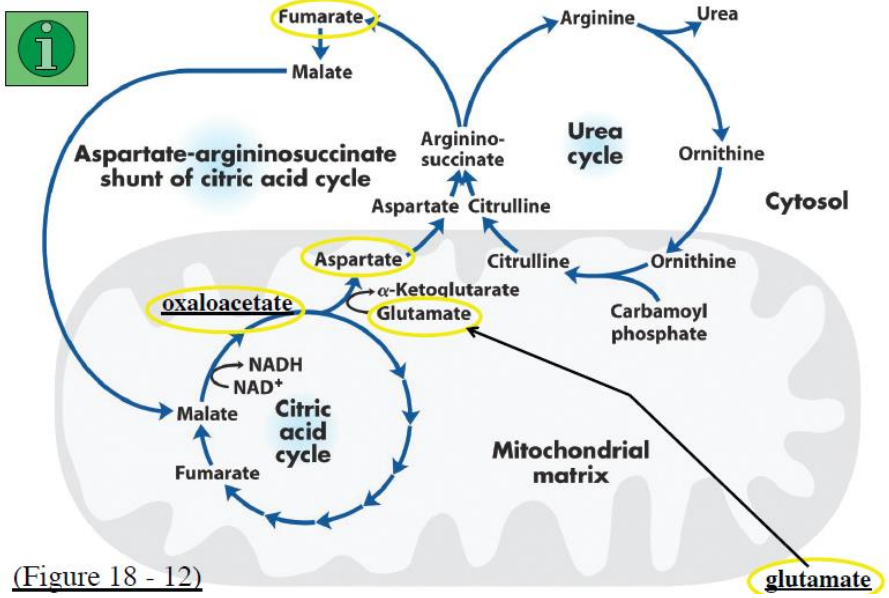
How is metabolic traffic disciplined and controlled?

- **Cell compartimentalisation**

- *Pathways having cytosolic and mitochondrial reactions*

Glutamate can receive an amino group from any other amino acid, therefore, the amino group of any amino acid will be found in aspartate

Linkage of urea cycle to citric acid cycle: fumarate "re-cycled" to oxaloacetate to be "re-transaminated" to aspartate.



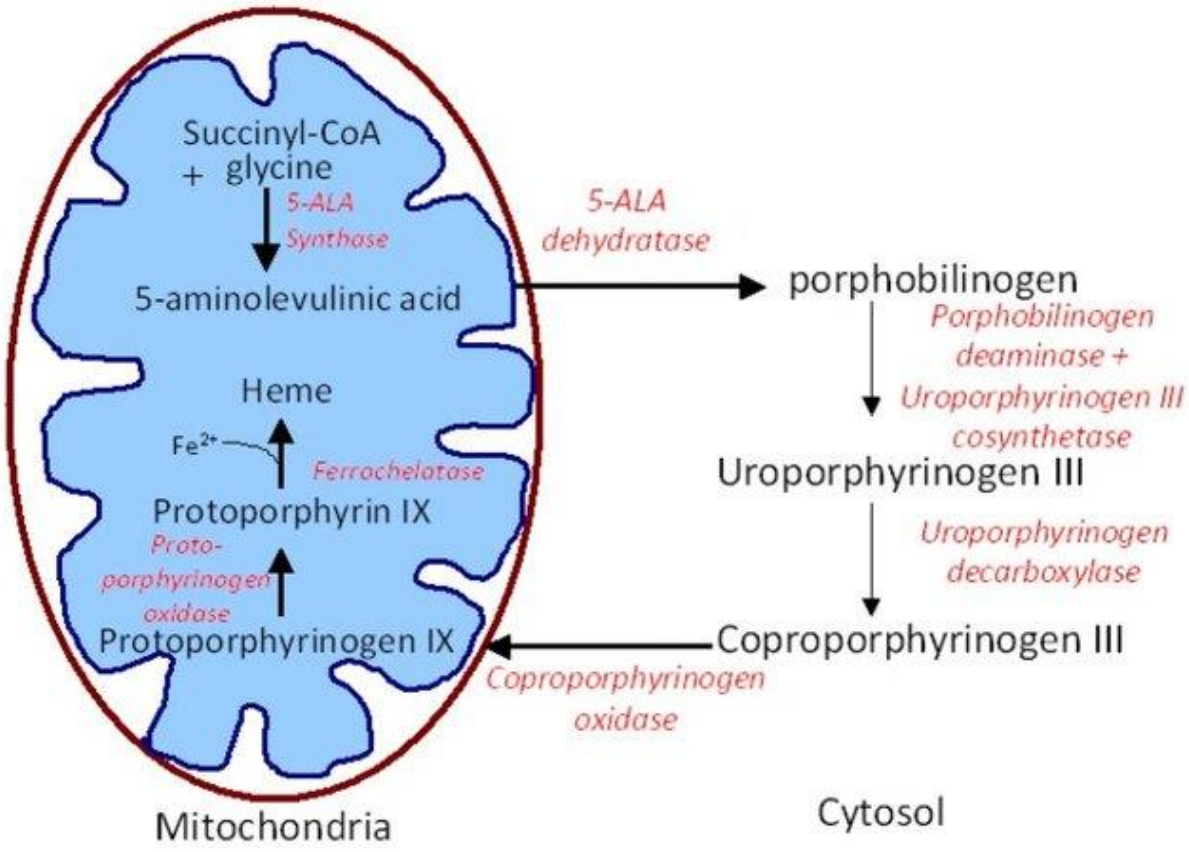
(Figure 18 - 12)

METABOLIC INTEGRATION

How is metabolic traffic disciplined and controlled?

- **Cell compartimentalisation**

- *Pathways having cytosolic and mitochondrial reactions*



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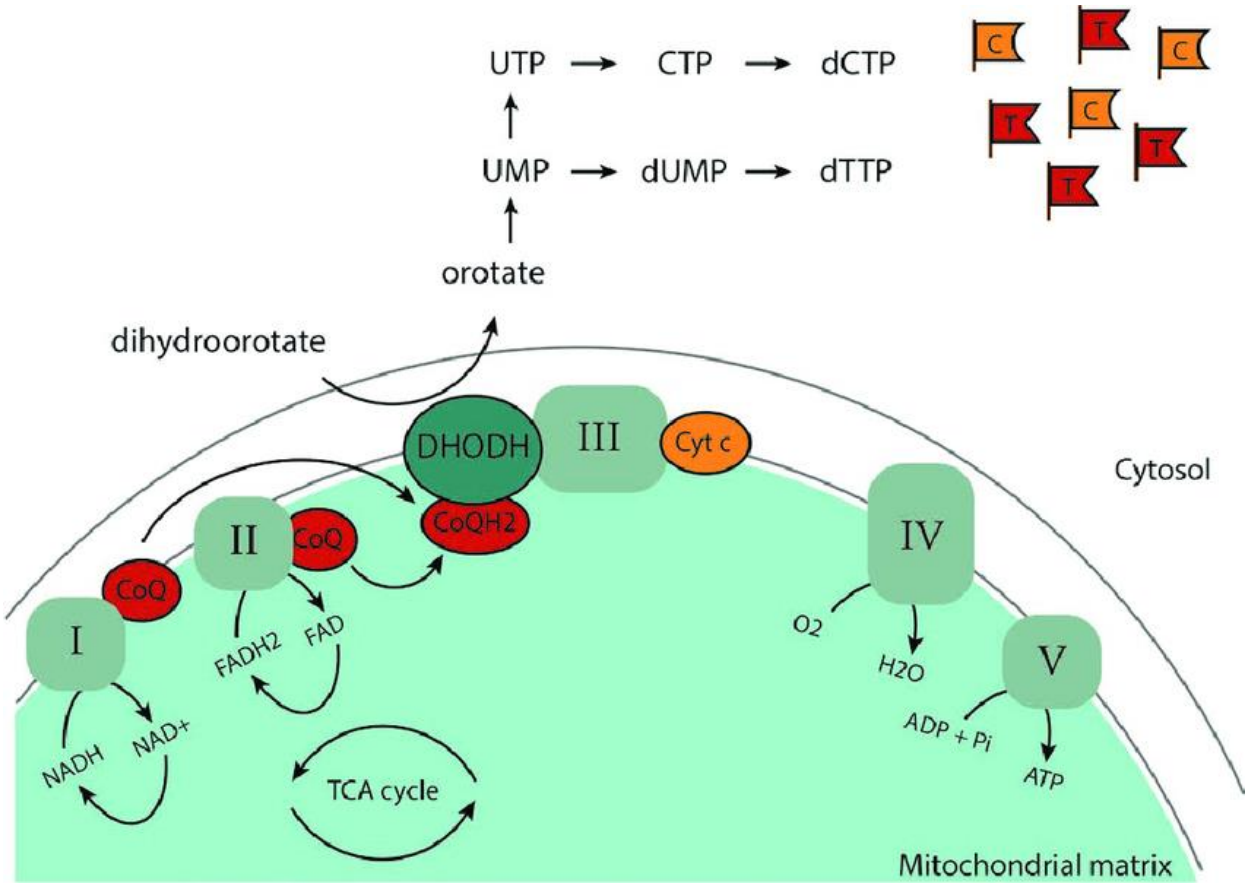


METABOLIC INTEGRATION

How is metabolic traffic disciplined and controlled?

- **Cell compartimentalisation**

- Key transported intermediates

Pyruvate (produced in cytosol and transported to matrix for its further metabolism: PDH).

Malate (from cytosol to matrix in malate/aspartate shuttle; from matrix to cytosol in initial steps of gluconeogenesis).

Aspartate, *Glutamate*, and other amino acids.

Some *TCA cycle intermediates* (citrate, isocitrate, α-ketoglutarate, succinate).

Acylcarnitines (transport of long-chain fatty acids).

METABOLIC INTEGRATION

How is metabolic traffic disciplined and controlled?

- **Cell compartimentalisation**

- Key transported intermediates

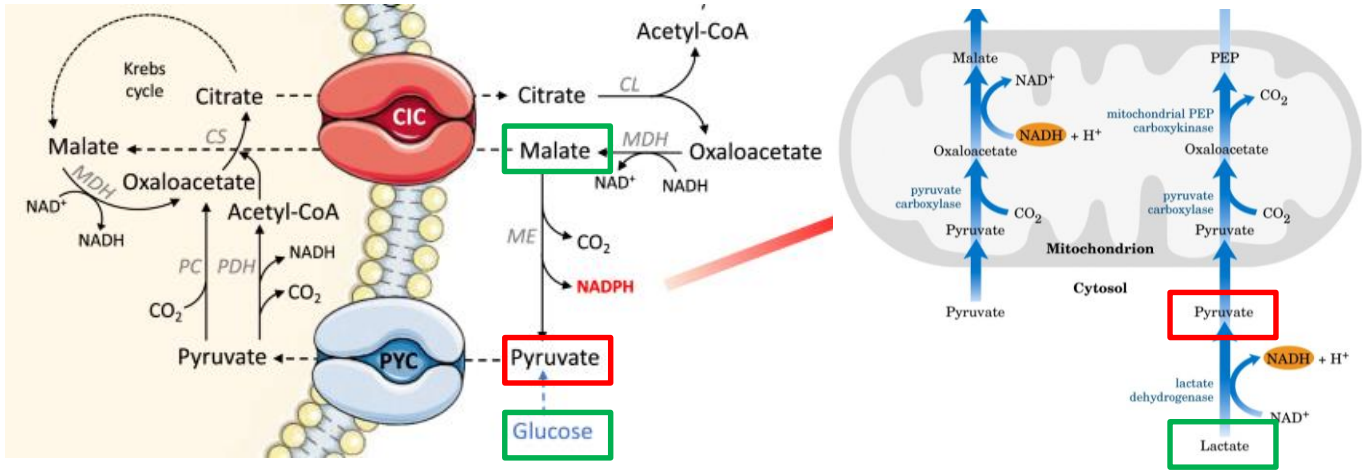
Pyruvate

Glycolysis: glucose → pyruvate (pyruvate kinase)

From amino acids: Serine, Alanine, Cysteine, Glycine, Tryptophan

From malate: malic enzyme; export of mitochondrial acetyl-CoA.

From lactate (lactate oxidation in heart, gluconeogenesis from lactate)



METABOLIC INTEGRATION

How is metabolic traffic disciplined and controlled?

- **Cell compartimentalisation**

- Key transported intermediates

Pyruvate

Carboxylation to oxaloacetate (pyruvate carboxylase). Anaplerotic reaction, gluconeogenesis.

Reduction to lactate: anaerobic glycolysis.

Oxidation to acetyl-CoA: for entry to the TCA cycle, fatty acid and cholesterol biosynthesis.

Transamination (synthesis of alanine, non-essential AA)

METABOLIC INTEGRATION

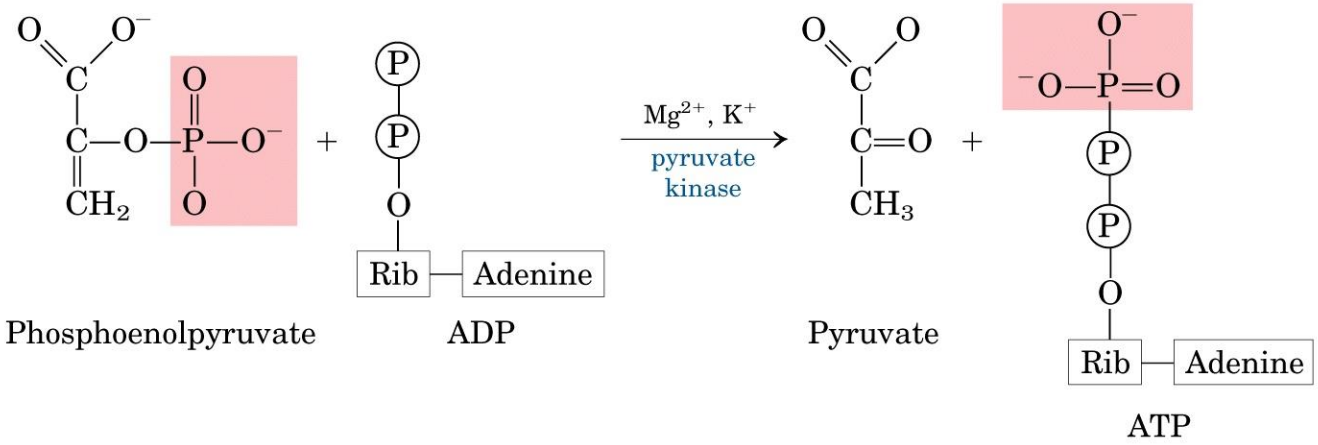
How is metabolic traffic disciplined and controlled?

- **Cell compartimentalisation**

- Key transported intermediates

Pyruvate

Glycolysis: glucose → pyruvate (pyruvate kinase)



Phosphoenolpyruvate ADP Pyruvate ATP

$\Delta G'^{\circ} = -31.4$ kJ/mol

METABOLIC INTEGRATION

How is metabolic traffic disciplined and controlled?

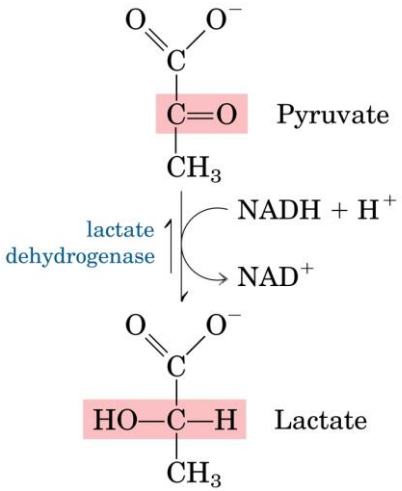
- **Cell compartimentalisation**

- Key transported intermediates

Pyruvate

Reduction to lactate: anaerobic glycolysis

Lactate oxidation in the heart, and gluconeogenesis from lactate



$\Delta G'^{\circ} = -25.1$ kJ/mol

METABOLIC INTEGRATION

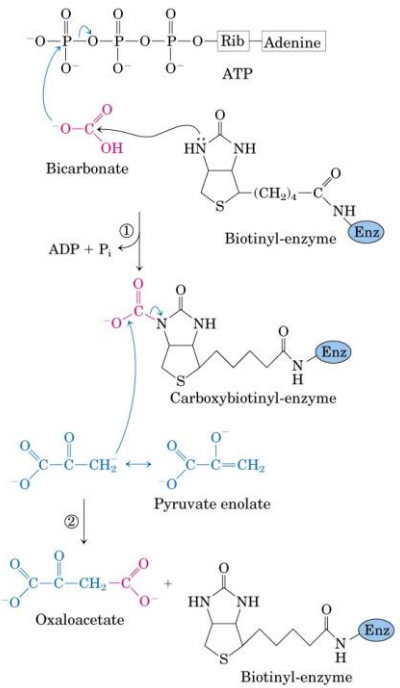
How is metabolic traffic disciplined and controlled?

- **Cell compartimentalisation**

- Key transported intermediates

Pyruvate

Carboxylation to oxaloacetate (pyruvate carboxylase). Anaplerotic reaction, gluconeogenesis.



METABOLIC INTEGRATION

Focus on the role of pyruvate carboxylase in liver

- *Activated by acetyl-CoA*
- *After a meal : anaplerotic*

- Insulin secreted

Glucose → pyruvate (+) Fructose-2,6-P

Pyruvate → acetyl-CoA (+) PDH dephosphorylated

Acetyl-CoA activates pyruvate carboxylase → OAA activates the TCA cycle

OAA cannot be used for gluconeogenesis because insulin blocks FBPase (high F2,6bP).

METABOLIC INTEGRATION

Focus on the role of pyruvate carboxylase in liver

- *Activated by acetyl-CoA*
- *At fasting: gluconeogenesis*

- glucagon secreted

Pyruvate from amino acids, not from glucose

PDH phosphorylated, inhibited

Fatty acid oxidation (+) produces acetyl-CoA

Acetyl-CoA activates pyruvate carboxylase → OAA

OAA is reduced to malate by high mitochondrial NADH from β-oxidation.

Malate exported from mitochondria initiates gluconeogenesis (activated by glucagon).

METABOLIC INTEGRATION

Focus on the role of pyruvate carboxylase in the liver

- *After a meal, secretion of insulin* (all key enzymes dephosphorylated)

Insulin → Tandem E kinase (PFK-2) → F2,6bP → PFK (+) → Glycolysis (+)

Insulin → Tandem E kinase → F2,6bP → FBPase (-) → Gluconeogenesis (-)

Insulin → PK (+) → Glycolysis (+)

Insulin → PDH (+) → Acetyl-CoA

Insulin → Lipolysis (-) → No FA oxidation

Insulin → Acetyl-CoA carboxylase (+) → Malonyl-CoA (+) → Inhibits CAT 1 and FA oxidation while starting Lipogenesis.

No NADH accumulation from excessive FA oxidation, the TCA cycle can proceed (NADH inhibits Isocitrate DH).

Acetyl-CoA activates Pyruvate Carboxylase as an anaplerotic reaction.

The TCA cycle is stimulated: OAA is not reduced to malate as in gluconeogenesis because NADH is low.

METABOLIC INTEGRATION

Focus on the role of pyruvate carboxylase in the liver

- *At fasting, secretion of glucagon* (all key enzymes phosphorylated)

Glucagon → Tandem E phosphatase (FBPase-2) → F2,6bP (-) → PFK (-) → glycolysis (-)

Glucagon → Tandem E phosphatase → F2,6bP (-) → FBPase (+) → Gluconeogenesis (+)

Glucagon → PK-P (-) → Glycolysis (-)

Glucagon → PDH-P (-) → No acetyl-CoA from pyruvate

Glucagon → Lipolysis (+) → FA oxidation with accumulation of NADH

Glucagon→ Acetyl-CoA carboxylase(P) → (-) No lipogenesis

NADH accumulation from excessive FA oxidation inhibits the TCA cycle (isocitrate DH)

Pyruvate carboxylase is activated by acetyl-CoA → OAA

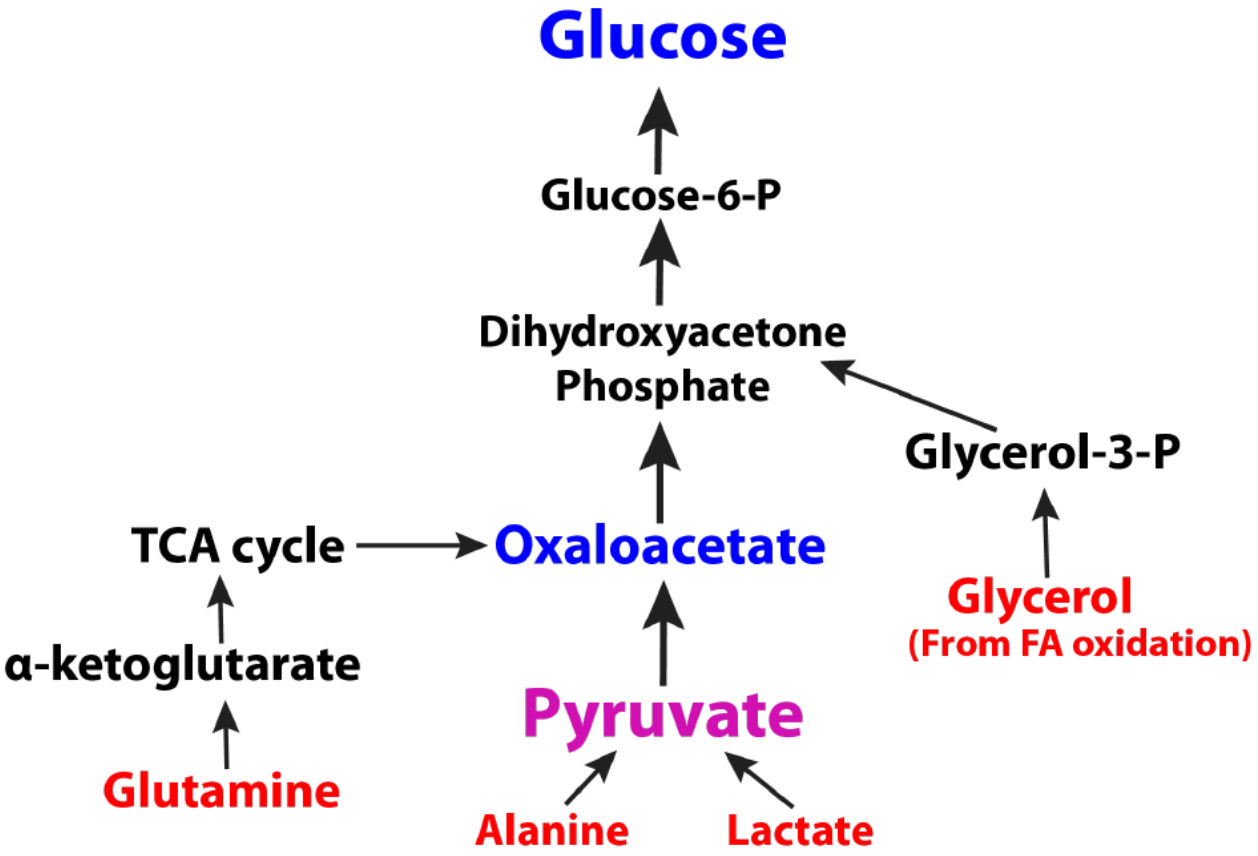
OAA cannot proceed in the TCA cycle that is inhibited

OAA is reduced to malate by excess NADH and follows gluconeogenesis

Acetyl-CoA cannot follow TCA cycle and forms ketone bodies

METABOLIC INTEGRATION

Focus on the role of pyruvate carboxylase in the liver



METABOLIC INTEGRATION

Reducing power for gluconeogenesis

Gluconeogenesis requires cytosolic *NADH* for the reduction of 1,3-BPG to glyceraldehyde-P.

If the carbon source is *lactate*, NADH is derived from oxidation of lactate to pyruvate in the cytosol

$$\text{lactate} + NAD^+ \rightarrow \text{pyruvate} + NADH + H^+$$

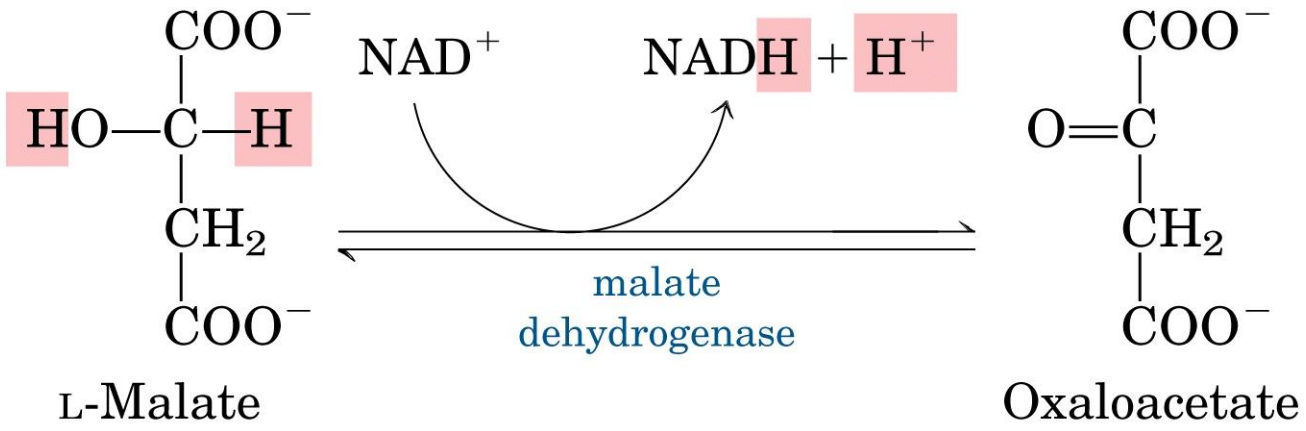
If the carbon source is *amino acids*, NADH is derived from malate export from the mitochondria followed by its oxidation to oxaloacetate in the cytosol

$$\text{malate} + NAD^+ \rightarrow \text{oxaloacetate} + NADH + H^+$$

METABOLIC INTEGRATION

Reducing power for gluconeogenesis

malate + NAD^+ → oxaloacetate + NADH + H^+



$\Delta G'^{\circ} = 29.7$ kJ/mol

METABOLIC INTEGRATION

Gluconeogenesis from aminoacids

Alanine, others → Pyruvate → Oxaloacetate

Aspartate → Oxaloacetate

Oxaloacetate + NADH + H^+ → **Malate** + NAD^+

Other aminoacids → TCA cycle intermediates → **Malate**

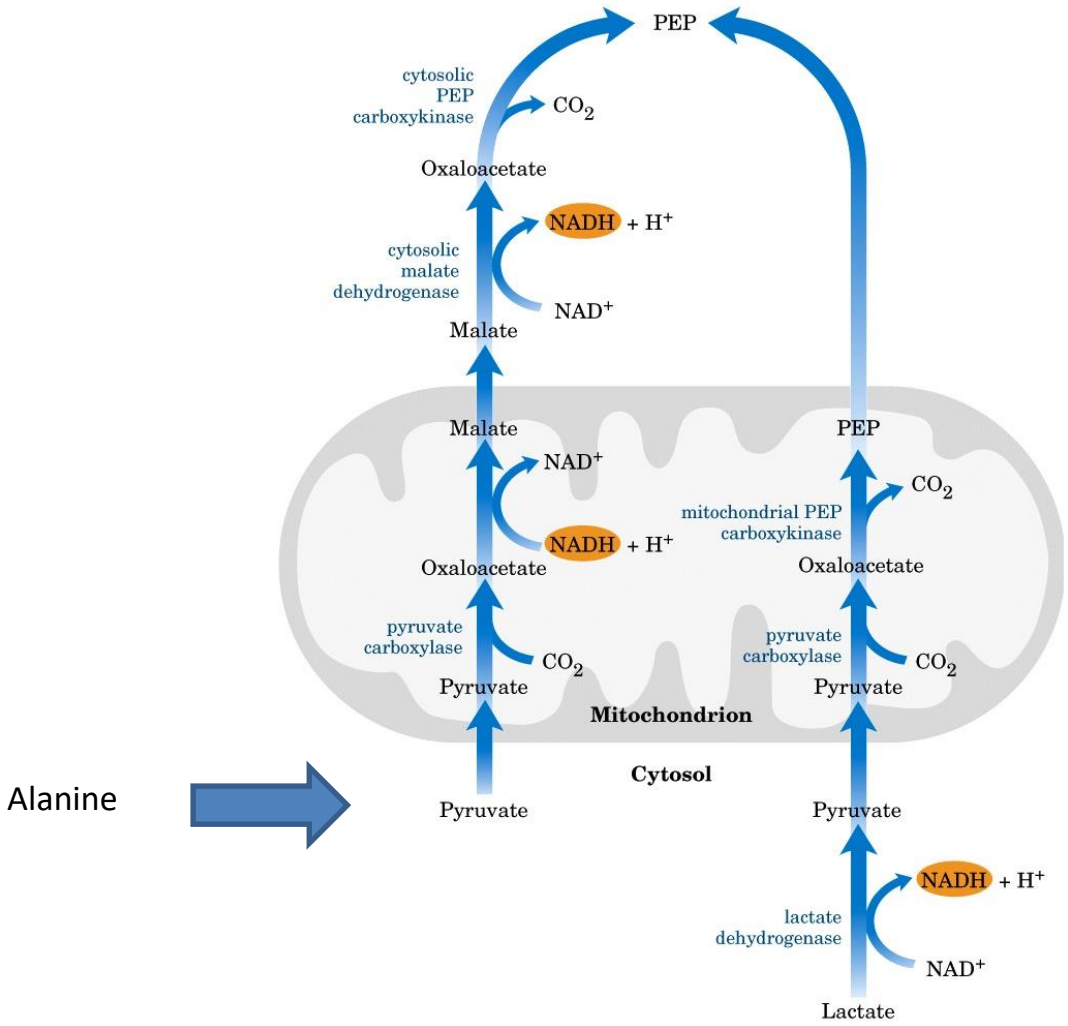
Malate → to cytosol

Malate + NAD^+ → Oxaloacetate **+ NADH + H^+**

Oxaloacetate → Phosphoenolpyruvate

METABOLIC INTEGRATION

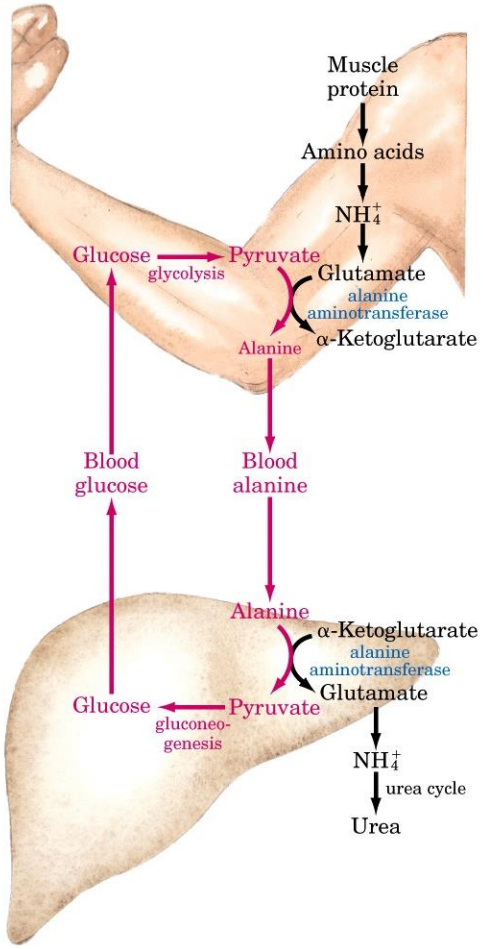
Gluconeogenesis from aminoacids



METABOLIC INTEGRATION

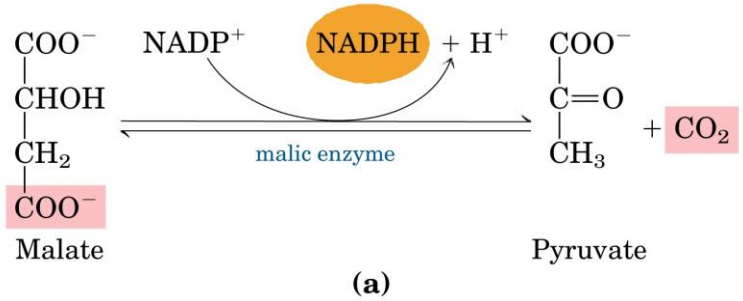
Gluconeogenesis from aminoacids

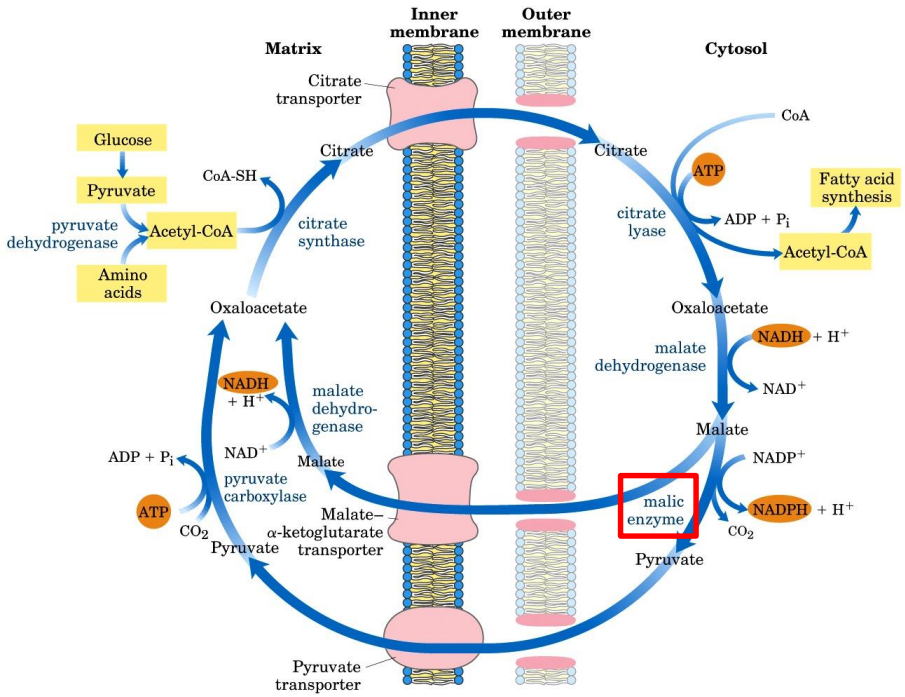
Alanine cycle



METABOLIC INTEGRATION

Gluconeogenesis from aminoacids





METABOLIC INTEGRATION

Gluconeogenesis from aminoacids:

All amino acids can be oxidised to acetyl-CoA:

Acetyl-CoA is then:

- oxidized in the TCA cycle
- used for fatty acid or cholesterol synthesis (liver, under insulin action)

Amino acid oxidation to acetyl-CoA:

Ketogenic → acetyl-CoA

AA → pyruvate → acetyl-CoA

AA→ oxaloacetate → malate → pyruvate → acetyl-CoA

AA → (α-ketoglutarate, succinyl-CoA, fumarate) → malate → pyruvate → acetyl-CoA

METABOLIC INTEGRATION

Gluconeogenesis from aminoacids:

Starting e.g. from glutamate, malate produced by the TCA cycle in hepatocytes can take the way of gluconeogenesis (export from mitochondria) or oxidation to acetyl-CoA. What dictates the choice?

It is the **hormonal state.**

During *fasting*, glucagon activates gluconeogenesis (PEPCK, FBPase…) that pulls malate out of mitochondria. Malic enzyme and PDH are inactive.

After a *meal*, insulin activates malic enzyme (increased expression) and PDH (dephosphorylation). Acetyl-CoA is directed to lipogenesis.

METABOLIC INTEGRATION

Gluconeogenesis from aminoacids:

- Glutaminolysis:

In neoplastic cells pyruvate dehydrogenase is inhibited:

Glucose → pyruvate → **lactate**

Neoplastic cells largely utilize glutamine:

Glutamine → glutamate → α-ketoglutarate → malate → pyruvate → **lactate**

and

Glutamine → glutamate → α-ketoglutarate → isocitrate → citrate → membrane lipids

METABOLIC INTEGRATION

How is metabolic traffic disciplined and controlled?

- **Cell compartimentalisation**

- Key transported intermediates

Acetyl-CoA:

From pyruvate (glucose, some amino acids)

From fatty acid oxidation

From actoacetate in peripheral tissues

From ketogenic amino acids

From all amino acids via the cataplerotic reactions

METABOLIC INTEGRATION

How is metabolic traffic disciplined and controlled?

- **Cell compartimentalisation**

- Key transported intermediates

Acetyl-CoA:

To the TCA cycle

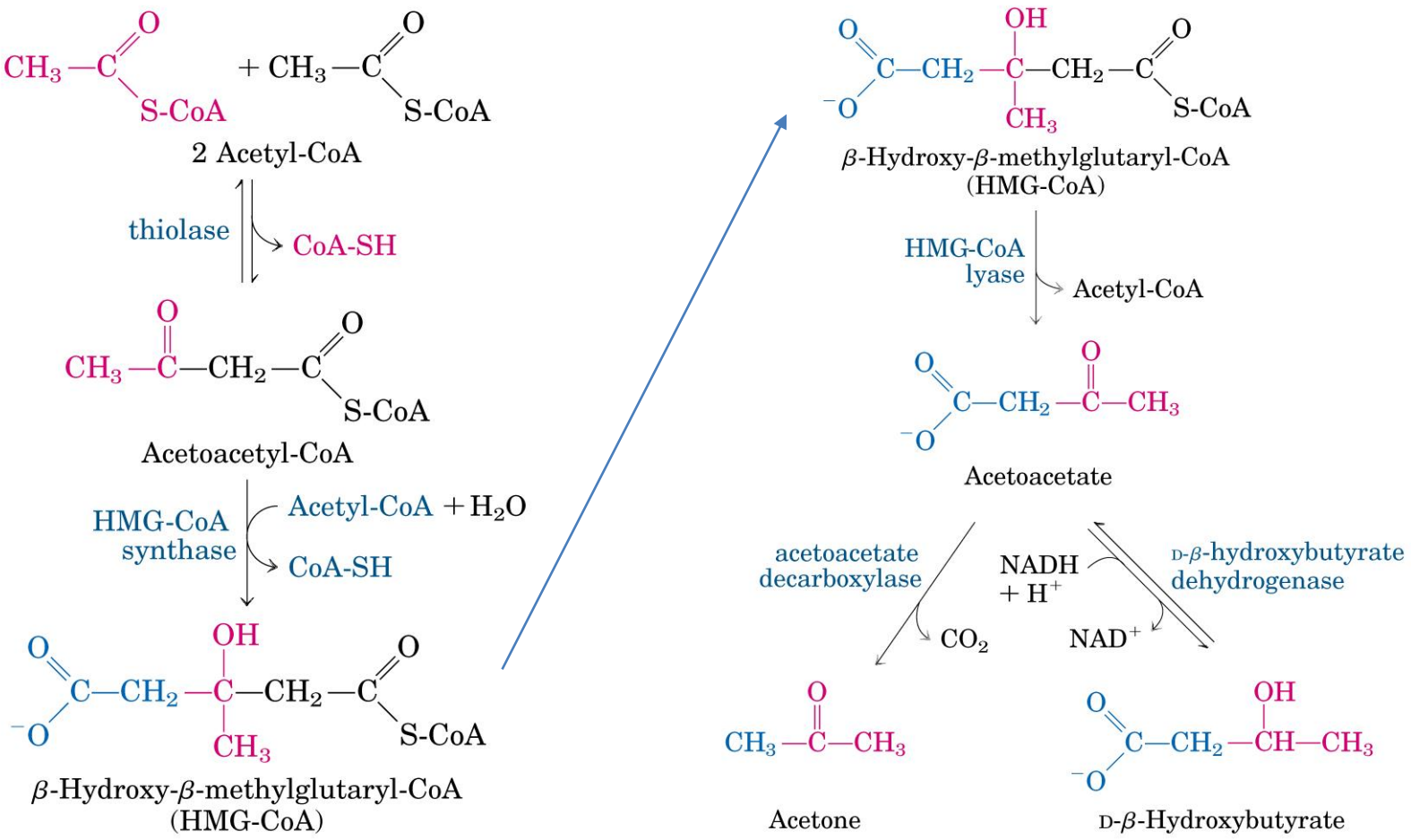
To produce ketone bodies in the liver

To fatty acid biosynthesis and elongation

To isoprenoid compounds (Coenzyme Q, cholesterol and derivatives)

METABOLIC INTEGRATION

Acetyl-CoA used in ketone body synthesis:



METABOLIC INTEGRATION

Acetyl-CoA produced in ketone body oxidation:

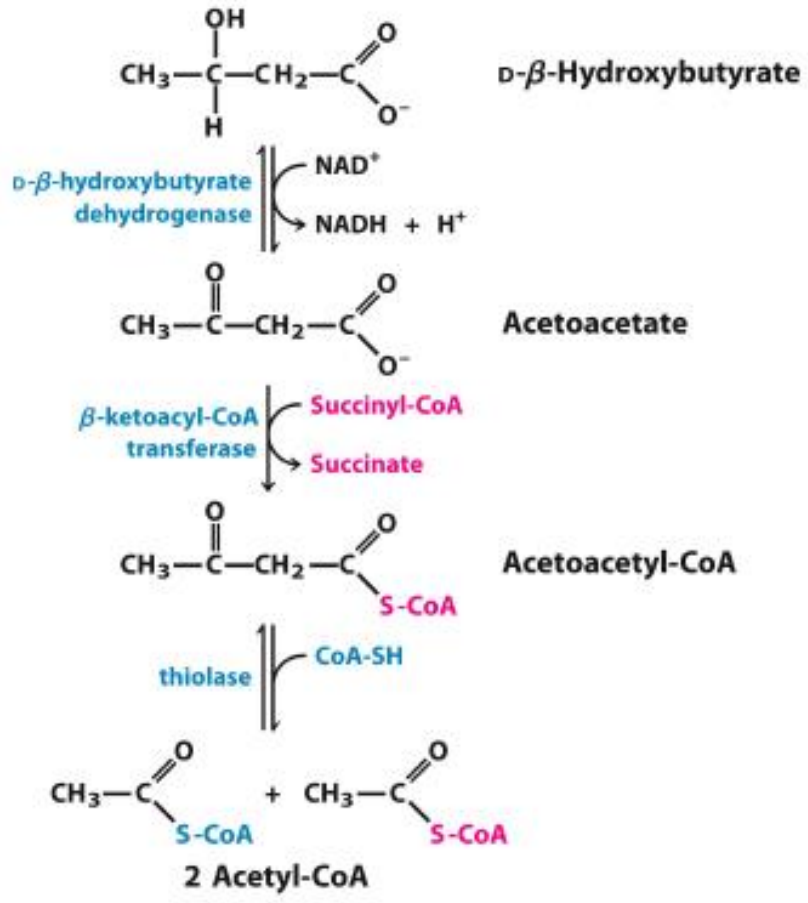


Figure 17-20
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METABOLIC INTEGRATION

Does activation of acetoacetate with succinyl-CoA interfere with the TCA cycle?

No!! The high-energy bond of succinyl-CoA is used to activate acetoacetate instead of making GTP, but the product, succinate, goes on in the TCA cycle.

$$\text{Succinyl-CoA} + \text{GDP} + P_i \rightarrow \text{Succinate} + \text{CoASH} + \text{GTP}$$

Succinyl-CoA + Acetoacetate → Succinate + Acetoacetyl-CoA

METABOLIC INTEGRATION

How is metabolic traffic disciplined and controlled?

- **Cell compartimentalisation**

- Key transported intermediates

Aspartate:

Transamination to oxaloacetate (for gluconeogenesis, for oxidation to acetyl-CoA)

In the malate/aspartate shuttle for the oxidation of glycolytic NADH

N donor in urea synthesis (Argininosuccinate synthetase) → fumarate

N donor in de novo purine synthesis (N1 of ring)

N donor for AMP synthesis from IMP → fumarate

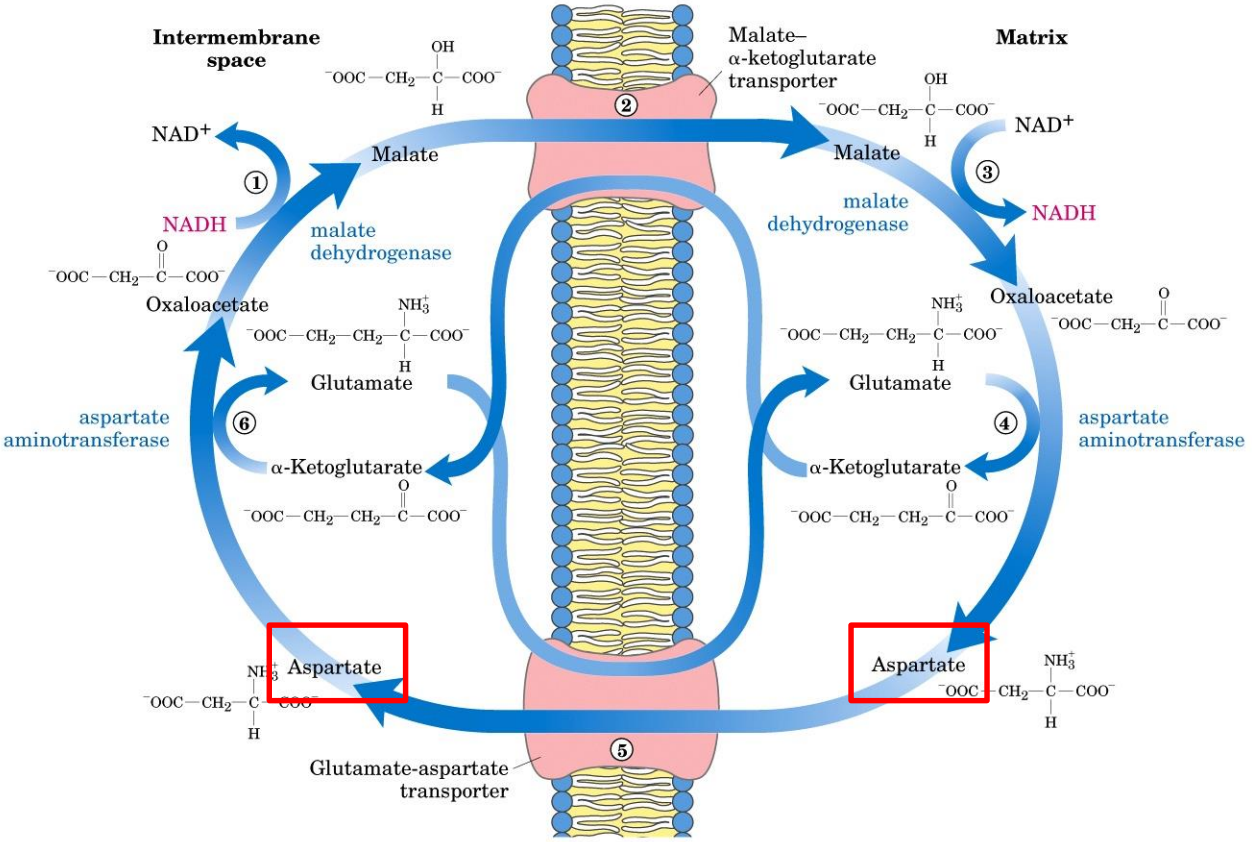
Pyrimidine biosynthesis (N3, C4, C5, C6)

Synthetized from oxaloacetate (Non-essential)

Precursor of Asparagine (asparagine synthetase)

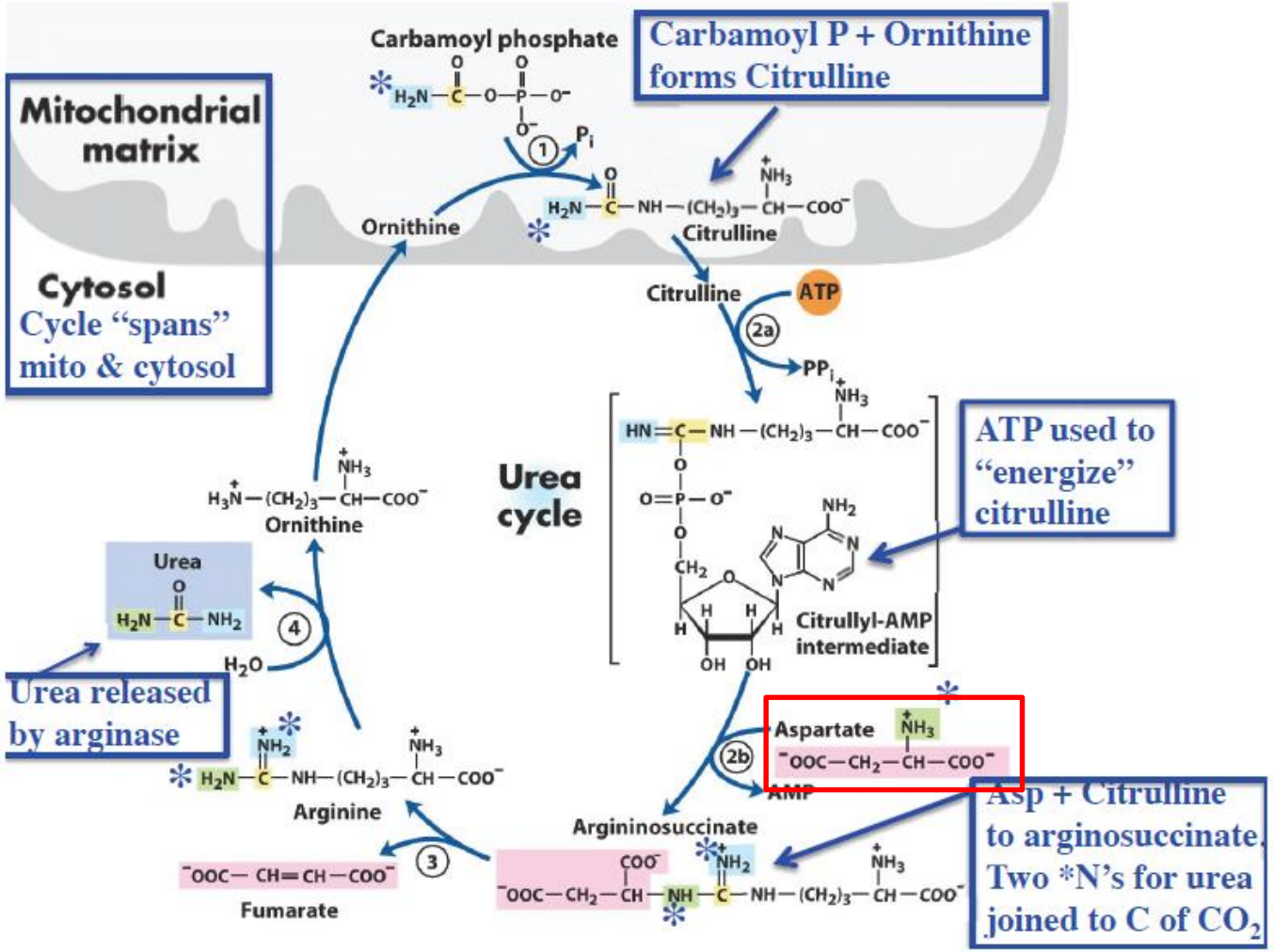
METABOLIC INTEGRATION

Aspartate:



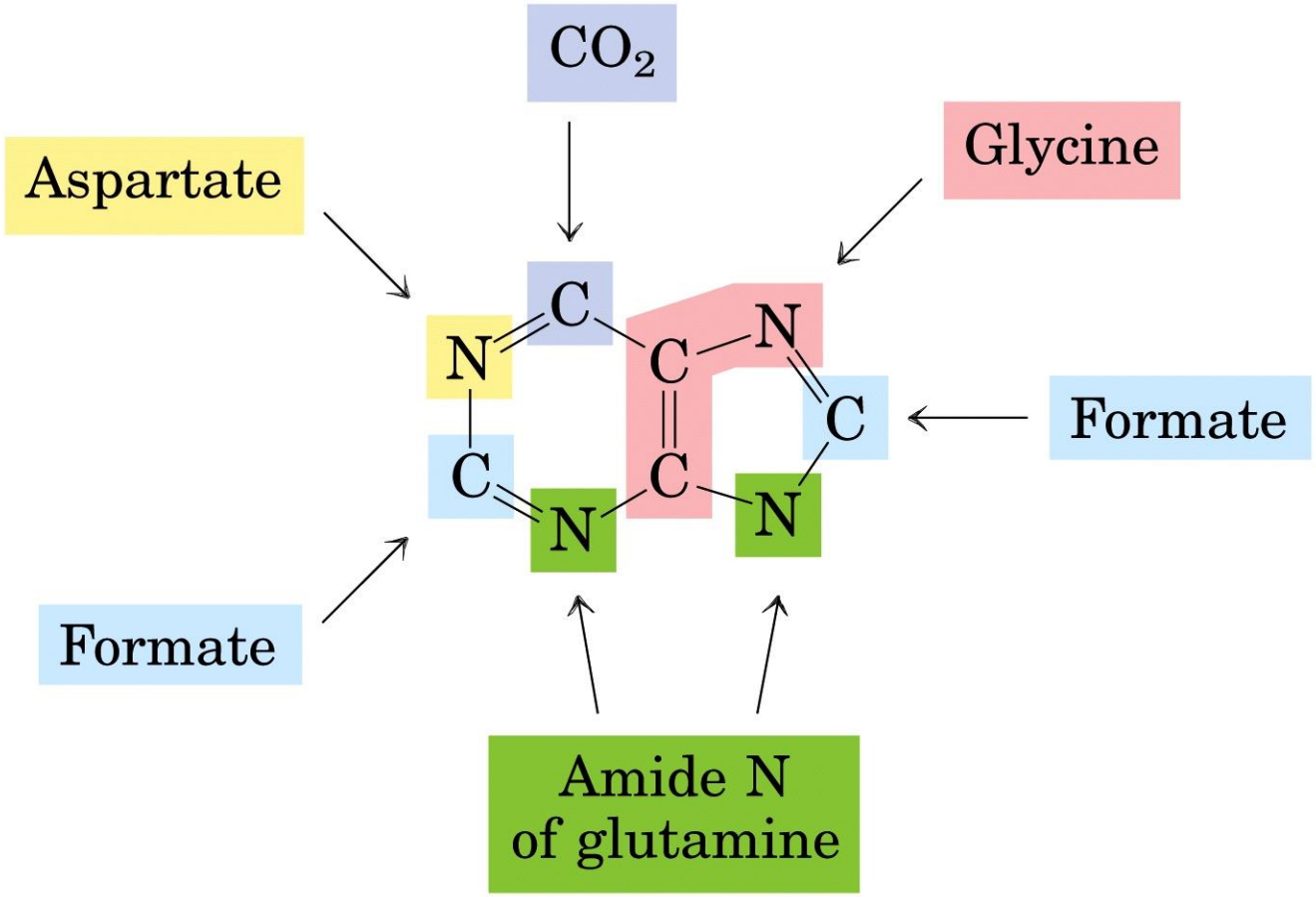
METABOLIC INTEGRATION

Aspartate:



METABOLIC INTEGRATION

Aspartate:



METABOLIC INTEGRATION

Aspartate:

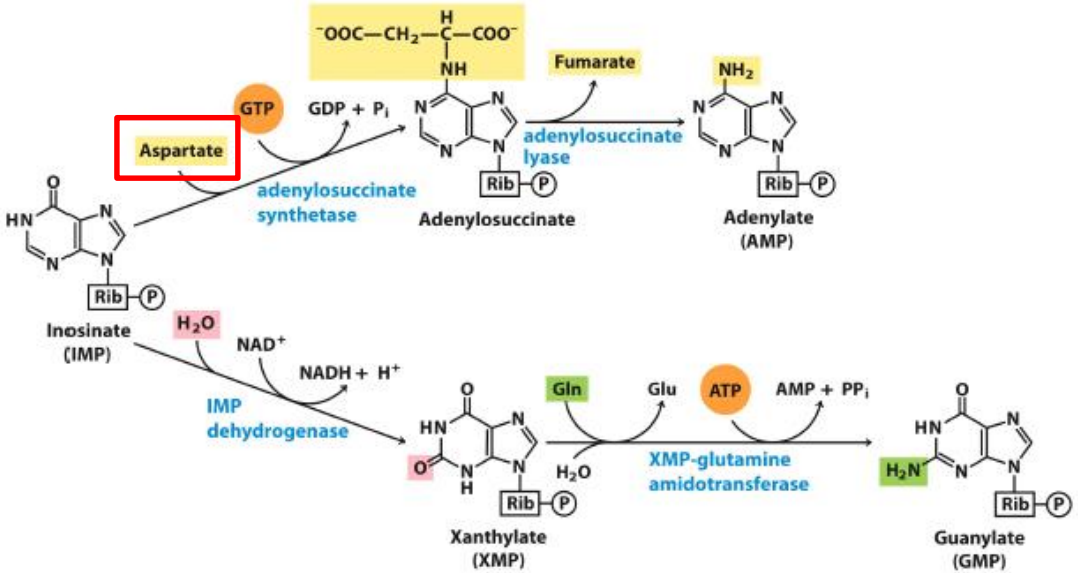


Figure 22-36
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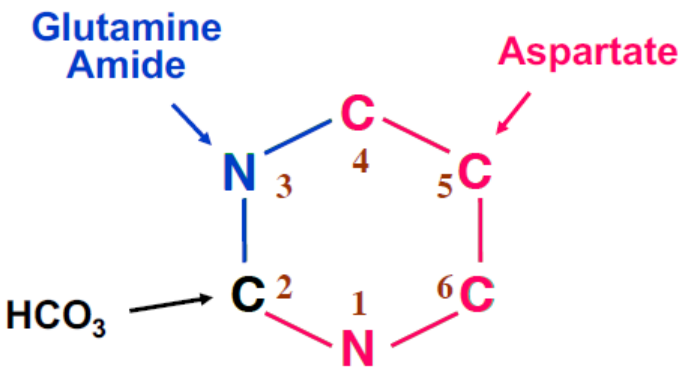


METABOLIC INTEGRATION

How is metabolic traffic disciplined and controlled?

- **Cell compartimentalisation**

- Key transported intermediates

Serine:

Deamination to pyruvate (Gluconeogenesis).

Decarboxylation to ethanolamine (Phospholipid metabolism).

Transfer of hydroxymethyl group to FH4.

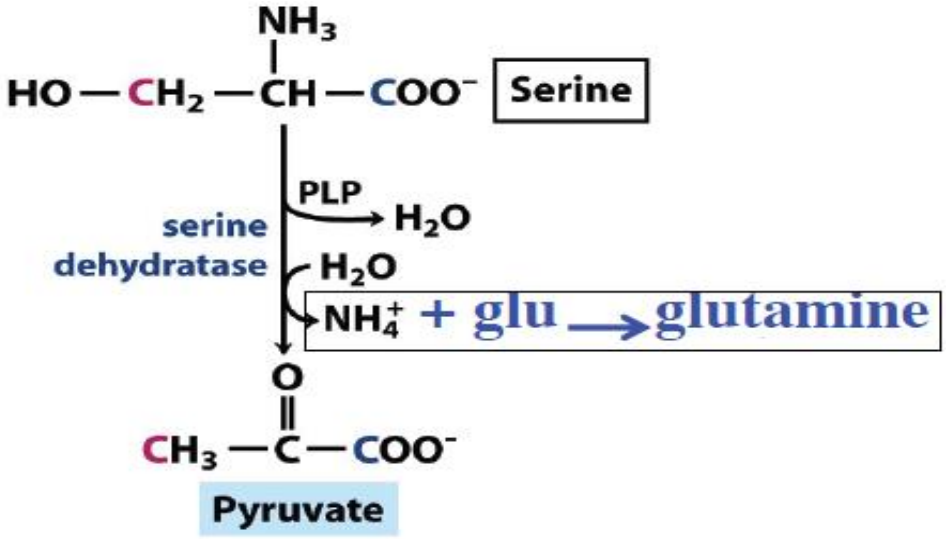
One-carbon metabolism (purine biosynthesis, TMP synthase, methionine resynthesis).

Biosynthesis of sphingosine.

METABOLIC INTEGRATION

Serine:

Deamination to pyruvate (Gluconeogenesis)



METABOLIC INTEGRATION

Serine:

Decarboxylation to ethanolamine (Phospholipid metabolism)

Serine → Ethanolamine + CO_2

requires PLP

Ethanolamine + 3 [CH_3] → Choline

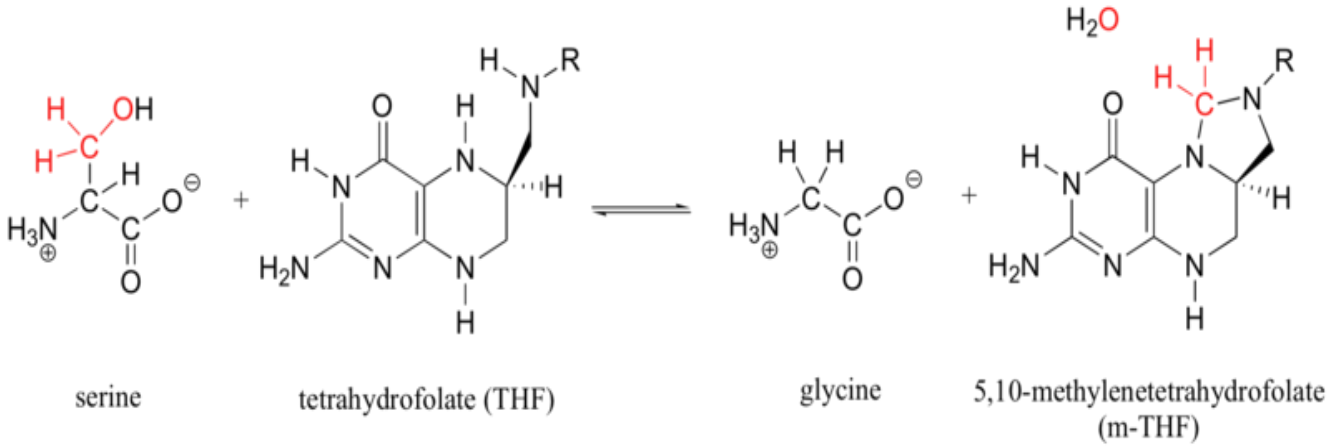
requires methyl FH_4

METABOLIC INTEGRATION

Serine:

Transfer of hydroxymethyl group to FH4:

Serine hydroxymethyl transferase requires PLP



METABOLIC INTEGRATION

Serine:

One-carbon metabolism (purine biosynthesis, TMP synthase, methionine resynthesis)

Serine + FH_4 → glycine + $FH_4{=}CH_2$

$FH_4{=}CH_2$ + NADH → FH_4-CH_3 + NAD^+

$FH_4{=}CH_2$ + $NADP^+$ → FH_4-CHO + NADPH

FH_4-CHO → C2, C8 purines

FH_4-CH_3 → re-synthesis methionine

$FH_4{=}CH_2$ → synthesis TMP from dUMP

METABOLIC INTEGRATION

Integration between metabolic pathways depends on **feeding/ fasting** cycles:

- *Lipogenesis* and *cholesterol* synthesis from glucose
- *Amino acid* metabolism and *gluconeogenesis*
- *Gluconeogenesis* and *ketogenesis*
- Prevention of opposite pathways from occurring at the same time

METABOLIC INTEGRATION

Integration between **subcellular compartments**

- *Carbohydrate catabolism* (cytosol and mitochondria)
- *Gluconeogenesis*, *fatty acid* and *cholesterol* synthesis (mitochondria and cytosol)
- *Amino acid* metabolism, *urea* synthesis (mitochondria and cytosol)
- *Protein* synthesis (cytosol and ER)
- Cellular traffic (plasma membrane, ER, Golgi, lysosomes)
- Calcium homeostasis (plasma membrane, ER, mitochondria)

METABOLIC INTEGRATION

Integration between **different organs and tissues**

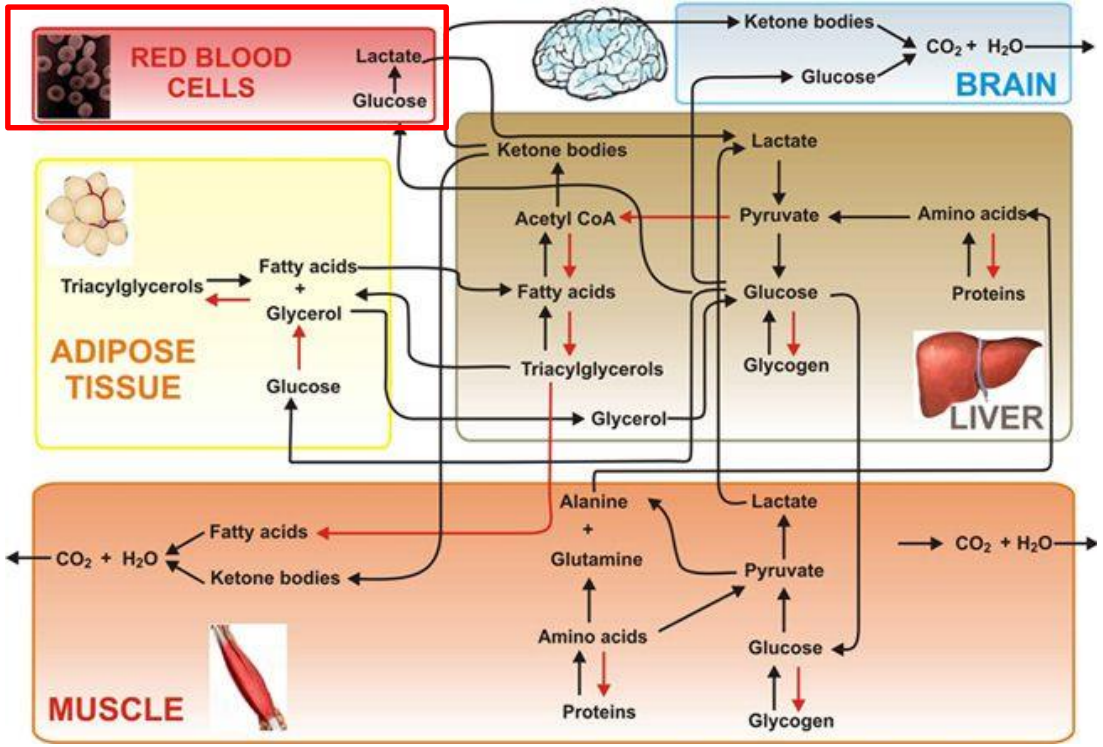
- Intestine, source of exogenous molecules
- Liver, the major metabolic factory for carbohydrates, lipids and proteins
- Adipose tissue, fat storage and metabolism
- Skeletal muscle, storage for amino acids
- Endocrine glands for regulation

METABOLIC INTEGRATION

Relationship between the utilization and production of substrates by different cells

Red Blood cells:

- Rely on glucose for energy
- Convert pyruvate to lactate

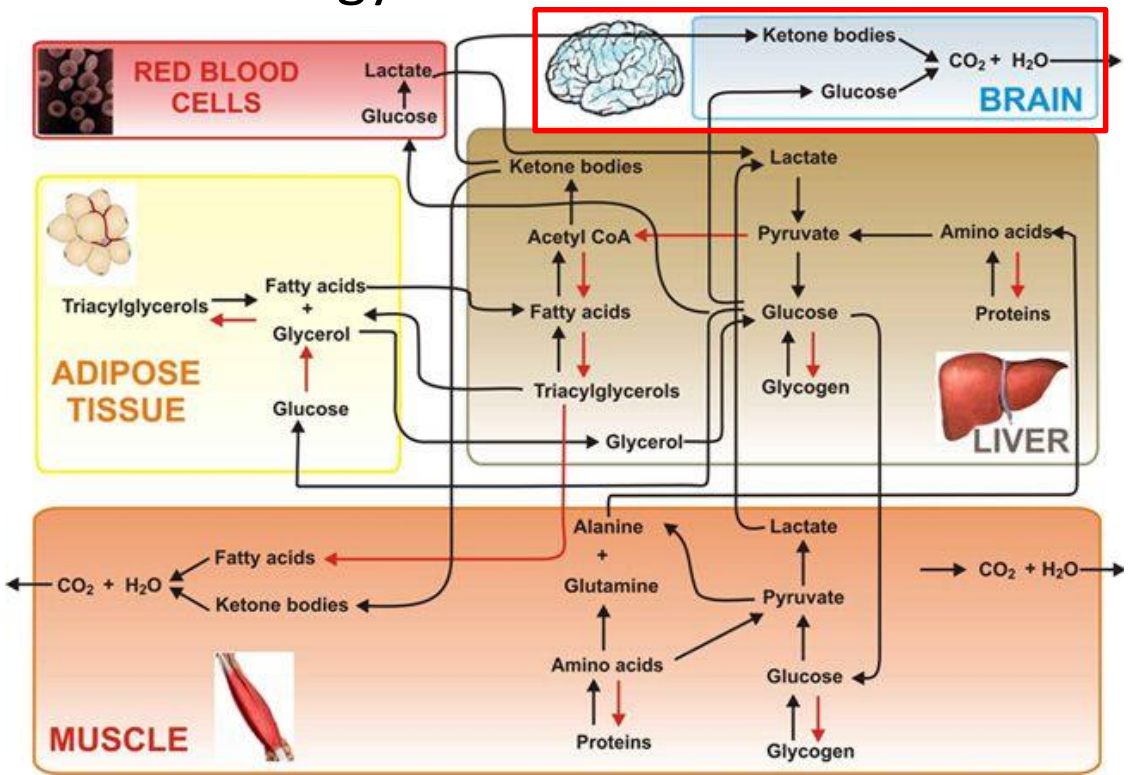


METABOLIC INTEGRATION

Relationship between the utilization and production of substrates by different cells

Brain:

- uses glucose and
- ketone bodies for energy

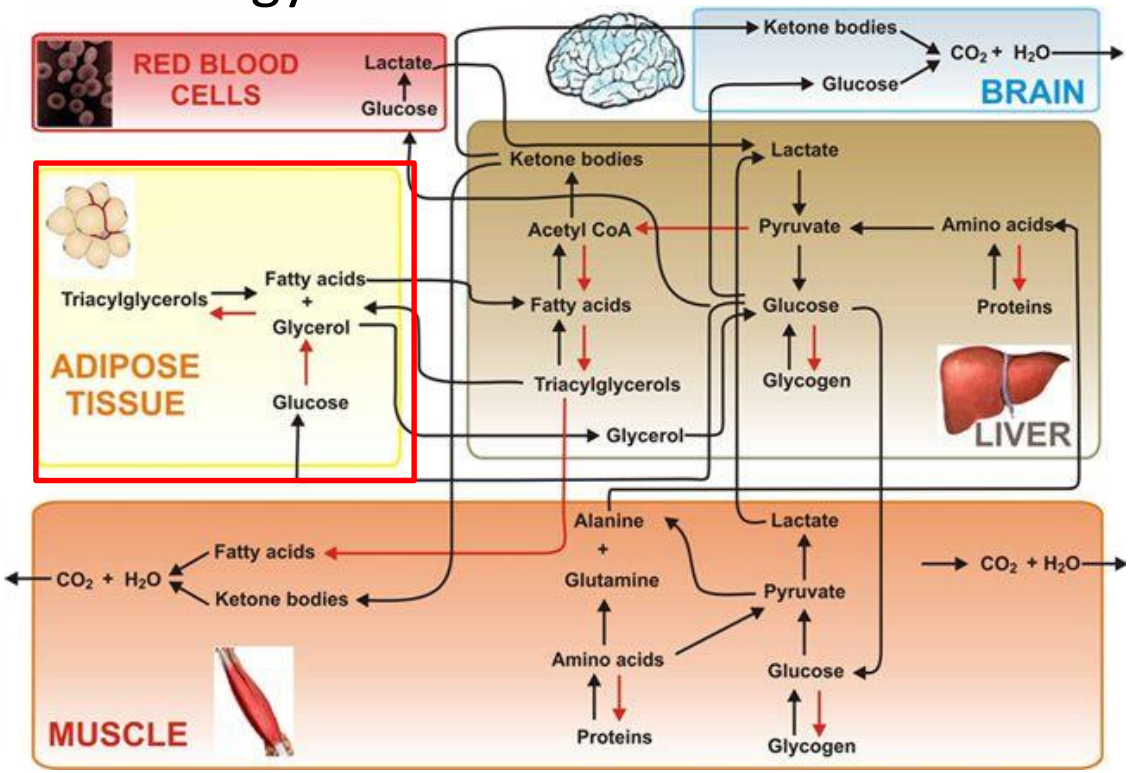


METABOLIC INTEGRATION

Relationship between the utilization and production of substrates by different cells

Adipose tissue:

- uses glucose and
- fatty acids for energy

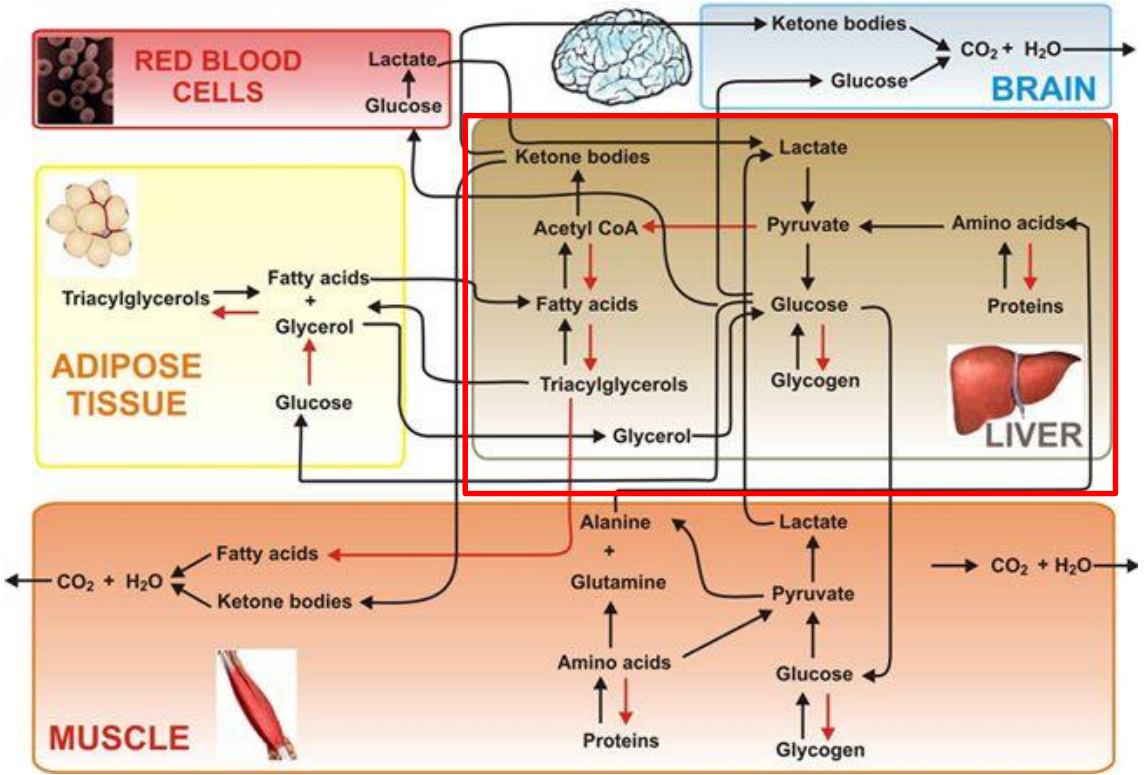


METABOLIC INTEGRATION

Relationship between the utilization and production of substrates by different cells

liver:

- primarly uses fatty acids oxidation for energy

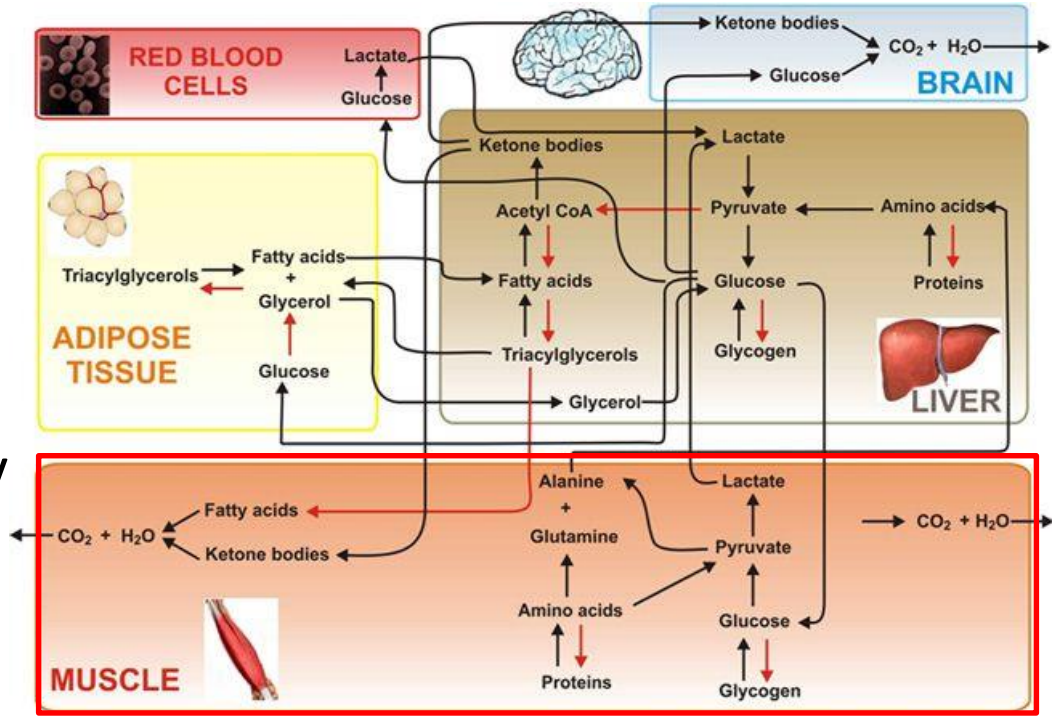


METABOLIC INTEGRATION

Relationship between the utilization and production of substrates by different cells

muscle cells:

- use fatty acids
- use ketone bodies
- use glucose
- use amino acids for energy



METABOLIC INTEGRATION

Hormones regulation

Hormones	Glucose uptake	Muscle glucose utilization	Protein synthesis	Glucose output	Ketogenesis	Liver gluconeo-genesis	Glycogeno-lysis	Glyco-genesis	Protein synthesis	Adipose fat synthesis	Tissue lipolysis
Anabolic hormones											
Insulin	↑↑	↑↑	↑↑	↓↓	↓↓	↓↓	↓↓	↑	↑↑	↑	↓↓
Counter-regulatory hormones											
Glucagon	-	-	-	↑↑	↑	↑	↑↑	-	-	-	↑
Epinephrine and norepinephrine	-	↑	-	↑↑	-	↑	↑↑ (initial)	↓	-	-	↑↑
Glucocorticoids	↓	↓	↓	↑	↑	↑ (mainly permissive)	-	↑	↓	-	↑ (permissive)
Growth hormone	↓ (weakly)	↓ (weakly)	↑	↑	↑	↑	-	-	↑	-	↑ (permissive)
Thyroid hormone	-	↑	↑	↑	↑	↑	-	-	↑	-	↑ (permissive)
Somatostatin	-	-	-	-	-	-	-	-	-	-	-
	Somatostatin's effects on metabolism are indirect via suppression of secretion of insulin, glucagon, growth hormone and thyroid hormone, and by effects on gastric acid secretion, gastric emptying time, and pancreatic exocrine secretion.										

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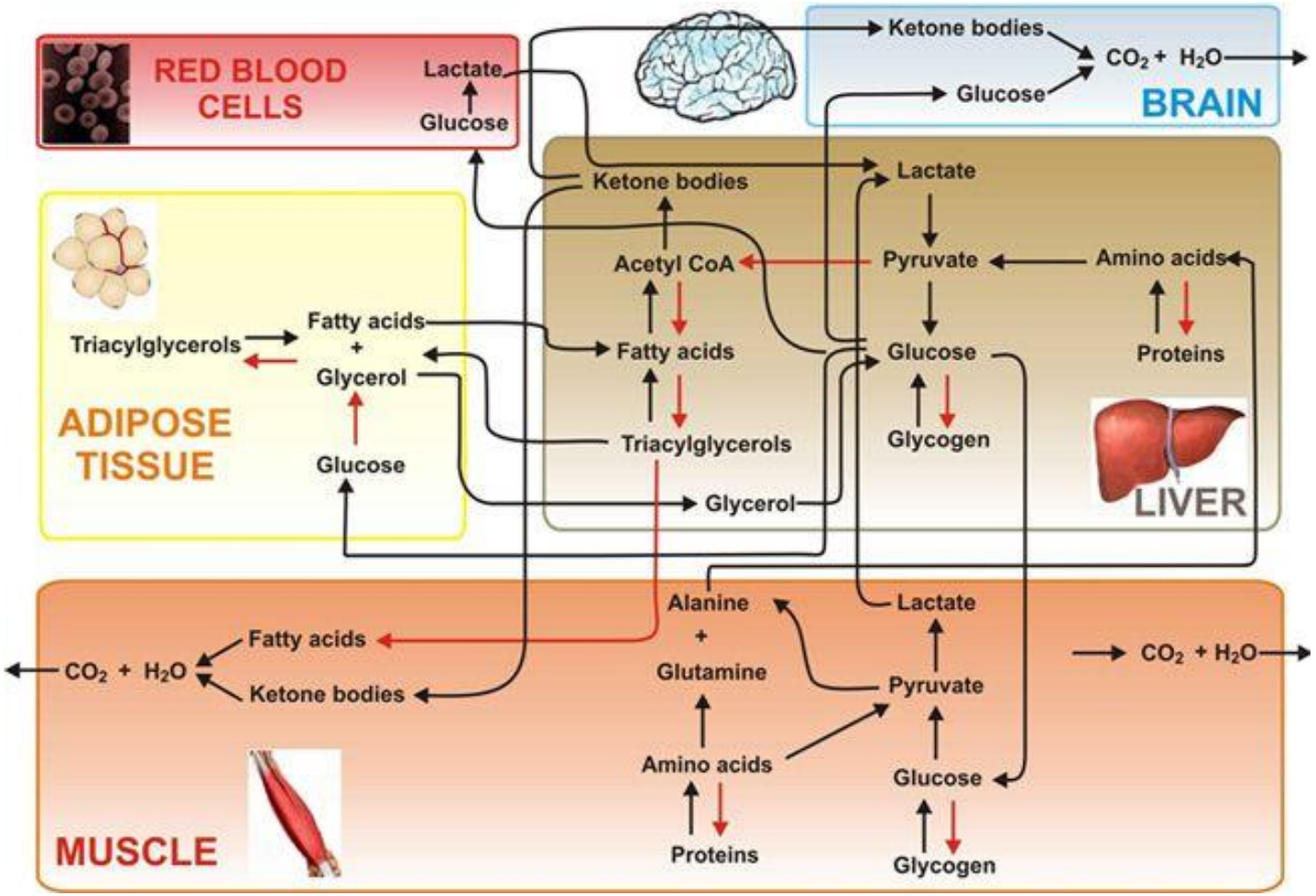
METABOLIC INTEGRATION

Liver – extrahepatic tissues crosstalk:

- *Liver* has close communication with *adipose tissue* and *skeletal muscle.*
- Liver-produced *glucose* and *ketone bodies* are delivered to *muscle* and other tissues (fasting and exercise).
- *Skeletal muscle* provides the liver with *lactate* and *amino acids* used as gluconeogenic substrates.
- Adipose tissue produces *NEFAs* and *glycerol* through lipolysisu
- *Hepatocytes* oxidise FA to generate *ketone bodies* or pack NEFAs into *VLDL.*
- *Ketone bodies and VLDL are secreted by the* liver and used by other tissues.
- *Hepatocytes use glycerol* to synthesise *glucose* or *TAG.*

METABOLIC INTEGRATION

Liver – extrahepatic tissues crosstalk:



METABOLIC INTEGRATION

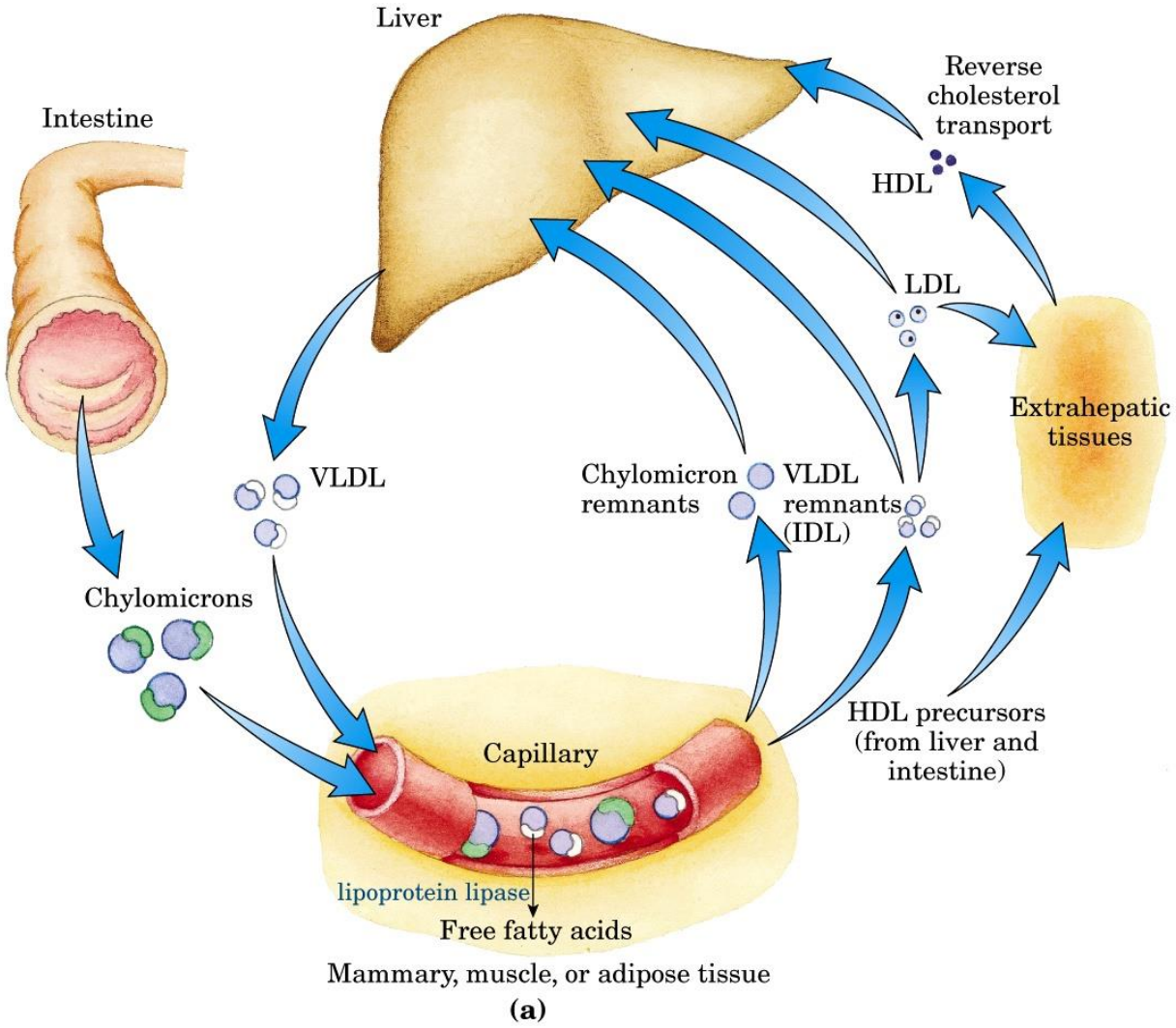
Fatty acids towards liver:

- After a *meal*, *chylomicron remnants* are taken by hepatocytes and provide residual fatty acids, cholesterol and proteins to build *lipids* and *VLDL* (in addition to fatty acid biosynthesis). *Glycerol* left after the action of lipoprotein lipase reaches the liver and is used for *lipid synthesis.*

- At *fasting* NEFA produced by lipolysis in adipose tissue are taken by hepatocytes to make *ketone bodies*. *Glycerol* from lipolysis is used for *gluconeogenesis*.

METABOLIC INTEGRATION

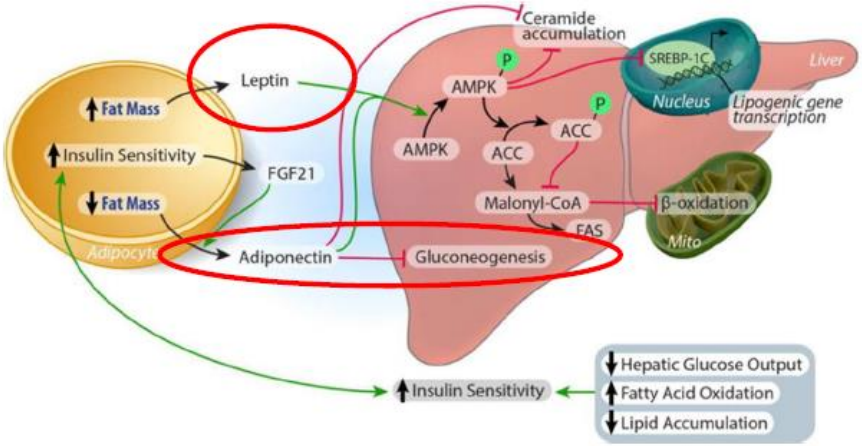
Fatty acids toward liver:



METABOLIC INTEGRATION

Liver – adipose tissues crosstalk:

- Adipose tissue regulates liver energy metabolism by secreting *adiponectin* (protein hormone).
- *Adiponectin* stimulates β-oxidation and inhibits gluconeogenesis.
- Adipose tissue is able to regulate liver metabolism indirectly by secreting hormones.
- *Leptin* acts on the brain, which communicates to the liver through the vagus nerve (suppresses the hepatic glucose production by reducing both glycogenolysis and gluconeogenesis).



METABOLIC INTEGRATION

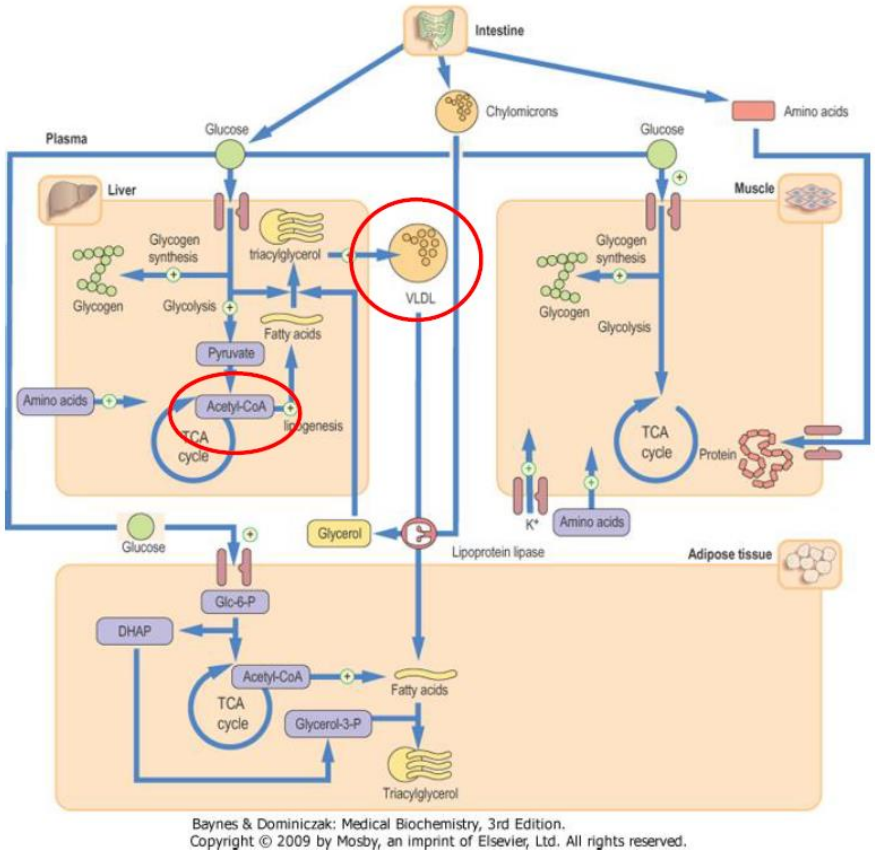
Glycogen and triacylglycerol synthesis in the liver in a fed state:

- After a meal, the liver synthesises *glycogen* and *triacylglycerols.*
- Glycogen stored in the liver can increase from 80 g after an overnight fast to a limit of 200-300 g
- The liver synthesises *triacylglycerols* and packs them in *VLDL* and secretes them.
- The fatty acids of the VLDL secreted from the liver are stored as adipose *triacylglycerols*.

METABOLIC INTEGRATION

Metabolism in a fed state:

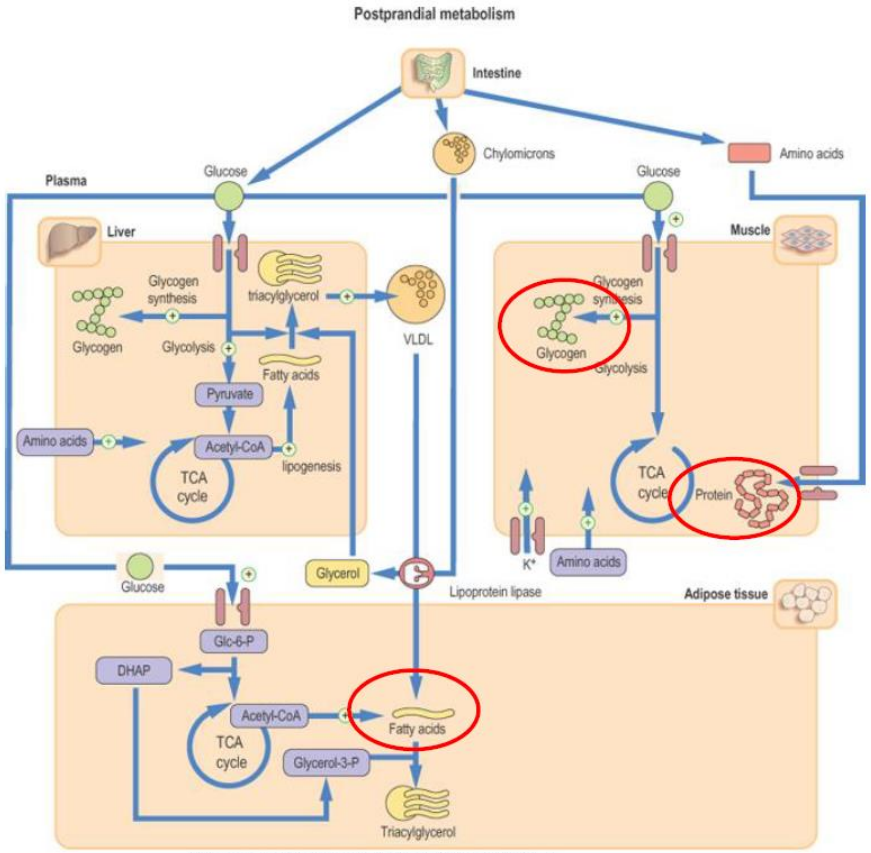
- *Carbohydrates, amino acids and fats* are absorbed in the intestine and insulin secretion is stimulated.
- *Insulin* directs metabolism towards *storage* and *anabolism*.
- In the liver, *glucose* is taken up by GLUT-2 and channelled into *glycolysis* and *glycogen* synthesis.
- Aerobic glycolysis supplies *acetyl-CoA* (lipogenesis).
- Fatty acids are esterified by glycerol (derived from glycolysis), forming *triacylglycerols*.
- Tryacylglycerols are packed into *VLDL* for transport.



METABOLIC INTEGRATION

Metabolism in a fed state:

- Muscle *glycogen synthesis*, amino acid uptake and *protein synthesis* are stimulated.
- In the *adipose tissue*, VLDL triacylglycerols are hydrolysed, and *fatty acids* are taken up by cells
- *Triacylglycerols* are resynthesized intracellularly as adipocyte storage material.



METABOLIC INTEGRATION

Mechanisms that affect glycogen and triacylglycerol synthesis in liver

Both synthesis are regulated by mechanisms involving key enzymes in these pathways

- *Glucokinase*

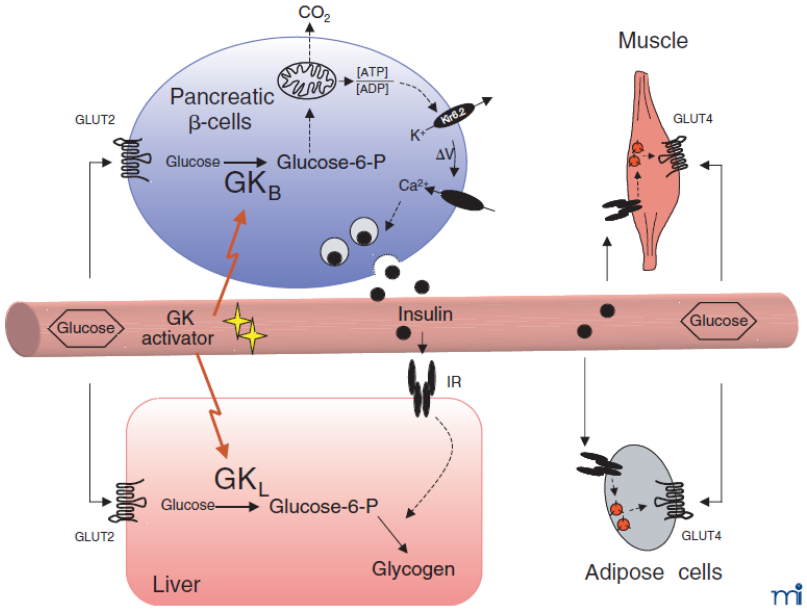
- Liver
- Pancreatic islets
- Intestinal cells
- Brain

METABOLIC INTEGRATION

Mechanisms that affect glycogen and triacylglycerol synthesis in liver

- *Glucokinase*

- Regulates glucose metabolism in liver, acts as a glucose sensor in other tissues.
- High K_m for glucose (low affinity); the enzyme is active in the fed state, when [glucose] is high (20 mM).
- The synthesis of glucokinase is induced by insulin and repressed by glucagon.

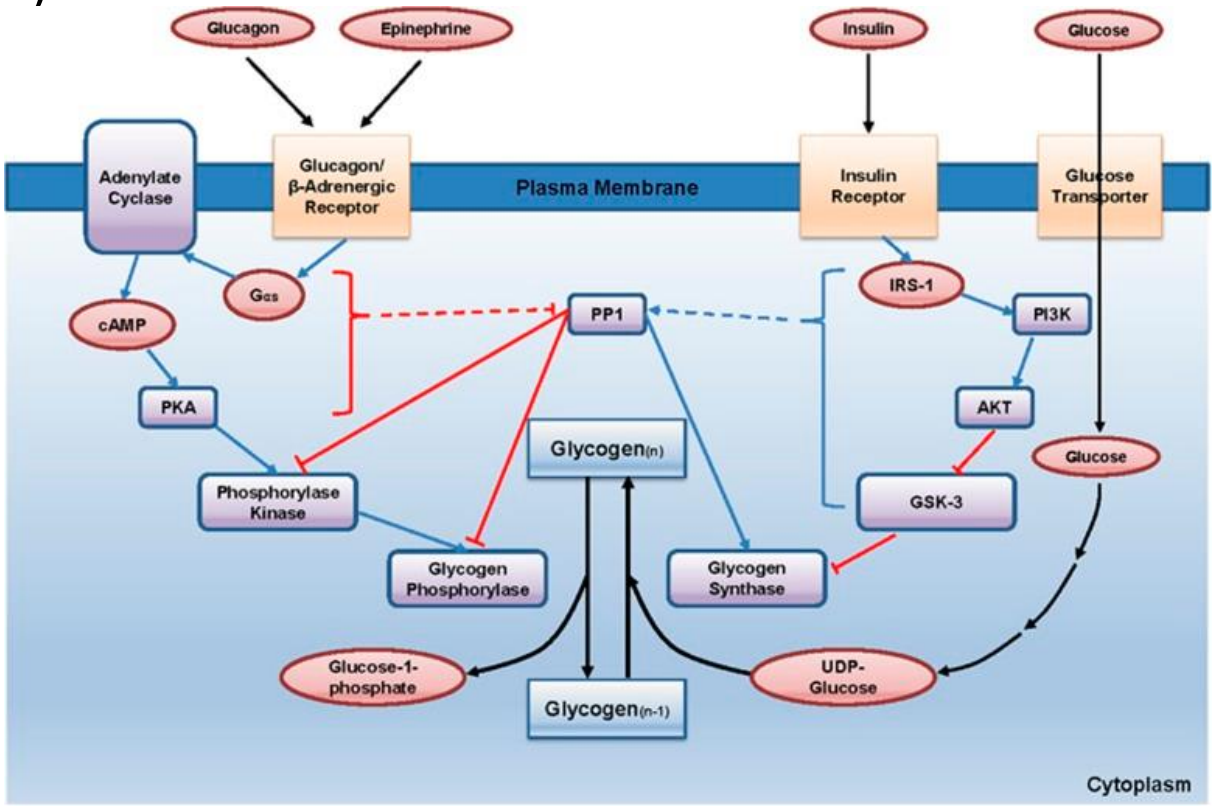


METABOLIC INTEGRATION

Mechanisms that affect glycogen and triacylglycerol synthesis in the liver

- *Glycogen synthase*

- Key regulatory enzyme in glycogen synthesis
- Regulated by dephosphorylation that occurs when insulin is elevated (fed state).

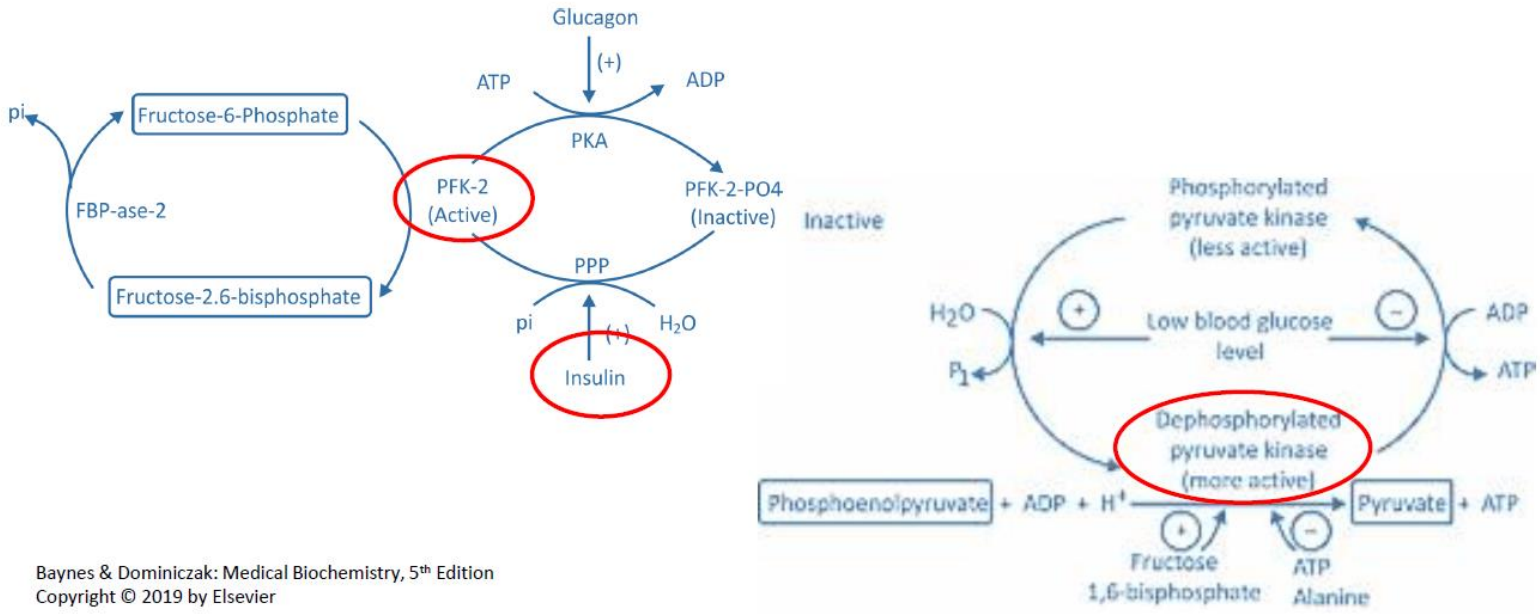


METABOLIC INTEGRATION

Mechanisms that affect glycogen and triacylglycerol synthesis in liver

- *Phosphofructokinase-1 and pyruvate kinase*

- *PFK-1* is allosterically activated in the fed state by fructose-2,6-bisphosphate (F-2,6-BP) and AMP.
- *PFK-2* (produces F2,6-BP) is dephosphorylated and active after a meal.
- *PK* is also activated by dephosphorylation, which is stimulated by the increase of the insulin/glucagon ratio in the fed state.



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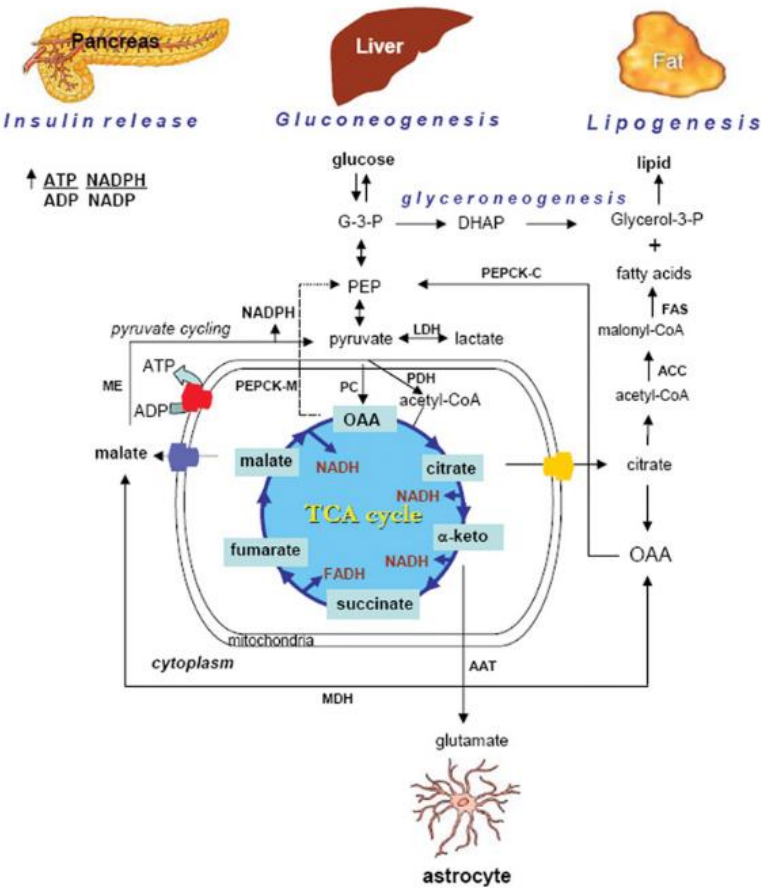
METABOLIC INTEGRATION

Mechanisms that affect glycogen and triacylglycerol synthesis in liver

- *Pyruvate dehydrogenase and pyruvate carboxylase*

- The conversion of pyruvate to fatty acids requires acetyl-CoA in the cytosol.
- Pyruvate can only be converted to acetyl-CoA in mitochondria, so it enters mitochondria.
- PDH is dephosphorylated and active in the fed state.
- Pyruvate is also converted to oxaloacetate by PC and activated by acetyl-CoA.

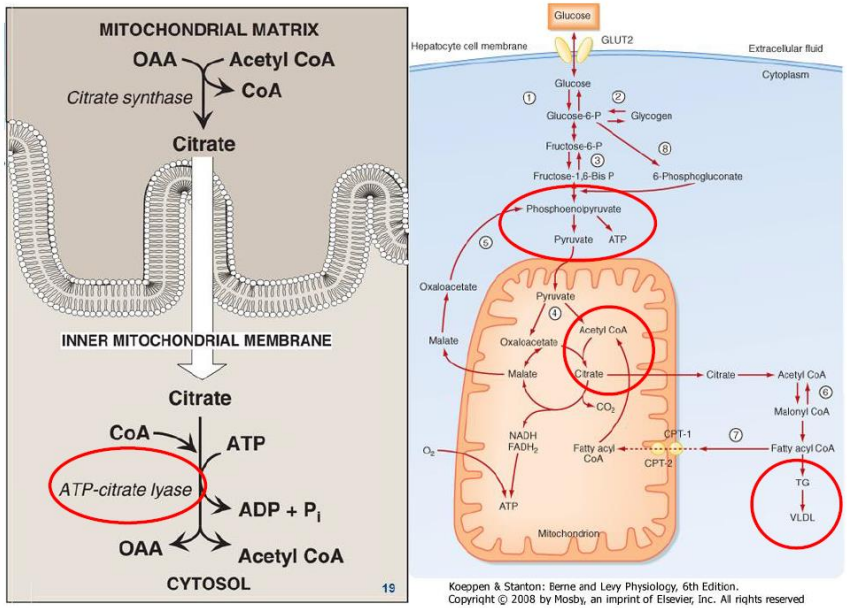


METABOLIC INTEGRATION

Mechanisms that affect glycogen and triacylglycerol synthesis in the liver

- *Citrate lyase*

- In the cytosol, citrate is cleaved by citrate lyase to form oxaloacetate and acetyl-CoA.
- Acetyl-CoA is used for FA biosynthesis and cholesterol synthesis, pathways activated by insulin.



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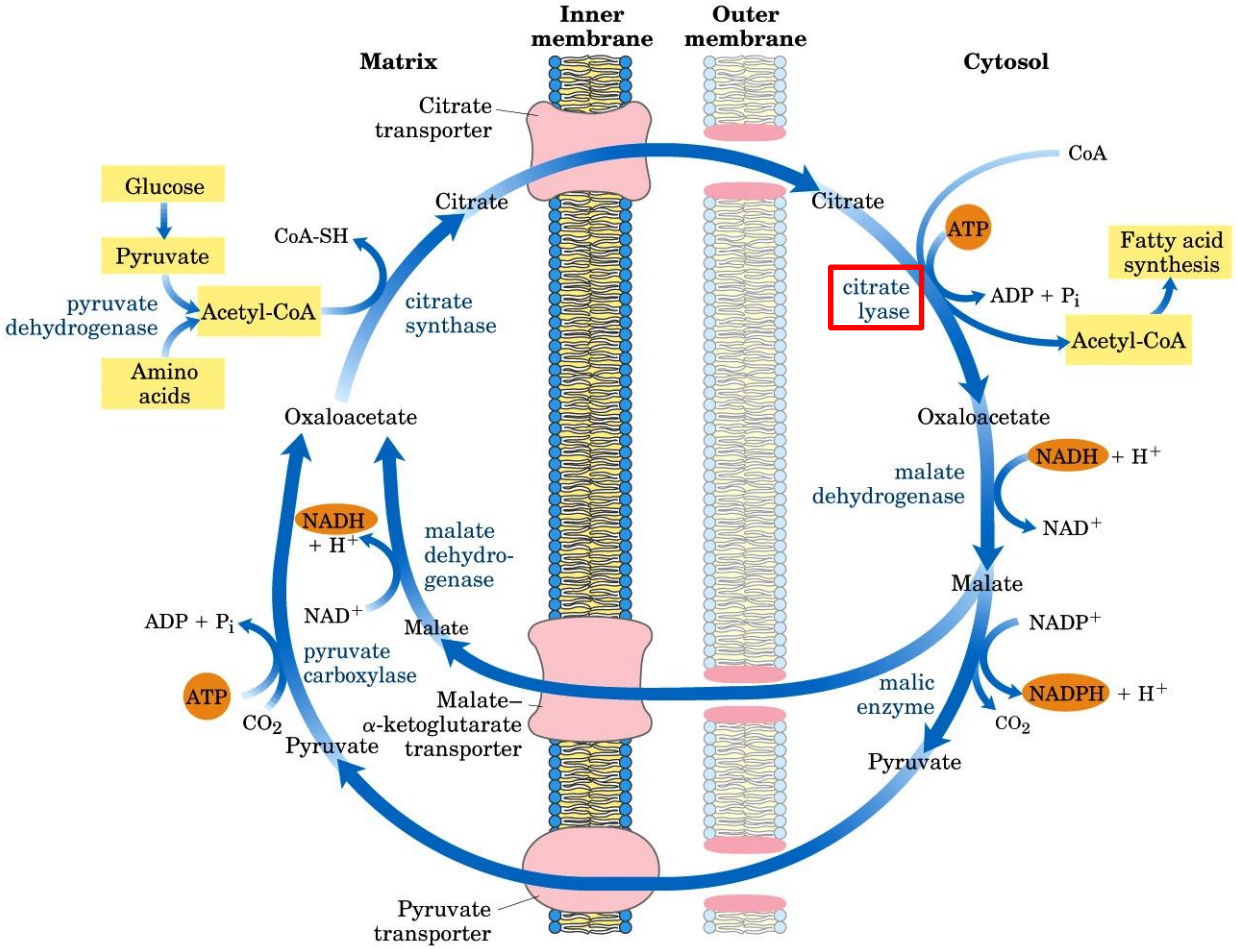
Marks' Basic Medical Biochemistry, A Clinical Approach. M. A Lieberman, A. Marks and A. Peet. Wolters Kluwer , Lippincott, Williams and Wilkins, 4th ed., 2013

METABOLIC INTEGRATION

Mechanisms that affect glycogen and triacylglycerol synthesis in liver



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