Metabolic Interrelationships

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Key Concepts

- Metabolic pathway are controlled in different nutritional and disease states to maintain sources of energy and amino acids in the blood for all tissues.
- Pathways that remove excess fuels from the blood (glycogenesis, glycolysis, fatty acid synthesis and lipogenesis) are active in the fed state.
- Pathways that maintain adequate levels of fuel in the blood (glycogenolysis, gluconeogenesis, lipolysis, proteolysis, and ketogenesis) are active in the starved state.
- Pathways are controlled by substrate availability, allosteric effectors, covalent modification, and induction or repression of key enzymes.
- The changes in metabolism that accompany common disease state are variations on the themes that function in the fed and fasted states

How does this happen in the starved and fed cycle

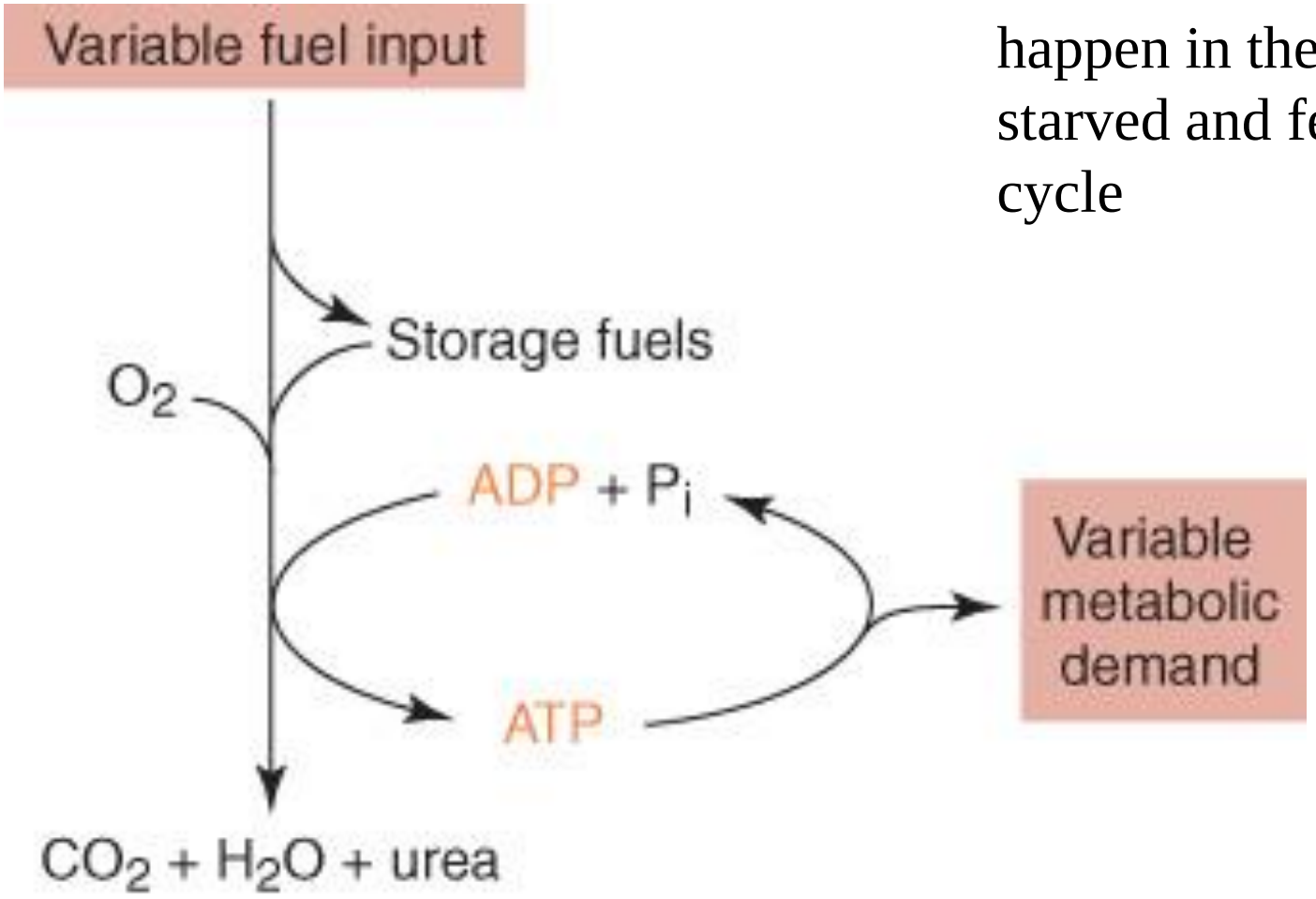


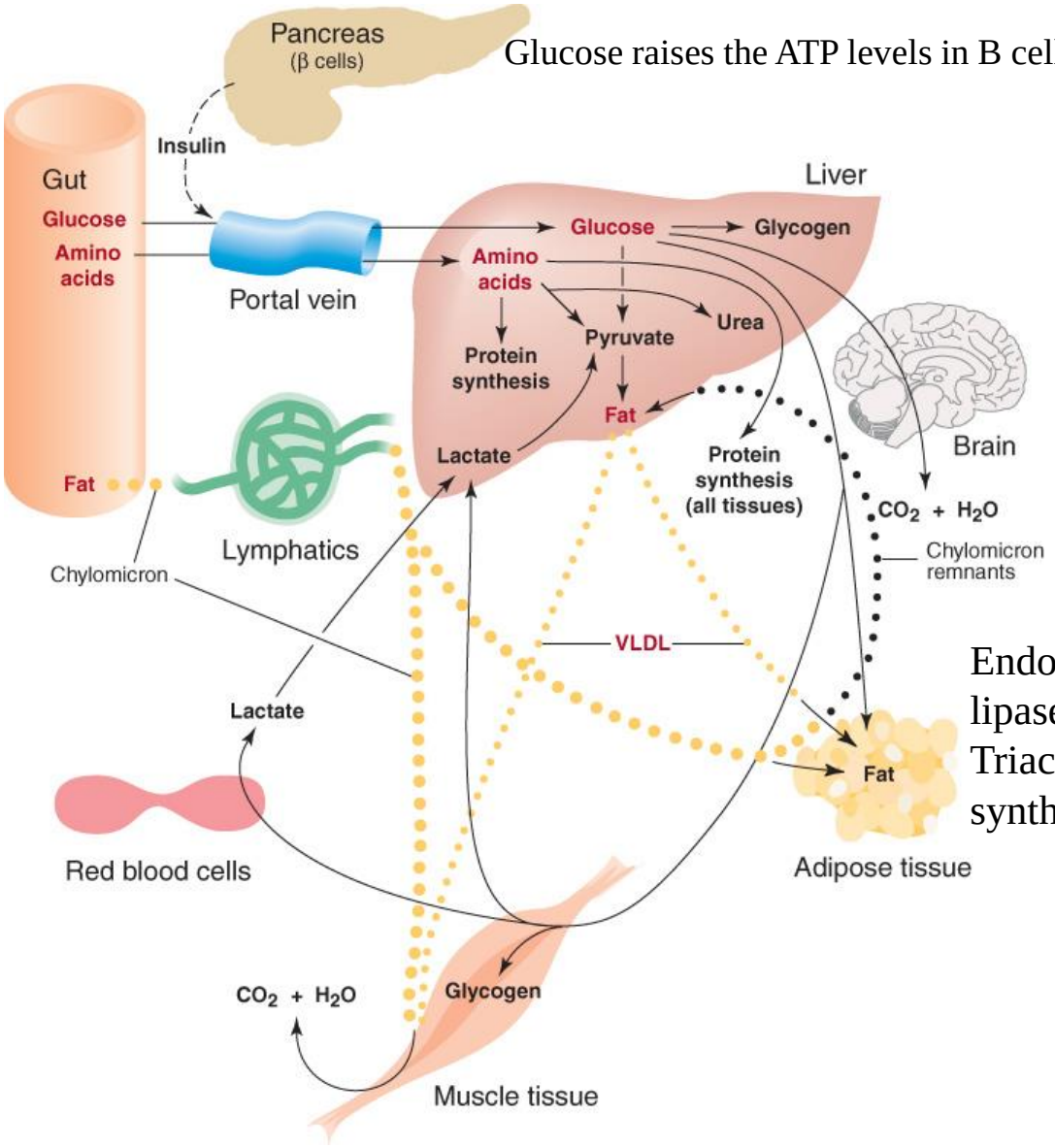
Figure 21.1 Humans can use a variable fuel input to meet a variable metabolic demand.

Metabolic Processes

- Glycogenolysis
- Gluconeogenesis
- Fatty Acid Synthesis
- Lipogenesis
- TCA Cycle Activity
- Amino Acid Oxidation
- Proteolysis

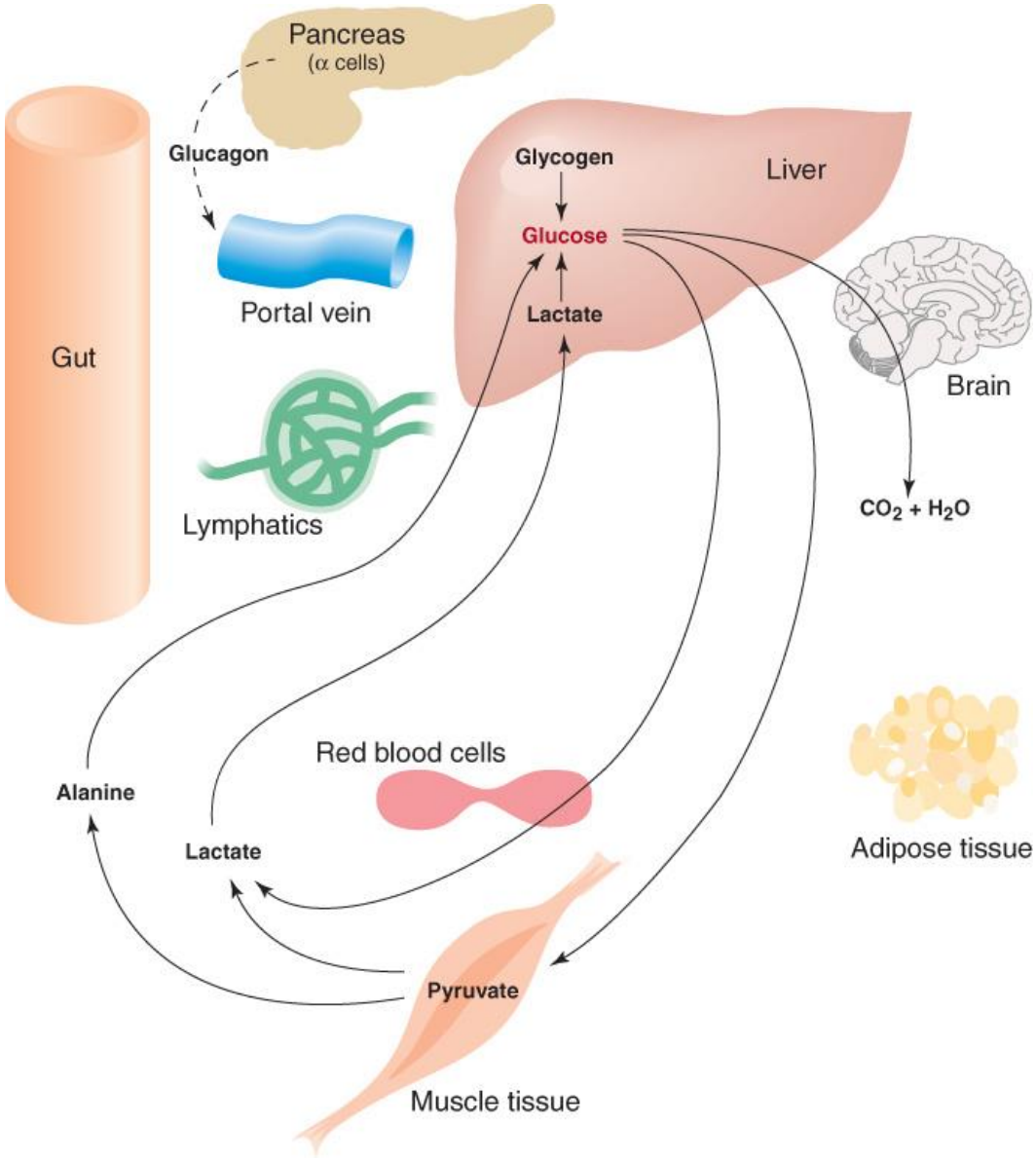
- Glycogenesis
- Glycolysis
- Lipolysis
- Glutaminolysis
- Ketogenesis
- Protein Synthesis
- Urea Synthesis

Glucose raises the ATP levels in B cells



Endothelial lipoprotein lipase hydrolyze Triacylglycerol, and then synthesis

Figure 21.2 Disposition of glucose, amino acids, and fat by various tissues in the well-fed state.



Cori cycle
Glucose from
Amino acid

Figure 21.3 Metabolic interrelationships of major tissues in early fasting state.

Fatty acids** can not be used for the synthesis of Glucose.

Alanine and Glutamine released in large quantities others go to intermediate (puruvate, aKetoglutarate) which also can yield Glutamine and Alanine. Enterocytes use Glutamine to form pyrimidine and purine. aKetoglutarate to malate to pyruvate by malic enzyme and then to alanine. Ketone bodies can reduce alanine release and proteolysis and branched AA oxidation decreasing muscle wasting.

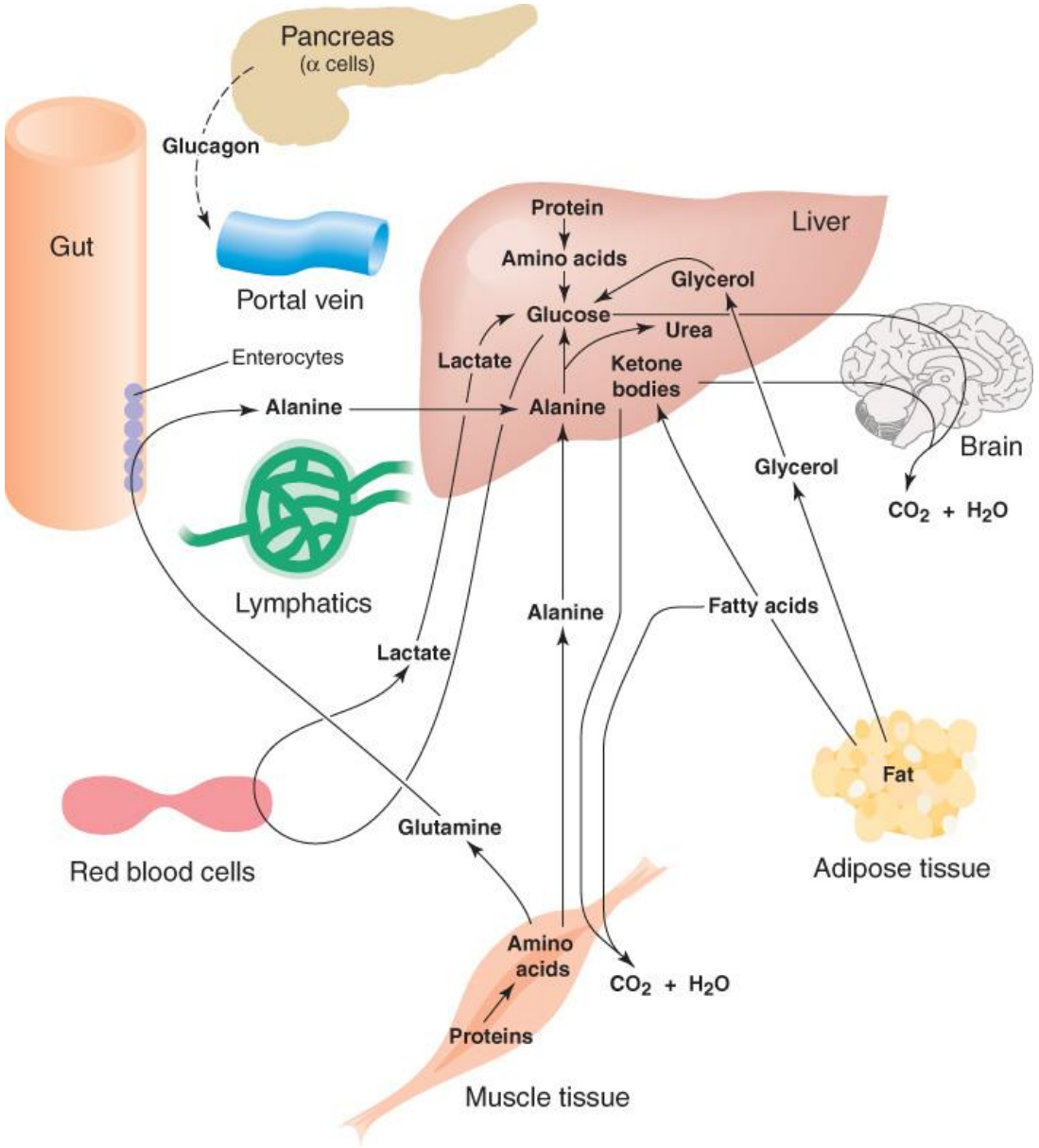


Figure 21.4 Metabolic interrelationships of major tissues in fasting state.

Glutamate provides the two N for Urea, glutamate oxidative deamination and from aspartate (Ox, Glu).

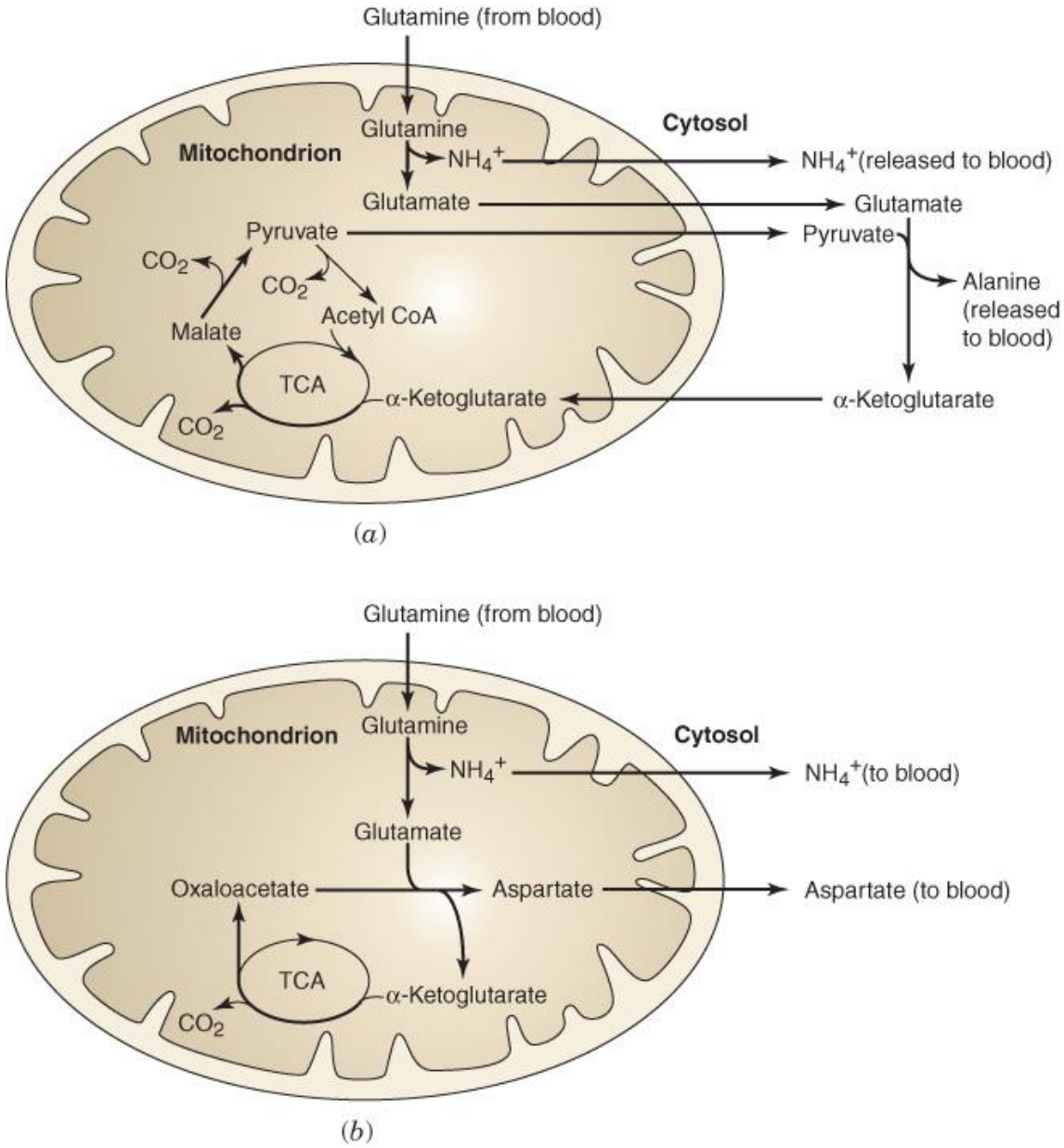


Figure 21.5 Glutamine catabolism by rapidly dividing cells.

Intestinal epithelium converts glutamine to citrulline, the only tissue that express an ATP dependent glutamate reductase that converts Glu to the Glu semialdehyde that forms Ornithine. This rx is irreversible in liver.

This pathway can be used to regulate arg and protein degradation under restricted protein intake.

The most important use of SAM in the body (production of Creatine)

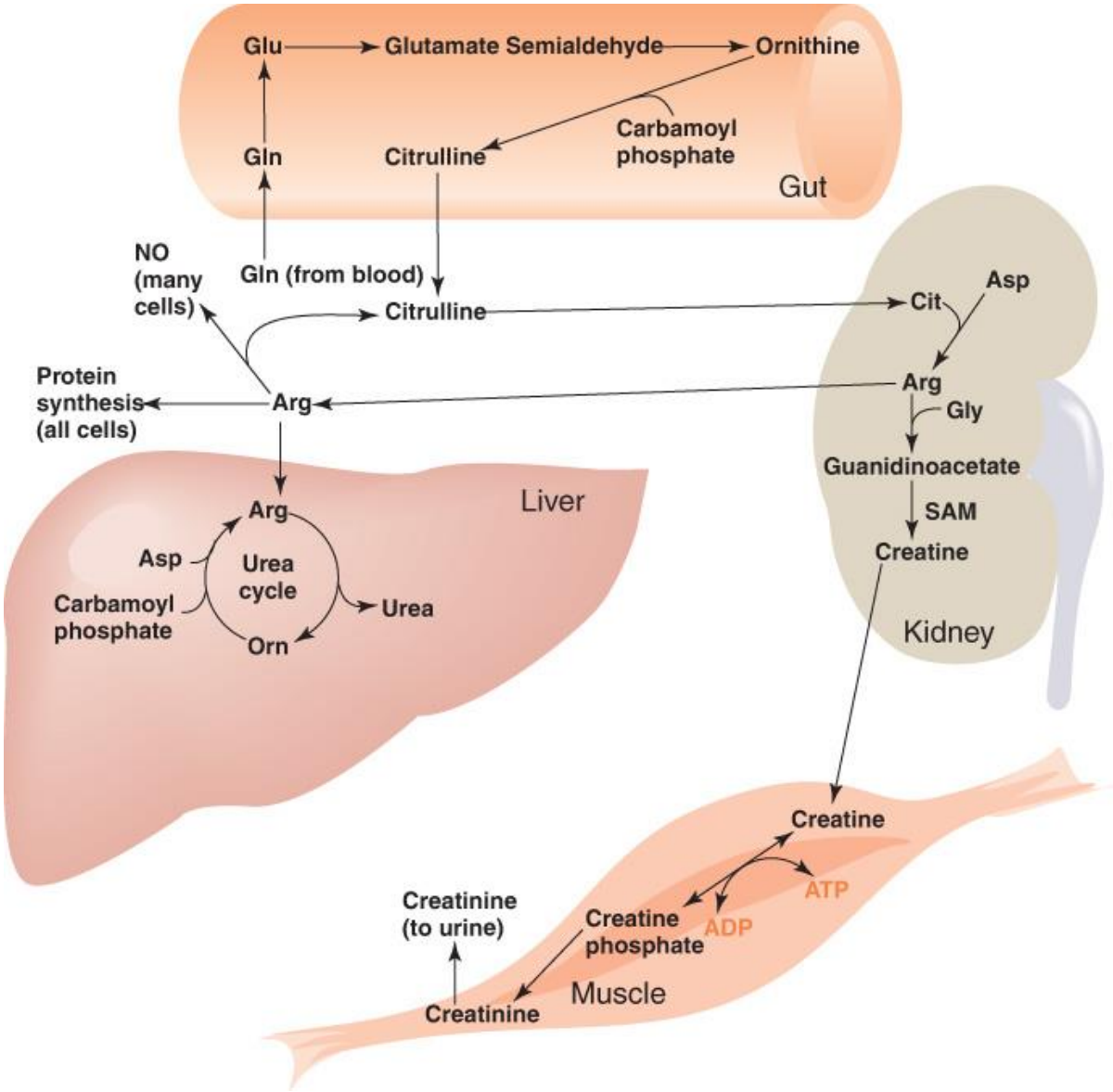
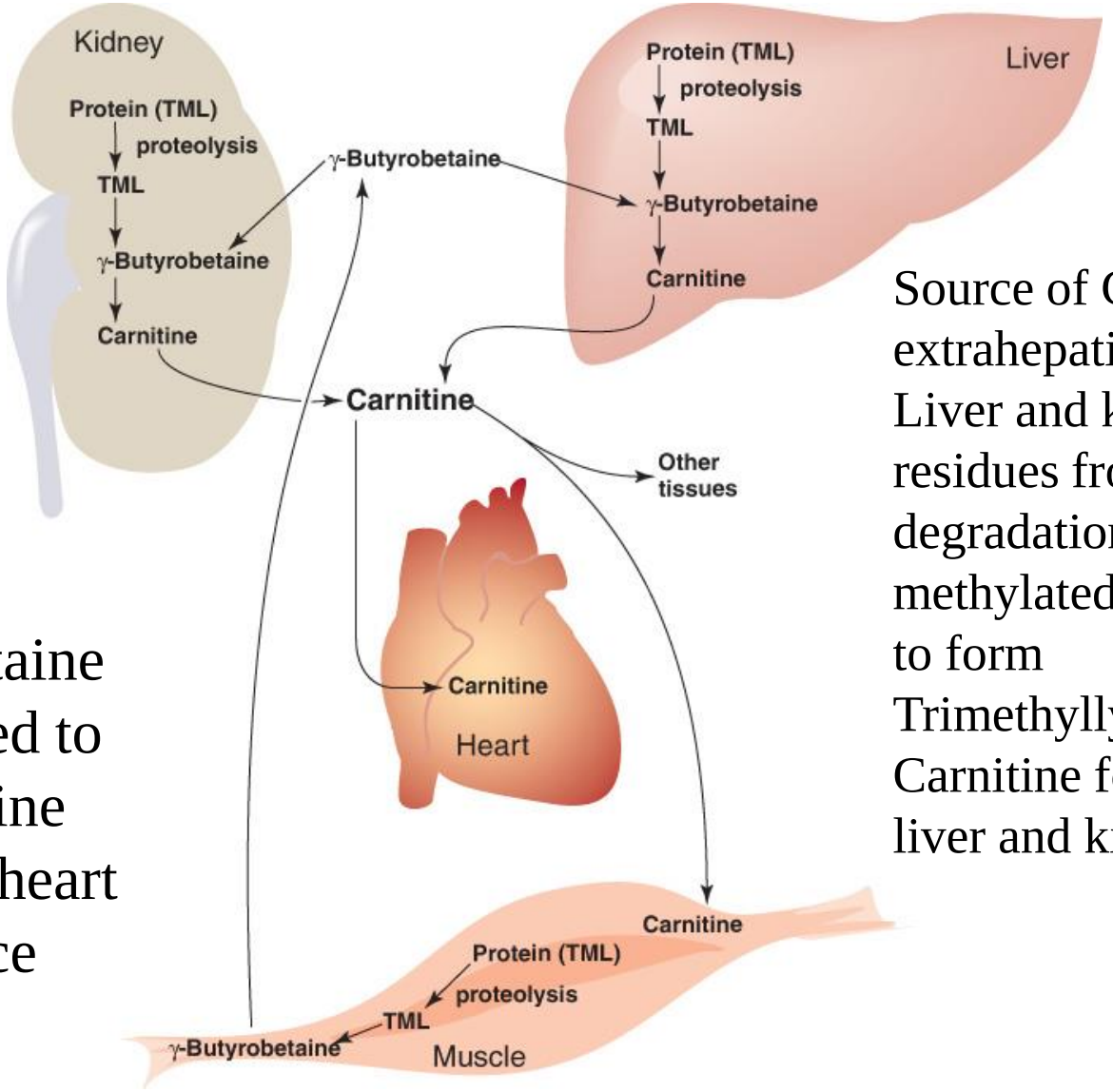


Figure 21.6 Gut and kidney function together in synthesis of arginine from glutamine.

This controls urea cycle in the liver.



G-butyrobetaine Hydroxylated to form Carnitine Muscle nor heart can't produce Carnitine

Source of Carnitine for extrahepatic tissue is the Liver and kidney, lysine residues from protein degradation are N-methylated using SAM to form Trimethyllysine TML. Carnitine formed from liver and kidney.

Figure 21.7 Kidney and liver provide carnitine for other tissues.

Energy requirements, reserves and caloric Homeostasis

The average person consumes 180-280 g of carbohydrates, 70-100g of protein and 70-100g of fat daily. This meets a daily requirement of 1600-2400 kcal.

Glucose levels need to be well regulated <1.5 mM coma and death

Hyperglycemia needs to also be avoided since glucose will be lost in urine and blood vol altered much glucose results in glycation of proteins

TABLE 21.1 • Energy Reserves of Humans[a]

		Fuel Reserves	
Stored Fuel	*Tissue*	*(g)*	*(kcal)*
Glycogen	Liver	70	280
Glycogen	Muscle	120	480
Glucose	Body fluids	20	80
Fat	Adipose	15,000	135,000
Protein	Muscle	6,000	24,000

[a]Data are for a normal subject weighing 70 kg. Carbohydrate supplies 4 kcal/g; fat, 9 kcal/g; protein, 4 kal/g.

Figure

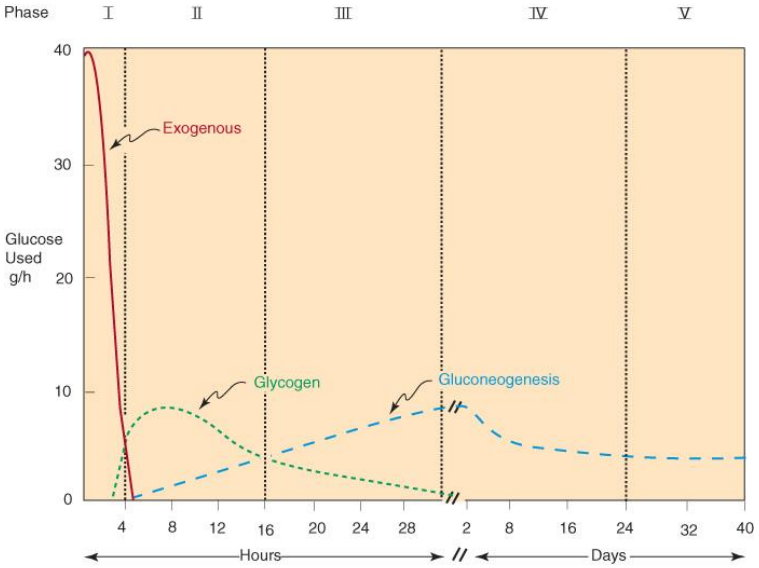
TABLE 21.2 • Substrate and Hormone Levels in Blood of Well-Fed, Fasting, and Starving Humans[a]

Hormone or Substrate (units)	*Very Well Fed*	*Postabsorptive 12 hours*	*Fasted 3 days*	*Starved 5 weeks*
Insulin (μU/mL)	40	15	8	6
Glucagon (pg/mL)	80	100	150	120
Insulin/glucagon ratio (μU/pg)	0.50	0.15	0.05	0.05
Glucose (mM)	6.1	4.8	3.8	3.6
Fatty acids (mM)	0.14	0.6	1.2	1.4
Acetoacetate (mM)	0.04	0.05	0.4	1.3
β-Hydroxybutyrate (mM)	0.03	0.10	1.4	6.0
Lactate (mM)	2.5	0.7	0.7	0.6
Pyruvate (mM)	0.25	0.06	0.04	0.03
Alanine (mM)	0.8	0.3	0.3	0.1
ATP equivalents (mM)	262	235	301	428

Source: From Ruderman, N. B., Aoki, T. T., and Cahill, G. F. Jr. Gluconeogenesis and its disorders in man. In: R. W. Hanson and M. A. Mehlman (Eds.), *Gluconeogenesis, Its Regulation in Mammalian Species.* New York: Wiley, 1976, p. 515.

[a]Data are for normal-weight subjects except for the 5-week starvation values, which are from obese subjects undergoing therapeutic starvation. ATP equivalents were calculated on the basis of the ATP yield expected on complete oxidation of each substrate to CO_2 and H_2O: 32 molecules of ATP for each molecule of glucose; 106 for the average fatty acid (palmitate); 19 for acetoacetate; 21.5 for β-hydroxybutyrate; 15 for lactate; 12.5 for pyruvate; and 13 (corrected for urea formation) for alanine.

Figure



Phase	ORIGIN OF BLOOD GLUCOSE	TISSUES USING GLUCOSE	MAJOR FUEL OF BRAIN
I	Exogenous	All	Glucose
II	Glycogen Hepatic gluco–neogenesis	All except liver. Muscle and adipose tissue at diminished rates	Glucose
III	Hepatic gluconeogenesis Glycogen	All except liver. Muscle and adipose tissue at rates intermediate between II and IV	Glucose
IV	Gluconeogenesis, hepatic and renal	Brain, RBCs, renal medulla. Small amount by muscle	Glucose, ketone bodies
V	Gluconeogenesis, hepatic and renal	Brain at a diminished rate, RBCs, renal medulla	Ketone bodies, glucose

Phase IV ketone bodies predominate to compensate for fuel needs

Figure 21.8 The five phases of glucose homeostasis.

Reproduced with permission from Ruderman, N. B., Aoki, T. T., and Cahill, G. F., Jr. Gluconeogenesis and its disorders in man, in R. W. Hanson, and M. A. Mehlman (Eds.), *Gluconeogenesis, Its Regulation in Mammalian Species. New York: Wiley, 1976, 515.*

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

Substrate availability controls metabolic pathways

Fatty acids in blood and entering liver determines ketogenesis

Glucose synthesis in liver is affected by the rate of which gluconeogenic substrate enter

In diabetes delivery of amino acids stimulate gluconeogenesis and exacerbates hyperglycemia. Failure to supply gluconeogenic substrate explain some hypoglicemia (pregnancy and advanced starvation)

Ammonia and amino acids stimulate urea cycle, the intestine release citrulline after rich protein meal, protein deficiency urea formation declines.

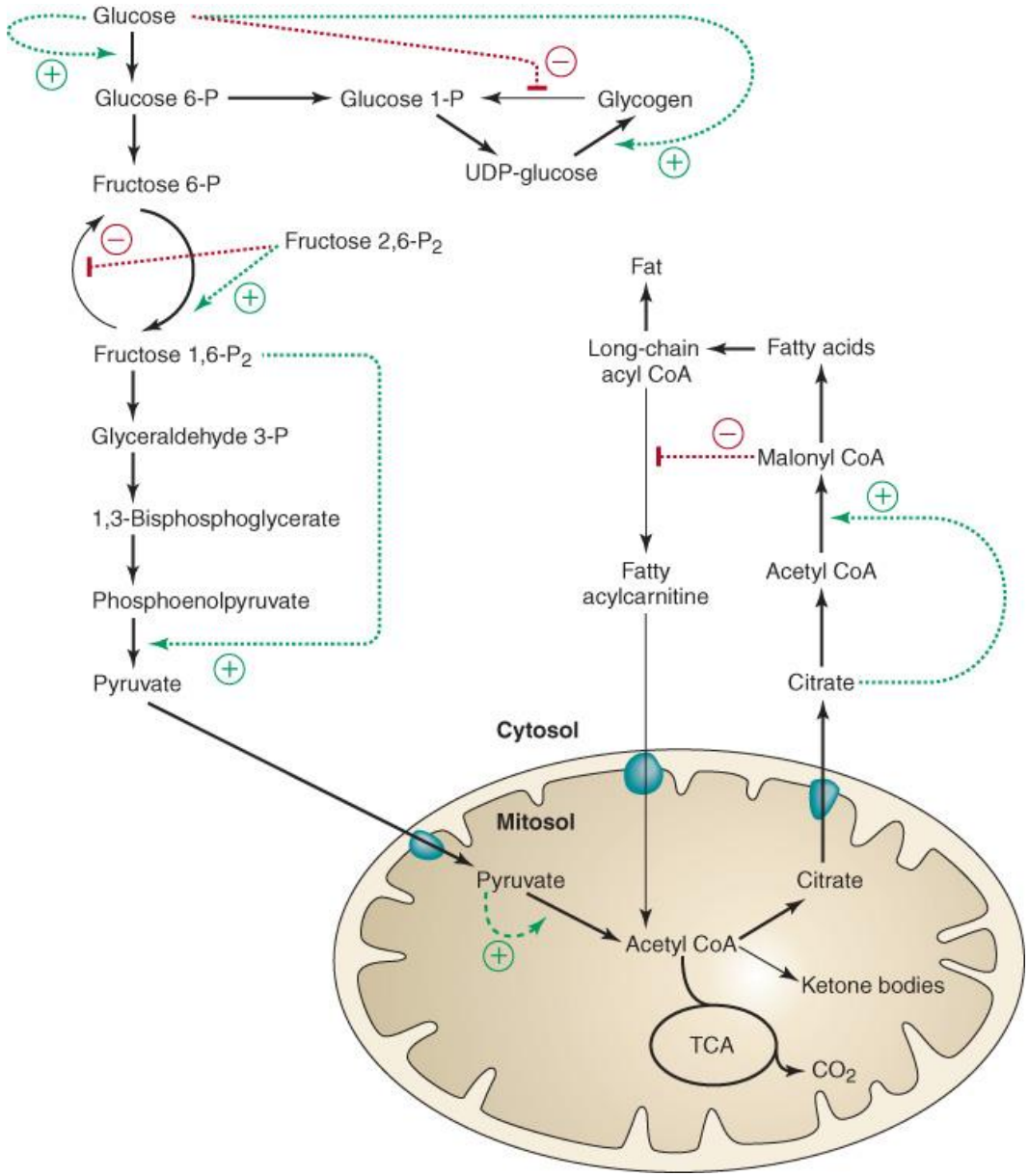
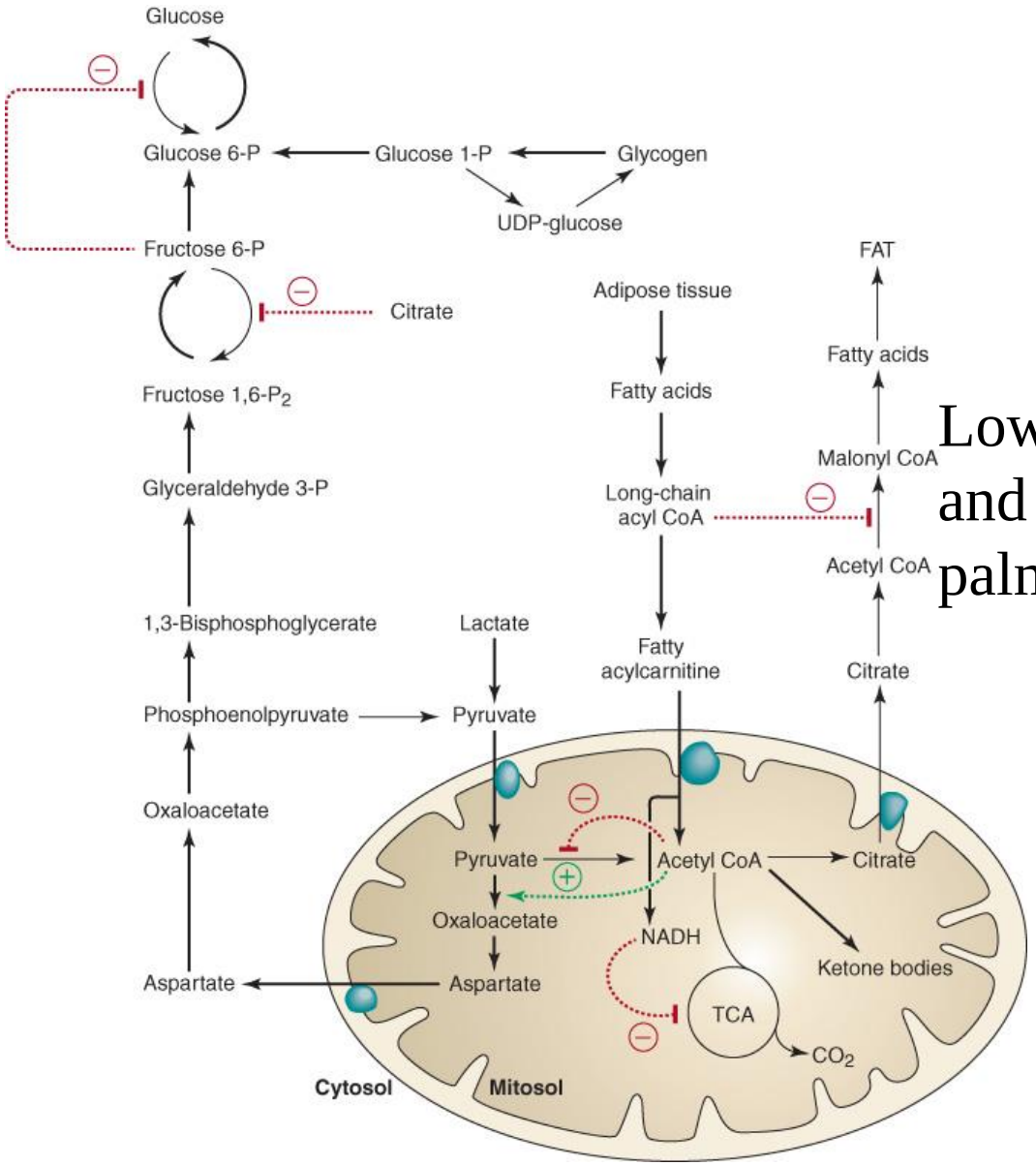
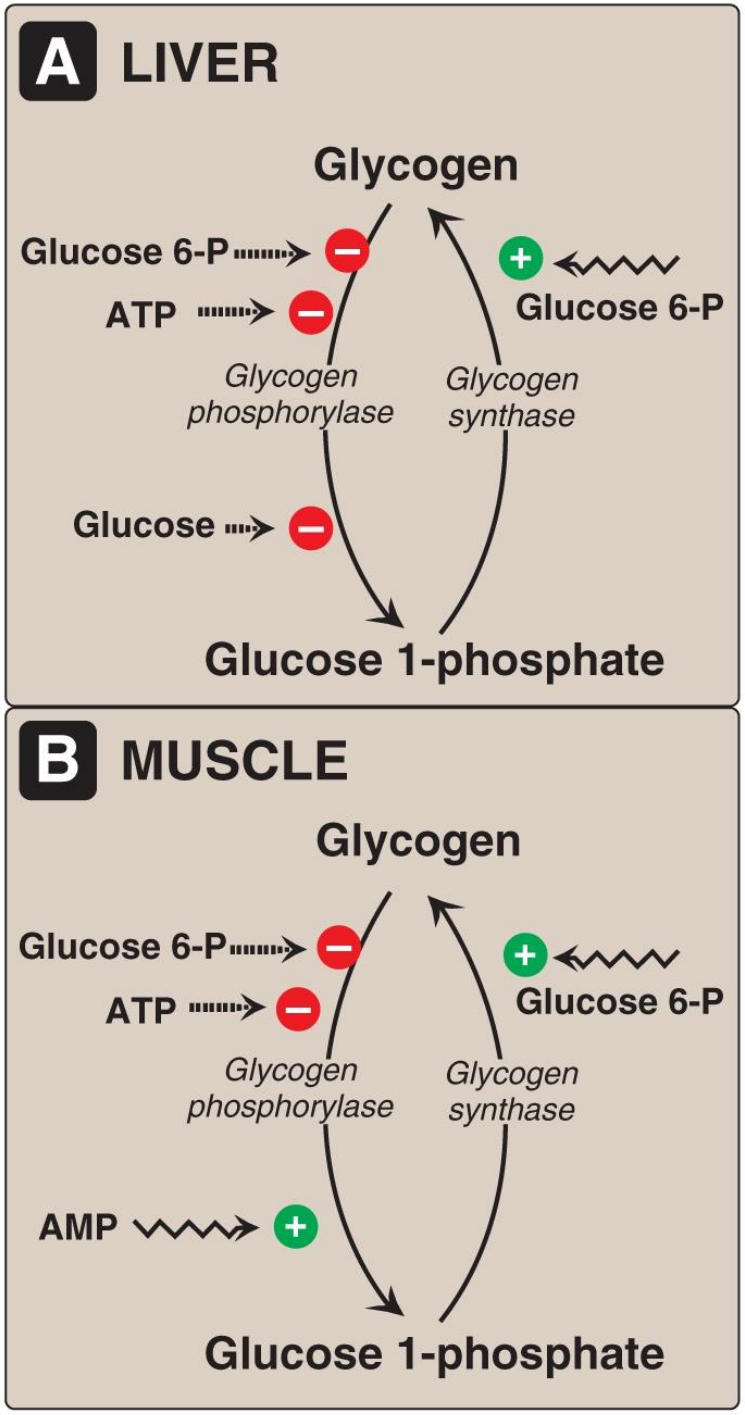


Figure 21.9 Control of hepatic metabolism by allosteric effectors in the well-fed state.

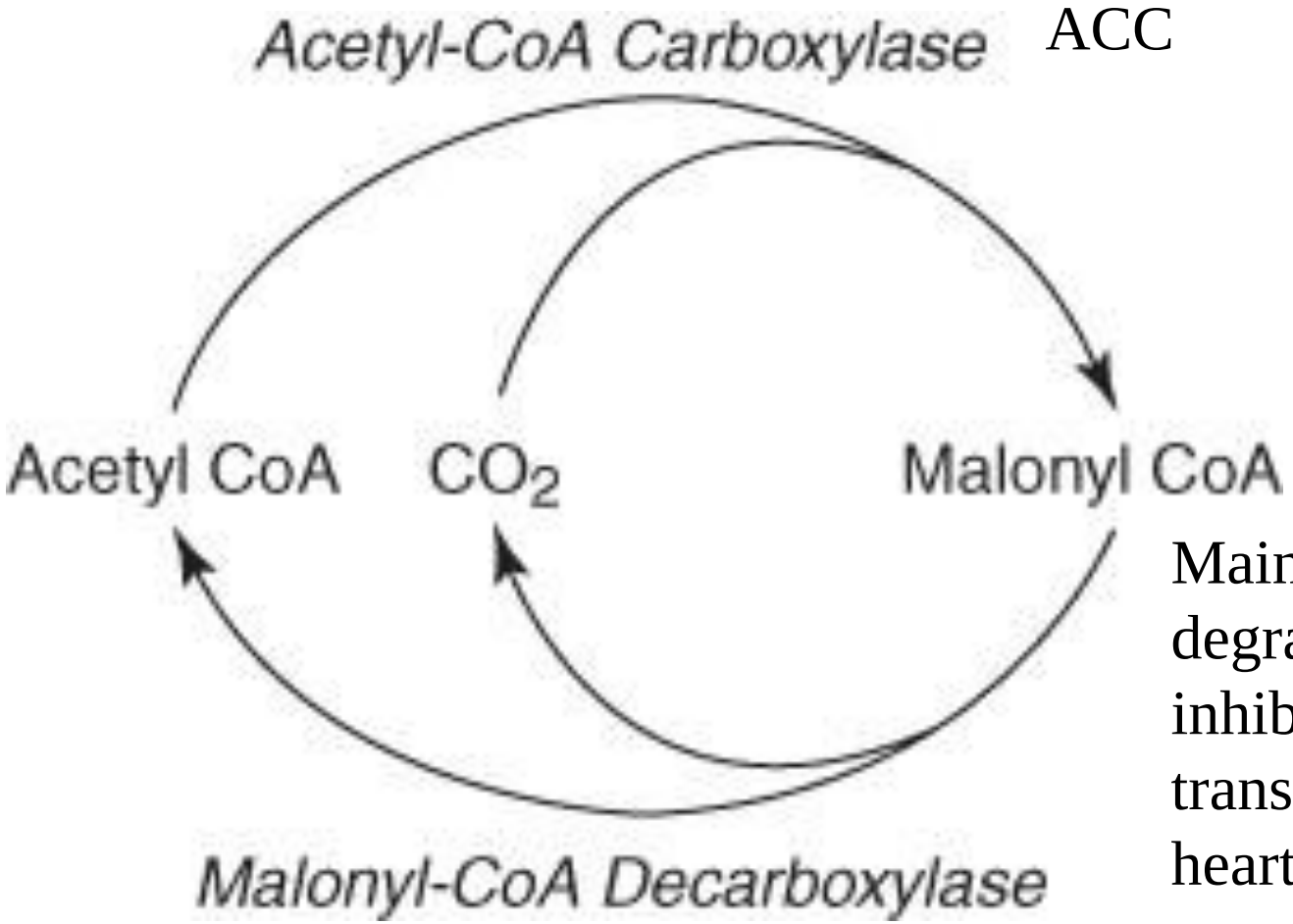


Lowers malonyl Co-A and induces carnitine palmitoyltransferase I

Figure 21.10 Control of hepatic metabolism by allosteric effectors in the fasting state.



Regulation of Glycogen Synthesis The synthesis and degradation of glycogen are tightly regulated. Glycogen synthase and glycogen phosphorylase are allosterically controlled and are hormonally regulated. Glycogen synthesis is stimulated when energy levels and substrate availability are high. Glycogen degradation is increased when energy levels and available glucose supplies are low. In muscle, contraction requires ATP hence AMP is accumulated. Ca^{2+} is released due to depolarization of nerve impulses. Ca^{2+} binds to calmodulin (a subunit of phosphorylase kinase) and activates this enzyme (glycogen phosphorylase).



ACC

MCD

Mainly degradation and inhibit facilitate transport in heart and muscle tissue and both in liver

Figure 21.11 Relative activities of acetyl-CoA carboxylase and malonyl-CoA decarboxylase determine the concentration of malonyl CoA.

Covalent modifications regulating key enzymes

cAMP
AMP when low ATP
hypoxia, excessive energy demand, AMP induces AMPK activated kinase to get ATP levels back

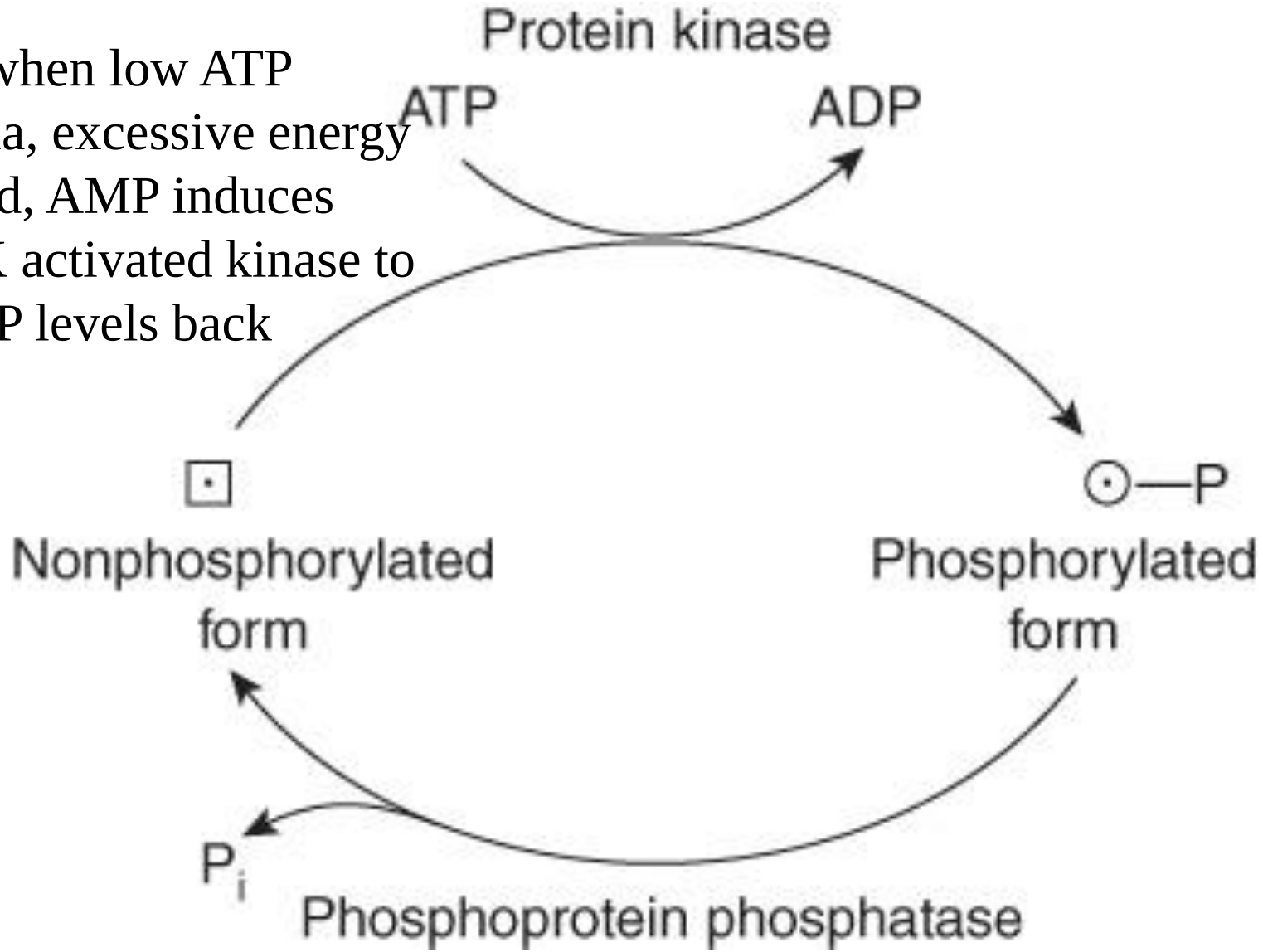


Figure 21.12 Regulation of the activity of key enzymes by covalent modification.

Covalent Modifications

Insulin
Phosphoprotein phosphatases
Opposite

Serine and threonine

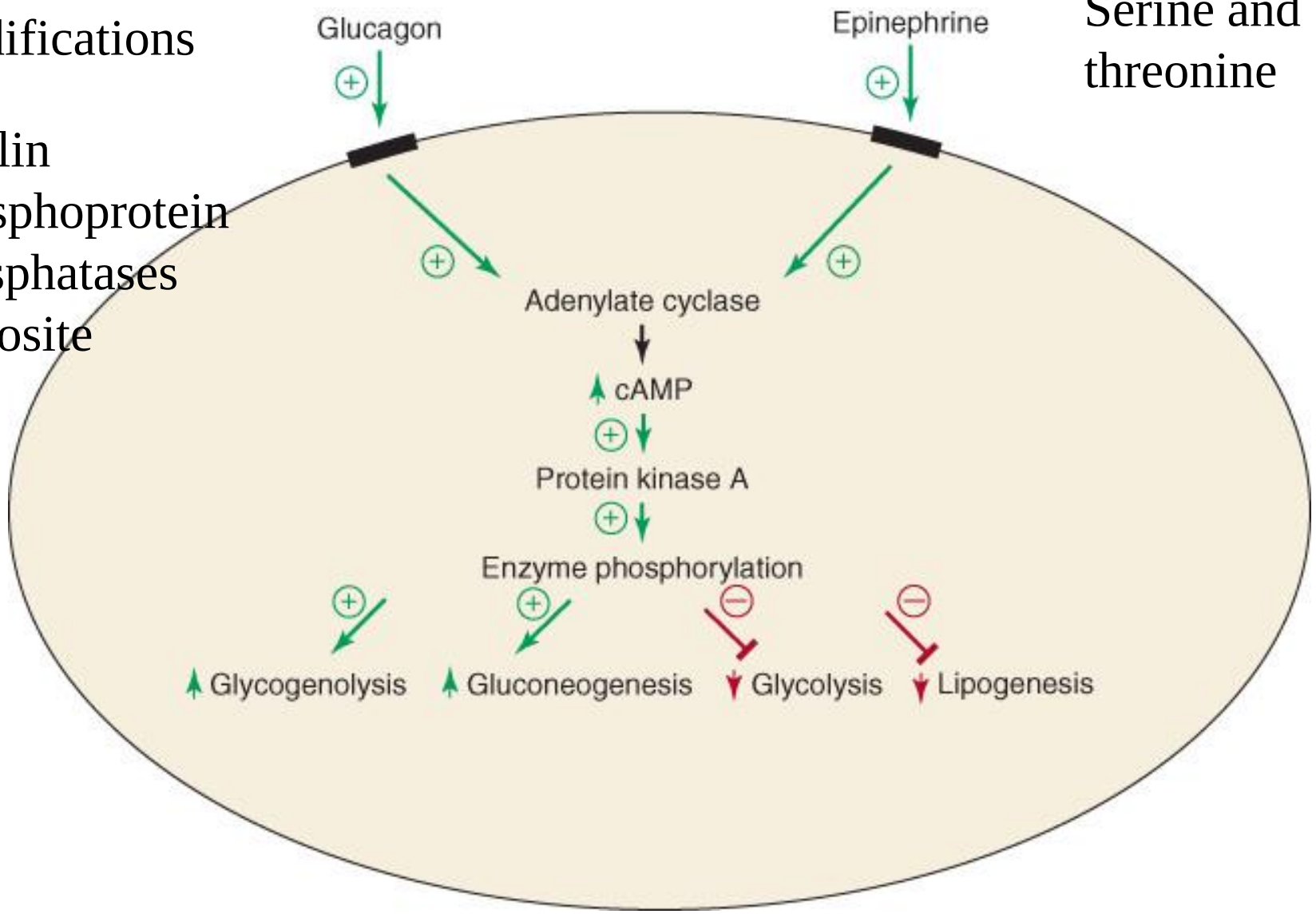


Figure 21.13 Glucagon and epinephrine stimulate glycogenolysis and gluconeogenesis and inhibit glycolysis and lipogenesis in liver.

Deprived state
energy is low

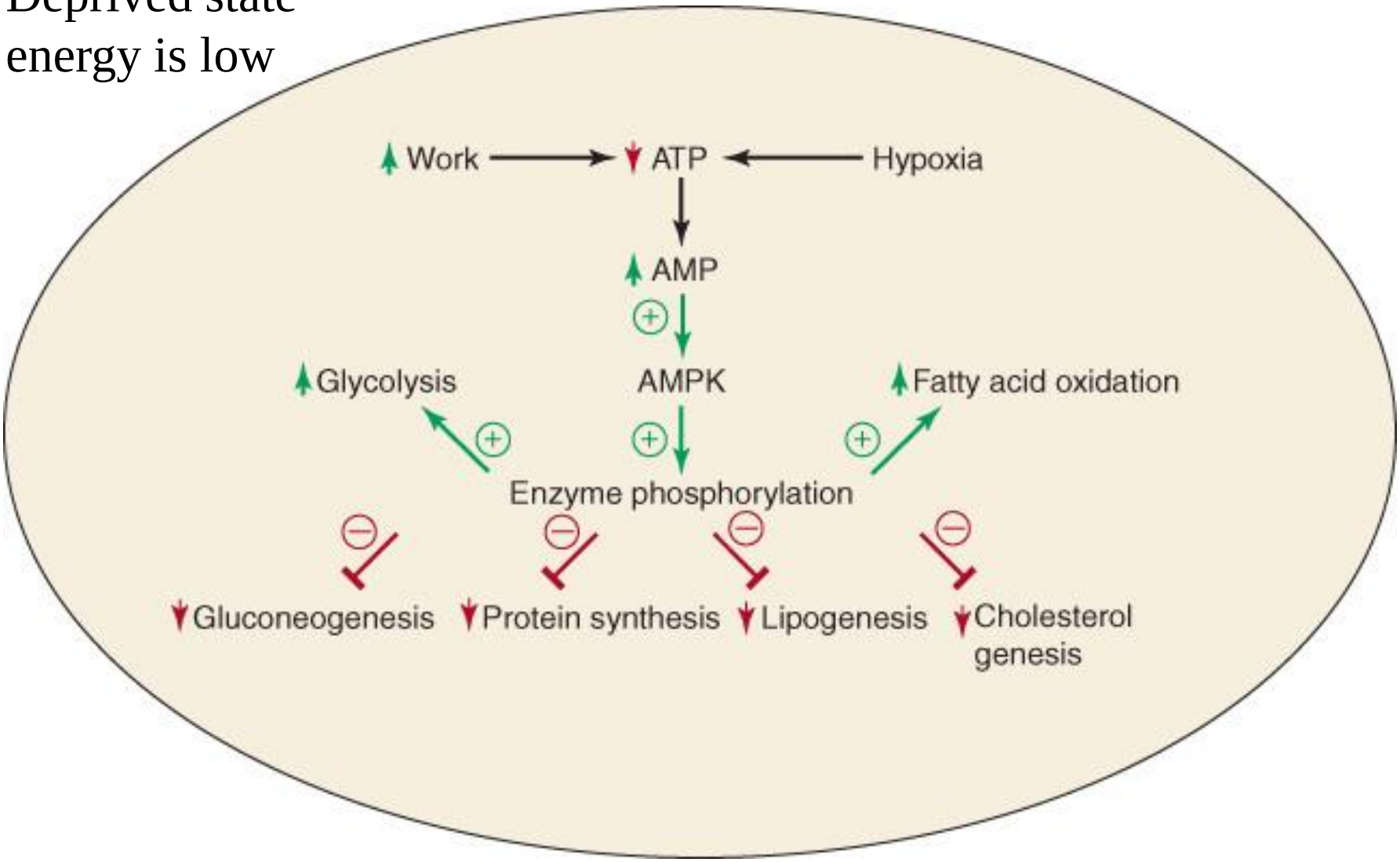
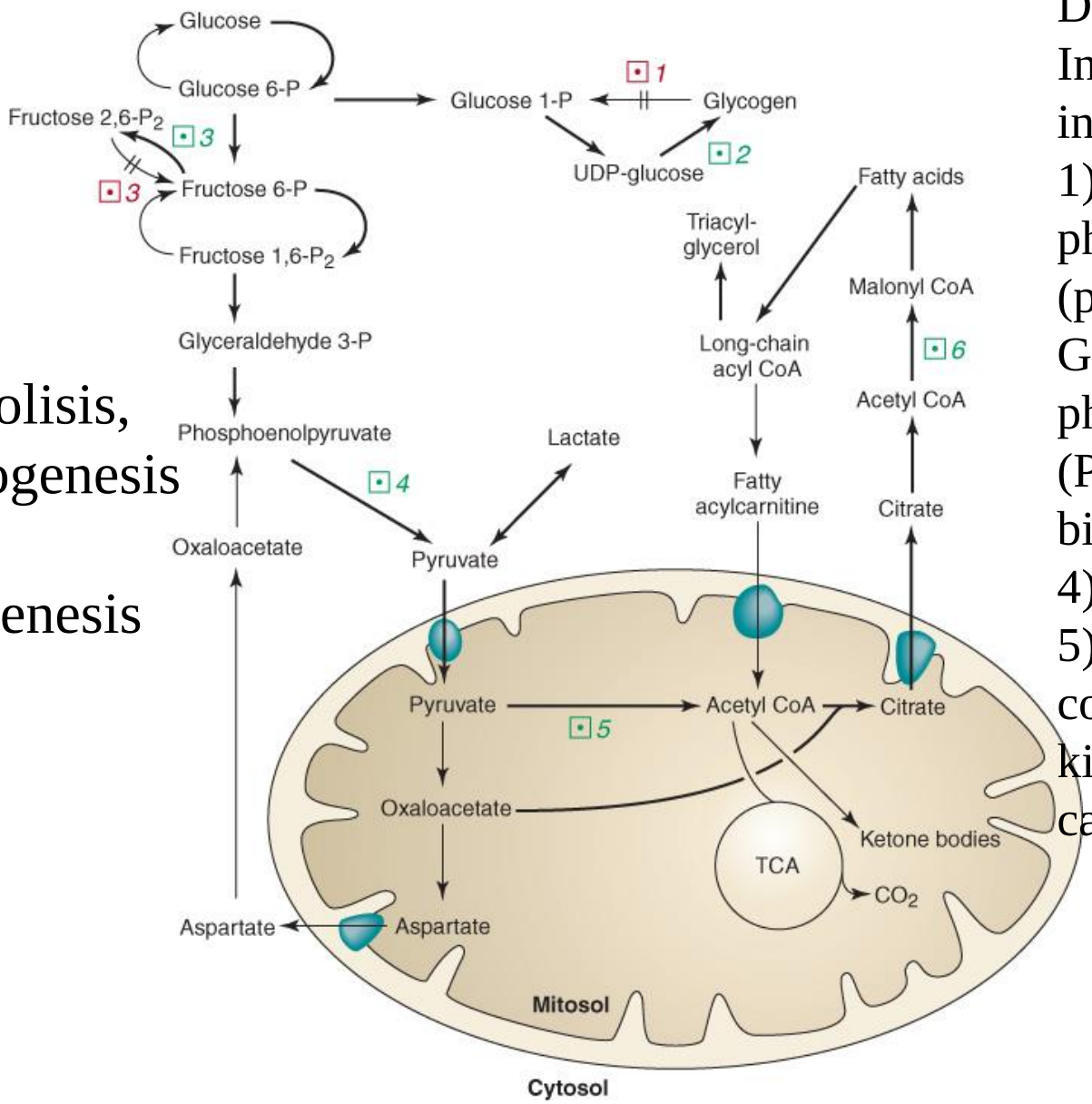


Figure 21.14 Activation of AMPK shuts down ATP-requiring processes and stimulates ATP-producing processes.

Glycolisis, glycogenesis , lipogenesis



Dephosphorylated state, Insulin high, glucagon low in blood (low cAMP) 1) glycogen phosphorylase, (phosphorylase kinase), 2) Glycogen synthase, 3) 6 phosphofructose 2 kinase (PFK2), /3) fructose 2,6 bisphosphatase (FBP2), 4)pyruvate kinase, 5)pyruvate dehydrogenase complex (low activity of kinase) 6) acetyl CoA carboxylase

Figure 21.15 Control of hepatic metabolism by covalent modification in the well-fed state.

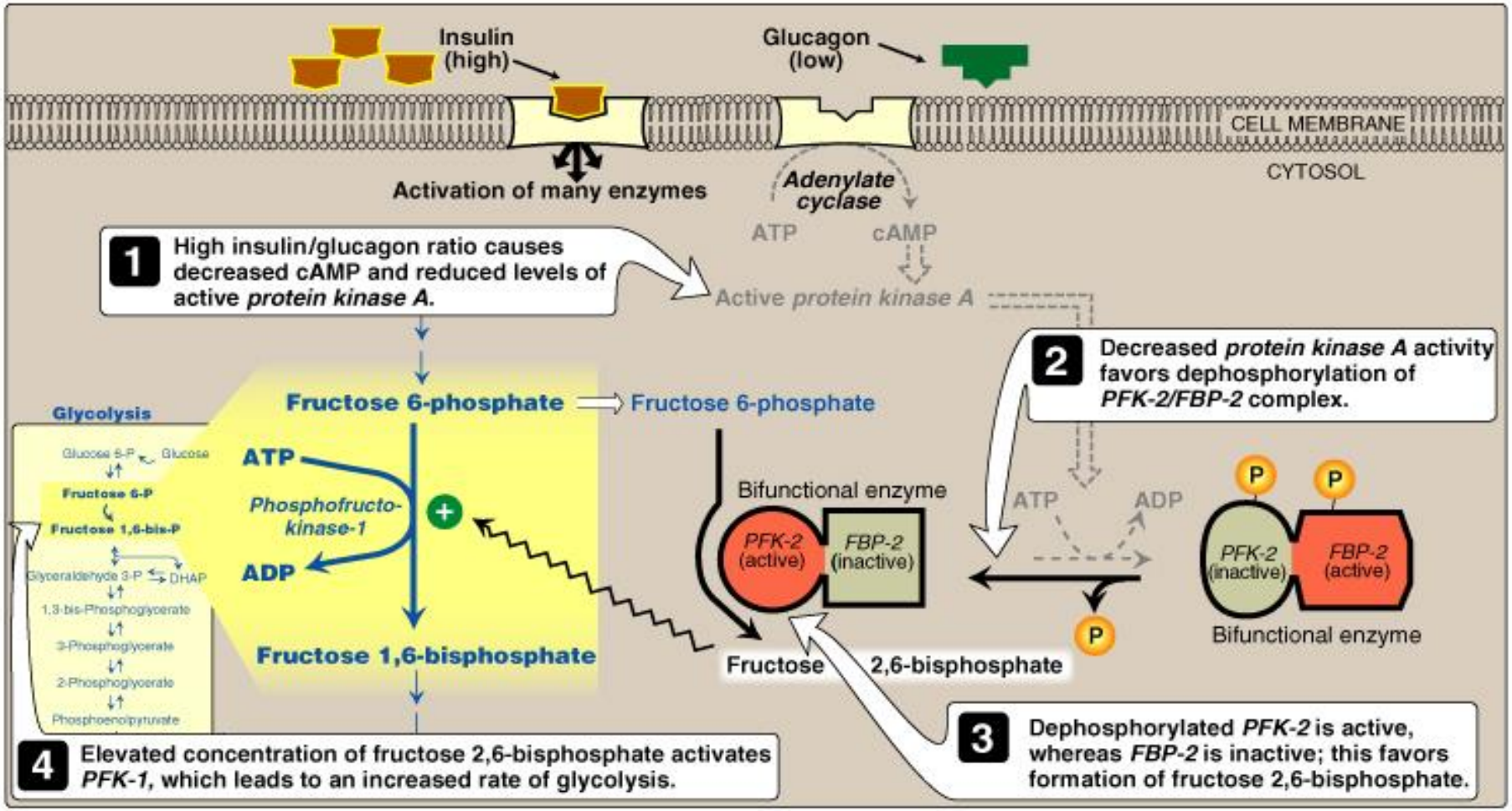
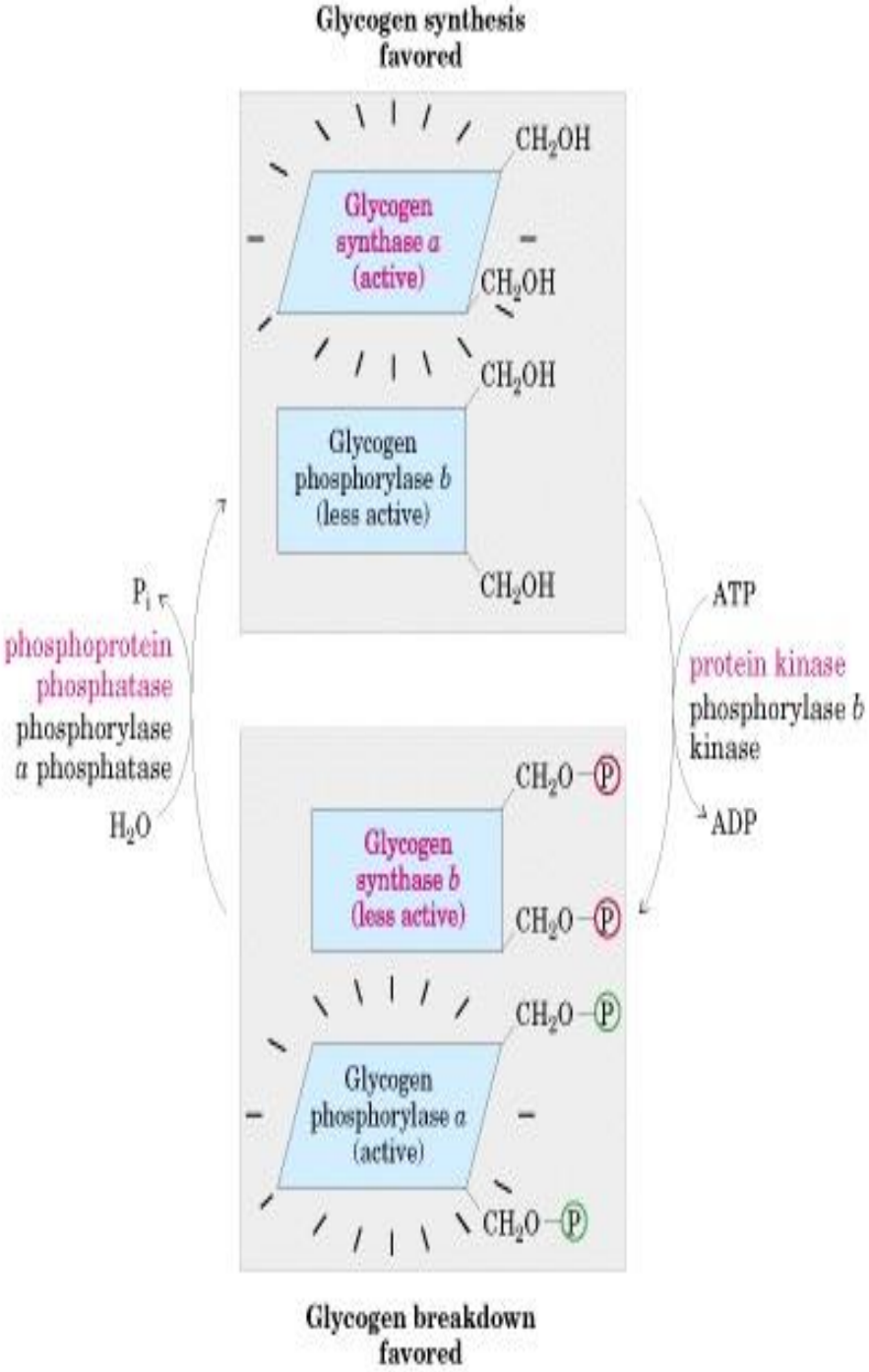
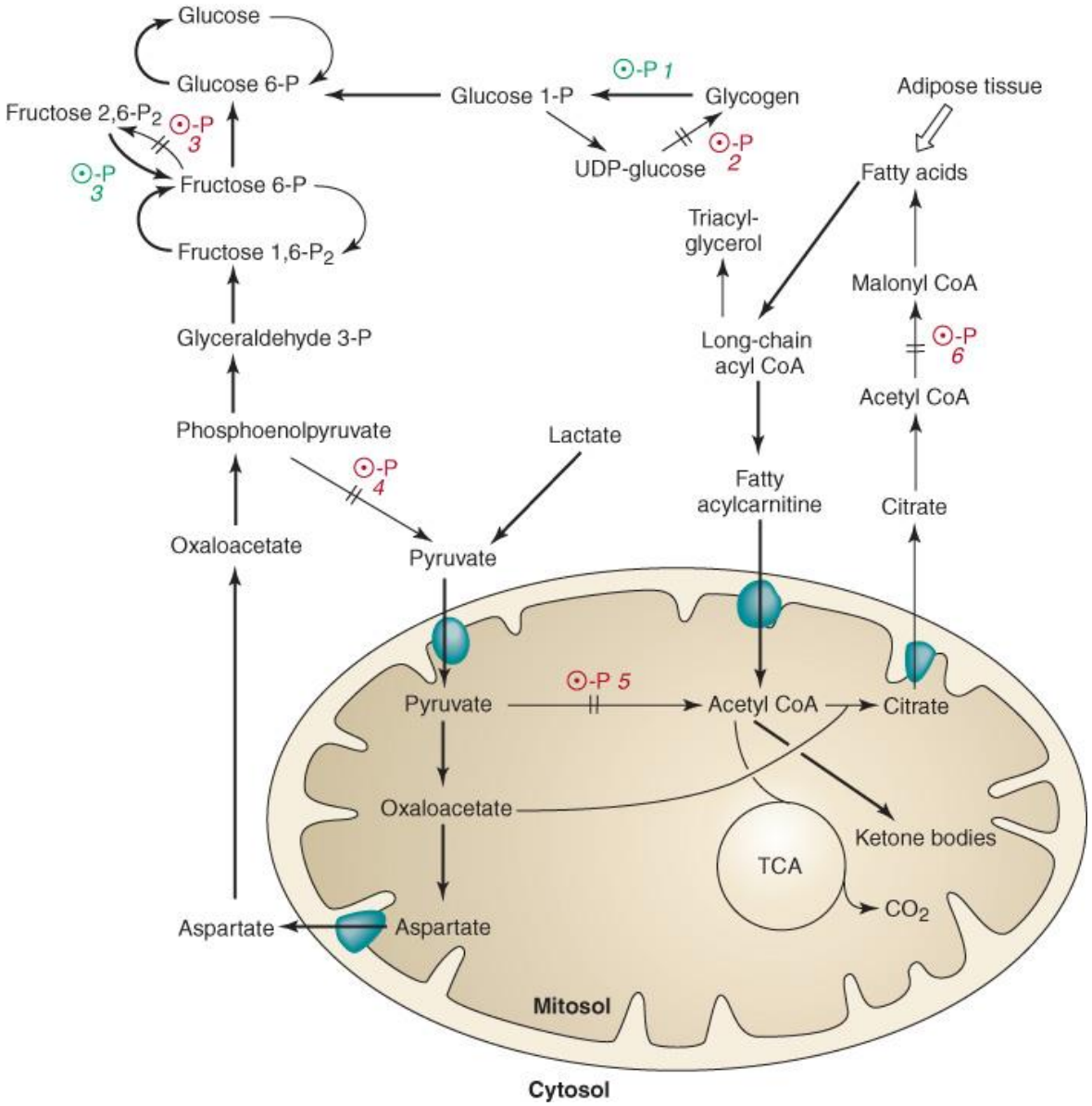


Figure 8.17

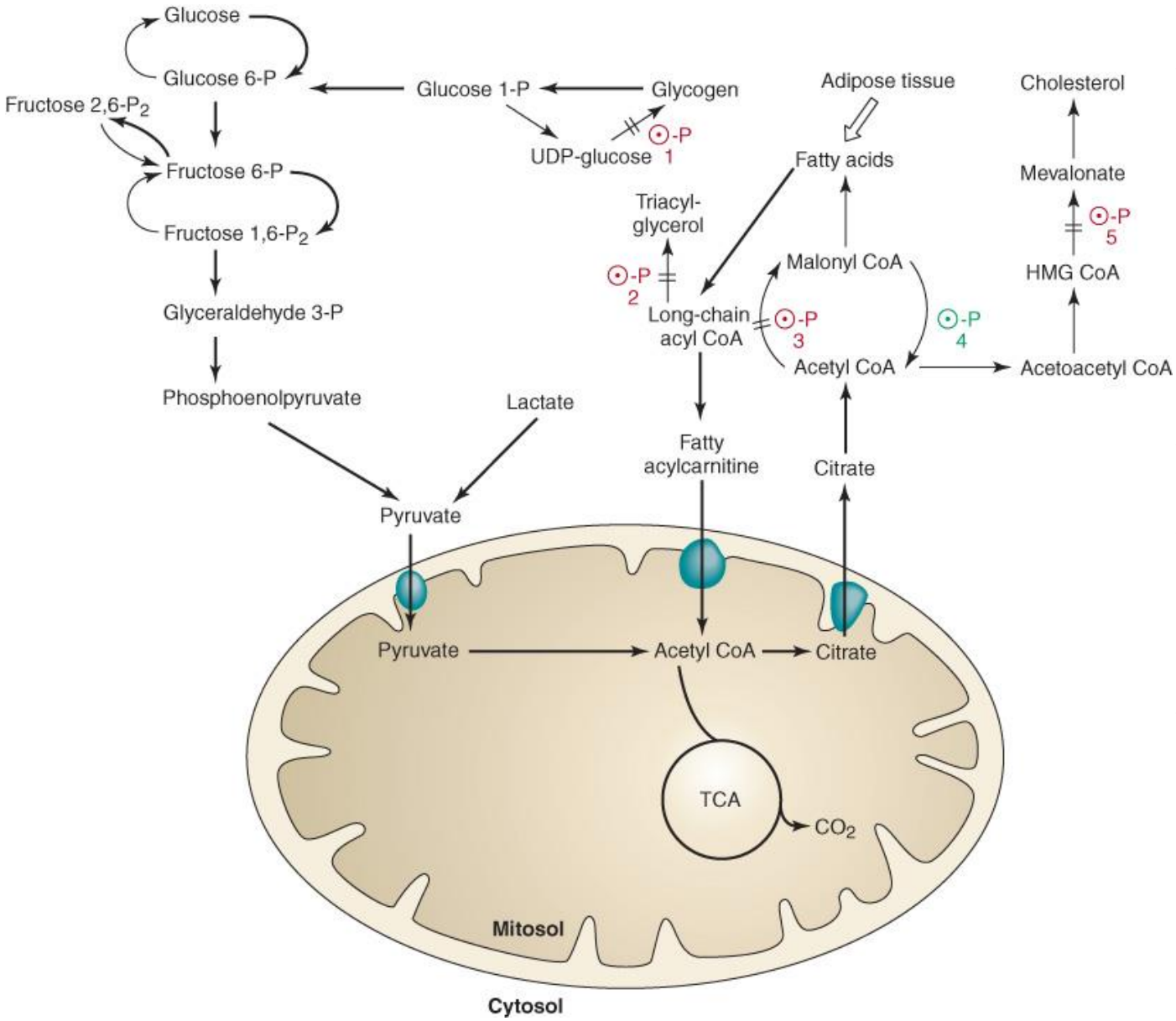
Effect of elevated insulin concentration on the intracellular concentration of fructose 2,6-bisphosphate in liver. *PFK-2 = phosphofructokinase-2*; *FBP-2 = Fructose bisphospate phosphatase-2*.


Glycogen synthesis favored
CH2OH
Glycogen synthase a (active)
CH2OH
CH2OH
Glycogen phosphorylase b (less active)
CH2OH
Pi
phosphoprotein phosphatase
phosphorylase a phosphatase
H2O
ATP
protein kinase
phosphorylase b kinase
ADP
CH2O—P
Glycogen synthase b (less active)
CH2O—P
CH2O—P
Glycogen phosphorylase a (active)
CH2O—P
Glycogen breakdown favored



High levels of glucagon, high levels of cAMP turn on Protein Kinase A, glycogen phosphorylase, phosphorylase kinase, PFK2/FBP2. Also AMPK activated turn off anabolic pathways that use ATP turns on catabolism.

Figure 21.16 Control of hepatic metabolism by covalent modification in the fasting state.



Phosphorylates Acetyl CoA Carboxylase, glycerol 3 phosphate acyltransferase, HMG reductase, glycogen synthase. Also inhibits protein synthesis (mRNA translation) so the strategy is to minimize use of ATP and helping B-oxidation lowering malonyl and activating MCoA decarbox

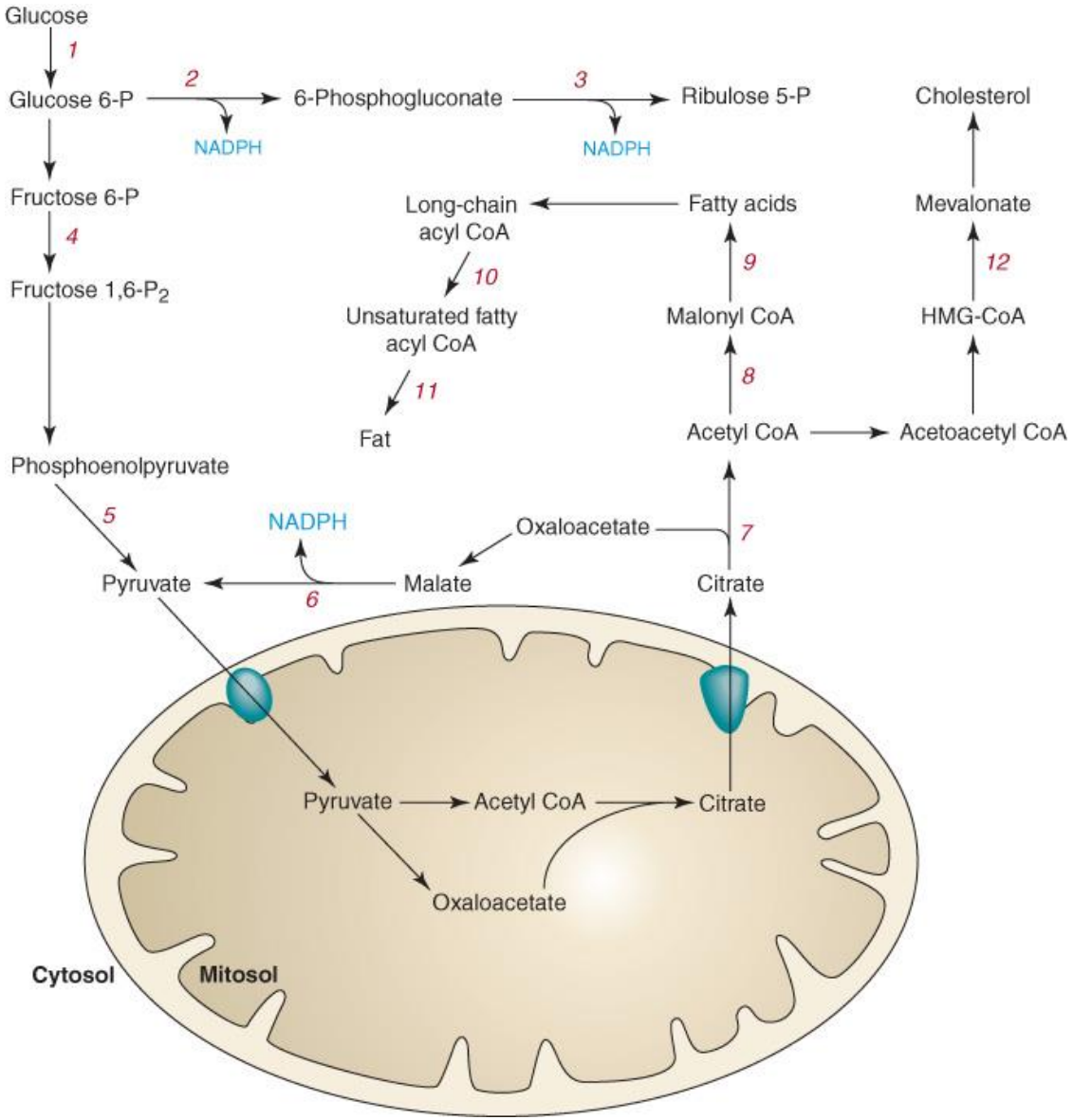
Figure 21.17 Control of hepatic metabolism by AMPK-mediated phosphorylation during energy deprivation.

In adipose tissue during well fed Pk, PDHC, Acetyl CoA carboxylase and hormone sensitive lipase (not found in liver) all are dephosphorylated. Hormone sensitive lipase is inactive.

Phosphorylation by cAMP Protein Kinase A and low Insulin levels in blood turn on lipid degradation.

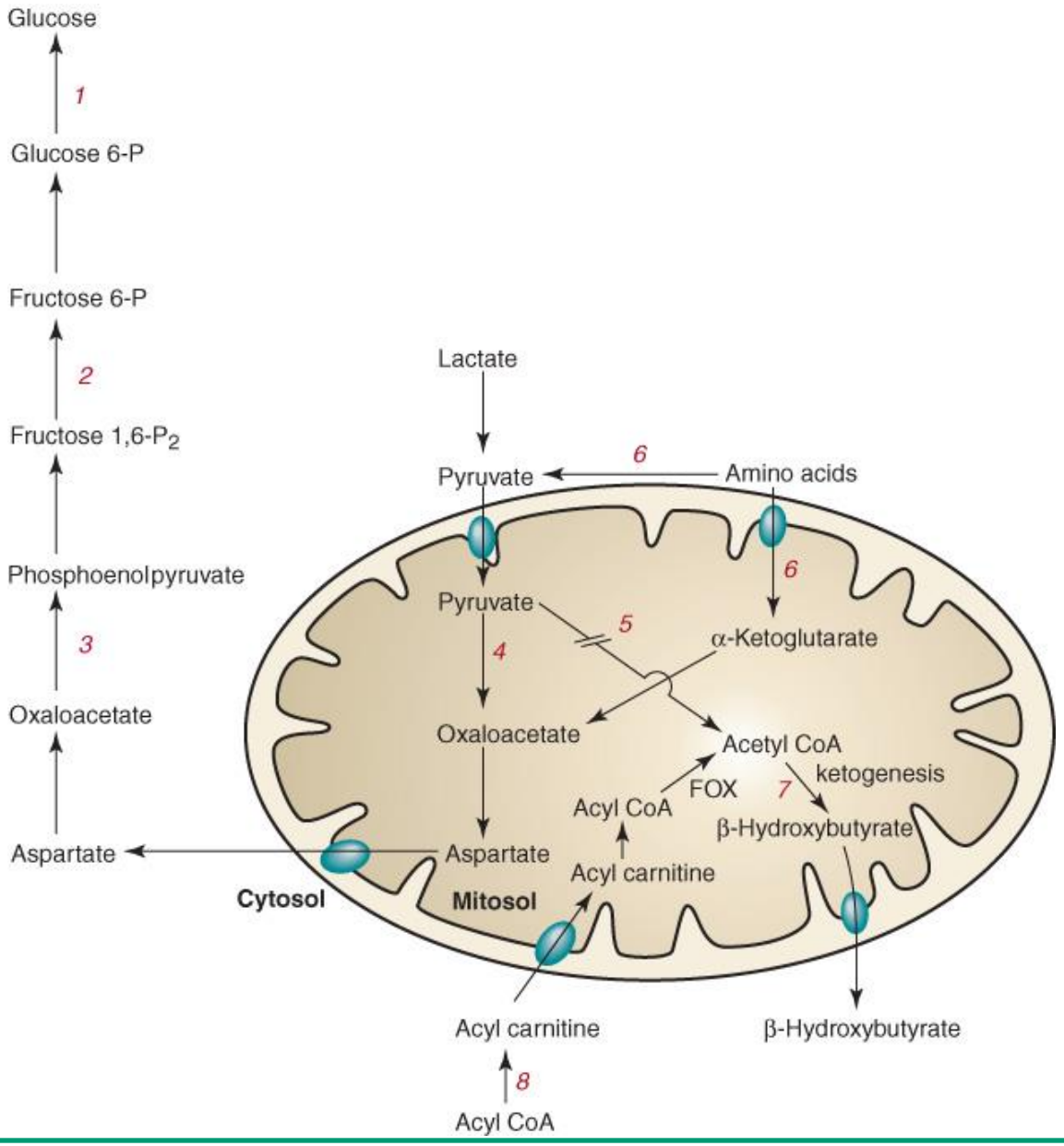
In skeletal muscle, Glycogen synthase, glycogen phosphorylase PDHC, Acetyl CoA carboxylase, and malonyl CoA decarboxylase are dephosphorylated in fed state. GLUT4 insulin stimulated.

In starved state the turn off of PDHC is critical to conserve 3 carbon compounds. This occurs with high levels of Acetyl CoA and NADH generated by B-oxidation



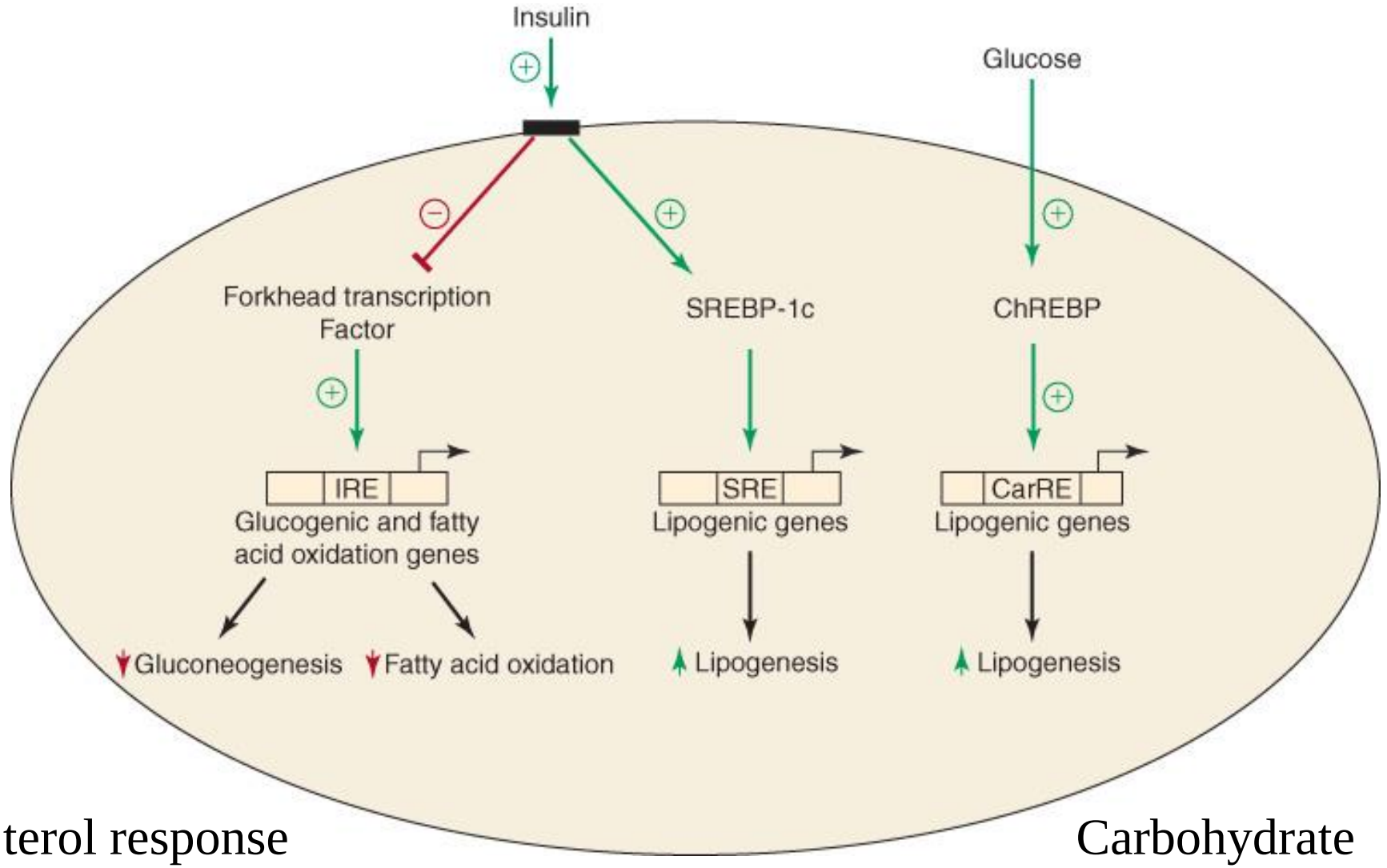
Enzymes induced in well fed state, all in synchronization to favor the formation of triacylglycerol and formation of NADPH for synthesis including de novo synthesis of Cholesterol enzyme names are in the book.

Figure 21.18 Hepatic enzymes induced in the well-fed state.



On the other hand under starvation lipogenic enzymes decrease dramatically in quantity while gluconeogenic enzymes are increased. Ketone bodies increase 7) Mitochondrial HMG CoA synthase (and the one in cytosol to mevalonate) . Induces PDK inhibiting PDHC, avoiding Pyruvate to metabolize to Acetyl CoA conserving lactate and some amino acids. Induction of 8) Carnitine Palmitoyltransferase I to induce B oxidation and ketone bodies

Figure 21.19 Hepatic enzymes induced in the fasted state.



Sterol response element binding proteins SREP

Carbohydrate response Binding P ChREBP dephosphorylated is active

Figure 21.20 Regulation of gene transcription in liver by insulin and glucose.

Another transfactor involved in the synthesis of gluconeogenic genes when phosphorylated by Protein K A

cAMP-response-element binding protein CREB

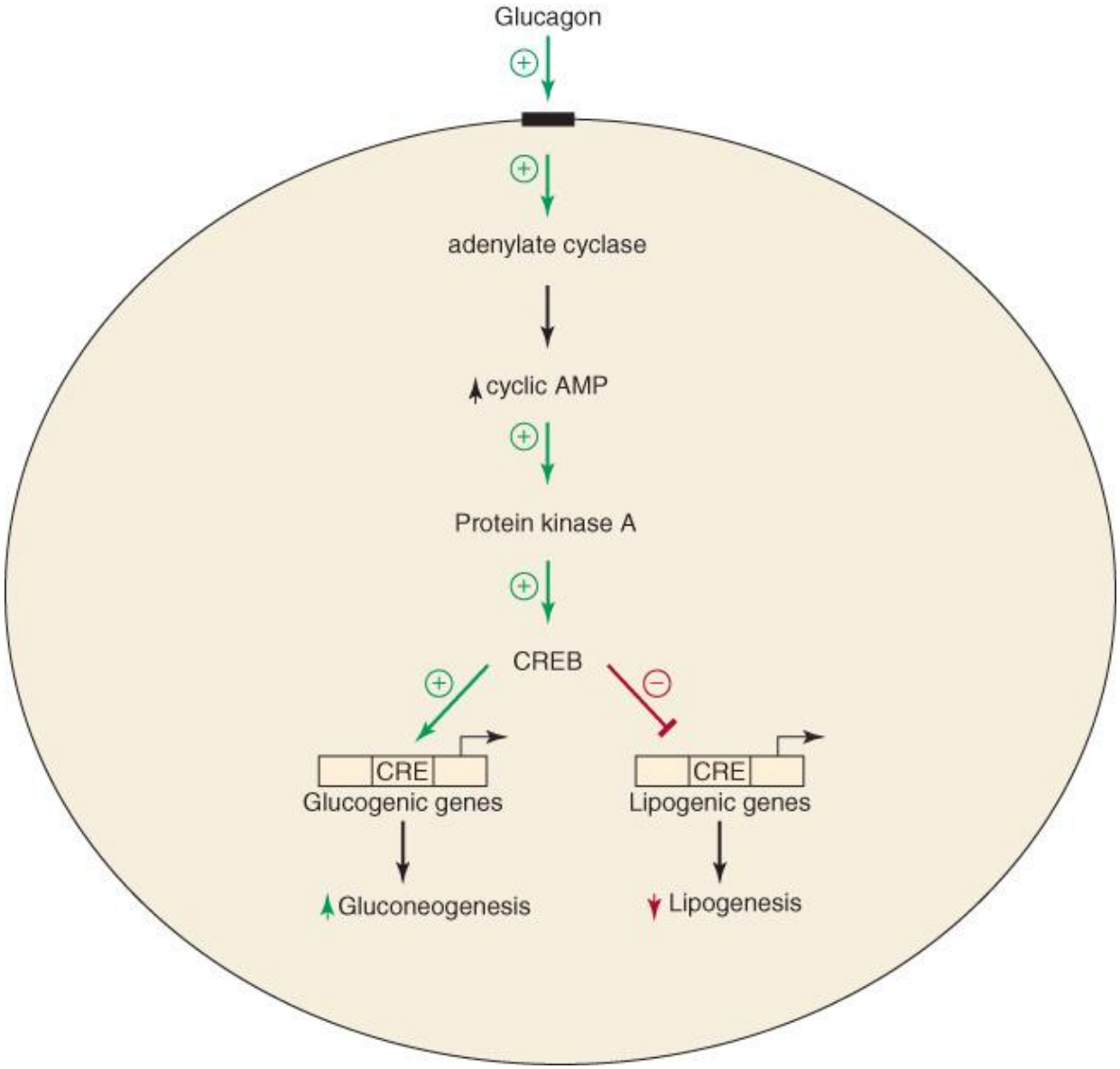
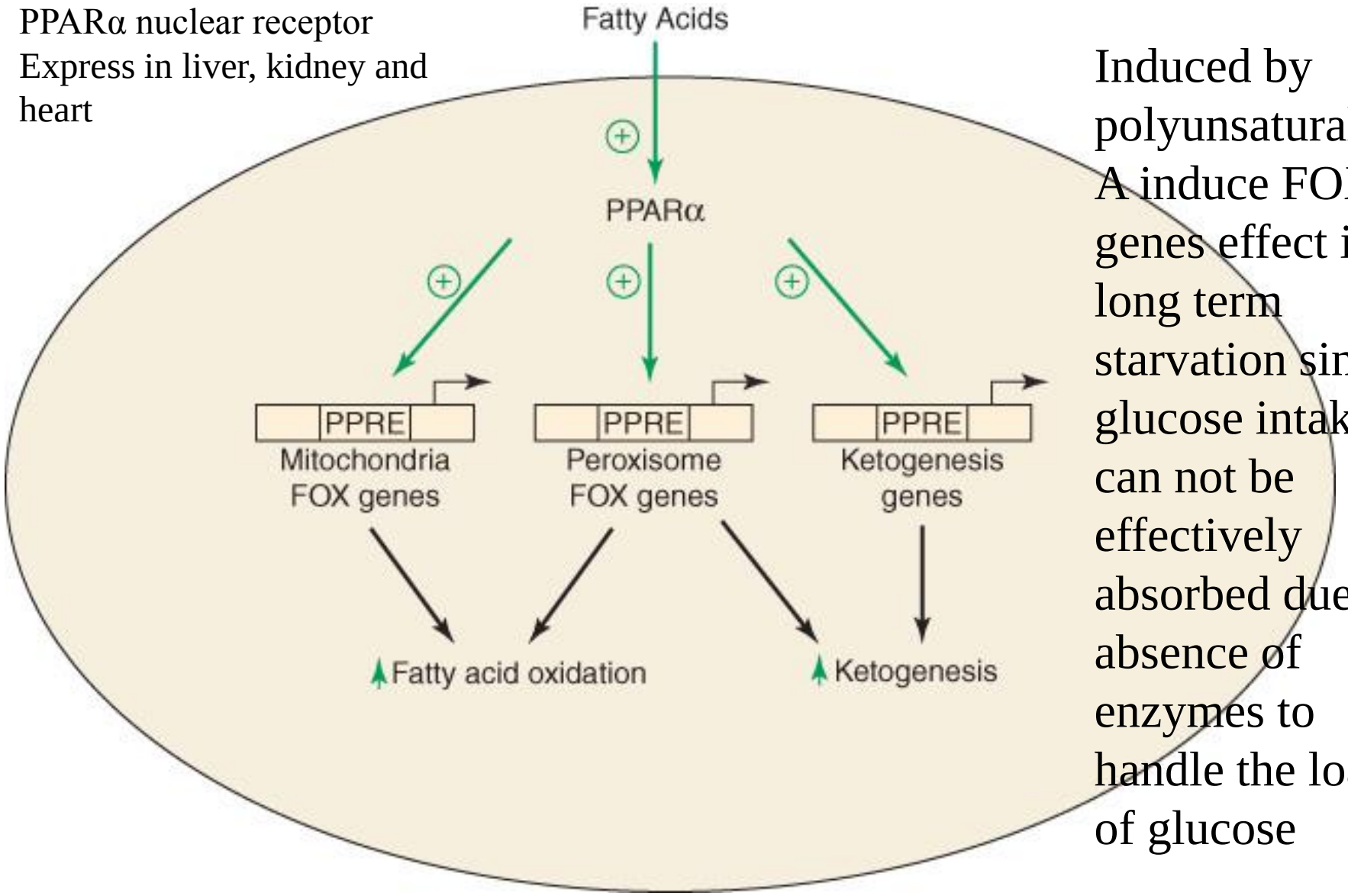


Figure 21.21 Regulation of gene transcription in liver by glucagon.

PPARα nuclear receptor
Express in liver, kidney and heart



Induced by polyunsaturaledF A induce FOX genes effect in long term starvation since glucose intake can not be effectively absorbed due to absence of enzymes to handle the load of glucose

Figure 21.22 PPAR activation by fatty acids promotes transcription of fatty acid oxidation (FOX) and ketogenesis genes. Abbreviation: PPRE, PPAR responsive element.

Metabolic syndrome associates with atherosclrerosis, high blood lipids and insulin resistance

Obesity results from over eating most fat comes from diet well fed too long. Caloric restriction benefit. From obesity increase risk to diabetes type 2 and cardiovascular disease

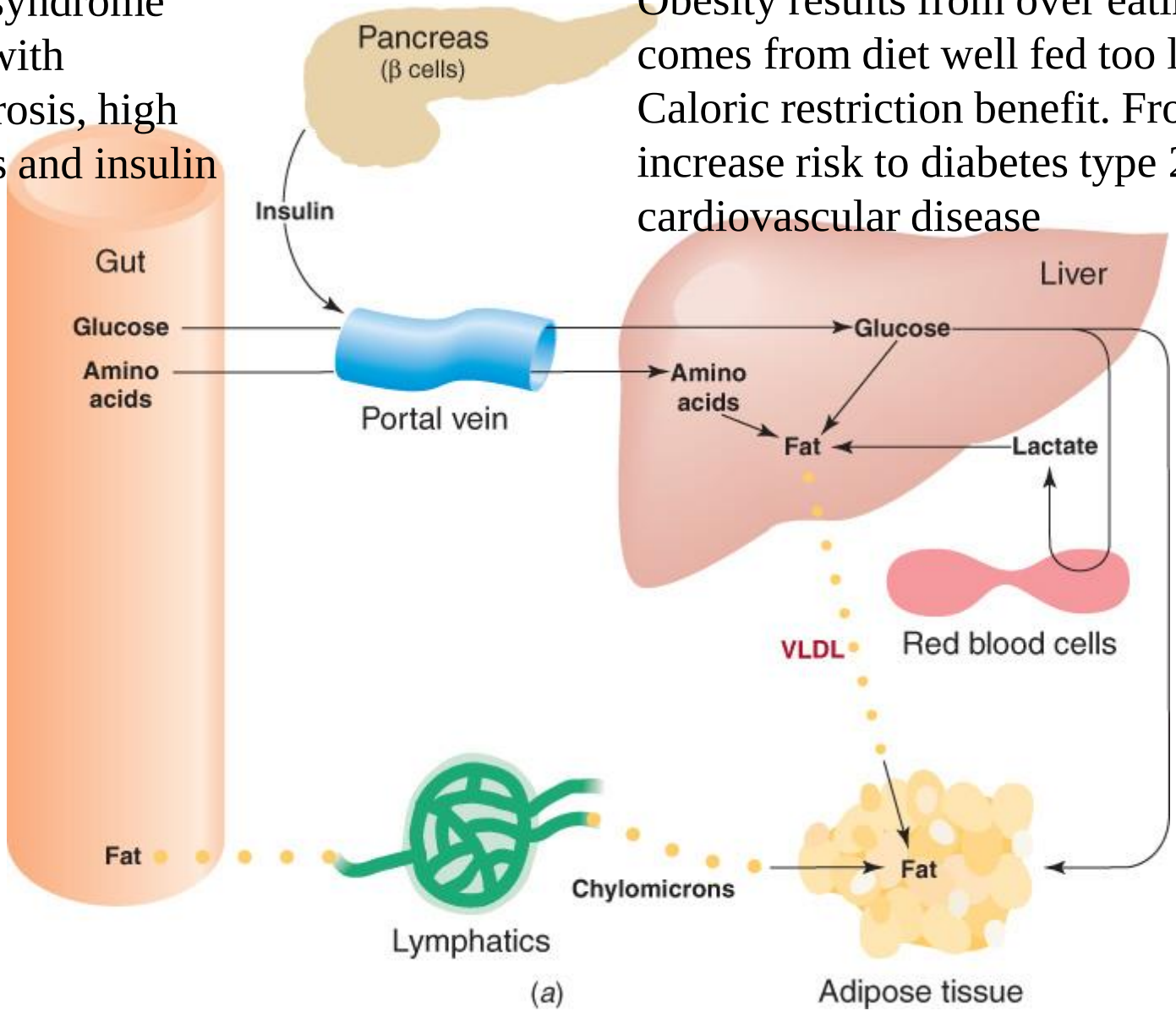
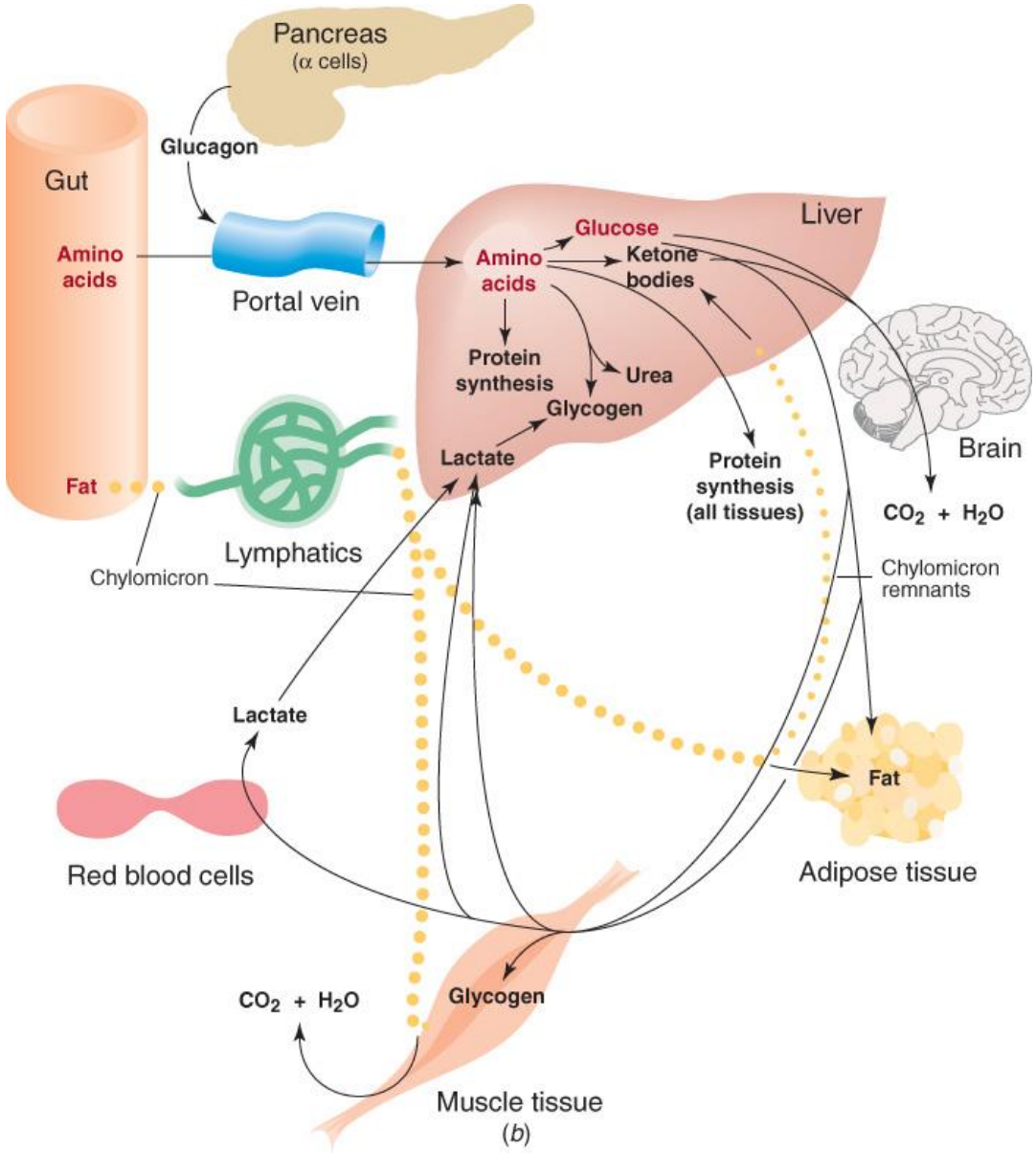


Figure 21.23 Metabolic interrelationships of tissues in various nutritional, hormonal, and disease states: Obesity.



Keton bodies and glucose are being produced fat is being used to produce ketone bodies to supply the ATP needs for glucose synthesis, Atkin diet low carbohydrate, moderate fat high protein.

Figure 21.24 Metabolic interrelationships of tissues in dieting.

Subjects are mainly obese resistant to insulin, low levels of insulin and defective B cells. Hyperglycemia

a. Increase in Fructose 2,6 bisphosphate
b. No Down regulation of phosphoenolpyruvate carboxykinase

Glut4 translocation to membrane is reduced in skeletal and adipose tissue
No ketoacitosis like in Diabetes type 1
Increase in fatty acid synthesis and Esterification leads to TA overproduction. High levels of TNFa

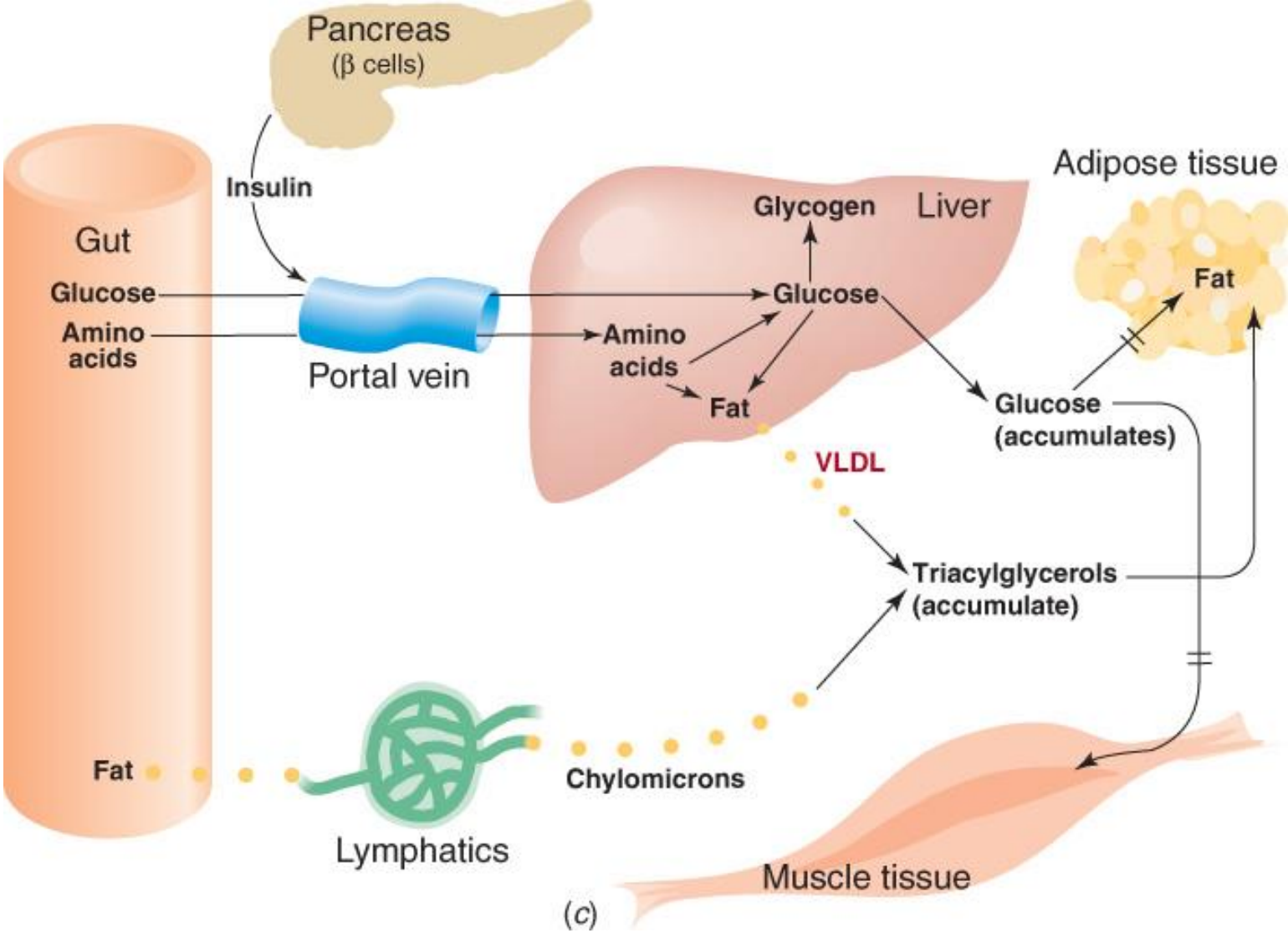


Figure 21.25 Metabolic interrelationships of tissues in type 2 diabetes mellitus.

Usually appears in childhood, liver always gluconeogenic and ketogenic since insulin/glucagon rations are low and fatty acids are high. Uncontrolled lipolysis in adipose tissue and lipogenesis is reduced, proteolysis in skeletal muscle, Glut4 remain inside cell (in muscle and adipose tissue).
Hyperglycemia in the well fed state.
Low lipoprotein lipase in adipose tissue hydrolizes TA in endothelial cells which depends on insulin for synthesis (hyperchylomicronemia)

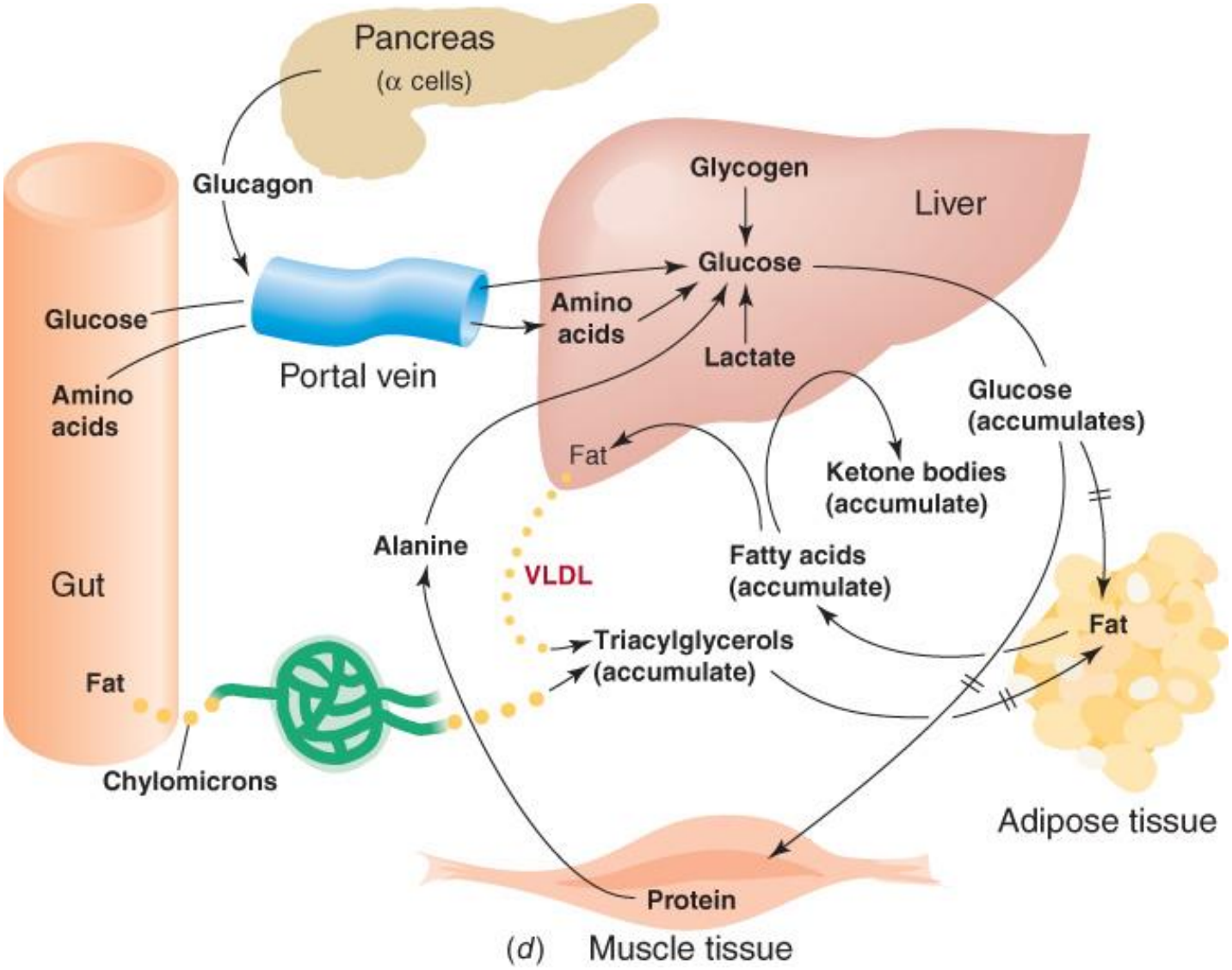


Figure 21.26 Metabolic interrelationships of tissues in type 1 diabetes mellitus.

They establish a Cori cycle with the liver very glucose dependent but need Oxygen. In core usually **hypoxic** which leads to increase hypoxia inducible factor HIF-1a factor which induces glucose transporters, glycolysis enzymes and pyruvate dehydrogenase kinase 1 (-PDHC)

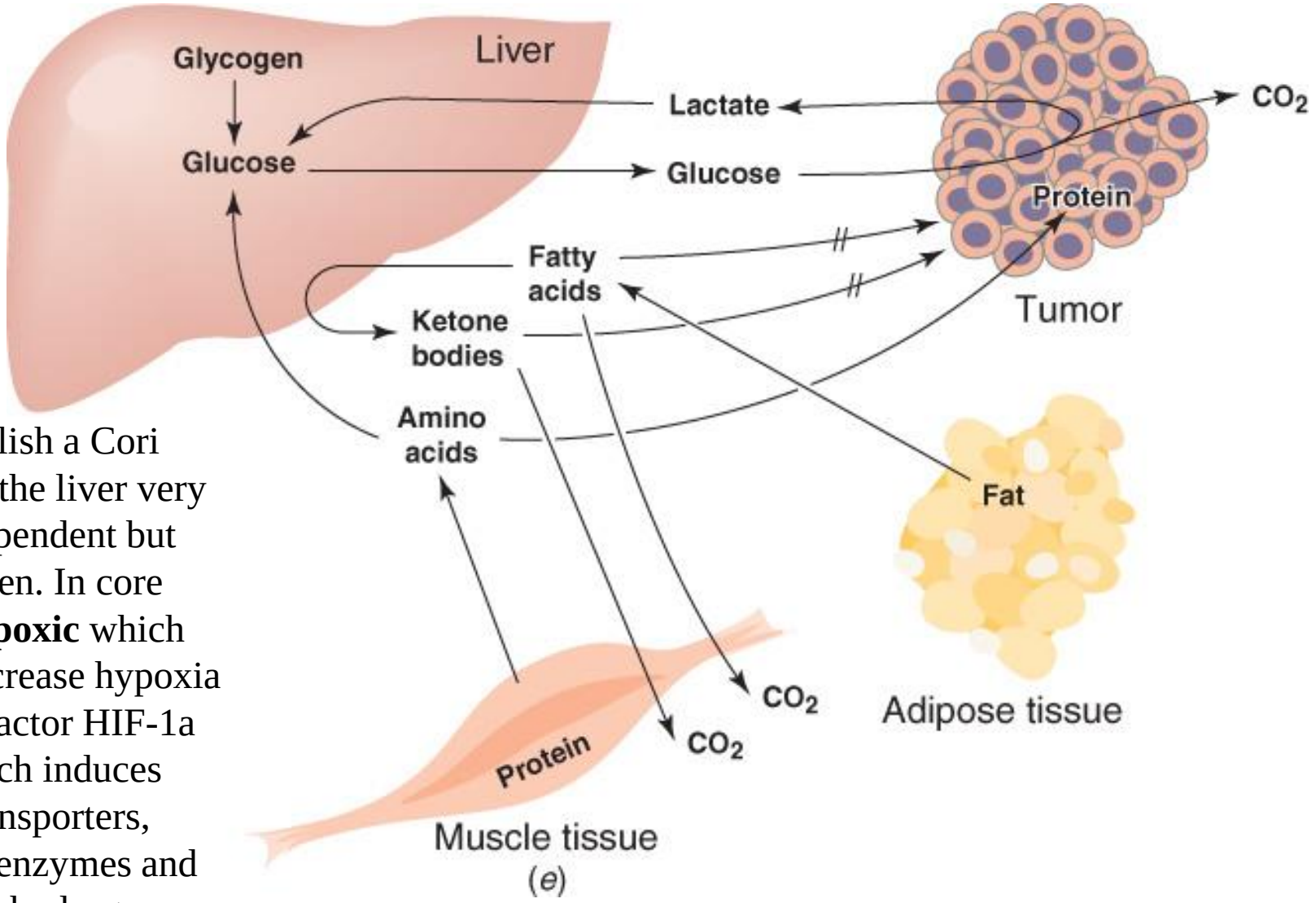


Figure 21.27 Metabolic interrelationships of tissues in cancer.

Increase in AMP allosterically activates glycogen phosphorilase, 6 phosphofructose 1 kinase (PFK1) and AMPK (+ fatty acid oxidation and Glycolysis). AMPK inactivates acetyl-CoA carboxylase . Therefore there is greater carnitine palmitoyltransferase 1 since ATP is in demand for contracting muscle. Lactate accumulates since glucose breakdown overrides glucose synthesis, lactate can become a fuel for the brain at 10-20 mM

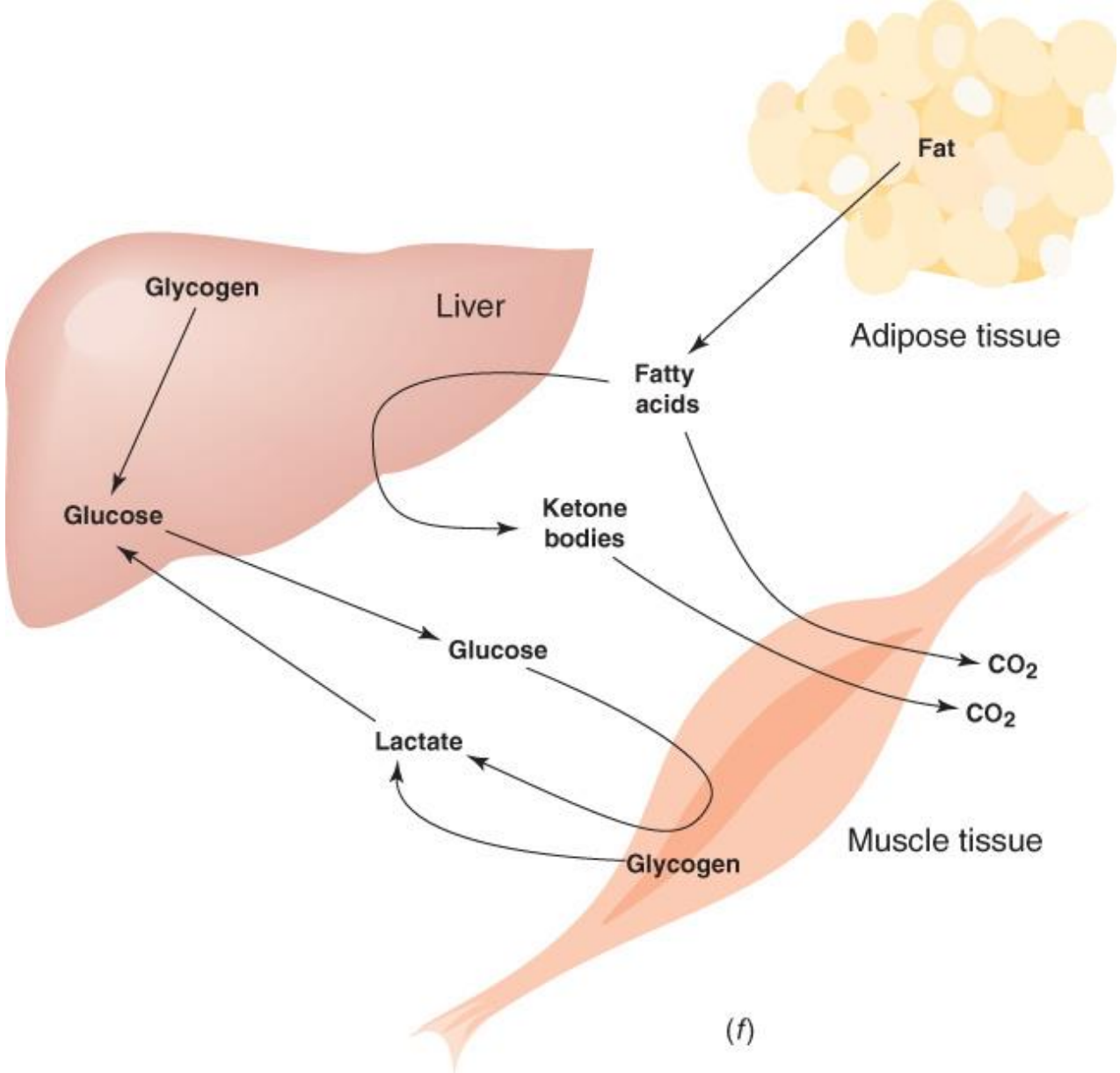


Figure 21.28 Metabolic interrelationships of tissues in exercise.

During pregnancy the starved state is perturbed, placenta secretes estradiol and progesterone (CYP11A) and lactogen which stimulates lipolysis in adipose tissue. After meals a pregnant woman can go into the starved phase faster than normal due to the fetus.

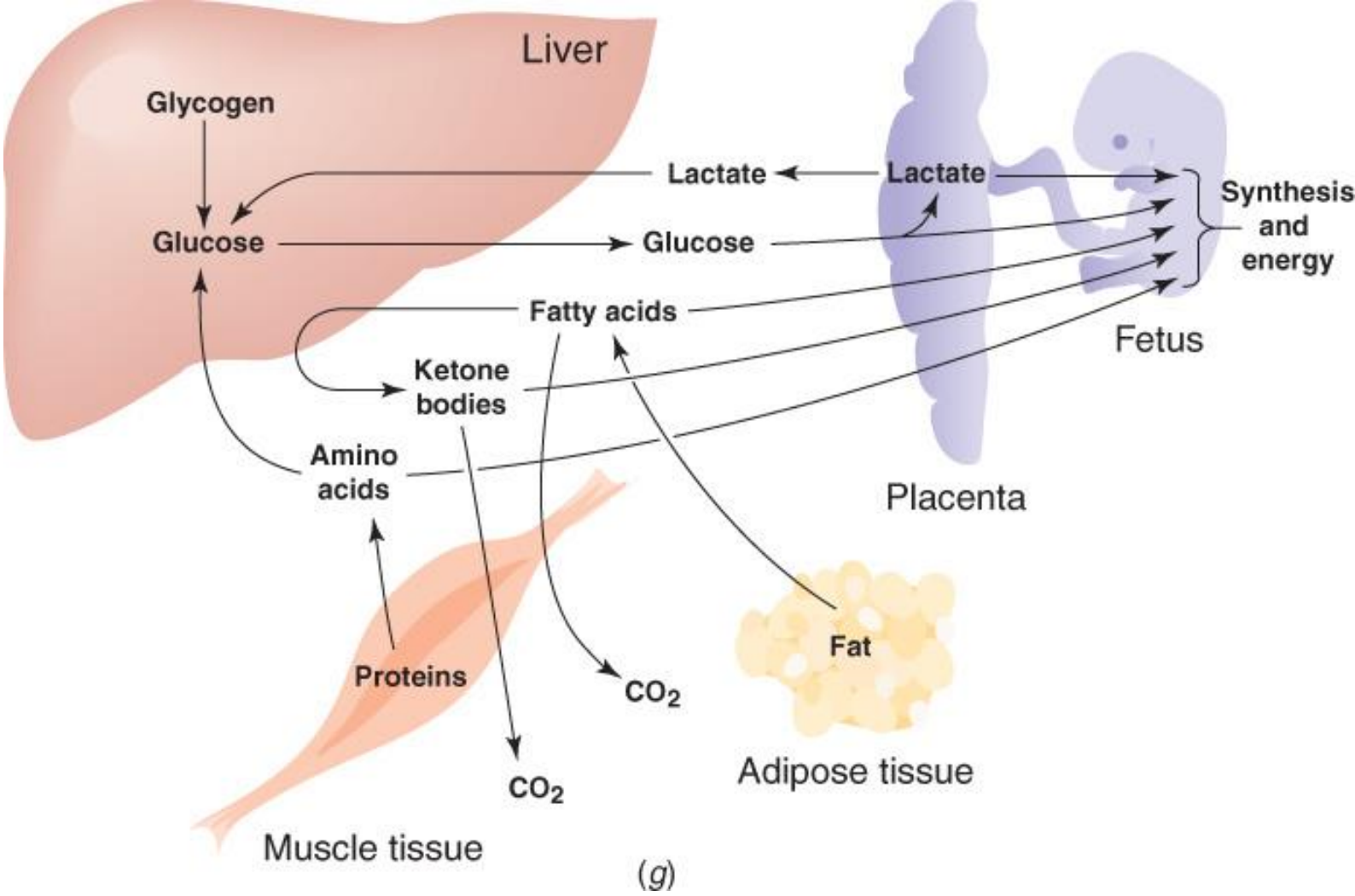
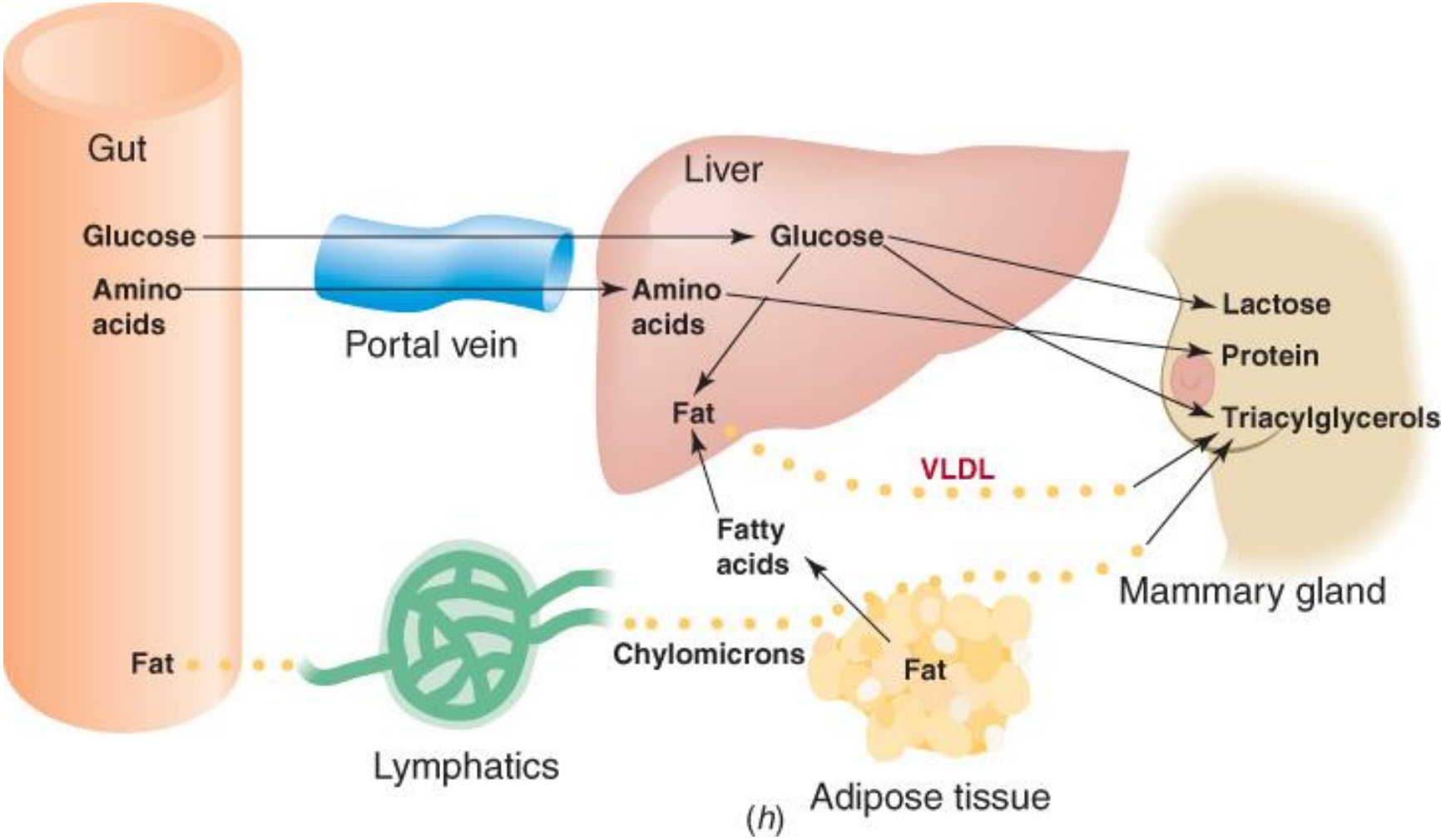


Figure 21.29 Metabolic interrelationships of tissues in pregnancy.



In late pregnancy placental (progesterone) and maternal (prolactin) induce lipoprotein lipase in mammary glands. Promotes milk secretion during lactation it produces PTHrP parathyroid hormone-related protein which stimulates Ca absorption.

Figure 21.30 Metabolic interrelationships of tissues in lactation.

Characteristics blood cortisol, glucagon, catecholamines, growth hormones and resistance to insulin. Gln and branched AA are reduced in muscle inducing proteolysis with the help of IL-1. IL6 induce fibrinogen, complement protein and clotting factors, α2 macroglobulin (injury and infection). TNFα suppresses TA synthesis, (-)lipoprotein lipase and stimulates lipolysis inhibits insulin release promotes insulin resistance.

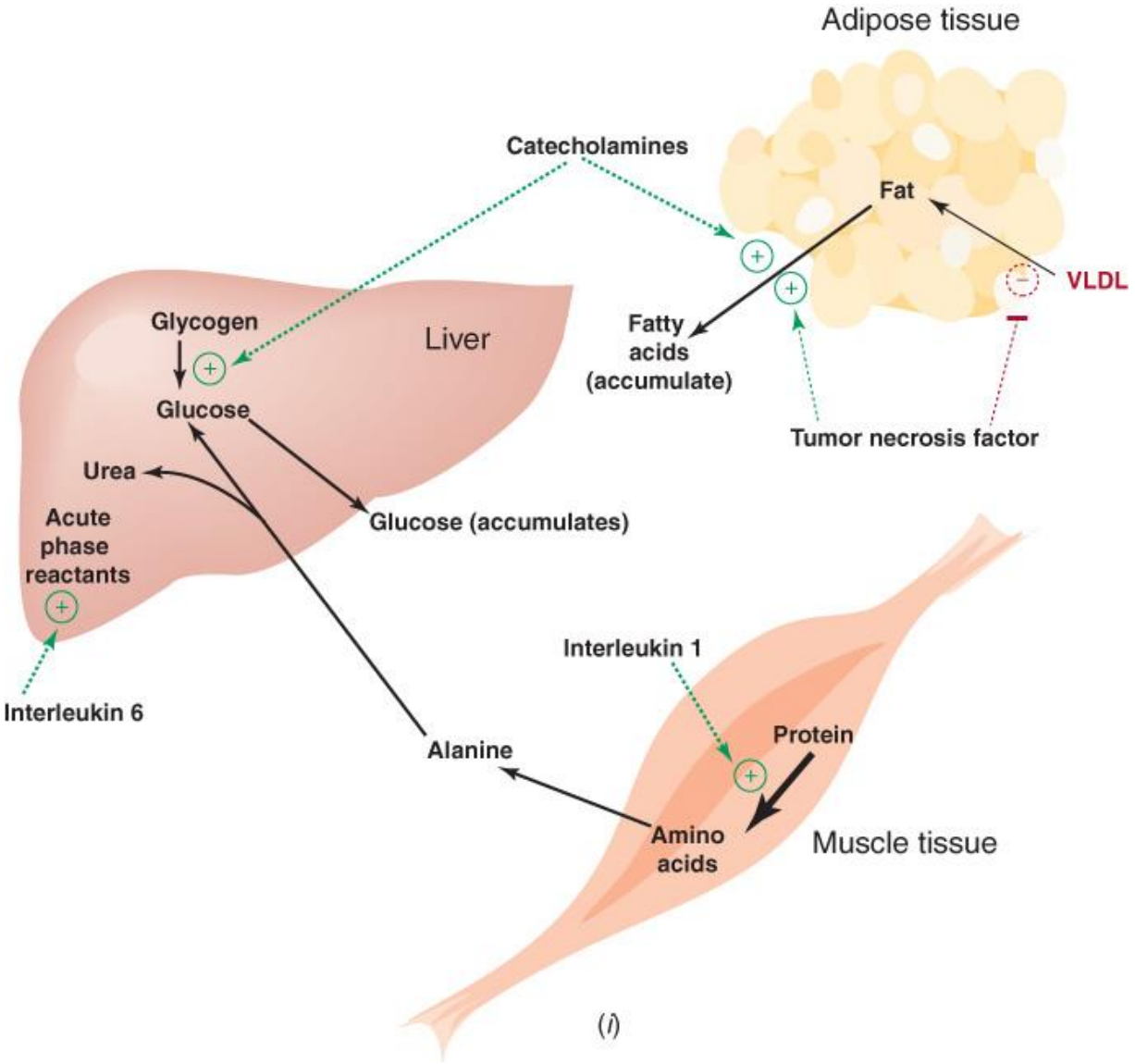
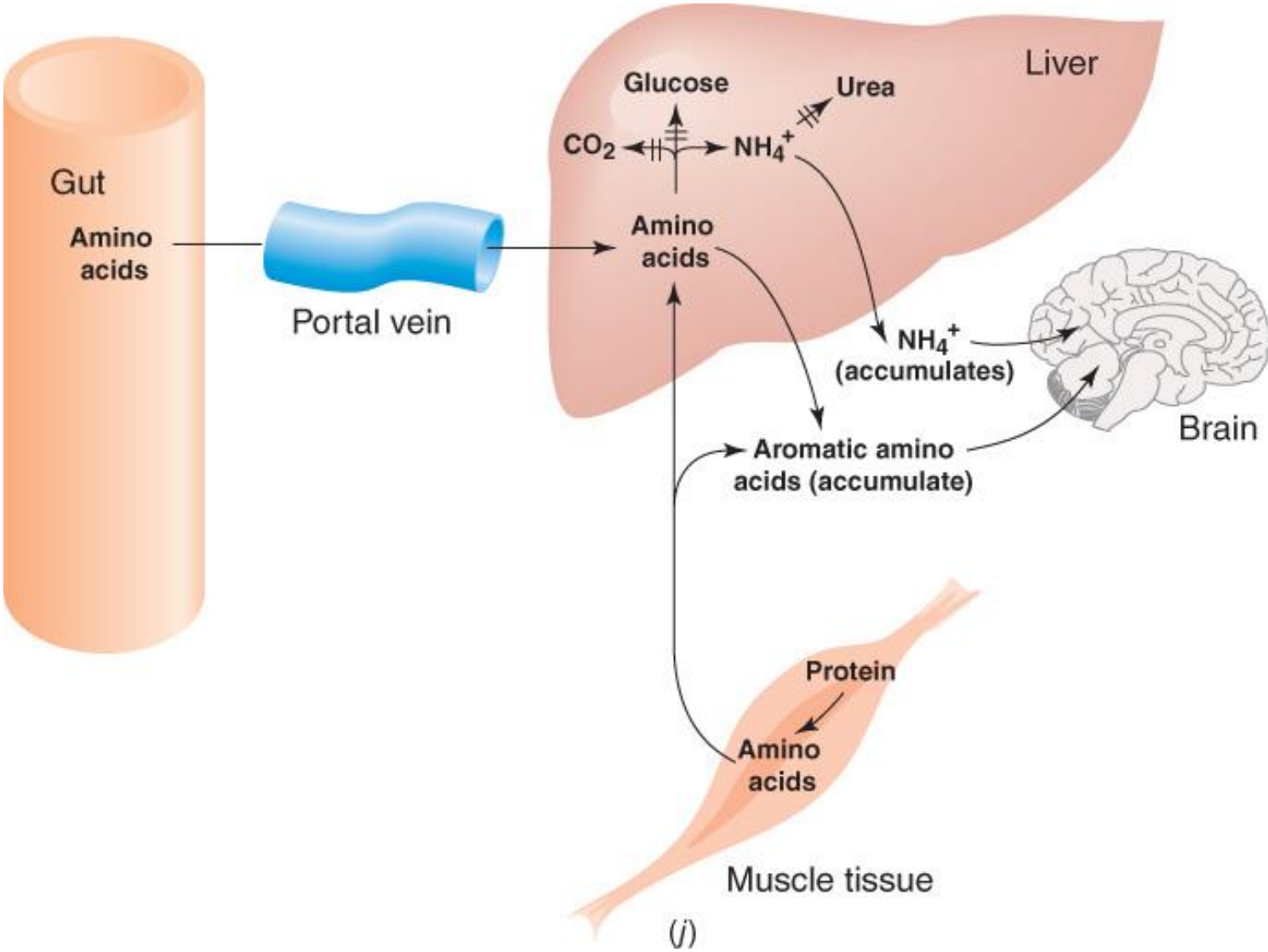


Figure 21.31 Metabolic interrelationships of tissues in stress and injury.

Major metabolic disarrangement for AA . Cirrhosis, cant convert ammonia into urea and Gln fast enough. Here we have ammonia built up. High Ammonia are caused by glutaminase and Glu dehydrogenase. Cause bleeding of upper GI. High AA increase net rate of Protein degradation. NH_4 toxic to brain interferes with AA metabolism and neurotransmitters. Deficient in Insulin like growth factor (IGF-1) and are insulin resistant may have diabetes.



Branched chain AA are reduced while aromatics AA are elevated in blood this results in a reduced Fisher ratio the molar ratio of branched AA/aromatic AA. Both transported to brain by same carrier mechanism less comp by the branch so more aromatic go into brain increasing serotonin.

Figure 21.32 Metabolic interrelationships of tissues in liver disease.

AA normally metabolized by kidney (proline, Gln, Glysine and citrulline) build up as well as Nitrogen products, urea, uric acid, creatinine. We need to reduce protein intake (only essential AA) diet high in carb so non-essential AA are biosynthesized by the TCA cycle intermediates. Can complicate by the removal of carnitine from blood during dialysis, increasing the risk of cardiac and skeletal myopathy

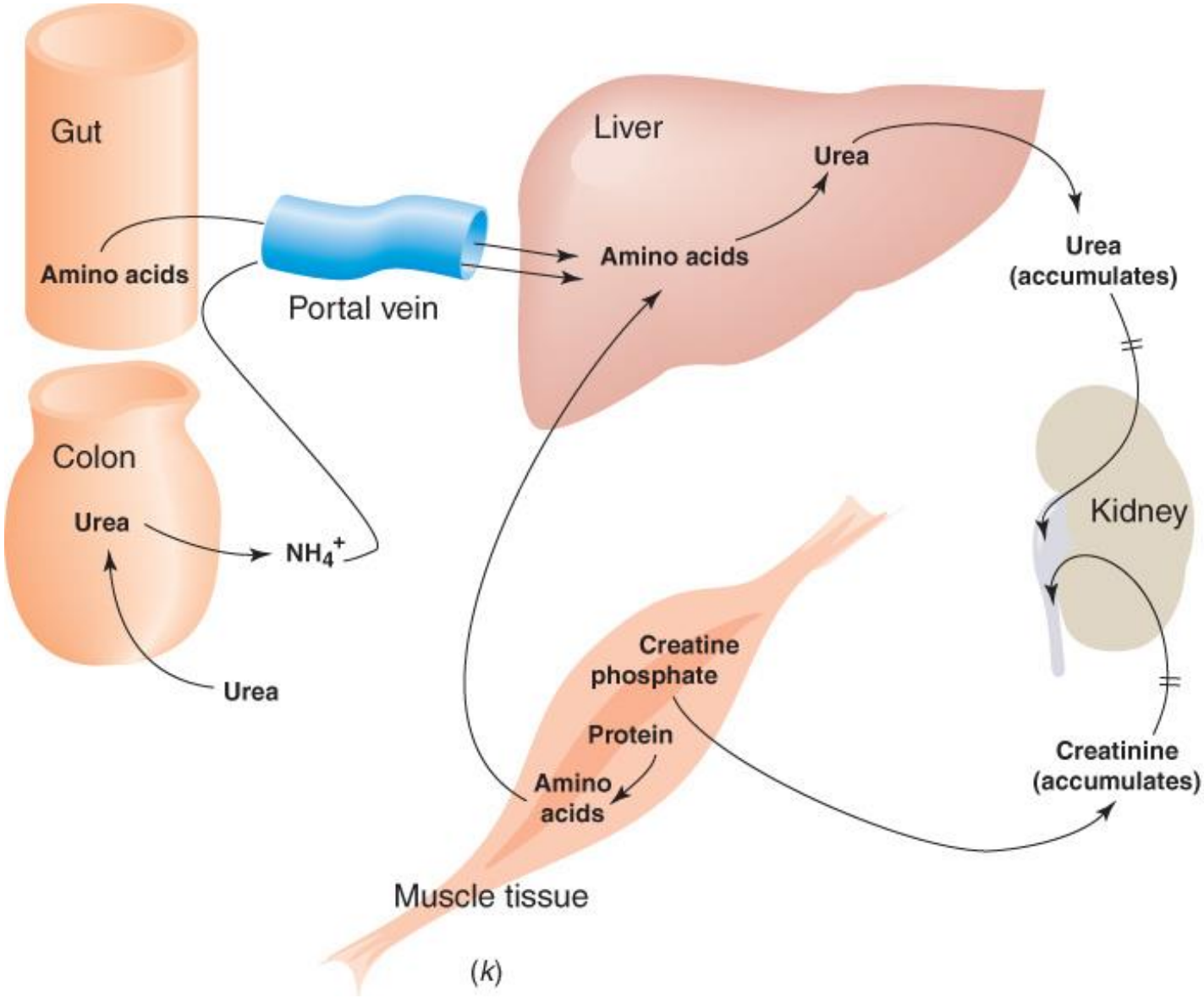


Figure 21.33 Metabolic interrelationships of tissues in kidney failure.

Liver involved in ethanol metabolism. Ethanol-acetaldehyde, ethanol dehydrogenase generates NADH and aldehyde dehydrogenase also generates NADH. Gluconeogenic Enzymes that use NAD are inhibited (lactate dehydrogenase and malate dehydrogenase) and fatty acid oxidation B-hydroxyacyl-CoA dehydrogenase as well as Glycerol phosphate dehydrogenase which reduces the formation of DHA and then glycerol is used for TA synthesis. Acetaldehyde can form covalent bonds with other functional groups enhancing toxicity

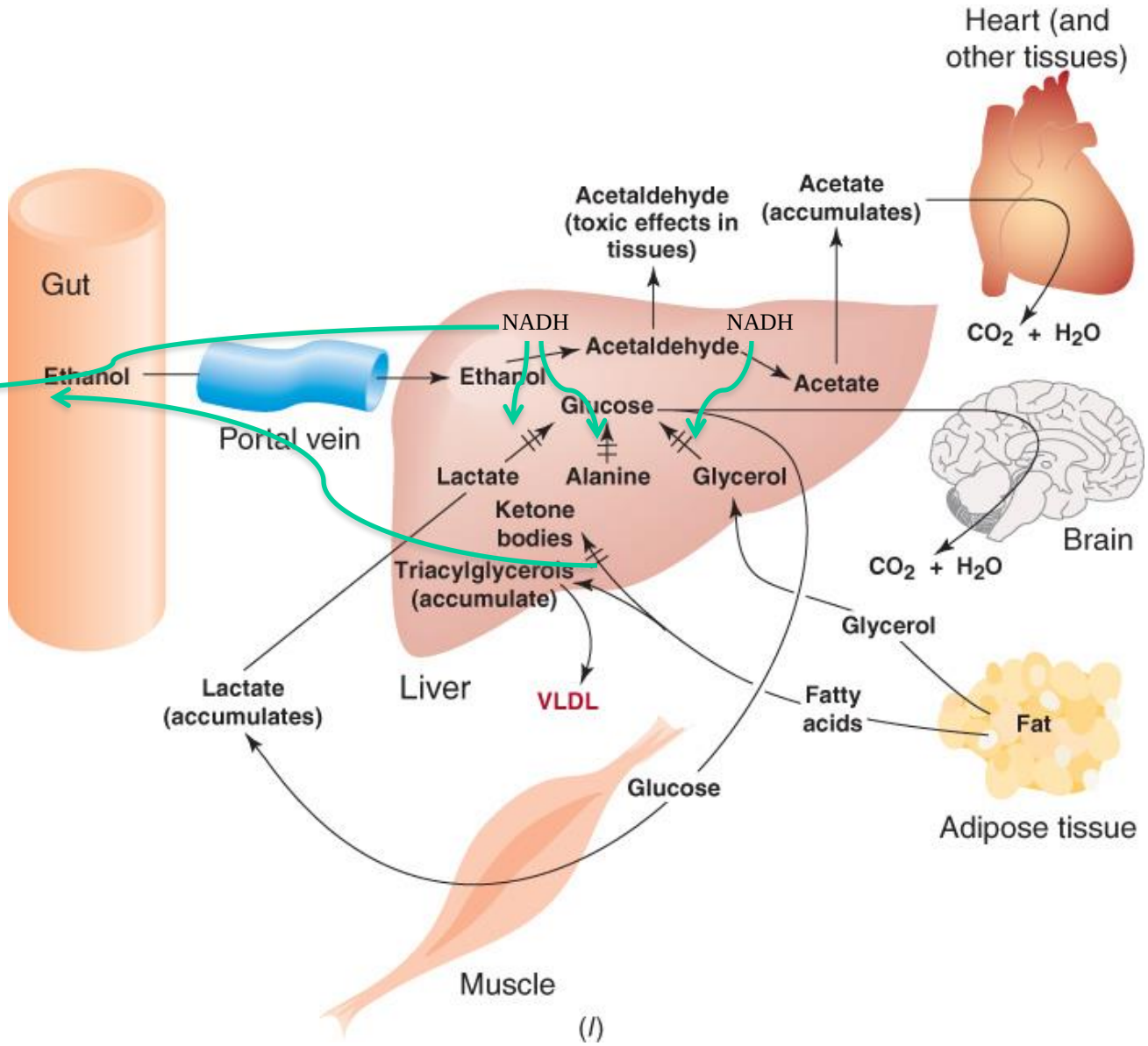
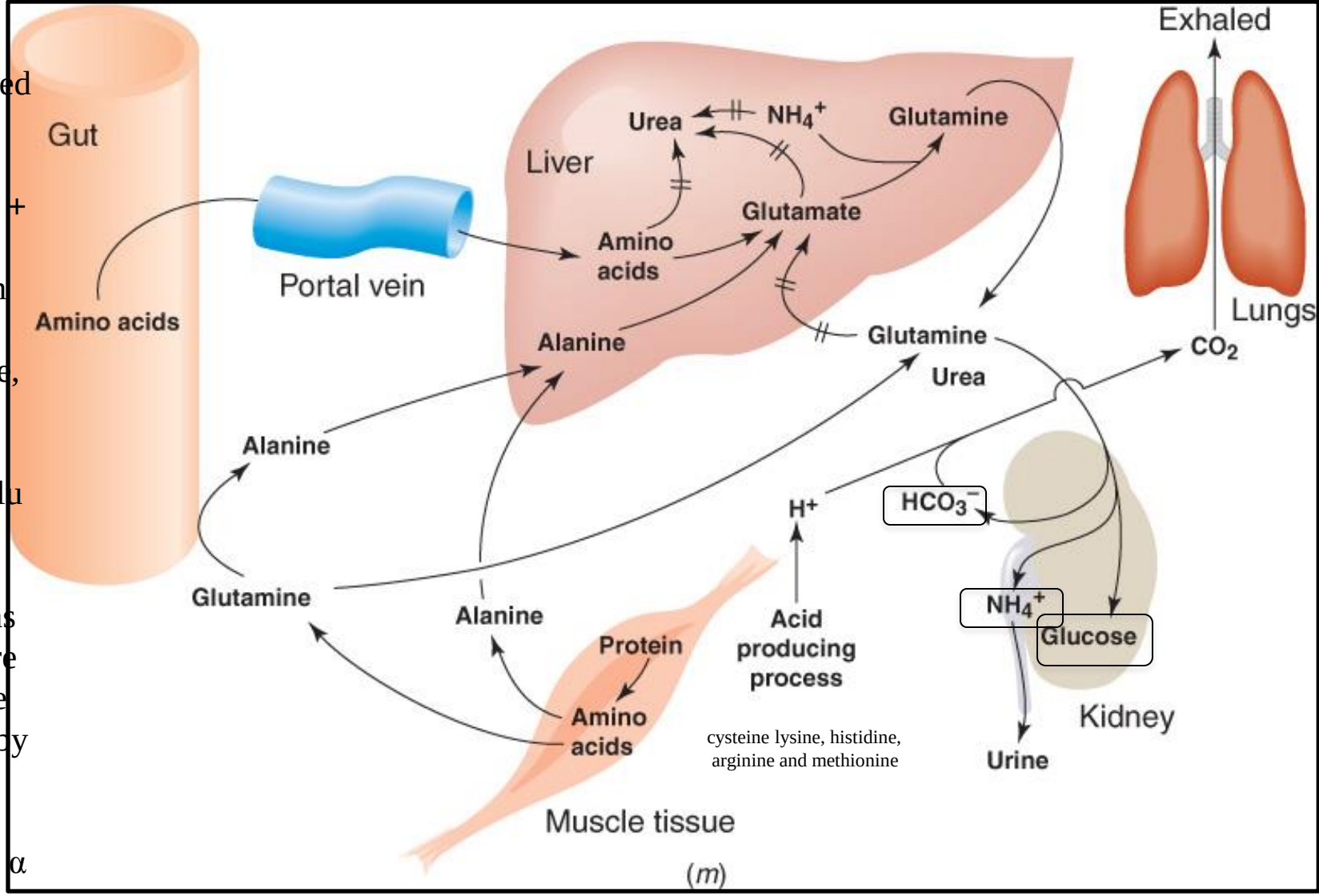


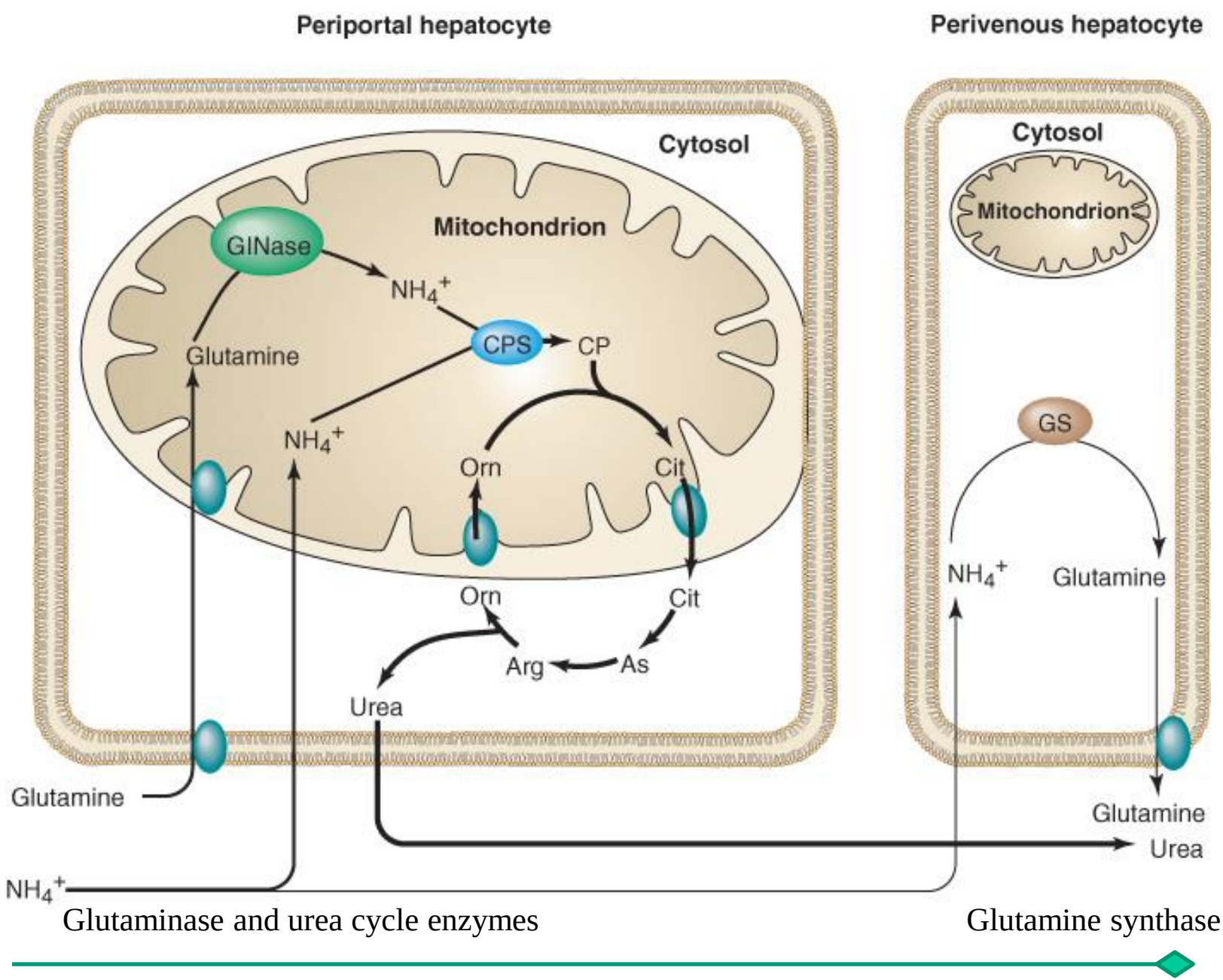
Figure 21.34 Metabolic interrelationships of tissues in consumption of alcohol.

Acid-base balance is shared between Liver and kidney. Metabolism of + charged AA result in proton formation (cysteine lysine, histidine, arginine and methionine) Glu and Aspartate consume some of these protons but the most are taken up by the uptake of Gln by the kidney as Gln is metabolized to α ketoglutarate to glucose and bicarbonate



The liver adapts synthetize less urea and making more Gln for the kidney

Figure 21.35 Metabolic interrelationships of tissues in acidosis.



Fall in Blood pH controls the uptake of Gln and activity of glutaminase in the periportal section and CPS1 is also less active at low pH therefore reducing urea synthesis and more Gln available for bicarbonate to neutralize pH.

Figure 21.36 Intercellular glutamine cycle of the liver.

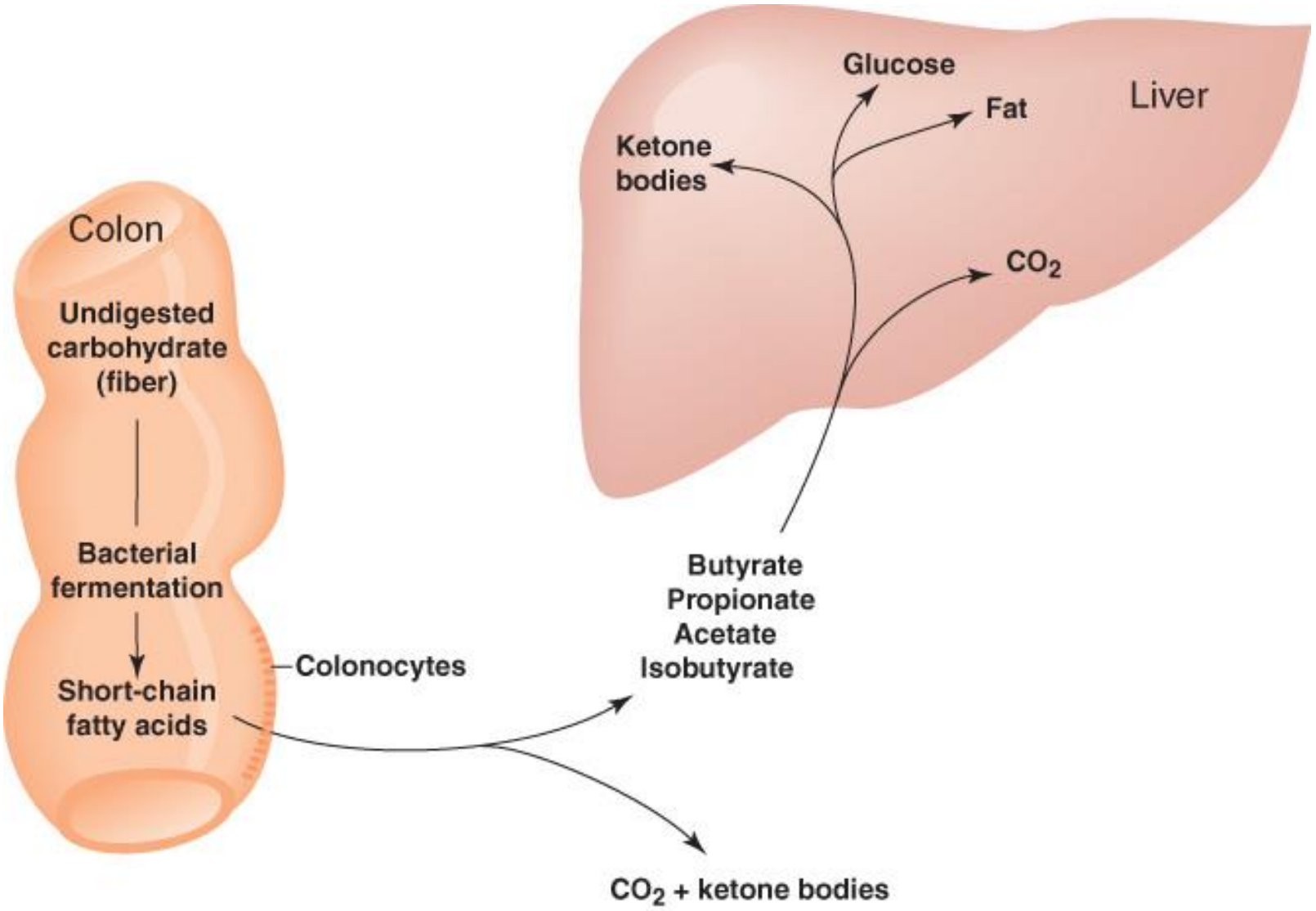


Figure 21.37 Bacterial fermentation generates fuel for colonocytes.