Chapter 18

Interorgan and Intracellular Coordination of Energy Metabolism in Vertebrates

Outline:

- Interdependence of the Major Organs in Vertebrate Fuel Metabolism
- Hormonal Regulation of Fuel Metabolism
- Responses to Metabolic Stress: Starvation, Diabetes

the metabolic profiles of the major organs in vertebrates:

1. fuels they use and generate, and how the organs interact under stress to maintain appropriate energy balance.
2. how these interactions are controlled in large part by hormonal signals

Interdependence of the Major Organs in Vertebrate Fuel Metabolism

- Metabolite concentrations represent a significant intracellular control mechanism.

The major fuel depots are ***triacylglycerols*** (adipose tissue), ***protein*** (muscle), and ***glycogen*** (muscle and liver).

which substrates are catabolized for energy — is the concentration of each of the usable substrates.

major organs plays in fuel metabolism— brain, muscle, liver, adipose tissue, and heart

an organ specialized to produce a particular fuel lacks the enzymes to use that fuel

Interdependence of the Major Organs in Vertebrate Fuel Metabolism

TABLE 18.1 Profiles of the major vertebrate organs in fuel metabolism

Tissue	Fuel Store	Preferred Fuel	Fuel Sources Exported
Brain	None	Glucose (ketone bodies during starvation)	None
Skeletal muscle (resting)	Glycogen	Fatty acids	None
Skeletal muscle (during exertion)	None	Glucose	Lactate, alanine
Heart muscle	None	Fatty acids	None
Adipose tissue	Triacylglycerols	Fatty acids	Fatty acids, glycerol
Liver	Glycogen, triacylglycerols	Amino acids, glucose, fatty acids	Fatty acids, glucose, ketone bodies

Skeletal muscle stores ~3/4 of the total glycogen in humans, ¼ in the liver.

1760 kj/day, ~15% of the total energy consumed by one person

Transport in blood and convert to glucose in liver

From glucose-alanine cycle

From Citric acid cycle

generate ATP in large quantities to maintain the membrane potentials essential for transmission of nerve impulses.

lipolysis

also glucose, lactate, and ketone bodies

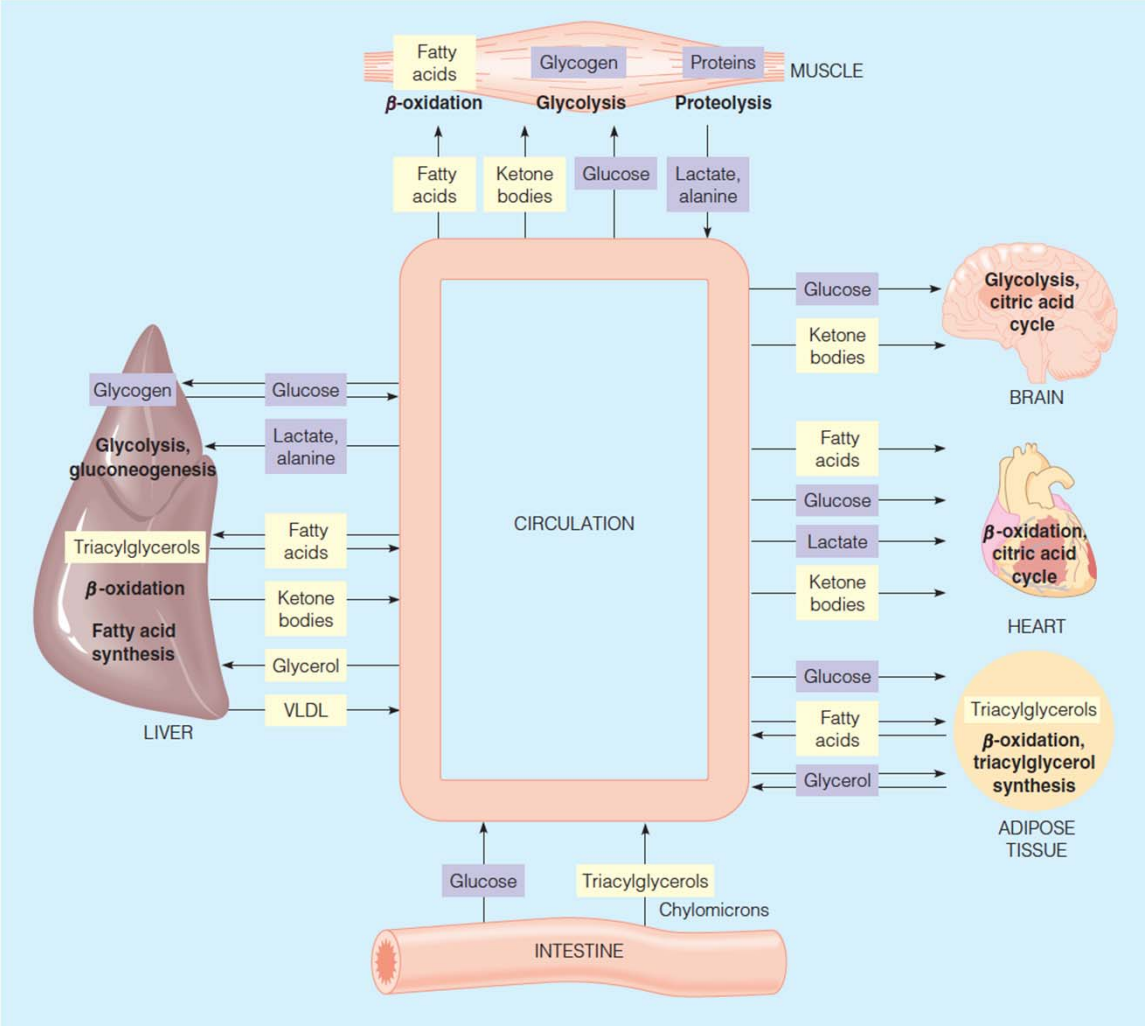
most of the low-molecular-weight metabolites that appear in the blood through digestion are taken up by the liver for metabolic processing.

Interdependence of the Major Organs in Vertebrate Fuel Metabolism

Metabolic interactions among the major fuel-metabolizing organs:

Lipid-derived metabolites

Carbohydrate-derived metabolites



Hormonal Regulation of Fuel Metabolism

TABLE 18.2 Major hormones controlling fuel metabolism in mammals

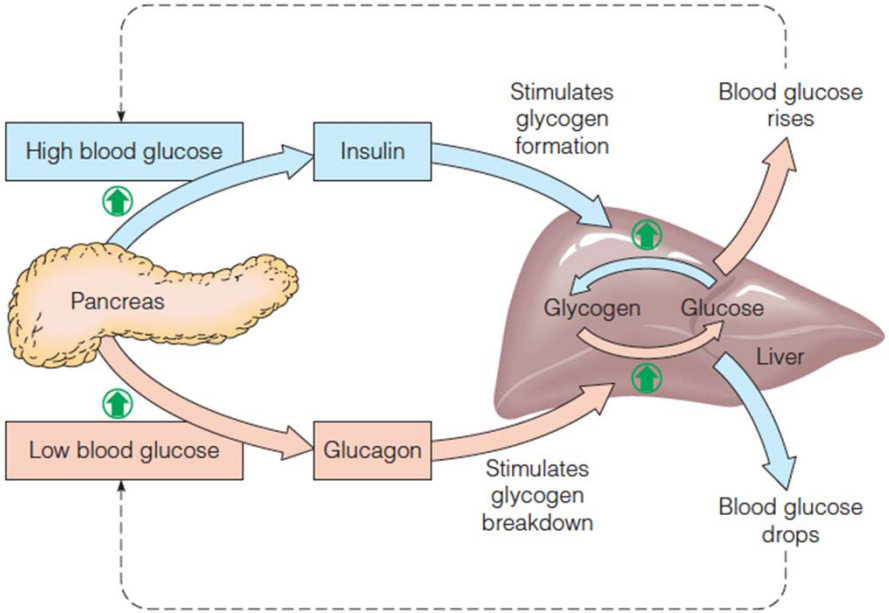
Hormone	Biochemical Actions	Enzyme Target	Physiological Actions
Insulin	↑ Glucose uptake (muscle, adipose tissue)	GLUT4	Signals fed state: ↓ Blood glucose level ↑ Fuel storage ↑ Cell growth and differentiation
	↑ Glycolysis (liver, muscle)	PFK-1 (via PFK-2/FBPase-2)	
	↑ Acetyl-CoA production (liver, muscle)	Pyruvate dehydrogenase complex	
	↑ Glycogen synthesis (liver, muscle)	Glycogen synthase	
	↑ Triacylglycerol synthesis (liver)	Acetyl-CoA carboxylase	
	↓ Gluconeogenesis (liver)	FBPase-1 (via PFK-2/FBPase-2)	
	↓ Lipolysis		
	↓ Protein degradation		
	↑ Protein, DNA, RNA synthesis		
Glucagon	↑ cAMP level (liver, adipose tissue)		Signals fasting state: ↑ Glucose release from liver ↑ Blood glucose level ↑ Ketone bodies as alternative fuel for brain
	↑ Glycogenolysis (liver)	Glycogen phosphorylase	
	↓ Glycogen synthesis (liver)	Glycogen synthase	
	↑ Triacylglycerol hydrolysis and mobilization (adipose tissue)	Hormone-sensitive lipase, perilipin, adipose triglyceride lipase	
	↑ Gluconeogenesis (liver)	FBPase-1 (via PFK-2/FBPase-2), pyruvate kinase, PEPCK	
	↓ Glycolysis (liver)	PFK-1 (via PFK-2/FBPase-2)	
	↑ Ketogenesis (liver)	Acetyl-CoA carboxylase	
Epinephrine	↑ cAMP level (muscle)		Signals stress: ↑ Glucose release from liver ↑ Blood glucose level
	↑ Triacylglycerol mobilization (adipose tissue)	Hormone-sensitive lipase, perilipin, adipose triglyceride lipase	
	↑ Glycogenolysis (liver, muscle)	Glycogen phosphorylase	
	↓ Glycogen synthesis (liver, muscle)	Glycogen synthase	
	↑ Glycolysis (muscle)	Glycogen phosphorylase, providing increased glucose	

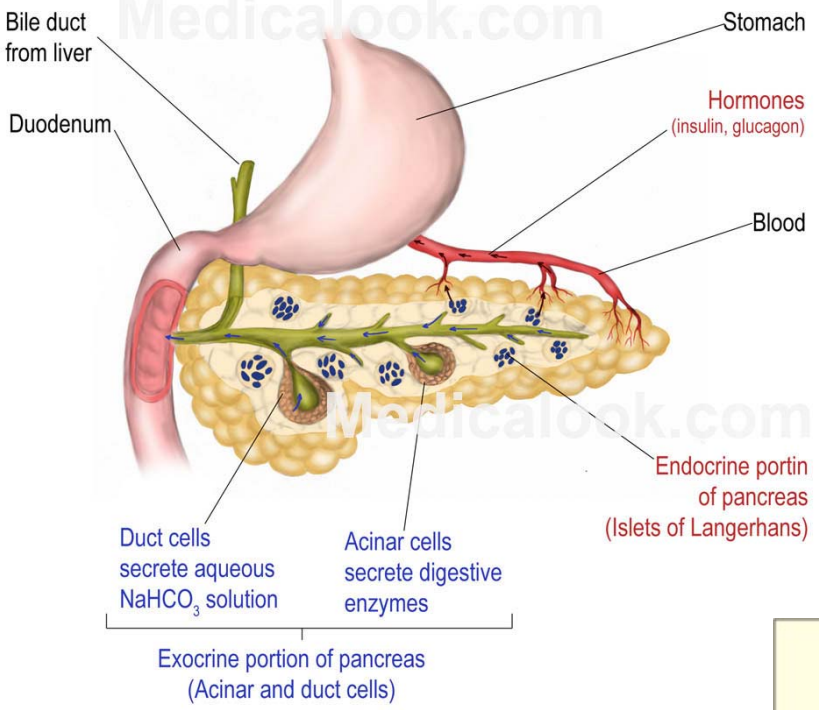
Hormonal Regulation of Fuel Metabolism

- One of the most important roles of ***liver*** is to serve as a "***glucostat***" monitoring and stabilizing blood glucose levels.
- Maintenance of blood glucose within narrow limits is critical to brain function.
- The key hormones regulating fuel metabolism are ***insulin***, which ***promotes glucose use***, and ***glucagon*** and ***epinephrine***, which ***increase blood glucose***.

synthesized in the pancreas

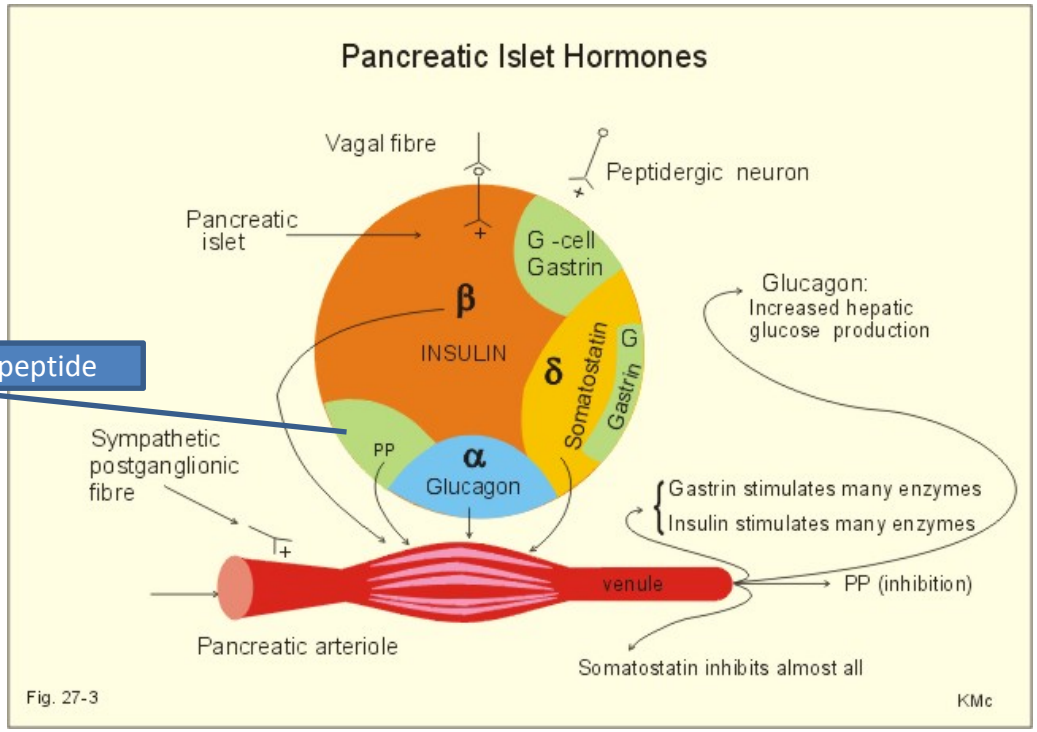
liver senses the fed state and acts to store fuel derived from glucose. Liver also senses the fasted state and increases the synthesis and export of glucose when blood glucose levels are low.





islets of Langerhans and pancreatic hormone

F cells, pancreatic polypeptide



insulin

insulin signals the fed state and thereby promotes:

(1) uptake of fuel substrates into some cells,
(2) storage of fuels (lipids and glycogen),
(3) biosynthesis of macromolecules (nucleic acids and protein).

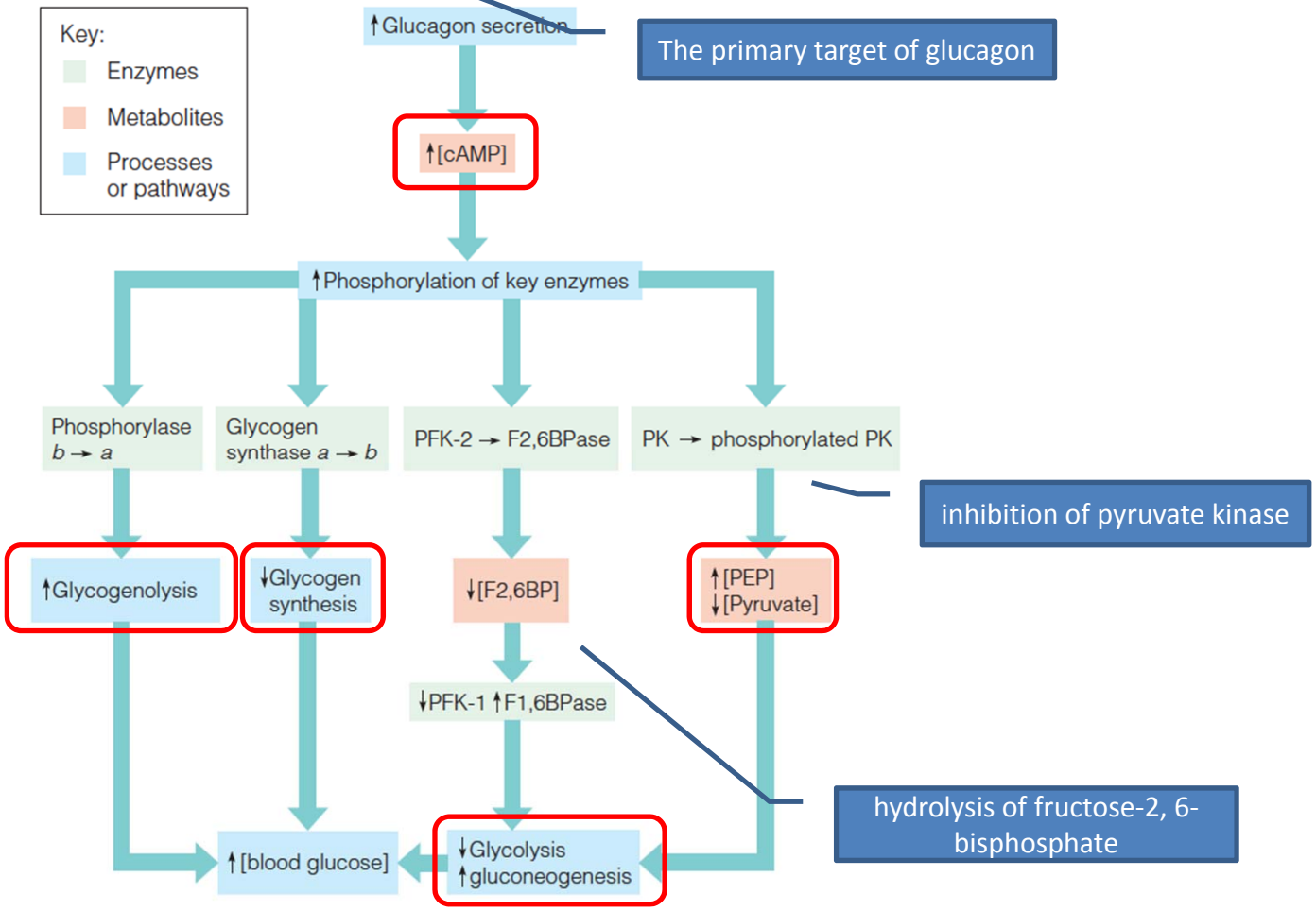
Other effects of insulin:

- increased uptake of glucose in muscle and adipose tissue;
- activation of glycolysis in liver;
- increased synthesis of fatty acids and triacylglycerols in liver and adipose tissue;
- inhibition of gluconeogenesis in liver;
- increased glycogen synthesis in liver and muscle;
- increased uptake of amino acids into muscle with consequent activation of muscle protein synthesis;
- inhibition of protein degradation.

Hormonal Regulation of Fuel Metabolism

synthesized by alpha cells of the islets of Langerhans

Actions of ***glucagon*** in liver that lead to a rise in blood glucose:



Hormonal Regulation of Fuel Metabolism

- **AMPK** and **mTOR** protein kinases play central roles in orchestrating the metabolic activity of mammalian cells.

- AMPK (AMP-activated protein kinase) is activated when the energy charge of the cell is low (high AMP/ATP ratio).

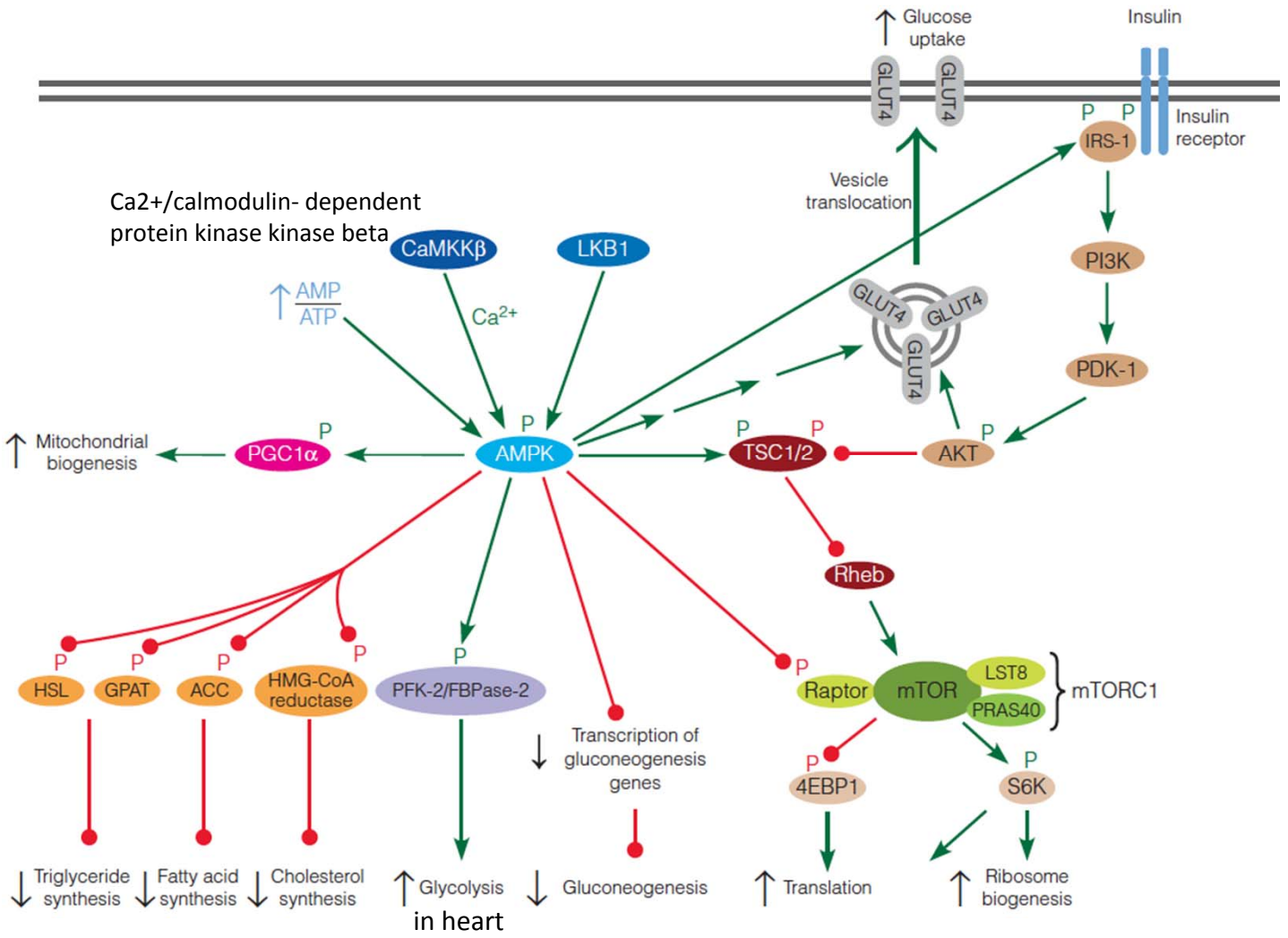
- AMPK initiates a signaling process that conserves cellular energy by stimulating pathways that lead to ATP production while inhibiting pathways that utilize ATP.

  enhance energy-producing pathways:
  - stimulate glucose uptake (GLUT4 translocation)
  - glycolysis in heart (via stimulats PFK-2/FBPase-2 activity)
  - mitochondrial biogenesis.

  inhibit energy-requiring pathways:
  - hepatic gluconeogenesis (decreased transcription of gluconeogenic enzymes)
  - fatty acid synthesis (via acetyl-CoA carboxylase)
  - triacylglycerol synthesis (via glycerophosphate acyltransferase and hormone-sensitive lipase)
  - cholesterol synthesis

Hormonal Regulation of Fuel Metabolism

AMPK and mTOR signaling pathways play opposing roles in controlling the metabolic activity



Hormonal Regulation of Fuel Metabolism

- **mTOR** (mammalian target of rapamycin) was discovered during biochemical studies with the bacterial macrolide, ***rapamycin*****,** a potent immunosuppressant.

- mTOR, in contrast to AMPK, is active under nutrient-rich conditions, and inactive under nutrient-poor conditions.

- Activated mTOR promotes anabolic processes, including cell proliferation, protein synthesis, and biosynthesis, but inhibits catabolic processes.

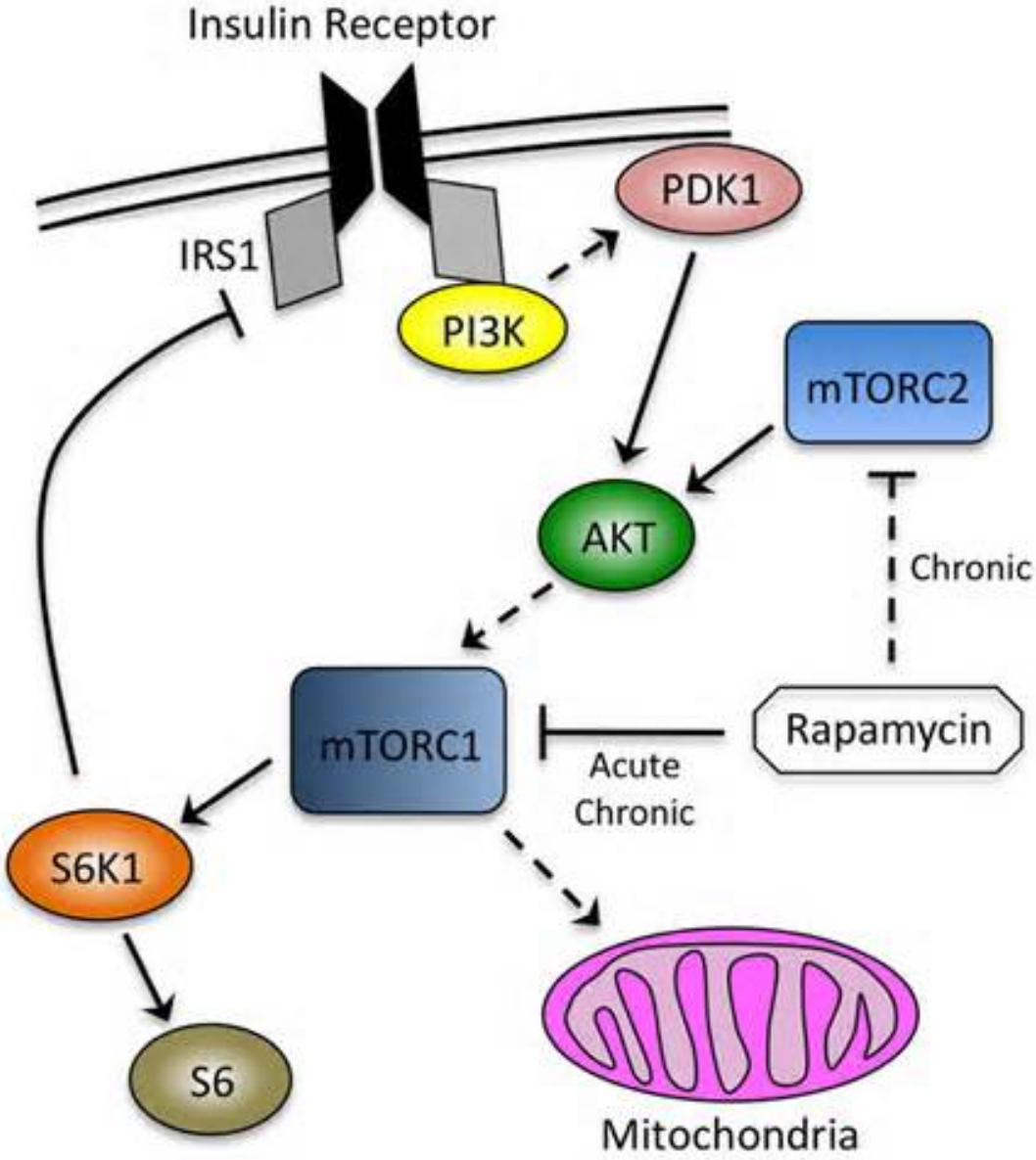
mTORC and target proteins

- mTOR exists as two distinct multiprotein complexes: a rapamycin-sensitive complex (mTORCl) composed of mTOR, mLST8, raptor, and PRAS40; and a rapamycin- insensitive complex (mTORC2) composed of mTOR, mLST8, rictor, Sinl, and PRR5/Protor.

- Rapamycin binds to a small cellular protein, FKBP12, and this FKBP12-rapamycin complex allosterically inhibits mTORC1, but has no effect on mTORC2.

- Substrates of mTORCI are 4EBP1 (eukaryotic initiation factor 4R-hinding protein 1) and S6K (ribosomal protein S6 kinase).

- 4EBP1 normally inhibits the translation initiation factor eIF4E, ; phosphorylation of 4EBP1 by mTORCI suppresses its ability to bind eIF4E and inhibit translation.


Insulin Receptor
IRS1
PI3K
PDK1
mTORC2
AKT
Chronic
mTORC1
Rapamycin
Acute
Chronic
S6K1
S6
Mitochondria

Insulin-AKT-TSC-mTORC signaling pathway

upstream signal of mTORC1: tuberous sclerosis complex (TSC).

TSC1 (hamartin) and TSC2 (tuberin).

TSC2 contains a GTPase activating protein (GAP) domain that inactivates the small Ras-like GTPase Rheb. Rheb normally activates mTORC1, thus loss of TSC1 or TSC2 leads to hyperactivation of mTORC1.

Insulin signaling:

- Insulin receptor (tyrosine kinase) phosphorylates insulin receptor substrate (IRS) protein.
- IRS proteins integrate the activated insulin receptor to downstream adaptor proteins and enzymes.
- Phosphorylated IRS activates phosphoinositide 3-kinase (PI3K), converts membrane phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-trisphosphate (PIP3).
- PIP3 activates PDK-1, which then activates Akt, Akt then phosphorylates TSC, inactivating the complex, resulting in activation of mTORC1.

Hormonal Regulation of Fuel Metabolism

- ***Sirtuins*** (encoded by *SIRT*1-7) are a highly conserved family of NAD^+-dependent protein deacetylases, catalyze the deactylation of acetylated lysine residues in target proteins.

- ***Sirtuins*** are named after the founding member of the family, yeast Sir2 (silent information regulator 2), which deacetylates histones to regulate gene expression of the mating type locus in yeast.

- Sirtuins are now known to act on many proteins besides histones, and they are structurally conserved from bacteria to humans.

- For most protein targets, deacetylation increases the activity of the target protein.

- The deacetylase activity of sirtuins is sensitive to changes in the cellular NAD+ levels, being enhanced at high NAD+/NADH ratios.

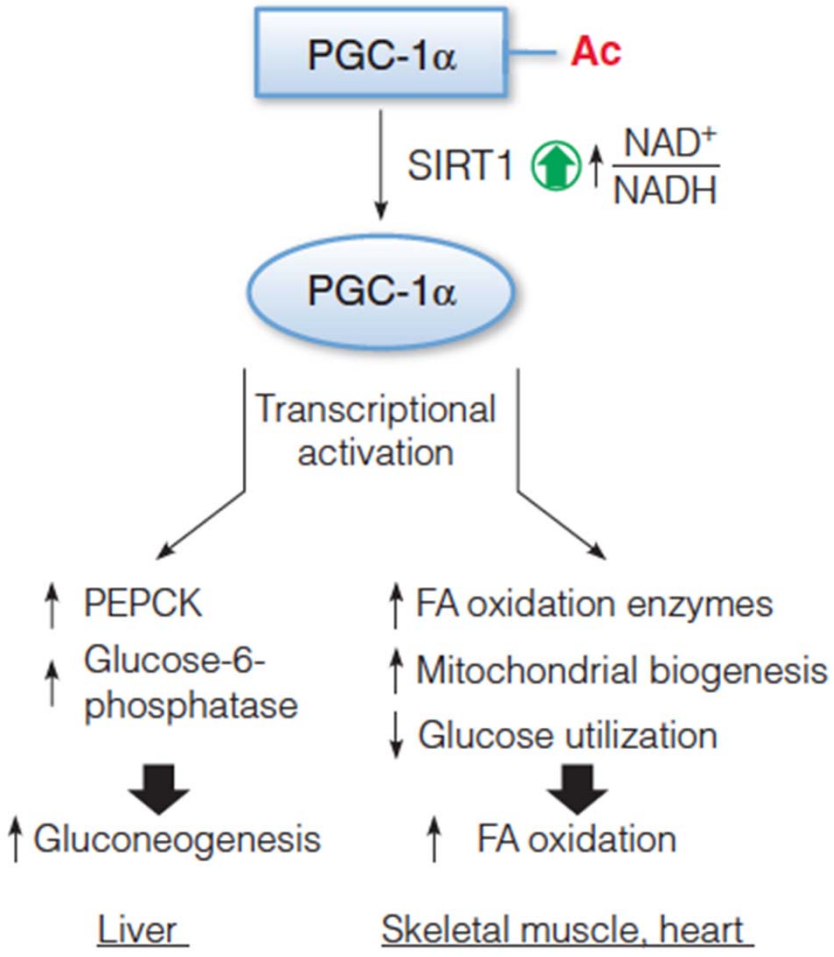
- Thus, sirtuins act as metabolic sensors of the cellular redox state.

peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α)

- A co-activator of the transcription factor peroxisome proliferator-activated receptor-y (PPARy).
- Binds to and stimulates the transcriptional activity of several transcription factors, including p53, nuclear respiratory factors 1 and 2 (NRF-1, NRF-2), and forkhead box O (FOXO).

PGC-1α is sensitive to its acetylation status, and PGC-1α can be deacetylated by SIRT1.

Hormonal Regulation of Fuel Metabolism



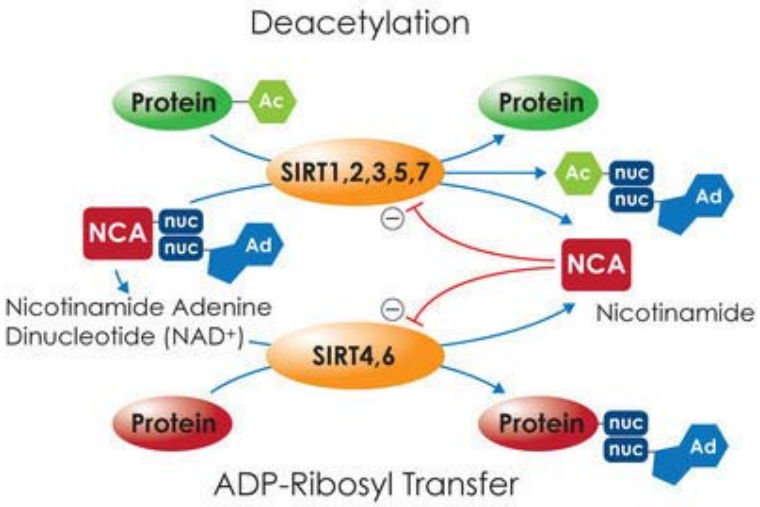
PGC-1 and SIRT1 control the reprogramming of fuel utilization pathways in response to fasting:

- A high NAD/NADH ratio, in response to low nutrients (fasting), activates SIRT1 to deacetylate PGC-1 upregulating its transcriptional coactivator function.
- Tissue-specific transcriptional activation programs result in increased gluconeogenesis (liver) and increased fatty acid oxidation (skeletal and heart muscle).
- Deacetylated PGC-1α also coactivates the transcription of nuclear-encoded genes that encode subunits of the mitochondrial respiratory chain.
- AMPK phosphorylates PGC-lα, which also causes its activation.

Hormonal Regulation of Fuel Metabolism

TABLE 18.3 Substrates and cellular locations of mammalian sirtuins

	Subcellular Location	Deacetylation Substrates
SIRT1	Nucleus, cytoplasm	Histones PGC-1α, FOXO, and many other transcription factors IRS-2
SIRT2	Nucleus, cytoplasm	Histones FOXO and other transcription factors
SIRT3	Mitochondrial matrix	Acetyl-CoA synthetase 2 (Chapter 17) Long-chain acyl-CoA dehydrogenase (Chapter 17) Complex I of electron transport chain (Chapter 15) Glutamate dehydrogenase (Chapter 20) Ornithine transcarbamoylase (Chapter 20) $NADP^+$-dependent isocitrate dehydrogenase (Chapter 14) Superoxide dismutase (Chapter 15)
SIRT4[1]	Mitochondrial matrix	Glutamate dehydrogenase[2] (Chapter 20)
SIRT5	Mitochondrial matrix	Carbamoyl phosphate synthetase I (Chapter 20)
SIRT6	Nucleus	Histones
SIRT7	Nucleolus	RNA polymerase I[3]



Hormonal Regulation of Fuel Metabolism

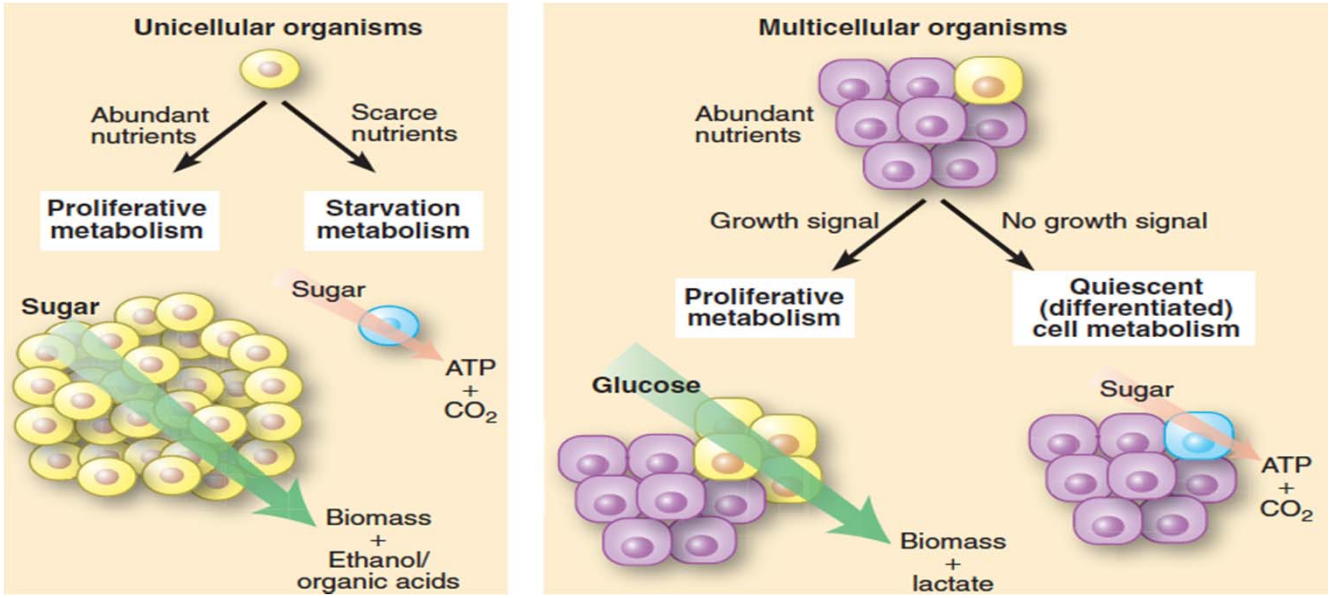
- sirtuins play important roles in cellular stress responses, genomic stability, tumorigenesis and aging.

- Calorie restriction (CR; reduction in food intake of 30-40%) extend lifespan by up to 50% and delays the onset of age-associated disease in animal models.

- *SIRT1* knockout mice do not exhibit the longevity normally associated with calorie restriction. Conversely, transgenic mice that overexpress SIRT1 exhibit many CR responses even when without food restriction. But the mechanisms are not fully understood.

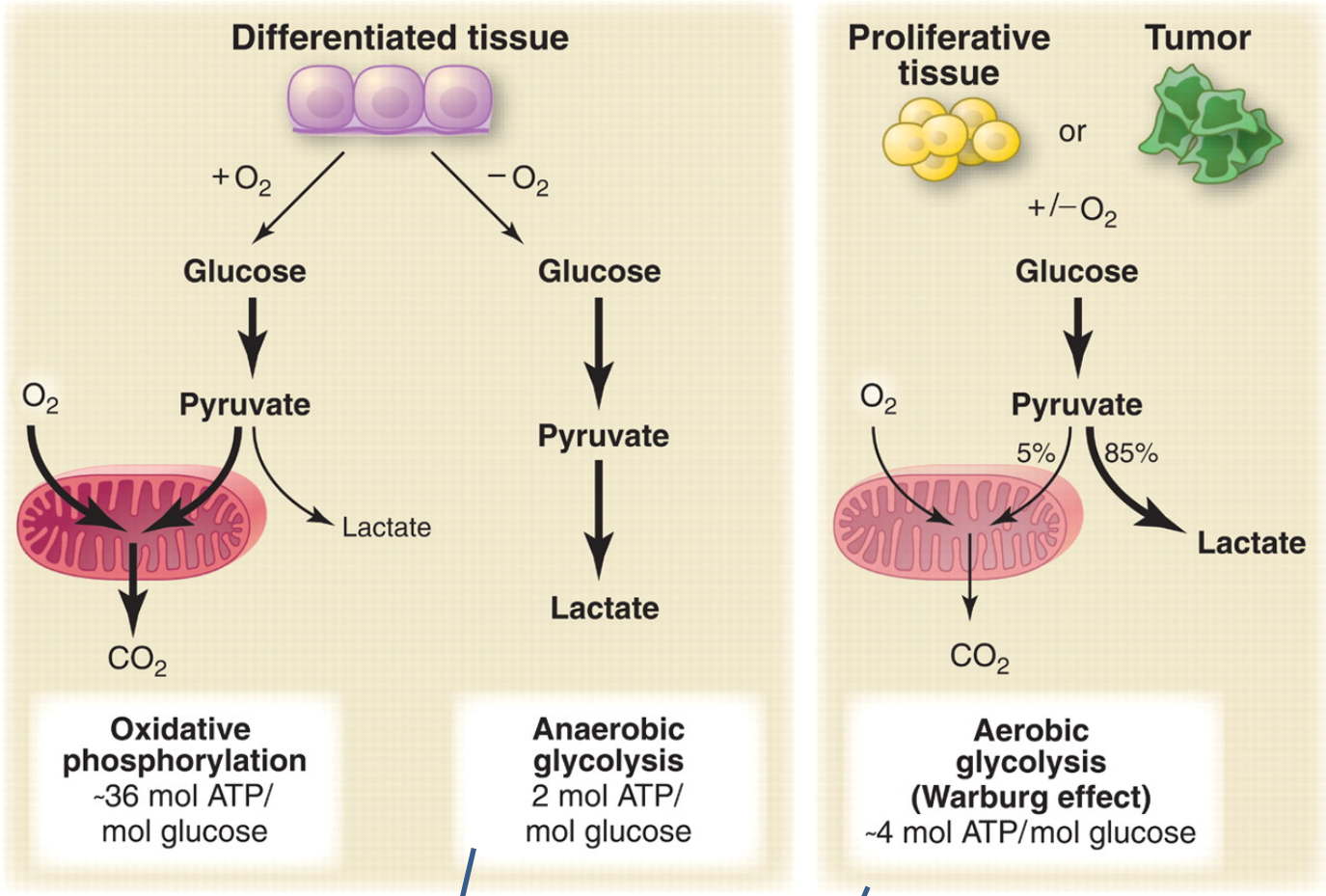
- ***resveratrol*** (chemical compound in red grapes) and newer classes of ***SIRT1 activators*** provide promise for treatment of aging-related diseases.

Hormonal Regulation of Fuel Metabolism



- Proliferating and nonproliferating cells use different metabolic strategies to generate energy.
- Proliferative metabolism relies on glycolysis, a rapid but relatively inefficient process for generating ATP, which requires abundant nutrients.
- When nutrients are scarce, unicellular organisms adapt to a starvation metabolism, characterized by the slower, but more efficient, oxidative metabolism.
- This same efficient oxidative metabolism is used by nondividing, differentiated mammalian cells.
- Nutrient abundance is rarely an issue in multicellular organisms so that the switch between proliferative and quiescent metabolism is determined by the presence or absence of appropriate growth factors (hormones) , rather than by nutrient availability.

the differences between oxidative phosphorylation, anaerobic glycolysis, and aerobic glycolysis (Warburg effect).

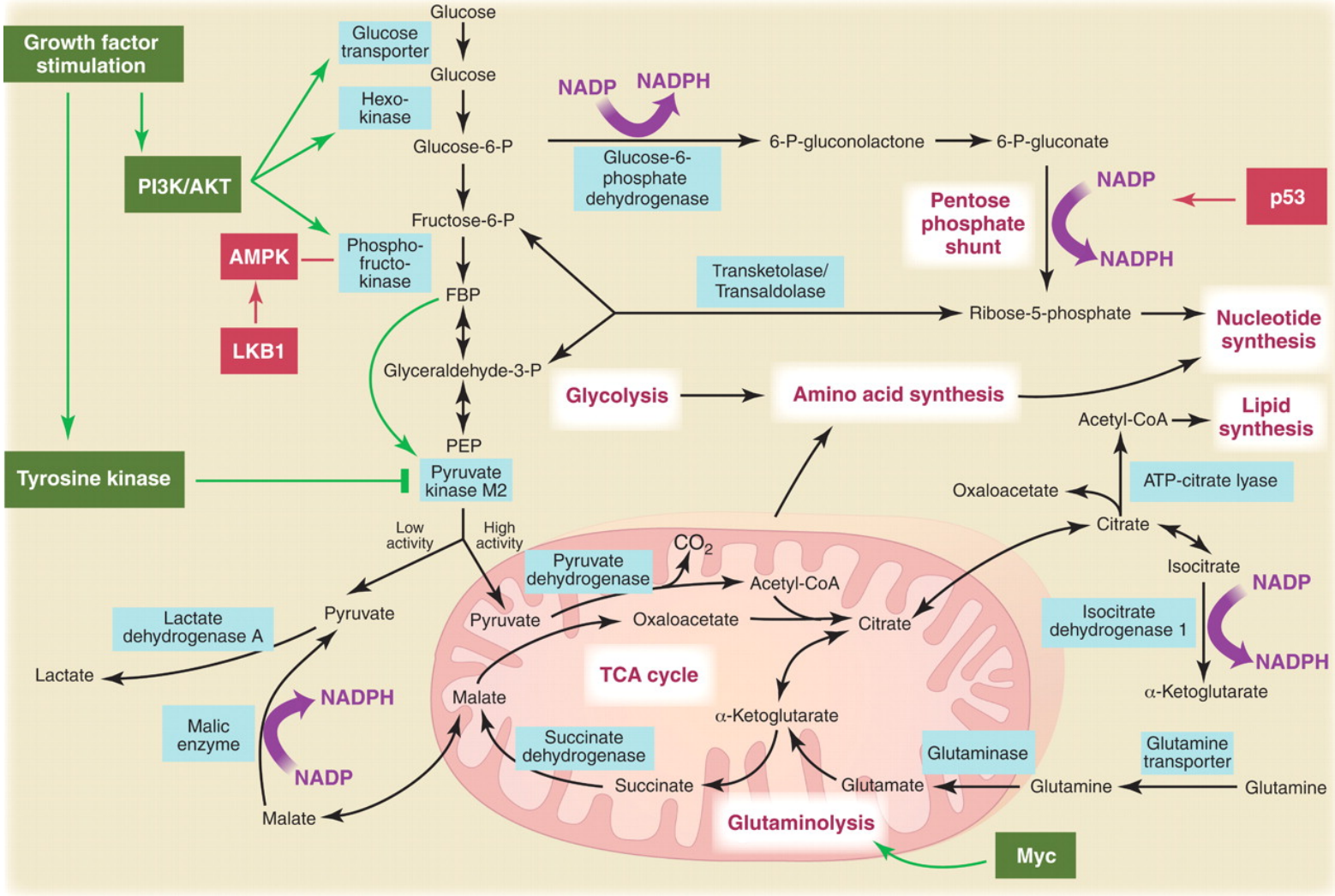


oxygen is essential for this process.

minimal ATP production

regardless of whether oxygen is present

how glycolysis, oxidative phosphorylation, the pentose phosphate pathway, and glutamine metabolism are interconnected in proliferating cells.

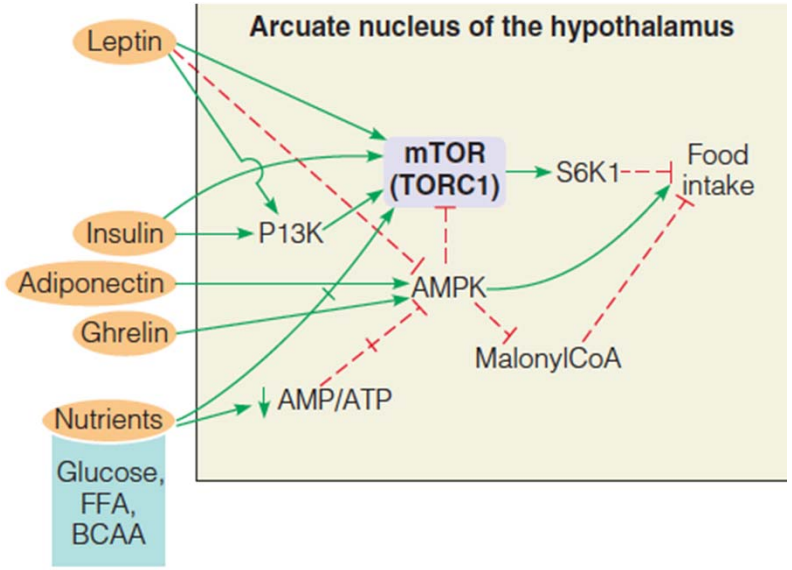


Hormonal Regulation of Fuel Metabolism

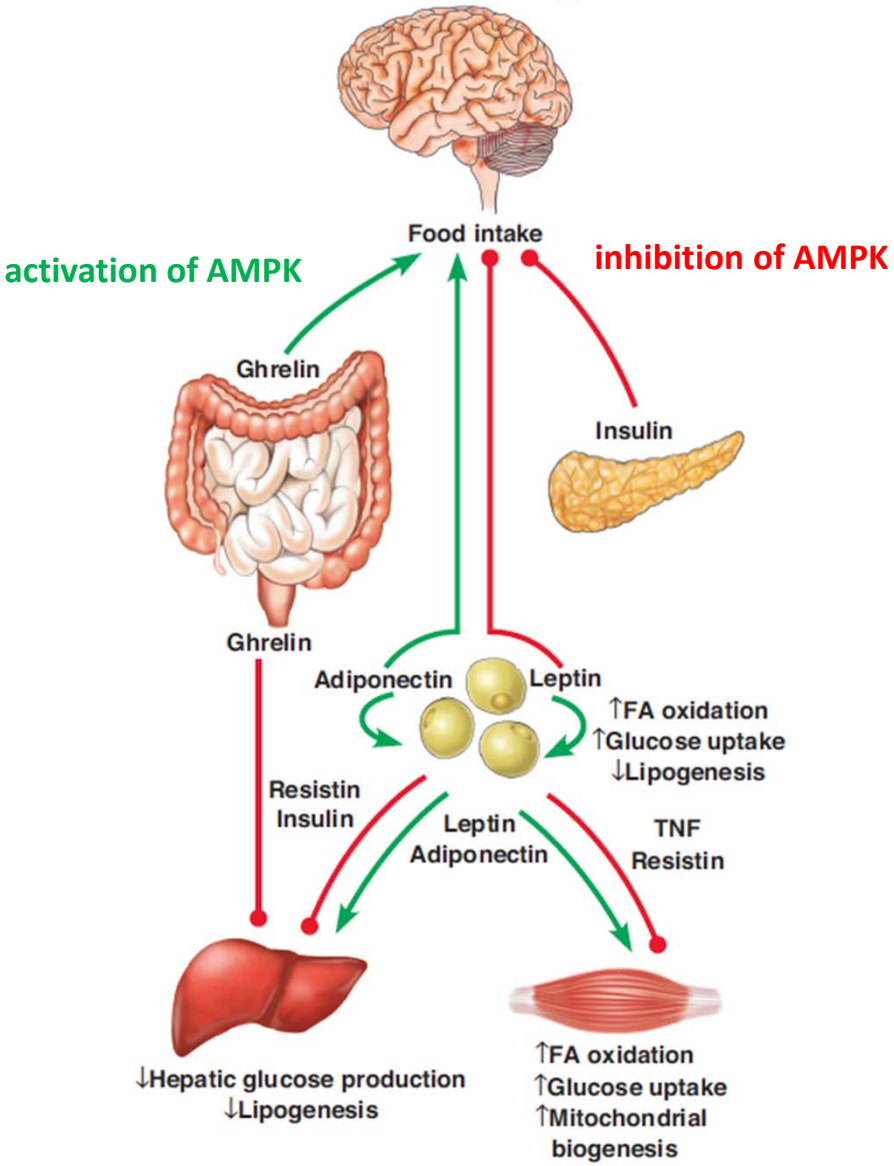
Fuel and hormonal control of food intake in the arcuate nucleus of the hypothalamus, intergrated by AMPK and mTOR.

- Activation of AMPK promotes food intake; inhibition suppresses food intake.
- Insulin acts through the PI3K-mTOR cascade to inhibit food intake.
- Leptin (from adipocytes) activates mTOR and inhibits AMPK function in hypothalamus, suppressing food intake.
- Adiponectin and ghrelin stimulate food intake by activating AMPK.

AMPK is activated in response to low levels of nutrients



Hormonal Regulation of Fuel Metabolism



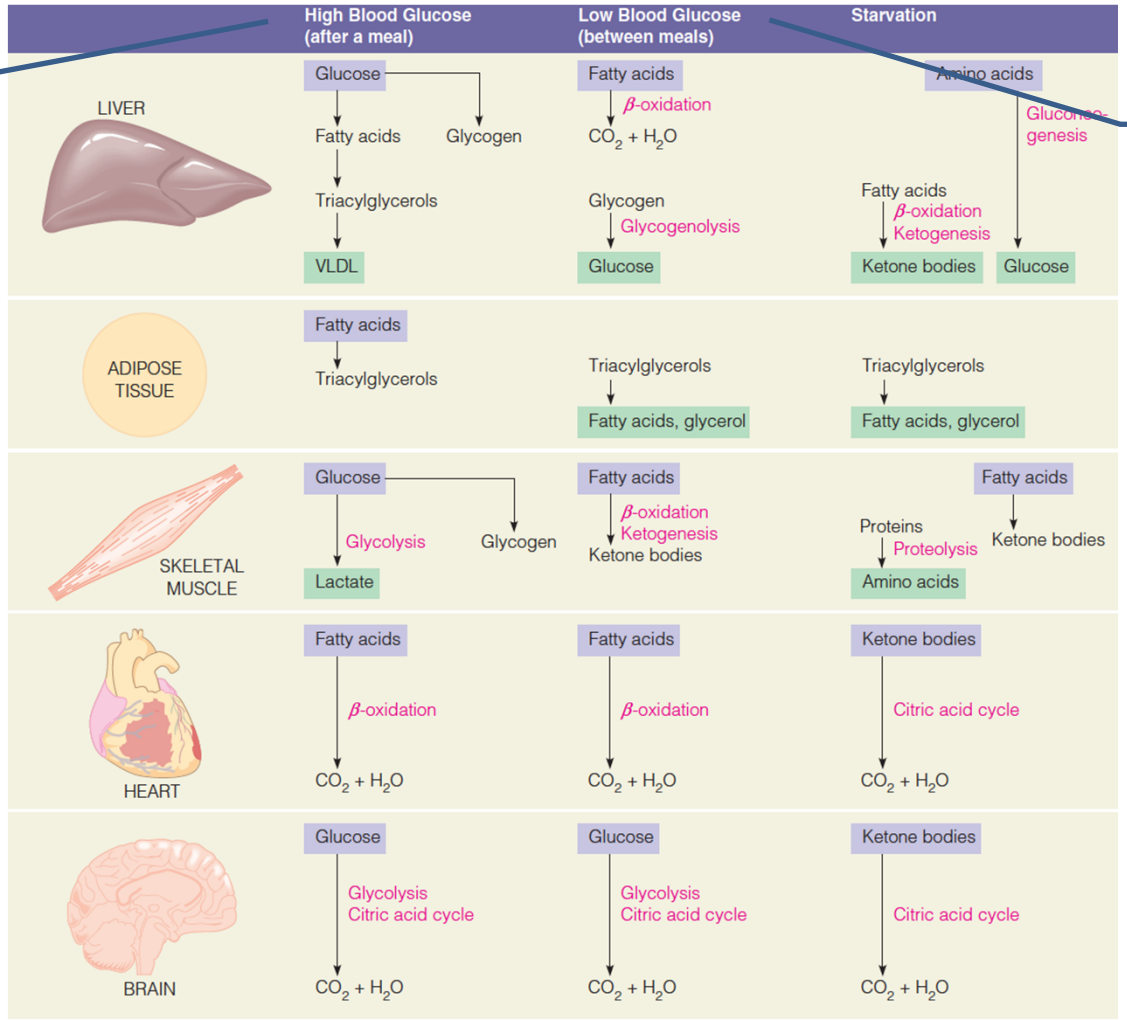
Endocrine regulation of food intake and energy homeostasis in mammals:

•The effects of the major endocrine regulators on AMPK signaling in brain, adipose tissue, liver, and skeletal muscle.

Responses to Metabolic Stress: Starvation, Diabetes

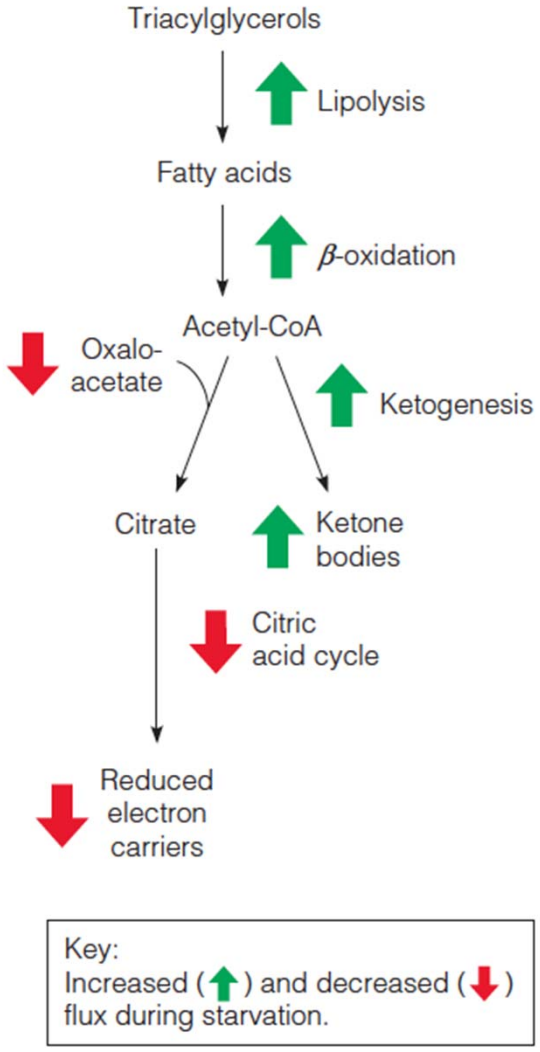
Major events in the storage, retrieval, and use of fuels in the fed and unfed states and in early starvation:

meal stimulates the secretion of insulin and suppresses the secretion of glucagon



Insulin secretion slows and glucagon secretion increases, promotes glycogen mobilization in liver via the cAMP-dependent cascade mechanisms that activate glycogen phosphorylase and inactivate glycogen synthase.

Starvation



- During starvation, organism adapts metabolically to increase the use of fuels other than carbohydrate, primarily fat.
- Metabolic adaptations promote alternative fuel use during starvation so that glucose homeostasis is maintained for several weeks.

Diabetes

- Diabetes results either from insulin deficiency or from defects in the insulin response mechanism, glucose is actually present in excessive amounts.

- Type 1 diabetes is characterized by insulin deficiency; Type 2 diabetes is characterized by insulin resistance — patients cannot respond to therapeutic doses of insulin. Type 2 diabetes accounts for more than 95% of people with diabetes.

- Two related mechanisms have been proposed as causes of type 2 diabetes: the lipid overload hypothesis and the inflammation hypothesis.

- Diabetes can be thought of as "starvation in the midst of plenty" because cells are unable to utilize the glucose that accumulates in the blood.

Diabetes

The metabolic abnormalities in diabetes:

• The insulin deficiency blocks the uptake of glucose into muscle and adipose tissue and reduces glucose catabolism in all tissues.

• Proteolysis in muscle and lipolysis in adipose tissue are enhanced.

• In the liver, gluconeogenesis from amino acids and citric acid cycle intermediates is stimulated as the cells attempt to remedy the perceived lack of usable glucose, and fatty acid oxidation and ketogenesis are also increased.