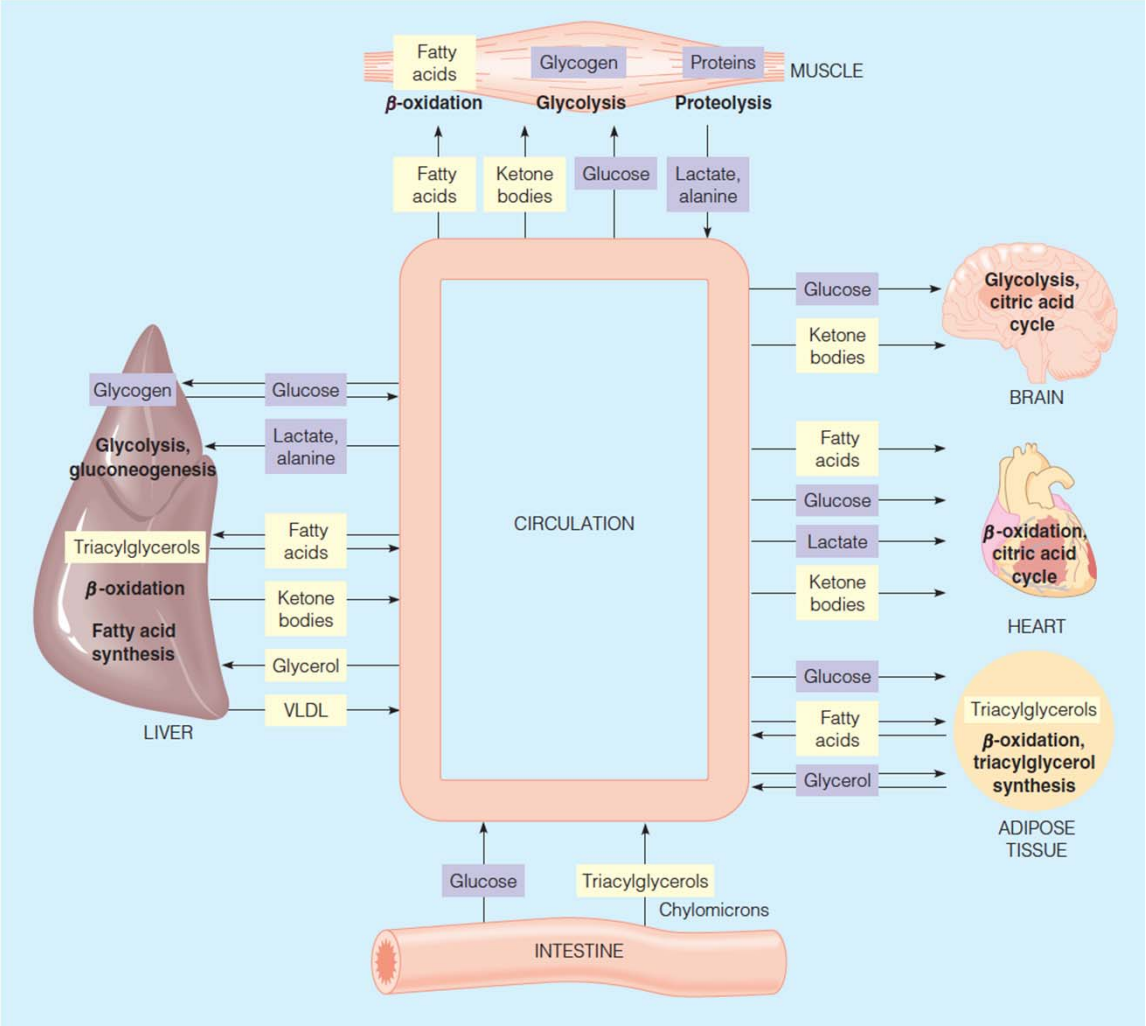
Interdependence of the Major Organs in Vertebrate Fuel Metabolism

Metabolic interactions among the major fuel-metabolizing organs:

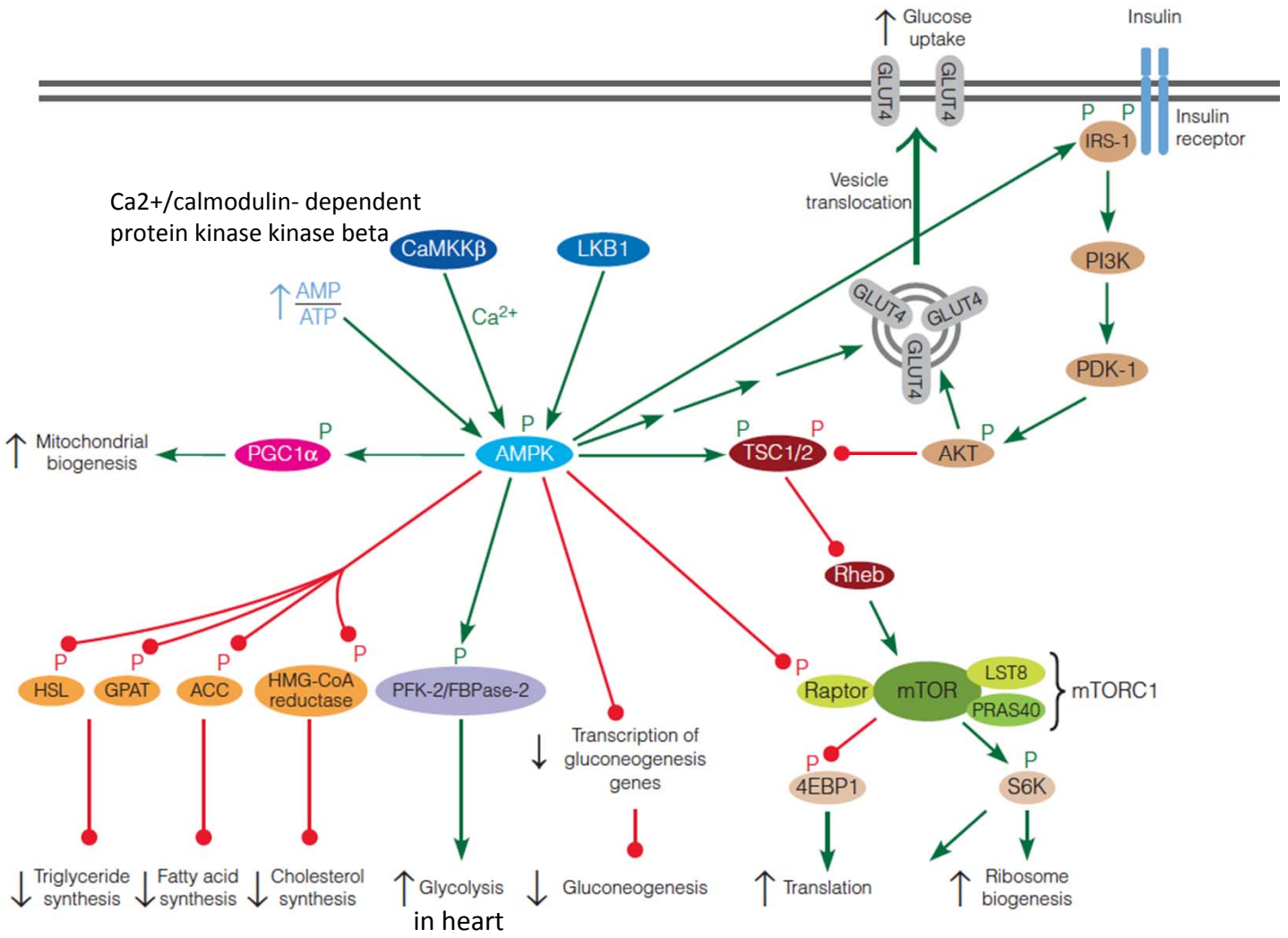
Lipid-derived metabolites

Carbohydrate-derived metabolites



Hormonal Regulation of Fuel Metabolism

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



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.

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.

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

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

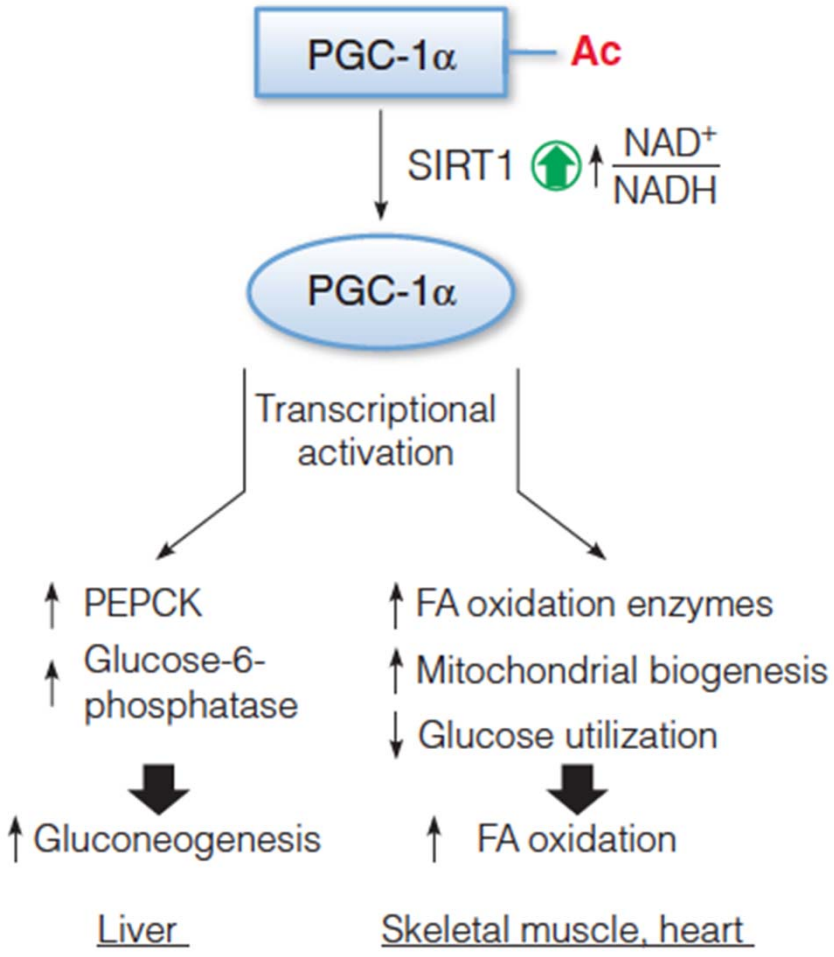
- AMPK (AMP-activated protein kinase) is activated when the energy charge of the cell is low (high AMP/ATP ratio).

- 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

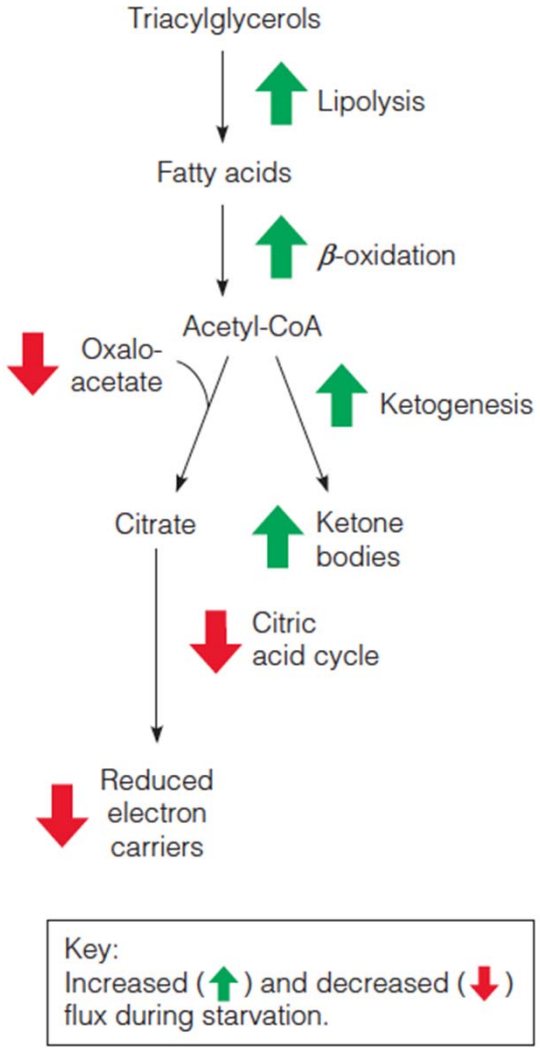
Hormonal Regulation of Fuel Metabolism



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.

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.

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