**Regulation of Mammalian Fuel Metabolism**

**19.1: Integration of Fuel Metabolism**

* **Summarize the metabolic functions of liver, kidney, muscle, and adipose tissue.**
	+ **Identify the major sources of fuel in each organ.**
	+ **Describe the mobilization of stored fuel in each organ.**
	+ **Trace the movement of metabolites between organs.**

organ/cellular compartmentalization

* Compartmentalization = regulation
* Organ specialization = compartmentalization
* Organ functions respond to fed/fasted/active state
* Liver: gluconeogenesis, ketogenesis, urea production
* Adipose: fat storage

liver

* Fed: glucose/fat stored; TAGs synthesized from glucose and amino acids exported
* Fasted: glucose mobilized and released to circulation; TAGs converted to Acetyl-CoA for ketogenesis; amino acids converted to glucose or Acetyl-CoA
* Lactate/alanine converted to glucose, nitrogen disposal via urea synthesis

muscle

* Fed: glucose stored as glycogen
* Active: glycogen catabolized for ATP production; f.a.s and ketones burned as well (CAC); cardiac muscle is constantly active and burns f.a.s as primary fuel
* Sustained activity: pyruvate converted to lactate and alanine, exported to liver
* Starvation: proteins hydrolyzed to amino acids for gluconeogenesis

adipose tissue

* Fed: glucose converted to glycerol + f.a.s = TAGs for storage
* Fasted: TAGs released for f.a. oxidation

kidney

* Primarily waste eliminating organ
* Minor role: converts a-ketoglutarate to glucose via gluconeogenesis

Cori cycle

* Liver releases glucose to tissues via circulatory system
* Amino groups travel to liver and kidney for disposal
* Lactate produced during sustained exercise is exported to liver and converted to glucose
* Transport back to muscle feeds activity post glycogen depletion
* Recycles waste from NAD+ regeneration
* Energetic transfer from liver (from fatty acid oxidation) to muscles = energy cycle

glucose-alanine cycle

* Muscle breakdown during sustained exercise generates intermediates to feed CAC (a-KG)
* Alanine produced via transamination is exported to liver
* Amino group removed via deamination, then used for urea synthesis
* pyruvate converted to glucose via gluconeogenesis
* Transport back to muscle feeds activity post glycogen depletion
* Energetic transfer from liver to muscles
* Disposes of nitrogenous waste; transported from muscles to liver (as alanine)

**19.2: Hormonal Control of Fuel Metabolism**

* **Describe the effects of insulin, glucagon, and epinephrine on fuel metabolism.**
	+ **Summarize the effects of insulin on muscle, adipose tissue, and liver.**
	+ **Recount how epinephrine and glucagon signaling lead to fuel mobilization.**
	+ **Describe the role of AMP-dependent protein kinase.**
* Metabolic processes are continually adjusted to accommodate cellular needs
* Fuels are continually stored, mobilized, and replenished
* Brain requires continual supply of glucose
* Cardiac muscle preferentially to burns fat
* Activity is hormonally controlled: insulin, glucagon, epinephrine and norepinephrine
* Also regulated are appetite regulation, fuel allocation, and body weight

insulin signaling

* Stimulates glucose uptake; inhibits glycogen breakdown
* Post-prandial rise in blood glucose stimulates insulin release from b-islet cells
* Glucose metabolism generates insulin-releasing signal
* Glucokinase ~ hexokinase (liver and pancreatic); high KM decreases saturation, increases sensitivity to [glucose]
* Kinetics of glucokinase indicate cooperativity within the monomeric enzyme
* Substrate-induced conformational change could increase affinity for subsequent substrate binding
* Cooperativity enhances glucose binding when [glucose] rises
* Insulin binding to receptor initiates RTK signal transduction; IRS-1 and IRS-2 are downstream targets

insulin action (muscle/adipose/liver)

* Hormone response depends on cell-specific receptors
* Generally, insulin = abundance (fuel storage)
* Glucose transport is increased by translocation of transporters (GLUT4) to membrane; passive transport
* Transporters returned once insulin signal is removed
* Insulin binding to adipose receptors causes f.a. uptake via activation of extracellular lipoprotein lipase
* Alters activity of glycogen metabolism



glycogen synthase/glycogen phosphorylase

* Glycogen synthase activated by G-6-P
* Glycogen phosphorylase activated by AMP/ inhibited by ATP
* Primarily regulated by phosphorylation
* phosphatases activate synthase
* Kinases activate phosphorylase
* Reciprocal regulation by single kinase/phosphatase

glucagon/epinephrine signaling: GPCRs

* Post-dietary uptake, cells rely upon glucose from glycogenolysis
* Pancreatic a-cells release glucagon at low [glucose]
* Binding of glucagon and catecholamines triggers GPCR cascade; + PKA
* Glucagon stimulates glucose release from stored glycogen as well as lipolysis in adipose tissue (muscle responds to catecholamines)
* +PKA activates phosphorylase kinase, promoting glycogenolysis via glycogen phosphorylase; phosphorylase kinase activity increased by Ca2+ from PI signaling = pathways converge
* +PKA relocates and activates hormone-sensitive lipase, mobilizing stored TAGs.

hormonal regulation of fuel metabolism

* Leptin: signals satiety; suppresses appetite via hypothalamus; levels proportional to adipose tissue
* Adiponectin: activates AMPK to increase catabolism of fuels and insulin sensitivity
* Resistin: blocks insulin activity; levels rise with obesity



AMP-dependent protein kinase

* Cellular fuel sensor
* Regulated by AMP, ADP, ATP
* Ser/Thr kinase with regulatory and catalytic subunits
* Activated by phosphorylation at Thr residue
* ADP binding to regulatory subunit prevents dephosphorylation, maintaining kinase activity
* ATP inhibits AMPK, competes with AMP and ADP for binding to regulatory subunit
* AMPK regulates ATP consumption and production, i.e., PFK-2 activation in muscle; acetyl-CoA carboxylase inactivation (- f.a. synthesis, + oxidation)
* Promotes mitochondrial production



**19.3: Disorders of Fuel Metabolism**

* **Compare the metabolic changes that occur in starvation, obesity, and diabetes**
	+ **Describe how fuel use changes during starvation.**
	+ **Compare brown and white fat and their contributions to obesity.**
	+ **Describe the causes and symptoms of type 1 and type 2 diabetes.**

sources of metabolic fuels

* Metabolic switch to burning fat shuts down insulin secretion, making more glucose available for brain tissue
* Liver and kidneys increase gluconeogenesis from proteins and fats
* Liver begins ketogenesis to prevent muscle degradation

dysregulation of fuel metabolism

* Physiological costs: lungs, heart, mechanical stress, increased risk of cardiovascular disease, diabetes, cancer
* Complex disorder of regulation of fuel metabolism
* Body weight set-point, leptin involved
* Leptin resistance leads to weight gain and higher set-point

adipose tissue: brown vs. white

* Brown: specialized for thermogenesis; high mitochondrial content; resembles muscle
* Responds to norepinephrine to activate lipase via PKA; liberates f.a.s from TAGs
* Expresses UCP in mitochondria

diabetes

* Type I = autoimmune, juvenile-onset; Tx with insulin and blood glucose monitoring
* Type II = insulin resistant, adult-onset
* Insulin insensitivity causes hyperglycemia and increased gluconeogenesis
* Increased glycosylation of proteins can cause tissue damage
* Conversion of glucose to sorbitol causes accumulation and disruption of osmotic balance; renal stress, protein precipitation leads to cataracts; neuropathies and circulatory problems from tissue damage; renal failure, heart attack, stroke, amputation
* Ketogenesis results in overproduction of ketone bodies, resulting in diabetic ketoacidosis

metabolic syndrome

* Related set of symptoms correlated with development of diabetes
* Obesity, insulin resistance, atherosclerosis, hypertension, increased cancer incidence
* High proportion of visceral fat leads to altered hormone profile (decreased leptin and adiponectin, increased resistin)
* TNFa promotes inflammation, insulin insensitivity
* Fat toxicity, impairment of GLUT4 translocation, increase in liver gluconeogenesis, b cell exhaustion from overstimulation

**19.4: Clinical Connection: Cancer Metabolism**

* **Relate metabolic changes to the rapid growth of cancer cells**

metabolic changes in cancer metabolism

* High rate of glycolysis, independent of O2 levels
* Warburg effect: aerobic glycolysis
* Large consumption of glucose and disposal of waste as lactate
* Conversion of glucose to anabolic precursors promote cell division
* Diversion of intermediates to nucleotide and protein synthesis
* Glutamate dehydrogenase (amino group transfer) is regulatory point for cancer cells; inhibited when f.a. synthesis is high
* GDH activated by ADP; inhibited by GTP

