Metabolism

The goal of this lectures is to discuss basic physiology associated with the control of metabolism, such as the neuroendocrine control of pre- and post-absorptive states. The sections for this lecture are:

Introduction

Neuroendocrine control of metabolism
- Insulin and Glucagon
- Growth hormone (GH) and growth factors (IGF)
- Thyroid hormones (tri / tetra iodotyronin, T3 and T4)
- Catecholamines (Cus, Epi and Norepinephrine)
- Glucocorticoids (Cortisol in humans)

Major metabolic pathways of the absorptive state

Major metabolic pathways of the post-absorptive state
Introduction

FUEL METABOLISM IN ANABOLIC / CATABOLIC PHASES

<table>
<thead>
<tr>
<th>State</th>
<th>Hormones</th>
<th>Fuel Source</th>
<th>Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>anabolism</td>
<td>Insulin</td>
<td>diet</td>
<td>Glycogen synthesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Triglyceride synthesis</td>
</tr>
<tr>
<td></td>
<td>Glucagon</td>
<td></td>
<td>Protein synthesis</td>
</tr>
<tr>
<td>catabolism</td>
<td>Insulin</td>
<td>storage depots</td>
<td>Glycogenolysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lipolysis</td>
</tr>
<tr>
<td></td>
<td>Glucagon</td>
<td></td>
<td>Proteolysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ketogenesis</td>
</tr>
</tbody>
</table>

Introduction

<table>
<thead>
<tr>
<th>Form absorbed across GI tract</th>
<th>Form circulating in blood</th>
<th>Form stored</th>
<th>Storage site</th>
<th>Percent of total energy stored</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrates</td>
<td>Glucose</td>
<td>Glucose</td>
<td>Liver, skeletal muscles</td>
<td>1%</td>
</tr>
<tr>
<td>Proteins</td>
<td>Amino acids, some small peptides</td>
<td>Amino acids</td>
<td>Skeletal muscle*</td>
<td>22%</td>
</tr>
<tr>
<td>Lipids</td>
<td>Monoglycerides and fatty acids (in chylomicrons)</td>
<td>Free fatty acids, lipoproteins</td>
<td>Adipose tissue</td>
<td>77%</td>
</tr>
</tbody>
</table>

*Even though proteins are found in all cells of the body, most of the proteins mobilized for energy come from skeletal muscle cells.

<table>
<thead>
<tr>
<th>Glycogen</th>
<th>Triglycerides</th>
<th>Proteins (mobilizable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal muscle</td>
<td>71</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Liver</td>
<td>24</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>5</td>
<td>99</td>
</tr>
<tr>
<td>Brain</td>
<td>&lt; 1</td>
<td>0</td>
</tr>
</tbody>
</table>
Introduction

glycogen phosphorilase  
G-6-Pase  
glucose  
G-6-Pase  
G - 1 - P  
glycogen synthetase  
hexokinase  
glucose  
F-1,6-diPase  
transaminases  
amino acids  
proteins  
F - 6 - P  
F - 1,6-diP  
triose  
pyruvate  
acetyl CoA  
Krebs cycle  
proteins  
Fatty acids  
glycogen phosphorilase  
G-6-Pase  
glucose  
G-6-Pase  
G - 1 - P  
glycogen synthetase  
hexokinase  
glucose  
F-1,6-diPase  
transaminases  
amino acids  
proteins  
F - 6 - P  
F - 1,6-diP  
triose  
pyruvate  
acetyl CoA  
Krebs cycle  
proteins  
Fatty acids  

Introduction

Absortive State

TABLE 16-1 Summary of Nutrient Metabolism during the Absorptive Period

1. Energy is provided primarily by absorbed carbohydrate in a typical meal.
2. There is net uptake of glucose by the liver.
3. Some carbohydrate is stored as glycogen in liver and muscle, but most carbohydrate and fat in excess of that used for energy are stored mainly as fat in adipose tissue.
4. There is some synthesis of body proteins, but some of the amino acids in dietary protein are used for energy or converted to fat.
Introduction

Post-Absorptive State

TABLE 16-2 Summary of Nutrient Metabolism during the Postabsorption Period

1. Glycogen, fat, and protein synthesis are curtailed, and net lipolysis occurs.
2. Glucose is formed in the liver both from the glycogen stored there and by gluconeogenesis from blood-borne lactate, pyruvate, glycerol, and amino acids. The kidneys also perform gluconeogenesis during a prolonged fast.
3. The glucose produced in the liver (and kidneys) is released into the blood, but its utilization for energy is greatly reduced in muscle and other nonessential tissues.
4. Lipolysis releases adipose tissue fatty acids into the blood, and the oxidation of these fatty acids by most cells and of ketones produced from them by the liver provides most of the body’s energy supply.
5. The brain continues to use glucose but also starts using ketones as they build up in the blood.

Critical Points of Transition

<table>
<thead>
<tr>
<th>ABSORPTIVE STATE</th>
<th>PREABSORPTIVE STATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROTEINS TRIACYLGLYCEROL GLYCOCEN</td>
<td>PROTEIN TRIACYLGLYCEROL GLYCOCEN</td>
</tr>
<tr>
<td>Amino acids → Glycogen → Fatty acids → Glucose</td>
<td>Amino acids → Glucose → Fatty acids → Glucose</td>
</tr>
<tr>
<td>Glucose → CO₂ + H₂O + Energy</td>
<td>Fatty acids and ketones → CO₂ + H₂O + Energy</td>
</tr>
<tr>
<td>Glucose → Liver → Glycogen, Lactate, Glycerol, and Amino acids</td>
<td>Glucose → Liver</td>
</tr>
</tbody>
</table>

Introduction
## Introduction

<table>
<thead>
<tr>
<th>Absorptive (anabolic) state</th>
<th>Postabsorptive (catabolic) state</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carbohydrates</strong> In liver and skeletal muscle, glucose is converted to glycogen (glycogenesis) for storage. Liver also converts some glucose to triglycerides, which are transported to adipose tissue by lipoproteins. In adipose tissue, glucose is converted to triglycerides for storage. In body cells, glucose undergoes oxidation for energy.</td>
<td>In liver, glycogen is catabolized to glucose (glycogenolysis) and new glucose is formed from noncarbohydrate precursors (gluconeogenesis); glucose is then transported into the bloodstream. In muscle, glycogen is catabolized to glucose-6-P, which can be used by the muscle cell for energy.</td>
</tr>
<tr>
<td><strong>Lipids</strong> Triglycerides are synthesized from ingested fats, proteins, and glucose by adipocytes; triglycerides synthesized in the liver are transported to adipose tissue for storage.</td>
<td>In adipose tissue, triglycerides are broken down to fatty acids and glycerol, which enters the bloodstream and travels to the liver, where it is converted to glucose (gluconeogenesis). Fatty acids enter the bloodstream and provide the primary energy source for most body cells. In liver, fatty acids are converted to ketones.</td>
</tr>
<tr>
<td><strong>Amino acids</strong> In all cell types, amino acids are used for protein synthesis. In liver, amino acids can be converted to ketone bodies for energy production or triglyceride synthesis. Triglycerides are then transported to adipose tissue by lipoproteins.</td>
<td>In muscle, proteins are catabolized to amino acids, which are transported to the liver for gluconeogenesis.</td>
</tr>
</tbody>
</table>

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**Diagram**

- **Carbohydrates**
  - Glucose → Glycogen
  - Glycogen → Other metabolism
- **Proteins**
  - Amino acids → Lipoproteins
  - Lipoproteins → Fatty acids
- **Lipids**
  - Triglyceride → Fatty Glycerol
  - Fatty Glycerol → Triglyceride

Liver → 2 NH₃ → Urea

Liver 2 NH₃ → Urea

LPL
Introduction

The main endocrine systems involved in the neuroendocrine control of metabolism are:

<table>
<thead>
<tr>
<th>Site of secretion</th>
<th>Primary stimuli for secretion (direct stimuli in parentheses)</th>
<th>Not effect on carbohydrate metabolism</th>
<th>Effect on glucose</th>
<th>Not effect on lipid metabolism</th>
<th>Not effect on protein metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>Adrenal medulla</td>
<td>Sympathetic nervous activity (stress, exercise)</td>
<td>1. Glycogenolysis</td>
<td>1. Plasma glucose</td>
<td>1. Lipolysis</td>
</tr>
<tr>
<td>Thyroid Hormones</td>
<td>Thyroid gland</td>
<td>TSH from anterior pituitary (GH from hypothalamus, cold temperatures in infants)</td>
<td>1. Thyroid function</td>
<td>None</td>
<td>1. Lipolysis</td>
</tr>
</tbody>
</table>
Insulin

- 51 aa, 2 chains, 3 disulfide bonds, C-peptide
- stimulates anabolism and favors energy storage
- increases glycogen storage and inhibits both glycogen breakdown and gluconeogenesis
- increases fatty acid synthesis and decreases lipolysis and ketogenesis
- stimulates transport of glucose and of some aminoacids into striated muscle / adipose tissue
- increases protein synthesis in liver, muscle, adipose
- like growth factors, has a growth promoting effect
Insulin

Target-Cell Responses

(A) 
- Muscle: 
  - Glucose uptake and utilization, net glycogen synthesis, net amino acid uptake, net protein synthesis
- Adipocytes: 
  - Glucose uptake and utilization, net triglycerol synthesis
- Liver: 
  - Glucose uptake and utilization, net triglycerol synthesis, no ketone synthesis

(B) 
- Muscle: 
  - Glucose uptake and utilization, net glycogen catabolism, net protein catabolism, net amino acid release, fatty acid uptake and utilization
- Adipocytes: 
  - Glucose uptake and utilization, net triglycerol catabolism and release of glycerol and fatty acids
- Liver: 
  - Glucose release due to net glycogen catabolism and gluconeogenesis, ketone synthesis and release

Insulin

- Cys rich
- Hydrophobic aa
- Kinase
- Insulin

NH2 → α 
ECF  membr 
ICF → COOH

Tyr-P of docking protein IRS-1

SH2-domain mediated complex formation
Ser - Thr kinase cascade
DNA synthesis and gene transcription

SOS ras raf MEKK MAPK p90rsk PP1G glycogen synthase

phosphatidylinositol -3-P

stimulation of glucose transport
Insulin

<table>
<thead>
<tr>
<th>CHIEF ACTIONS OF INSULIN ON METABOLIC PATHWAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liver</strong></td>
</tr>
<tr>
<td>glycogenolysis</td>
</tr>
<tr>
<td>gluconeogenesis</td>
</tr>
<tr>
<td>ketogenesis</td>
</tr>
<tr>
<td>fatty acid synthesis</td>
</tr>
<tr>
<td>phosphorylase (glucose-dependent de-P)</td>
</tr>
<tr>
<td>PEPCK (transcriptional regulation)</td>
</tr>
<tr>
<td>FDPase-2 (enzyme dephosphorylation)</td>
</tr>
<tr>
<td>substrate (alanine) delivery from muscle</td>
</tr>
<tr>
<td>substrate (FFA) delivery from fat</td>
</tr>
<tr>
<td>glycogen synthase (enzyme de-P)</td>
</tr>
<tr>
<td>acetyl CoA carboxylase (transcription)</td>
</tr>
<tr>
<td>fatty acid synthase</td>
</tr>
<tr>
<td><strong>Muscle</strong></td>
</tr>
<tr>
<td>proteolysis</td>
</tr>
<tr>
<td>protein synthesis</td>
</tr>
<tr>
<td>glucose uptake</td>
</tr>
<tr>
<td>glycogen synthesis</td>
</tr>
<tr>
<td>multiple mechanisms</td>
</tr>
<tr>
<td>activity at multiple steps</td>
</tr>
<tr>
<td>recruit Glut-4 to cell surface</td>
</tr>
<tr>
<td>glucose uptake</td>
</tr>
<tr>
<td>glycogen synthase (enzyme de-P)</td>
</tr>
<tr>
<td><strong>Fat</strong></td>
</tr>
<tr>
<td>lipolysis</td>
</tr>
<tr>
<td>triglyceride synthesis</td>
</tr>
<tr>
<td>hormone sensitive lipase (enzyme de-P)</td>
</tr>
<tr>
<td>delivery of tryglyceride from liver lipoprotein lipase</td>
</tr>
</tbody>
</table>
Anti insulin controls

<table>
<thead>
<tr>
<th>TABLE 16-4</th>
<th>Summary of Glucose-Counterregulatory Controls*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GLUCAGON</td>
</tr>
<tr>
<td>Glycogenolysis</td>
<td>✓</td>
</tr>
<tr>
<td>Gluconeogenesis</td>
<td>✓</td>
</tr>
<tr>
<td>Lipolysis</td>
<td>✓</td>
</tr>
<tr>
<td>Inhibition of:</td>
<td></td>
</tr>
<tr>
<td>glucose uptake</td>
<td></td>
</tr>
<tr>
<td>by muscle cells</td>
<td></td>
</tr>
<tr>
<td>adipose tissue cells</td>
<td></td>
</tr>
</tbody>
</table>

* ✓ indicates that the hormone stimulates the process; ✓ indicates that the hormone has no major physiological effect on the process. Epinephrine stimulates glycogenolysis in both liver and skeletal muscle, whereas glucagon does so only in liver.

Glucagon

[Diagram showing the effects of glucagon on various processes including plasma glucose, sympatetic activity, alpha cells in pancreas, glucagon secretion, liver, adipose tissue, glycogenolysis, gluconeogenesis, ketone synthesis, triglyceride synthesis, and protein breakdown/synthesis.]
Glucagon

- the main counterregulator to insulin together with catecholamines (epinephrine) & cortisol
- 29 aa, member of a family of related peptides that includes VIP, GIP, and secretin
- determines glycemia in postabsorptive state through glycogenolysis and gluconeogenesis
- glucose, insulin and SS inhibit its release
- aa, exercise and CAs stimulate its release
- gene expression is restricted to α cells in islet and is negatively regulated by insulin
- glycentin, GI specific proteolytic processing

Glucagon

Glucagon

<table>
<thead>
<tr>
<th>glucagon</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
</tr>
</tbody>
</table>

Glucagon receptor

- Cell membrane

- Gs

- AC

- Phosphodiesterase

- ATP → cAMP → 5’AMP

- Inactive PKA → active PKA

- Inactive PKb → active PKb

- Glycogen phosphorilase b → glycogen phosphorilase b

- Glycogen + Pi → glucose - 1 - P

- Blood glucose
**Glucagon**

**CHIEF ACTIONS OF GLUCAGON ON METABOLIC PATHWAYS**

<table>
<thead>
<tr>
<th>LIVER</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>glycogenolysis</td>
<td>glycogen phosphorylase (cAMP-dep-P)</td>
</tr>
<tr>
<td>glycogenesis</td>
<td>glycogen synthase (phosphorylation)</td>
</tr>
<tr>
<td>gluconeogenesis</td>
<td>F - 1,6 - diPase (phosphorylation)</td>
</tr>
<tr>
<td>glycolysis</td>
<td>pyruvate kinase (phosphorylation)</td>
</tr>
<tr>
<td>ketogenesis</td>
<td>substrate delivery, releasing inhibition of carnitine palmytoil transferase, allowing mitochondrial transfer and FA oxidation</td>
</tr>
</tbody>
</table>

**Glucagon and Glucose Metabolism**

**Glucagon and Fat Metabolism**

**Glucagon and Protein Metabolism**

**Plasma Glucose Control Over Glucagon Secretion**
Glucagon

Insulin / Glucagon

Plasma Concentrations of Glucose, Glucagon, and Insulin During Exercise
Growth Hormone

- lowers blood aminoacid concentrations
- lowers blood urea nitrogen. Positive N balance
- increases DNA, RNA, and protein synthesis
- elevates glycemia by decreasing CH utilization and the sensitivity to the insulin-hypoglycemic effect
- elevates fat oxidation. Lowers respiratory quotient
- induces growth in general mostly through IGFs
- stimulates growth and calcification of cartilage (IGF)
- GH abuse causes diabetes mellitus by exhaustion of β-cells overstimulated by high glycemia (meta-hypophyseal diabetes). Impaired glucose tolerance in acromegaly might be related to this interaction
Growth Hormone

- the GHRH peptide:
- G - protein linked receptor
- AC/cAMP, PLC / IP, PLA/ PGE
- sexual dimorphism (DHT)
- have receptors for SS
- the SS peptide:
- G - protein linked receptor
- Gi, AC, open K channels, hyperpolarization, lower Ca influx to cell
Growth Hormone

- GH receptors do not have a kinase
- Dimerization, if GH excess inhibition
- Ligand binding results in rapid phosphorylation of cell proteins on Tyr
- Janus (JAK) kinases are cytoplasmic tyrosine kinases which physically associate with the box 1 - box 2 domains of the ligand bound receptor leading to auto - phosphorylation on Tyr residues and phosphorylation of transcription factors called “signal transducers and activators of trans-cription” or in short “STATS”
- Most GH effects are mediated by IGFs
Growth Factors

- GFs have Tyr-K except TGFβ which phosphorilates Ser / Thr residues
- receptor dimerization
- amplification through multiple kinases & stats (signal transducers and activators of transcription)
- long-term effects of GFs are dependent on shifts in gene expression

Thyroid Hormones

- Hypothalamus
- TRH secretion
- Anterior pituitary
- TSH secretion
- Thyroid gland
- Thyroid hormone secretion
- Plasma T3
- Conversion to T3
- Many tissues

- Basal metabolic rate
- Heat production
- Responsiveness to sympathetic input
- Permits normal growth and development

- Permits normal growth and development
- Permits maintenance of normal activity
Thyroid Hormones

Major Functions of the Thyroid Hormones

1. Required for normal maturation of the nervous system in the fetus and infant
   Deficiency: Mental retardation (cretinism)

2. Required for normal bodily growth because they facilitate the secretion of and response to growth hormone
   Deficiency: Deficient growth in children

3. Required for normal alertness and reflexes at all ages
   Deficiency: Mentally and physically slow and lethargic; delayed reflexes
   Excess: Restless, irritable, anxious, wakeful; hyper-reflexic

4. Major determinant of the rate at which the body produces heat during the basal metabolic state
   Deficiency: Low BMR, cold intolerance; decreased food appetite
   Excess: High BMR, heat intolerance; increased food appetite, increased catabolism of nutrients

5. Facilitates the activity of the sympathetic nervous system by stimulating the synthesis of one class of receptors (beta receptors) for epinephrine and norepinephrine
   Excess: Symptoms similar to those observed with activation of the sympathetic nervous system (for example, increased heart rate)
Thyroid Hormones

<table>
<thead>
<tr>
<th>Hormone binding region</th>
<th>DNA binding region</th>
<th>COOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>563</td>
<td>NH₂</td>
</tr>
<tr>
<td>1</td>
<td>946</td>
<td>COOH</td>
</tr>
<tr>
<td>1</td>
<td>777</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>408</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>917</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>427</td>
<td></td>
</tr>
</tbody>
</table>

Structure of nuclear hormone receptors:
- estrogen
- progesterone
- glucocorticoid
- thyroid hormone
- androgen
- Vitamin D

Thyroid Hormones

Inactive:
- T3R
- T3R
- empty binding site
- HRE
- TFIIB
- RNA-Pol II
- TATA box

Active:
- T3
- T3R
- T3R
- co-repressor COOH
- co-repressor NH2
- TFIIB
- RNA-Pol II
- TATA box
- DNA
Thyroid Hormones

- Increased metabolism (ml O2/100g/h)
- Body weight (g)
- Time in days

Catecholamines

- Plasma glucose
- Glucose receptors in central nervous system
- Sympathetic activity
- Adrenal medulla
- Epinephrine secretion
- Liver
- Muscle
- Adipose tissue
- Glycogenolysis
- Gluconeogenesis
- Lipolysis
- Plasma fatty acids and glycerol

Negative feedback
Catecholamines

- Epi, NE, Ach, DA, glucagon
- Gs (ß1, ß2), Gi (α2), Gq (α1)
- adrenoreceptors are upregulated in the absence of stimulation and downregulated under continuous stimulation (eg. denervation supersensitivity vs continuous isoproterenol)
- adrenoreceptor responses to Cas are affected by gonadal steroids (eg. uterine contraction due to CAs in E2 vs P4 milieu)
- cortisol is permissive for cAMP metabolic and pressor effects
- T3 & sympathoadrenal activity
Catecholamines

- under stress blood glucose should be elevated for energy production by brain, heart, skeletal muscle
- Epi stimulates hepatic glycogenolysis (β receptor)
- muscle glycogen, lactic acid, liver (gluconeogenesis)
- Cas inhibit insulin / stimulate glucagon (β receptor)
- hypoglycemia stimulates adrenal Epi secretion by a CNS glucoreceptor (blocked by anesthetic in hypoth)
- Epi stimulates lipolysis by + HS-lipase and TG-lipase
- FFA used as energy source (glucose-sparing action)
- Epi decreases muscle proteolysis and aa release which might be of physiological importance to its short-term response associated with stress (β recept)

Glucocorticoids

- Facial tissues
- Adipose tissue
- Muscle and other tissues
- Liver
- Glucose uptake
- Amino acid uptake
- Lipolysis
- Protein breakdown
- Protein synthesis
- Gluconeogenesis

Stress → Circadian rhythm → Hypothalamus → CRH secretion → Anterior pituitary → ACTH secretion → Adrenal cortex → Cortisol secretion

Feedback loop: Many tissues → Glucose uptake, Amino acid uptake → Lipolysis → Protein breakdown → Gluconeogenesis
**Glucocorticoids**

**Effect of Cortisol on Organic Metabolism**

1. Basal concentrations are permissive for stimulation of gluconeogenesis and lipolysis in the postabsorptive state.

2. Increased plasma concentrations cause:
   a. Increased protein catabolism
   b. Increased gluconeogenesis
   c. Decreased glucose uptake by muscle cells and adipose tissue cells
   d. Increased triglyceride breakdown

**Net result:** Increased plasma concentrations of amino acids, glucose, and free fatty acids
Glucocorticoids

- increases gluconeogenesis by a genomic mechanism
- inhibits glucose transport thus decreases its utilization
- reduces aa use for protein formation except in the liver
- increases FA / glycerol mobilization from adipose depot

Zn fingers are binding regions of transcription factor proteins which attach to the promotor segment of DNA
**Glucocorticoids**

- Increase synthesis of gluconeogenic enzymes within hepatocytes (anabolic)
- Actions on skeletal muscle and adipose are catabolic (block glucose uptake, stimulate proteolysis, lipolysis, and promote FFA and glycerol mobilization)
- Glucose produced is either stored as glycogen or released into the blood
- Excessive secretion is antagonistic to insulin and promotes diabetes mellitus, an effect that is amplified since they reduce the affinity of certain cells for insulin, further aggravating the diabetes

**Metabolism**

- Nutrient molecules
- Oxidation
- Energy
- CO₂ + H₂O + NH₃
- ATP
- Heat
- Work: mechanical, chemical, transport
Absorptive State

Absorptive state
Absorption of small nutrients

Glucose
Liver, adipose tissue
Fatty acids
Liver
Amino acids

Glycerol

Liver, muscle

Liver, adipose tissue

Muscle, other cells

Most body cells
Catabolism

CO₂ + H₂O + energy

Glycogen
Triglycerides

Protein

Critical Points of Transition
Postabsorptive State