IX. Bioregulation of Feeding, Digestion, and Metabolism

- Bioregulation of Feeding
- Bioregulation of Digestion
- Bioregulation of Metabolism
- Pancrease
- Hormone Regulating metabolism
- Reading Assignment: textbook pp. 428-468

Bioregulation of Feeding (I)

- Feeding is regulated by a complex system of peptide hormones and neural factors
- Orexic agents: Bioregulators that stimulate appetite and feeding
- Anorexic agents: Bioregulators that inhibit appetite and feeding
- Orexic agents that stimulate feeding
  - Hypothalamic orexic agents:
    - **Neuropeptide Y (NPY)**: 36 amino acid residues
      - **NPY** gene encodes a neuropeptide that is widely expressed in the central nervous system and influences many physiological processes, including cortical excitability, stress response, food intake, circadian rhythms, and cardiovascular function. It functions through G protein-coupled receptors to inhibit adenylyl cyclase, activate mitogen-activated protein kinase (MAPK), regulate intracellular calcium levels, and activate potassium channels.
      - Repeated or continuous administration of NPY produces hyperphagia, weight gain and obesity; blocking NPY neuronal activity reduces hyperphagia
    - **Agouti-related protein (AgRP)**:
      - A paracrine signaling molecule with 132 amino acid residues. It is co-localized in NPY neurons and over expression can lead to obesity
Bioregulation of Feeding (II)

- Melanin-concentrating hormone (MCH): 19 amino acid residues
  - a cyclic amino acid orexinogenic hypothalamic peptide originally isolated from the pituitary gland of teleost fish where it controls skin pigmentation. It has been found that administration of MCH can elevate feeding. Furthermore, MHC knock out mice are hypophagic and are excessive lean
  - MCH actions through interacting with a G-protein coupled receptor to inhibit cAMP accumulation and stimulate intracellular calcium flux, and is probably involved in the neuronal regulation of food consumption.

- Endocannabinoid:
  - The endocannabinoid system refers to a group of neuromodulatory lipids and their receptors that are involved in a variety of physiological processes including appetite, pain-sensation, mood, and memory

- Ghrelin: A-28 amino acid peptide secreted from stomach, capable of binding to GH secretogogue receptor (GHS-1a) to cause release of GH from the pituitary gland. Plasma levels of ghrelin increase before mealtime and at night. It may be the hunger signal for the brain

- Galanin: 29-30 amino acid residues. Stimulates LH release from the pituitary gland, and stimulates craving for fatty foods

- Orexins: There are two orexins, hypocretin-1 and hypocretin-2. Stimulate feeding

Structure of Orexin A

- Orexin A (hypocretin-1), 33 amino acid residues
- Orexin B (hypocretin-2), 28 amino acid residues
- Orexin A and Orexin B are derived from the same prohormone
- Both orexin A and orexin B not only can stimulate appetite but also stimulate hormone release, gastrin secretion and affecting metabolic rates
- Orexin A and Orexin B are called hypocretin-1 and -2, both are synthesized in neurons in left hypothalamus and neurons in the gut
- Both orexin peptides bind to the two G-protein coupled receptors, OX₁ and OX₂ with Orexin-A binding to both OX₁ and OX₂ with approximately equal affinity while Orexin-B binds mainly to OX₂ and is 5 times less potent at OX₁
Ghrelin is a 28 amino acid peptide and hormone that is produced mainly by P/D1 cells lining the fundus of the human stomach epsilon cells of the pancreas that stimulates hunger.

- Ghrelin levels increase before meals and decrease after meals. It is considered the counterpart of the hormone leptin, produced by adipose tissue, which induces satiation when present at higher levels.
• Ghrelin is a potent stimulator of growth hormone from the anterior pituitary gland. Ghrelin binds to a G-protein coupled receptor, known as the growth hormone secretagogue receptor. Ghrelin binds to the GHSR1a splice-variant of this receptor which is present in high density in the hypothalamus, pituitary as well as vagal afferent cell bodies and vagal afferent endings throughout the gastro-intestinal tract.
• Ghrelin plays a significant role in neurotrophy, particularly in the hippocampus, and is essential for cognitive adaptation to changing environments and the process of learning. Recently, ghrelin has been shown to activate the endothelial isoform of nitric oxide synthase in a pathway that depends on various kinases including Akt.
• Ghrelin has emerged as the first identified circulating hunger hormone. Ghrelin and synthetic ghrelin mimetics (the growth hormone secretagogues) increase food intake and increase fat mass by an action exerted at the level of the hypothalamus.
• Reading assignment: Ghrelin

---

**Galanin and Galanin Receptor**

- **Galanin:**
  - Galanin is a neuropeptide encoded by the *GAL* gene, that is widely expressed in the brain, spinal cord, and gut of humans as well as other mammals. Galanin signaling occurs through three G-protein coupled receptors.
  - It is involved in the modulation and inhibition of action potential in neurons. Galanin has been implicated in many biologically diverse functions, including nociception, waking and sleep regulation, cognition, feeding, regulation of mood, regulation of blood pressure, it also has roles in development as well as acting as a trophic factor.

- **Galanin Receptor:**
  - Galanin receptor is a G-protein coupled receptor, or metabotropic receptor which binds galanin.
  - So far three subtypes are known to exist: **GAL-R1**, **GAL-R2**, and **GAL-R3**. The specific function of each subtype remains to be fully elucidated.
Bioregulation of Feeding (III)

- Inhibition of Feeding
  - There are numerous peptides that have been demonstrated to inhibit feeding and induce satiety. These are:
    - Cholecystokinin (pancreozymin; CCK): Produced in the I-cells in the mucosal epithelium of the small intestine to regulate digestion of fat and protein
    - Leptin: Isolated from the adipose tissue, a large peptide with 167 amino acids. It was discovered in mutant mice with ob/ob. Leptin binds to receptors in the hypothalamus that operate through a JAK – STAT pathway (i.e., through cytokine receptor). It may operate in part by blocking the orexic action of the peptide, ghrelin, in the brain. POMC (propiomelanocortin) neurons in the brain are associated with anorexia and have receptors for leptin. These neurons secret α-MSH which binds to MC4 receptor. Knockout mice for MC4 receptor gene exhibit obesity. POMC neurons co-express cocaine-amphetamine-regulated transcript (CART), a potent inhibitor of food intake, exhibit leptin receptors and may be mediators of leptin action
    - Neurotensin neurons also appear to be leptin targets and can stimulate neurons to that release CRH, a potent anorectic agent

Daily Pattern for Ghrelin and Laptin Levels in Blood

- Preproghrelin is cleaved to yield proghrelin which is then acylated by ghrelin O-acyltransferase to yield octanoyl ghrelin and decanoyl ghrelin. Only octanoyl ghrelin can bind to GH secretagogue receptor (GHS-1a) to exert its functions

- Secretion of ghrelin is inhibited by insulin, growth hormone (somatotropin), leptin, glucose, glucagon, and fatty acids. Secretion of ghrelin is stimulated by insulin-like growth factor-1 and muscarinic agonists.
- Ghrelin can also cause the release of GH from pituitary gland. Ghrelin level increases at meal-time and at night. It may be a hanger signal for brain
Actions of Leptin

- Leptin acts on receptors in the hypothalamus of the brain where it inhibits appetite by:
  - (1) counteracting the effects of neuropeptide Y (a potent feeding stimulant secreted by cells in the gut and in the hypothalamus)
  - (2) counteracting the effects of anandamide (another potent feeding stimulant that binds to the same receptors as THC [Tetrahydro-cannabinol])
  - (3) promoting the synthesis of α-MSH, an appetite suppressant. This inhibition is long-term, in contrast to the rapid inhibition of eating by CCK and the slower suppression of hunger between meals mediated by PYY3-36
- The absence of leptin (or its receptor) leads to uncontrolled food intake and resulting obesity. Several studies have shown that fasting or following a very-low-calorie diet (VLCD) lowers leptin levels
- It might be that, in the short-term, leptin is an indicator of energy balance. This system is more sensitive to starvation than to over-feeding; leptin levels change more when food intake decreases than when it increases. It might be that the dynamics of leptin due to an acute change in energy balance are related to appetite and eventually to food intake.
- Leptin interacts with six types of receptors (Ob-Ra–Ob-Rf, or LepRa-LepRf) which in turn are encoded by a single gene, \( \text{LEPR} \). Ob-Rb is the only receptor isoform that can signal intracellularly via the Jak-Stat and MAPK signal transduction pathways, and is present in hypothalamic nuclei

Molecular Action of Leptin in the Hypothalamus

Leptin binding to its receptor (Ob-Rb) induces activation of JAK, receptor dimerization, and JAK-mediated phosphorylation of the intracellular part of the receptor, followed by activation of STAT3. Activated STAT3 dimerizes, translocates into the nucleus and tans-activates target genes, including suppressor of cytokine signaling-3 (SOCS3), neuropeptide Y (NPY) and proopiomelanocortin (POMC). Leptin also activates PI3K, and phosphodiesterase 3B (PDE3B) and reduces cAMP levels in the hypothalamus, and that the PI3K–PDE3B–cAMP pathway interacting with the JAK2–STAT3 pathway constitutes a critical component of leptin signaling in the hypothalamus
Bioregulation of Digestion

• The GI tract secretes a variety of peptides that regulate digestion. Many of these peptides also have important roles in the nervous system and in the HP-system, e.g., Vasoactive intestinal peptide (VIP)
  - Secretin secreted from duodenal mucosa
  - Gastrin from the antral stomach to control acid secretion
  - Cholecystokinin (CCK) stimulates gallbladder secretion of bile into the gut
  - Pancreozymin stimulates enzyme secretion by the pancreas
  - GIP: glucose-dependent insulinotropic peptide
  - Motilin: stimulates migrating motor complex and cause intestinal contractions
  - Neurotensin: inhibits gastric acid secretion and motility
  - SST: Inhibits gastric acid secretion
  - VIP: Release arteriole smooth muscle and increase blood flow into intestine
  - Enteroglucagon: GLP-1, stimulates insulin release and inhibits glucagon release; anorexic

Vasoactive Intestinal Polypeptide (VIP)

• Vasoactive intestinal peptide also known as the vasoactive intestinal polypeptide or VIP is a peptide hormone containing 28 amino acid residues that is produced in many tissues of vertebrates including the gut, pancreas and suprachiasmatic nuclei of the hypothalamus in the brain
• Functions of VIP:
  ✓ VIP induces relaxation of lower esophageal sphincter, stomach, and gallbladder, stimulates secretion of water into pancreatic juice and bile, and causes inhibition of gastric acid secretion and absorption from the intestinal lumen.
  ✓ It also stimulates pepsinogen secretion by chief cells
  ✓ In the brain and some autonomic nerves (suprachiasmatic nuclei), VIP plays a key role in communication between individual brain cells within this region. Further, VIP is also involved in synchronising the timing of SCN function with the environmental light-dark cycle. Combined, these roles in the SCN make VIP a crucial component of the mammalian circadian timekeeping machinery.
  ✓ VIP helps to regulate prolactin secretion
  ✓ VIP has significant effects on the cardiovascular system
  ✓ VIP provokes vaginal lubrication in normal women
  ✓ GH-RH is a member of the VIP family and stimulates Growth Hormone secretion in the anterior pituitary gland.
Distribution of Endocrine Cells in the Gastrointestinal Tract and Pancreas

Table 12-1. Mammalian Regulators of Feeding and Digestion

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Number of amino acids</th>
<th>Cellular source</th>
<th>Primary function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrin</td>
<td>17, 34</td>
<td>Gastric G cell</td>
<td>Stimulates gastric acid secretion</td>
</tr>
<tr>
<td>Somatostatin (SS)</td>
<td>14, 28</td>
<td>Gastric D cell</td>
<td>Inhibits gastric acid secretion</td>
</tr>
<tr>
<td>Cholecystokinin (CCK)</td>
<td>8, 33, 39, 58</td>
<td>Intestinal L cell</td>
<td>Stimulates pancreatic enzyme secretion, gallbladder contraction, and bile release</td>
</tr>
<tr>
<td>CCK</td>
<td>27</td>
<td>Brain neurons</td>
<td>Laxative</td>
</tr>
<tr>
<td>Secretin</td>
<td>28</td>
<td>Intestinal S cell</td>
<td>Relaxes arteriole smooth muscle and increases blood flow to intestine</td>
</tr>
<tr>
<td>Vasoactive intestinal peptide (VIP)</td>
<td>43</td>
<td>Intestinal K cells</td>
<td>Stimulates insulin release in presence of glucose</td>
</tr>
<tr>
<td>Gliotoxin-dependent intramitopeptide (GIP)</td>
<td>36</td>
<td>Intestinal L cells (IG cells)</td>
<td>Stimulates migrating motor complex; causes intestinal contractions</td>
</tr>
<tr>
<td>Neuropeptide GLP-1</td>
<td>36</td>
<td>Intestinal N cells and neurons</td>
<td>May inhibit gastric acid secretion and motility</td>
</tr>
<tr>
<td>Neuropeptide NT (NT)</td>
<td>13</td>
<td>Intestinal N cells and neurons</td>
<td>Anorectic</td>
</tr>
<tr>
<td>Gastrin-releasing peptide (GRP)</td>
<td>27</td>
<td>Brain neurons</td>
<td>Stimulates gastric release</td>
</tr>
<tr>
<td>Calcitonin gene-related peptide (CGRP)</td>
<td>37</td>
<td>Gastric and intestinal neurons</td>
<td>May inhibit gastric secretion</td>
</tr>
<tr>
<td>Galanin</td>
<td>29/30</td>
<td>Brain neurons</td>
<td>May inhibit gastric acid secretion and motility</td>
</tr>
<tr>
<td>Peptide YY</td>
<td>36</td>
<td>Intestinal L cell</td>
<td>Analgesic</td>
</tr>
<tr>
<td>Peptide histidine-isoleucine (PHI)</td>
<td>27</td>
<td>Intestinal neurons</td>
<td>Released with VIP and may have some actions</td>
</tr>
<tr>
<td>Melanocortin-converting enzyme (MCH)</td>
<td>33</td>
<td>Brain neurons</td>
<td>Orexic</td>
</tr>
<tr>
<td>Neuropeptide Y (NPY)</td>
<td>36</td>
<td>Brain neurons</td>
<td>Orexic</td>
</tr>
<tr>
<td>Orexin A (Hyponorex N)</td>
<td>33</td>
<td>Brain neurons</td>
<td>Orexic</td>
</tr>
<tr>
<td>Orexin B (Hyponorex B)</td>
<td>28</td>
<td>Brain neurons</td>
<td>Orexic</td>
</tr>
<tr>
<td>Orexin C (Hyponorex C)</td>
<td>28</td>
<td>Brain neurons, visceral cells</td>
<td>Orexic</td>
</tr>
<tr>
<td>Prokinetic-releasing peptide (PKP)</td>
<td>31</td>
<td>Brain neurons</td>
<td>Anorexic</td>
</tr>
<tr>
<td>Leptin</td>
<td>167</td>
<td>Brain neurons, adipose cells</td>
<td>Anorexic</td>
</tr>
<tr>
<td>Melanocortin (a-MSH)</td>
<td>13</td>
<td>Brain neurons</td>
<td>Anorexic</td>
</tr>
</tbody>
</table>
The Human Digestive System

• In addition to the secretions of the GI epithelium, digestion is added by three exocrine glands: (i) salivary glands; (ii) the liver; and (iii) the exocrine pancreas
  ➢ Salivary gland: secretes saliva containing salts and salivary amylase
  ➢ Liver and pancreas secret enzyme and other substances into intestine (for details see Table 12-1)
• GI peptide secreting cells are derived from the neural crest cells during embryonic development
• Neural control of gastric secretion occurs at two levels:
  ➢ (i) Cephalic phase: stimulation of secretion via parasympathetic discharges by the same stimuli that cause salivation
  ➢ (ii) Gastric phase: the presence of food in the stomach elicits secretion through vago-vagal reflexes and/or through the gastrin mechanism. Neural factors can stimulate secretion of a hormone produced in the gastric epithelium that stimulates certain aspects of gastric secretion
  ➢ Edkins, in 1905, discovered that extracts prepared from the most posterior portion of the stomach, the antrum, stimulated acid secretion by the gastric glands

Gastrin and Acid Secretion

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Residues</th>
<th>Sequence</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human gastrin II</td>
<td>17</td>
<td>EEPLW Y</td>
<td>W M D F-NH₂</td>
</tr>
<tr>
<td>Caerulein</td>
<td>10</td>
<td>QQU Y T</td>
<td>W M D F-NH₂</td>
</tr>
<tr>
<td>CCK₄</td>
<td>8</td>
<td>D Y M</td>
<td>W M D F-NH₂</td>
</tr>
</tbody>
</table>

• There are three forms of gastrins in human: gastrin I (17 amino acids), gastrin II (with a sulfate group attached at position 6 near the C-terminus) and big gastrin (consists of gastrin I or gastrin II plus a different 17 amino acid peptide component)
• The prehormone of gastrin is a peptide of 104 amino acid residues, after processing big gastrin and small gastrin will be released
• The biological activities of gastrin resides on the four carboxyl-terminal amino acids consisting of Trp-met-Asp-Phe-NH₂
• Gastrin receptor is a G-protein coupled receptor that works through IP₃ and phospholipase C to cause activation of H⁺-ATPase and secretion of H⁺
• SST (somatostatin) released by D-cells in the antrial stomach will inhibit the release of gastrin
Neurocrine, Endocrine and Paracrine Mechanism Controlling Acid Secretion by the Stomach

Entergastrones

- Peptides released from small intestine that inhibit acid secretion in the stomach
- Several peptides secreted by the small intestine may be candidates as enterogastrones with by evoking SST release or through more direct inhibitory action
Gastrin Releasing Peptide

- GRP (gastrin releasing peptide) stimulates the release of **Gastrin** from the G cells of the stomach. The gene that GRP is derived encodes a number of bombesin-like peptides. The preproGRP contains 148 amino acid residues, following cleavage of the signal peptide, it is further processed to produce a 27-amino acid gastrin-releasing peptide and a 10-amino acid neuromedin C. These smaller peptides regulate numerous functions of the gastrointestinal and central nervous systems, including release of gastrointestinal hormones, smooth muscle cell contraction, and epithelial cell proliferation
- In stomach, GRP works as paracrine. In addition to regulate the release of gastrin, GRP also stimulates the release of pancreatic enzymes, contraction of gastric, intestinal and gallbladder smooth muscle, and release of several gastrointestinal and pancreatic hormones
- GRP also produces mitogenic effects resulting hyperplasia of pancreatic, intestinal, and other tissues
- It has been suggested that GRP plays multiple roles in modulating GI physiology

Secretion of Pepsinogen

- The major gastric enzyme in adult human is protease pepsin, that is secreted by the chief cells of the gastric mucosa
- Pepsinogen is the inactive form of pepsin. Activation of pepsinogen to pepsin takes place under excess H+ supplies by parietal cells
- The optimal pH for pepsin activity is between pH 1-2. When pH is above 4.5, pepsin is inactive
- Release of pepsinogen is triggered by parasympathetic stimulation via the vagus nerve causes release of pepsinogen
- Gastrin can cause the release of pepsinogen only when it is applied in doses large enough to inhibit acid secretion by the parietal cells, implying that gastrin is not normal factor cause release of pepsinogen
- Several other GI peptides can invoke pepsinogen release but do so only in applying pharmacological doses
- But motilin can cause the release of pepsinogen under physiological condition and SST inhibits the release
Motilin

- Motilin is a 22-amino acid polypeptide hormone in the motilin family that, in humans, is encoded by the *MLN* gene. It is secreted by endocrine M cells (these are not the same M cells that are in Peyer's patches) that are numerous in crypts of the small intestine, especially in the duodenum and jejunum.
- The amino acid sequence of motilin is: Phe-Val-Pro-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Met-Gln-Glu-Lys-Glu-Arg-Asn-Lys-Gly-Gln. It is unrelated to other hormones.
- Motilin receptors are found in the gastrointestinal tract of human, pigs, rats, cows, and cats, and in the central nervous system of rabbits.
- Functions of motilin:
  ✓ The main function of motilin is to increase the migrating myoelectric complex component of gastrointestinal motility and stimulate the production of pepsin.
  ✓ Motilin is also called "Housekeeper of the gut" because it improves peristalsis in the small intestine and clears out the gut to prepare for the next meal. A high level of motilin secreted between meals into the blood stimulates the contraction of the fundus and antrum and accelerates gastric emptying. It then contracts the gallbladder and increases the squeeze pressure of the lower esophageal sphincter. Other functions of motilin include increasing the release of pancreatic polypeptide and somatostatin.

Regulation of Intestinal Digestion

- Three phases of intestinal regulation can be identified:
  ✓ Cephalic phase of intestinal regulation: vagal stimulation that influence pancreatic secretion
  ✓ Gastric phase of intestinal regulation: vagal and vago-vagal stimulation gastric of gastrin that appears to influence pancreatic secretion
  ✓ Intestinal phase: relies primarily on release of peptides simulated directly by the composition of the intestinal content
- Secretin: 27 amino acid residues, chemically related to several peptides of PACAP family. The receptor is a G-protein coupled receptor and work through cAMP
- Cholecystokinin (CCK): I-cell in the intestinal mucosa secrets CCK. It is derived from a 33 amino acid peptide called pancreozymin-cholecystokinin (PZCCK). It functions together with secretin to release enzymes from pancreas.
Mammalian Pancreas

- The pancreas is a glandular organ of the digestive system and endocrine system of vertebrates. It produces several important hormones such as insulin, glucagon, somatostatin, and pancreatic polypeptide, and pancreatic digestive enzymes for the small intestine. The digestive enzymes help to break down the carbohydrates, proteins, and lipids in the chyme.

- Endocrine: Islet of Langerhans - secretes insulin, glucagon, somatostatin (SST), and pancreatic polypeptide (PP)

Mouse islet cells:
- B cells: producing insulin (stained green in this picture)
- A cells: producing glucagon (stained red in this picture)
- D cells: producing SST
- PP cells: producing pancreatic peptide, may play a role in post-absorptive metabolism

Comparison of Islets of Rat and Human

Size her resolutions
Discovery of Insulin

- Islet cells in the pancreas were first observed by a German scientist Paul Langerhans.
- Insulin was discovered by Frederick Banting and Charles Best. They started to work on the identification of insulin in 1921, and Bertran Collip joined the team in 1922 to purify insulin for conducting clinical studies.
- In 1923, Banting and Macleod were awarded with the Nobel Prize in Physiology or Medicine for the discovery of insulin.
- At the end, the money of the prize were shared among Banting, Best, Macleod and Collip.

Assigned Reading: Nobel Prize Lecture delivered by Frederick Banting in 1923

Prepro-insulin and Insulin

[Diagram showing the process of prepro-insulin transformation into mature insulin]
Actions of Insulin (I)

- Insulin is a hypoglycemic hormone
- Insulin is bioassayed \textit{in vitro} for its ability to stimulate uptake of glucose from the medium into muscle cells
- Glucose Tolerance Test: A standard assay to measure the ability of the pancreas to secret insulin. The assay is conducted as the following: following a period of fasting, a glucose load is administered orally or intravenously, and its rate of disappearance from the blood is measured. Results of this test could indicate whether the person is a diabetic mellitus

<table>
<thead>
<tr>
<th>Subject Status</th>
<th>Venous glucose levels (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fasting</td>
</tr>
<tr>
<td>Normal person</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Probable diabetes</td>
<td>100-120</td>
</tr>
<tr>
<td>Diabetic</td>
<td>~100</td>
</tr>
</tbody>
</table>

Actions of Insulin (II)

- Binding of insulin to its receptor, there is an increase of the transport glucose, amino acids, fatty acids, nucleotides, and various ions into the target cell
- Increase of anabolic pathways and decrease of catabolic pathways
- Cellular growth is stimulated via nuclear transcription and protein synthesis through interaction between insulin and IGFs
- Insulin stimulates uptake of glucose via activating GLUT 4 (a protein responsible facilitated diffusion of glucose from the blood). Insulin facilitates transport of glucose into muscle and fat cells, and transport of amino acids into muscle cells
- Insulin enhances the activity of hexokinase which stimulates glucose oxidation and favor lipogenesis in adipose tissue and protein synthesis in muscle
- Insulin prevents breakdown of glycogen (glycogenolysis) and enhances glycogen synthesis following uptake of glucose in muscle and liver (details see next slide). This is achieved by simultaneous inhibition of the cAMP dependent enzyme phosphorylase A and activation of the enzyme glycogen synthetase
Actions of Insulin (III)

- Glucose oxidation increases the intracellular pools of precursors for fat synthesis such as glycerol, acetyl-CoA and fatty acids.
- In addition to indirectly enhancing esterification by stimulating acylglycerol synthetase, insulin inhibits triglycerol lipase and prevent lipolysis in adipose tissue. This reduces release of NEFAs (non-esterified fatty acids) and monoacylglycerol into the blood and reduces hepatic fatty acid oxidation and ketogenesis.
- The actions of insulin on adipose tissue and lipid metabolism are marked in carnivores but not obvious in herbivores.
- The increase in intracellular glucose-6-phosphate and amino acids in both liver and muscle cells promotes protein, lipid and glycerol synthesis. These are important actions of insulin immediately following ingestion of meal and the entry of large quantities of digestive products such as glucose and amino acids into the blood.

Effect of insulin on glucose uptake and metabolism: Insulin binds to its receptor (1), which starts many protein activation cascades (2). These include translocation of Glut-4 transporter to the plasma membrane and influx of glucose (3), glycogen synthesis (4), glycolysis (5) and fatty acid synthesis (6).
Actions of Insulin

1. Pathways signaling through IP3 kinase and phosphatidylinositol-triphosphate (IP3 kinase and protein kinase B/Akt)
2. Mitogen-activated protein kinase (MAP Kinases)
3. Possible interaction via kinases not coupled to IRS (insulin receptor substrates)
Activation of PKB/Akt by Insulin

Akt, also known as Protein Kinase B (PKB), is a serine/threonine protein kinase that plays a key role in multiple cellular processes such as glucose metabolism, cell proliferation, apoptosis, transcription and cell migration.

The Central Role of Akt

Assigned Reading:
1. Insulin mechanism of action
2. Molecular basis of type-2 diabetes
Summary of Mechanism of Insulin Action

Types of Diabetes

- **Type I Diabetes**: Due to autoimmune-mediated destruction of pancreatic beta cells, resulting in insulin deficiency. Patients with type-1 diabetes amounts to nearly 10% of all diabetes cases.
- **Type 2 Diabetes**: Characterized by impaired insulin action and/or abnormal insulin secretion. Type-2 diabetes accounts for approximately 90% of all diabetes cases.
- An early abnormality of type 2 diabetes is insulin resistance (i.e., glucosr intolerance): a defective state in which insulin is unable to exert its biological effects at circulation concentrations that are effective in normal subjects.
- At the pre-onset of type-2 diabetes, resistance to glucose-lowering action of insulin, tends to lead a slight increase of blood glucose concentration, which stimulates insulin secretion and cause hyperinsulinemia. Initially, hyperinsulinemia is able to overcome insulin resistance. When insulin secretion is no longer be able to compensate insulin resistance, the state of hyperglycemia becomes apparent (diabetes state).
- It is now accepted defective post-receptor insulin signaling is the cause of insulin resistance in type-2 diabetes.
Is C-Peptide of Pro-Insulin Biologically Active?

- C-Peptide: a short 31-amino-acid protein that connects insulin’s A-chain to its B-chain in the pro-insulin molecule
- The first documented use of the C-peptide test was in 1972, in which it was used to determine the level of insulin
- During the past decade, however, C-peptide has been found to be a bioactive peptide in its own right, with effects on micro-vascular blood flow and tissue health
- C-peptide has been shown to bind to the surface of a number of cell types such as neuronal, endothelial, fibroblast and renal tubular, at nanomolar concentrations. The receptor is a G-protein coupled receptor
- The signal activates Ca^{2+}-dependent intracellular signaling pathways such as MAPK, PLCγ, and PKC, leading to upregulation of a range of transcription factors as well as eNOS (endothelial nitric oxide synthetase) and Na^{+}/K^{+}-ATPase activities
- The latter two enzymes are known to have reduced activities in patients with type I diabetes and have been implicated in the development of long-term complications of type I diabetes such as peripheral and autonomic neuropathy

Glucagon

- Glucagon is a hyperglycemic hormone. It is a single chain polypeptide with 29 amino acid residues (MW 3985 Daltons)
- Pro-glucagon is a protein of 160 amino acid residues, after processing gives rise to GRPP, GLP-1 GLP-2, oxyntomodulin and glucagon

```
NWt-Mis-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys--
1 2 3 4 5 6 7 8 9 10 11 12
Tyr-Leu-Asp-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-
13 14 15 16 17 18 19 20 21 22 23 24 25
Leu-Met-Asn-Thr-COOH
26 27 28 29
```

Mature Glucagon
Processing of Pro-glucagon in Pancreas and Small Intestine

- GRPP: glucagon related peptide
- GLP-1 and GLP-2: glucagon related peptide
- Oxyntomodulin: a naturally occurring 37-amino acid peptide hormone

---

Oxyntomodulin

- Oxyntomodulin is a naturally occurring 37-amino acid peptide hormone found in the colon, produced by the oxyntic (fundic) cells of the oxyntic (fundic) mucosa. It has been found to suppress appetite. A recent study has found that it can be used as a weight loss treatment.

- The mechanism of action of oxyntomodulin is not well understood. It is known to bind both the GLP-1 receptor and the glucagon receptor, but it is not known whether the effects of the hormone are mediated through these receptors or through an unidentified receptor.
Actions of Glucagon on Target Tissues

- Glucagon promotes glycogenolysis in liver cells in order to raising circulating glucose levels
- It is mediated through stimulation of adenylyl cyclase and production of intracellular cAMP and activation of phosphoylase-a
- Increased glycogenolysis is accompanied by decreased intracellular oxidation of glucose and directs the movement of glucose from liver cells into the blood
- Lipolysis is stimulated by glucagon in fasting animals through activation of hormone-dependent lipase (triglycerol lipase) in adipose tissues
- The release of NEFAs (none essential fatty acids) into the blood further increase β-oxidation followed by ketogenesis and gluconeogenesis in the liver
- Glucagon also increases levels of PEPCK, the critical enzyme in gluconeogenesis in liver cells

Example: Action of Glucagon in the Liver
How is homeostasis of glucose in the body of humans maintained?

How Do Insulin and Glucagon Regulate the Homeostasis of Glucose in the Blood

- **Insulin**: Stimulate glucose and amino acid uptake from the blood to various tissues; coupled with stimulation of anabolic processes (or synthetic reactions) such as glycogen, protein and lipid synthesis
- **Glucagon**: Causing release of glucose from glycogen, release of fatty acid from stored triglycerides and stimulation of gluconeogenesis
Glycogenesis and Glycogenolysis

Reading Assignment IX

1. Frederik G. Banting Nobel Prize lecture
2. AKT
3. Glucagon
4. Leptin
5. Molecular basis of type -2 diabetes
6. Molecular mechanism of insulin action