THE PANCREAS

Figure 11.26
The pancreas and the associated pancreatic islets (islets of Langerhans).


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Prof M Haag
NB: Exocrine fx
Endocrine fx
(Islands of Langerhans)

Cell types:
Alpha (α): glucagon
Beta(β): insulin
Delta(δ): somatostatin
Phi (θ): serotonin
Insulin Synthesis

Preproinsulin

Endoplasmic reticulum

"Folded" proinsulin

Secretion granule

Converting enzymes

Ganong, WF. Review of Medical Physiology. 21st rd. Fig 19-4 p339: Biosynthesis of insulin. Lange Medical books
INSULIN

Secreted as prepro- and prohormone, C peptide used diagnostically

**Regulation:** ↑ blood glucose

(Sensed by the Glucose sensor in the beta cells: GLUT-2 (low Affinity) and hexokinase)

↑ amino acids

↑ fatty acids, ketones

↑ parasympathetic stimulation

↑ intestinal glucagon

↓ sympathetic stimulation

↓ somatostatin
SECRETION PROCESS

(a) Beta cell at rest
1. Glucose in blood
7. No insulin secretion
2. Metabolism slows
3. ATP
4. K$_{ATP}$ channel open
5. Cell at resting membrane potential
6. Voltage-gated Ca$^{2+}$ channel closed

(b) Beta cell secretes insulin
8. Ca$^{2+}$ entry triggers exocytosis of insulin
1. Glucose in blood
GLUT transporter (GLUT 2)
2. Metabolism increases
3. ATP
5. Less K$^+$ leaves cell
4. K$_{ATP}$ channel closed
6. Cell depolarizes
7. Ca$^{2+}$ channel opens

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INSULIN ACTION MECHANISM
INSULIN CAN ALTER GENE ACTIVITY

**Figure 1–46.** One of the direct pathways by which growth factors alter gene activity. TK, tyrosine kinase domain; Grb2, Ras activator controller; Sos, Ras activator; Ras, product of the *ras* gene; MAP K, mitogen-activated protein kinase; MAP KK, MAP kinase kinase; TF, transcription factors. There is cross talk between this pathway and the cAMP pathway, as well as cross talk with the IP₃-DAG pathway.
Recruitment of intracellular GLUT4
General pathway for GLUT4 translocation

**Fig. 1.** General insulin signalling pathway leading to GLUT-4 translocation: insulin (green) binds to the insulin receptor (red), activating its tyrosine kinase activity. The activated insulin receptor tyrosine kinase phosphorylates IRS-1 on tyrosine residues allowing for the recruitment of the p85/p110 phosphatidylinositol 3' kinase (PI3K) to the plasma membrane. Activation and/or recruitment of PI3K generates PI(3,4,5)P_3 from PI(4,5)P_2, thereby recruiting the 3' phosphoinositide-dependent kinase-1 (PDK-1). PDK-1 phosphorylates and activates both protein kinase B (PKB/Akt) and the atypical PKC λ/ζ (αPKCs). PKB and the atypical PKCs promote GLUT-4 translocation by an as yet unknown downstream signalling pathway.
Fig. 2. Hypothesized additional pathway necessary for the insulin stimulation of GLUT-4 translocation: insulin (green) binds to the insulin receptor (red) located in caveolae/lipid rafts in the plasma membrane. Flotillin (F), located in the caveolae/lipid rafts, binds the Cbl associated protein (CAP). CAP targets Cbl to the lipid raft domains and the tyrosine phosphorylated Cbl recruits the CrkII/C3G complex. C3G, a guanine nucleotide exchange factor, exchanges GDP for GTP on TC10. Activated, GTP bound TC10 can now participate in GLUT-4 translocation, through modification of cortical actin or stimulating actin polymerization on GLUT-4 compartments.
Action of insulin on Glut4 and FAT

Functions: NB ANABOLIC!

A. Regulation of carbohydrate metabolism

1. Promotes glucose transport via GLUT-4 into muscle and fat tissue **THUS:** [blood glucose] ↓

2. Depresses gluconeogenesis in the liver via expression of glucose-6-phosphatase

3. Activates cAMP phosphodiesterase, decreases cAMP

4. Activates Ser/Thr phosphatases

5. Increases glycogenesis in liver and muscle (via decreased phosphorylation of glycogen synthase)

6. Decreases glycogenolysis (decreased cAMP)
GS = Glycogen synthase
HSL = Hormone sensitive lipase
GP = Glycogen phosphorylase

Adrenalin Glucagon cAMP Prot Kinases

Insulin Phosphatases

GS Inact → P

HS L Act → P

GP Act → P

GS act

HS L inact

GP inact
Regulation of fat and protein metabolism

- Promotes fatty acid uptake via FABP into fat & muscle cells
- Increases fat synthesis (Ac CoA carboxylase expression/phosphorylation?)
- Decreases lipolysis via decreased cAMP
- Promotes amino acid uptake
- Promotes growth
- Modulates specific protein expression

Other:
- Promotes cellular K⁺ uptake via synthesis/activation of the Na⁺,K⁺-pump
Effect of insulin on the overall flow of fuels

Berne RM, Levy MN. Principles of Physiology 1990; The C. V. Mosby Company; 11830 Westline Industrial Drive, St. Louis, Missouri 63146; pp 508
Metabolic effects of insulin deficiency

Normal: Glucose

DM: Ketones

Fatty acids
Metabolic effects of insulin deficiency 2

- Glucose in cells ↓
- Cells use fatty acids for energy instead
- Fat breakdown products accumulate in blood

- AcetylCoA + AcetylCoA (2+2C)
  - Aceto-acetic acid
  - Beta-hydroxy butyric acid
  - Acetone
    - 2H
    - -CO₂

Leads to keto-acidosis, blood pH ↓ coma
GLUCAGON

29 amino acids, from preproglucagon

Figure 5-9 Compounds derived from preproglucagon. GLP-1, Glucagon-like peptide-1; GLP-2, glucagon-like peptide-2; G, glucagon; GRPP, glucagon-related polypeptide; SP, signal peptide.

Of circulating glucagon only 30-40% from the liver
GLUCAGON

Control of secretion (α-cells)

+ 

- low blood glucose
- increased amino acids (Arg, Ala)
- bacterial pyrogens
- cholecystokinin
- Sympathetic stress, exercise
- Parasympathetic

- somatostatin
- insulin
- increase in blood glucose
**Function: via cAMP**

- ↑glycogenolysis – phosphorylase in liver
- ↑gluconeogenesis – fructose-6-phosphatase
- ↑Lipolysis - hormone-sensitive lipase
- ↑amino acid uptake by liver – GNG
- ↑Beta oxidation and ketogenesis
- ↑Urea synthesis in the liver

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*Figure 37-7  Effect of glucagon on the overall flow of fuels. Tissue release of glucose, free fatty acids, and ketoacids raises their plasma levels, whereas liver uptake of amino acids lowers their plasma levels.*

*Berne RM, Levy MN. Principles of Physiology 1990; The C. V. Mosby Company; 11830 Westline Industrial Drive, St. Louis, Missouri 63146; pp 512*
Figure 17-13. Cascade of reactions by which epinephrine activates phosphorylase. Glucagon has a similar action in liver but not in skeletal muscle.
7–31. Mechanism by which the activity of the hormone-sensitive lipase in adipose tissue.
## HORMONES THAT INFLUENCE BLOOD GLUCOSE LEVELS

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Effect</th>
<th>Action</th>
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<tr>
<td>Insulin</td>
<td>↓</td>
<td>Glucose transport into cells</td>
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<tr>
<td>Adrenalin</td>
<td>↑</td>
<td>Glycogenolysis</td>
</tr>
<tr>
<td>Glucagon</td>
<td>↑</td>
<td>Glycogenolysis</td>
</tr>
<tr>
<td>Cortisol</td>
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<td>Somatotropin</td>
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<tr>
<td>Thyroxin</td>
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<td>Duodenal glucose uptake</td>
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