Insulin and the brain

Mary ET Boyle, Ph. D.
Department of Cognitive Science
UCSD
“How long will the patient live?” was the only question to ask until a series of discoveries beginning with Langerhans’ description of pancreatic islets changed the lives of people with diabetes (1). Twenty years later, in 1889, pancreatic secretions were shown to control blood sugar levels; however, it took another 30 years until insulin was purified from the islets before patients could ask about the “quality of their life with insulin.”

For the next 50 years clinicians and scientists revealed the system-wide effects of insulin in liver, muscle, and adipose tissues, and recent work reveals insulin’s effect on longevity and the central nervous system. In the 1970s, the insulin receptor was discovered, and 10 years later the demonstration of its tyrosine kinase activity pointed us toward the mechanism of signal transduction (2). Remarkably, this steady progress has not stemmed the worldwide diabetes epidemic that will take a huge toll in premature morbidity and mortality in this new century (3).
Figure 27.15 Insulin secretion. The electron micrograph shows the release of insulin from a pancreatic β cell. One secretory granule is on the verge of fusing with the plasma membrane and releasing insulin into the extracellular space, and the other has already released the hormone. [Courtesy of Dr. Lelio Orci. L. Orci, J.-D. Vassalli, and A. Perrelet. Sci. Am. 259 (September 1988):85–94.]

**Diabetes**

Named for the excessive urination in the disease. Aretaeus, a Cappadocian physician of the second century A.D., wrote: “The epithet diabetes has been assigned to the disorder, being something like passing of water by a siphon.” He perceptively characterized diabetes as “being a melting-down of the flesh and limbs into urine.”

**Mellitus**

From Latin, meaning “sweetened with honey.” Refers to the presence of sugar in the urine of patients having the disease. *Mellitus* distinguishes this disease from diabetes *insipidus*, which is caused by impaired renal reabsorption of water.

TABLE 27.2 Fuel metabolism in starvation

<table>
<thead>
<tr>
<th>Fuel exchanges and consumption</th>
<th>Amount Formed or Consumed in 24 Hours (grams)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3d day</td>
</tr>
<tr>
<td><strong>Fuel use by the brain</strong></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>100</td>
</tr>
<tr>
<td>Ketone bodies</td>
<td>50</td>
</tr>
<tr>
<td>All other use of glucose</td>
<td>50</td>
</tr>
<tr>
<td><strong>Fuel mobilization</strong></td>
<td></td>
</tr>
<tr>
<td>Adipose-tissue lipolysis</td>
<td>180</td>
</tr>
<tr>
<td>Muscle-protein degradation</td>
<td>75</td>
</tr>
<tr>
<td><strong>Fuel output of the liver</strong></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>150</td>
</tr>
<tr>
<td>Ketone bodies</td>
<td>150</td>
</tr>
</tbody>
</table>

Cross-section of the pancreas

Pancreatic duct

Exocrine (out)
Acinar cells secrete pancreatic enzymes into pancreatic duct

Endocrine (in)
Islets of Langerhan cells secrete hormones into blood vessels
Pancreas basics

- α-cells: glucagon
- β-cells: insulin, amylin
- δ-cells: somatostatin
- ε-cells: pancreatic polypeptide
- F-cells: ghrelin

Cell types in the islets of Langerhans:

<table>
<thead>
<tr>
<th>Cell</th>
<th>Hormone</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-cells (15%)</td>
<td>glucagon</td>
<td>stimulate gluconeogenesis and release of glucose into blood stream</td>
</tr>
<tr>
<td>β-cells (75%)</td>
<td>insulin &amp; amylin</td>
<td>responsible for decreasing blood glucose levels and satiety (insulin 100:amylin 1)</td>
</tr>
<tr>
<td>δ-cells (5%)</td>
<td>somatostatin</td>
<td>inhibition of insulin and glucagon secretion</td>
</tr>
<tr>
<td>ε-cells (&lt;1%)</td>
<td>ghrelin</td>
<td>stimulating appetite hormone</td>
</tr>
<tr>
<td>F-cells (&lt;5%)</td>
<td>pancreatic polypeptide</td>
<td>self-regulate exocrine and endocrine pancreatic secretions</td>
</tr>
</tbody>
</table>

Insulin and glucagon are complementary

Insulin reduces blood glucose levels by activating glucose transporters (GLUT) enabling the uptake of glucose in:
# Tissue Distribution of glucose transporters

<table>
<thead>
<tr>
<th>Name</th>
<th>Tissue location</th>
<th>$K_M$</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLUT1</td>
<td>All mammalian tissues</td>
<td>1 mM</td>
<td>Basal glucose uptake</td>
</tr>
<tr>
<td>GLUT2</td>
<td>Liver and pancreatic β cells</td>
<td>15–20 mM</td>
<td>In the pancreas, plays a role in the regulation of insulin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>In the liver, removes excess glucose from the blood</td>
</tr>
<tr>
<td>GLUT3</td>
<td>All mammalian tissues</td>
<td>1 mM</td>
<td>Basal glucose uptake</td>
</tr>
<tr>
<td>GLUT4</td>
<td>Muscle and fat cells</td>
<td>5 mM</td>
<td>Amount in muscle plasma membrane increases with endurance training</td>
</tr>
<tr>
<td>GLUT5</td>
<td>Small intestine</td>
<td>—</td>
<td>Primarily a fructose transporter</td>
</tr>
</tbody>
</table>

Actions of glucagon:

After glucagon binds to its receptors on the liver cells, there is an increase in cyclic-AMP within hepatocytes. Cyclic-AMP activates a cascade of enzymes degrading glycogen into glucose.

Glycogenolysis = breakdown of glycogen
Gluconeogenesis = synthesis of glucose from amino acids in the liver

Glucose Tolerance Test:

Insulin deficiency

Glucose entry is blocked

Cells utilize their own stores of glycogen

Fat

Protein

Excessive fatty acid utilization leads to formation of ketone bodies by liver

Ketone bodies

Hyperphagia

Kidney tubules cannot reabsorb the excess filtered glucose. The extra glucose spills over in urine (glycosuria). The excess glucose causes osmotic diuresis (polyuria). Polyuria reduces plasma water, leading to excessive thirst (polydipsia).
Historically, there was little interest in insulin and the brain because:

“unlike [skeletal muscle], the brain does not require insulin to take up glucose

brain was considered to be insulin independent

insulin was considered too large to cross the blood brain barrier”

Innervation of islet of Langerhans

“From the large nerve trunk at one pole of the islet emerges the peri-insular plexus, the peri-insular ganglia (p.i.g.), and the “neural terminal” net in and around the islet.

The neural terminal is said to be composed of nerve fibers and interstitial Cajal’s cells (in black).

Part of the islet has been excised to show the interior structure of the islet. c capillary, 800.”

Image adapted from Honjin, 1956; courtesy of John Wiley & Sons, Inc

Nervous system divisions:

- Central Nervous System
- Peripheral Nervous System
  - Autonomic Nervous System
    - Parasympathetic nervous system
    - Sympathetic nervous system
    - Enteric nervous system
  - Slowly activated dampening system

Quick response mobilizing system
Autonomic Nervous System Control of insulin release:

Para sympathetic → Lateral hypothalamus

Vagus nerve

Parasympathetic

Celiac ganglion

Sympathetic nerve

Superior mesenteric ganglion

Ventromedial hypothalamus

Parasympathetic nerve input: B F A D

ACh: acetylcholine
GRP: gastrin releasing polypeptide
VIP: vasoactive intestinal polypeptide
PACAP: pituitary adenylate cyclase activating polypeptide

Parasympathetic nerve input:

- **ACh:** acetylcholine
- **GRP:** gastrin releasing polypeptide
- **VIP:** vasoactive intestinal polypeptide
- **PACAP:** pituitary adenylate cyclase activating polypeptide

- **ACh** – insulin release
- **VIP & PACAP** – glucose dependent insulin release
- **GRP** – may be involved in neuro regulation

- **ACh** – releases: glucagon somatostatin
- **PP** – is released by parasympathetic activity

Vagus Nerve stimulation


**ACh:** acetylcholine  
**GRP:** gastrin releasing polypeptide  
**VIP:** vasoactive intestinal polypeptide  
**PACAP:** pituitary adenylate cyclase activating polypeptide
Sympathetic nerve input:

NPY: Neuropeptide Y
NA: Noradrenalin

Sympathetic nerve input:

**β**
- NA – inhibits glucose dependent insulin release
- NPY & Galanin– inhibit insulin release

**α,F**
- NA– releases glucagon and PP

**δ**
- NA – inhibits somatostatin release

NA: Noradrenaline
NPY: Neuropeptide Y

Other & sensory nerve input: B F A D

Other nerve
CCK
NO

CCK: cholecystokinin
NO: nitric oxide
SP: Substance P
CGRP: Calcitonin gene-related polypeptide

Sensory nerve
CGRP
SP

CGRP: Calcitonin Gene-related peptide
SP: Substance P

Sensory nerve input:

- CGRP– inhibits insulin release
- CGRP – involved with Amylin
- SP – reported to increase and decrease insulin secretion

CGRP– stimulated glucagon release

Sensory nerve stimulation

CGRP is thought to exert a tonic inhibition of insulin secretion.

Other nerve input:

- CCK–stimulates insulin release
- NO– inhibition of NO-synthase inhibits insulin release (mice)
- Entero-pancreatic neuro regulation from the duodenum

CCK: Cholecystokinin
NO: Nitric Oxide

Review

**Autonomic regulation of islet hormone secretion – Implications for health and disease**

B. Ahrén

Department of Medicine, Lund University, Malmö, Sweden

Relationships Between the Autonomic Nervous System and the Pancreas Including Regulation of Regeneration and Apoptosis

Recent Developments

Takayoshi Kiba, MD, PhD

Kiba, T. Pancreas • Volume 29, Number 2, August 2004