Insulin and the brain

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“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 Orsi, 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>

**Pancreas basics**

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

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</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</td>
</tr>
<tr>
<td>ε-cells (&lt;1%)</td>
<td>ghrelin</td>
<td>stimulating appetite</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:

- **β-cells**
- **Glucose sensor (GLUT2)**
- **Insulin receptor**
- **Insulin**

## 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 most tissues, the brain does not require insulin to take up glucose

brain was considered to be insulin dependent

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.”

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
Autonomic Nervous System Control of insulin release:

Para sympathetic

Lateral hypothalamus

Ventricular hypothalamus

Sympathetic

Parasympathetic

Celiac ganglion

Superior mesenteric ganglion

Parasympathetic

Sensory

Sympathetic

Islets

Insulin/Amylin

Pancreatic Polypeptide

Glucagon

Somatostatin

Parasympathetic nerve input:

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

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Parasympathetic nerve input:

- 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

β

A, δ

α

F

Vagus Nerve stimulation

GLUT2

Sympathetic nerve input:

NA
NPY
Galanin

NPY: Neuropeptide Y
NA: Noradrenalin

Sympathetic nerve input:

- NA – inhibits glucose dependent insulin release
- NPY & Galanin– inhibit insulin release
- NA – releases glucagon and PP
- NA – inhibits somatostatin release

NA: Noradrenaline
NPY: Neuropeptide Y

Other & sensory nerve input:

Sensory nerve

CGRP
SP

Other nerve
CCK
NO

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

Sensory nerve input:

- **β**
  - CGRP—inhbits insulin release
  - CGRP—involved with Amylin
  - SP—reported to increase and decrease insulin secretion

- **α**
  - CGRP—stimulates glucagon release

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

CCK: Cholecystokinin
NO: Nitric Oxide

Other nerve input:

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

Other nerve stimulation

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