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 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>
<thead>
<tr>
<th>Fuel exchanges and consumption</th>
<th>3d day</th>
<th>40th day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fuel use by the brain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>Ketone bodies</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>All other use of glucose</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td><strong>Fuel mobilization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adipose-tissue lipolysis</td>
<td>180</td>
<td>180</td>
</tr>
<tr>
<td>Muscle-protein degradation</td>
<td>75</td>
<td>20</td>
</tr>
<tr>
<td><strong>Fuel output of the liver</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>150</td>
<td>80</td>
</tr>
<tr>
<td>Ketone bodies</td>
<td>150</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
- F-cells: pancreatic polypeptide
- ε-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:

- **β-cells**
- **Glucose sensor (GLUT2)**
- **Insulin**
- **Glucose transporter (GLUT4)**

Cell metabolism includes:

- Glycogen synthesis
- Protein synthesis
- Fatty Acid synthesis
- Glycerol
- Triglycerides

High levels of glucose in blood from:**

Insulin reduces circulating glucose by activating glucose transporters on cell membrane, enabling the uptake of glucose into most peripheral tissues where the glucose is used as a fuel or stored as glycogen.

In muscles, binding increases glucose entry (5) which is either oxidized for energy (6) or stored as glycogen (9), protein (10) and fatty acids (11). The fatty acids are used in liver and sent to fat cells (12). In fat cells, insulin promotes entry, enhancing its conversion to glycerol and fatty acids. These esterify to form triglycerides (13), which are stored.
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
Sympathetic-Fight or Flight Mode

Lower levels of insulin – leaves more glucose in the blood for fighting or “flight-ing” 😊
Autonomic Nervous System Control of insulin release:

Parasympathetic
Lateral hypothalamus
Parasympathetic
Celiac ganglion
Superior mesenteric ganglion
Sympathetic
Ventromedial hypothalamus

Anatomy of the ANS

**Somatic motor system**
- CNS
- Somatic motor neuron
- Skeletal muscle

**Autonomic motor system**
- CNS
- Autonomic ganglion
- Preganglionic fiber: acetylcholine as the NT
- Postganglionic fiber:
  - SNS: noradrenaline, ATP, acetylcholine (sweat glands and blood vessel) and NPY
  - PSN: acetylcholine, peptides
- Smooth muscle
- Gland cells
- Cardiac muscle

Slide from Lu Chen
Anatomy of the ANS

Sympathetic

Parasympathetic

Sympathetic Ganglia chain

Ganglia close to target

Ganglia close to spinal cord
Insulin Secretion from Beta Cells

1.) Close K+ channels -> depolarization ->
Activation of Calcium channels -> Calcium influx -> insulin containing vesicle exocytosis

2.) Activate adenylate cyclase ->
increase cAMP -> activation of PKA ->
insulin containing vesicle exocytosis

3.) Activate PLC -> PIP2 to IP3 and DAG
-> IP3 increases calcium and DAG activates PKC -> both cause insulin secretion via exocytosis

4.) Activate PLA2 -> converts phospholipids to arachidonic acid ->
AAs cause insulin release via exocytosis
Research report

Cephalic phase insulin release in healthy humans after taste stimulation?

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\textbf{ABSTRACT}

In humans little is known as to whether taste solutions applied to the tongue elicit cephalic phase insulin release (CPIR). The aim of this study was to re-examine if any effect of different taste solutions on CPIR occurs. Under fasting conditions healthy human subjects sipped, and washed out their mouths with eight taste solutions (sucrose, saccharin, acetic acid, sodium chloride, quinine hydrochloride, distilled water, starch, and sodium glutamate) for 45 s and spat them out again. The taste stimuli were not swallowed; they were applied in a randomized order, each on a separate day. Blood collection for determination of plasma glucose and plasma insulin concentrations was performed 3 min before and 3, 5, 7 and 10 min after taste stimulation. Ratings of quality, intensity and hedonic characteristics were also obtained. A significant increase of plasma insulin concentration was apparent after stimulation with sucrose and saccharin. In conclusion, the current data suggest that the sweeteners sucrose and saccharin activate a CPIR even when applied to the oral cavity only.

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Results

In the pilot study (\(n = 5\)), a significant rise of plasma insulin concentration was found 5 min after simulation using sucrose, saccharin, starch and distilled water, while the blood glucose concentrations remained unchanged (Table 1). With regard to starch and distilled water, outliers caused the increase of insulin concentration, while after sucrose and saccharin stimulation in all five subjects CPIR was suggested.
Fig. 2. (a) Effect of taste stimulation with sucrose on plasma insulin concentrations from baseline (μIU/mL) of healthy humans (n = 20) (means, S.E.M.) after subjects sipped and spat out the solutions after 45 s. An arrow indicates t = 0 min. Significant differences (*) were found between concentration before stimulation and 5 min after sucrose stimulation (p < 0.05). (b) Effect of taste stimulation with saccharin on plasma insulin concentrations from baseline (μIU/mL) of healthy humans (n = 20) (means, S.E.M.) after subjects sipped and spat out the solutions after 45 s. An arrow indicates t = 0 min. Significant differences (*) were found between concentration before stimulation and 5 min after sucrose stimulation (p < 0.05).
Interactions between the central nervous system and pancreatic islet secretions: a historical perspective

Denovan P. Begg and Stephen C. Woods

This article has been cited by other articles in PMC.
unconditioned stimulus: insulin
unconditioned response: hypoglycemic
neutral stimulus: odor
conditioned response: hypoglycemic
saline

insulin secretion could be conditioned reflex

Note: For this experiment a non-physiological level of insulin was injected.

Cephalic phase of insulin secretion:

- Autonomic and endocrine response not related to nutrient absorption.
- Humans: increase in circulating insulin in response to eating imaginary food (hypnosis).
- Sight, smell and expectation of food.
- Cephalic phase is also subject to being conditioned.

“...A rapid increase in circulating insulin after oral glucose, before any increase in circulating glucose, has been shown in normal subjects.”

Blocking vagus nerve input abolishes cephalic phase of insulin release:

trimetophane (trimethaphane) blocks the descending parasympathetic activity nicotinic receptor blocker.

the importance of the cephalic phase of insulin response:

1-3% of the total insulin released after a meal is associated with the cephalic phase

looks diabetic!

glucose intolerant without cephalic phase

amount of insulin secreted during cephalic phase is inversely related to circulating glucose

insulin released during cephalic phase

circulating glucose

insulin administration right after food intake improves glucose tolerance in obese and type 2 diabetic individuals

### 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. cAMP 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”

“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.”
Figure 1 The homeostatic pathway of energy balance

Pathways: afferent (blue), central (brown), and efferent (white)


parasympathetic

sympathetic

sensory

islets

B
Insulin/Amylin

F
Pancreatic Polypeptide

A
Glucagon

D
Somatostatin
Parasympathetic nerve input:

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

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 para-sympathetic 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

NA
NPY
Galanin

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:

- CCK
- NO
- CGRP
- SP

Sensory nerve

Other nerve

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

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 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)
- Enteropancreatic neuro regulation from the duodenum

CCK: Cholecystokinin
NO: Nitric Oxide

Review

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

B. Ahren

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