GIT hormones and blood glucose regulation
Most cells in the human body use glucose as a major source of energy. Glucose molecules are delivered to cells by the circulating blood and therefore, to ensure a constant supply of glucose to cells, it is essential that blood glucose levels be maintained at relatively constant levels. Level constancy is accomplished primarily through negative feedback systems, which ensure that blood glucose concentration is maintained within the normal range.
<table>
<thead>
<tr>
<th>Hormone</th>
<th>Tissue of Origin</th>
<th>Metabolic Effect</th>
<th>Effect on Blood Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Pancreatic β Cells</td>
<td>1) Enhances entry of glucose into cells; 2) Enhances storage of glucose as glycogen, or conversion to fatty acids; 3) Enhances synthesis of fatty acids and proteins; 4) Suppresses breakdown of proteins into amino acids, of adipose tissue into free fatty acids.</td>
<td>Lowers</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>Pancreatic D Cells</td>
<td>1) Suppresses glucagon release from α cells (acts locally); 2) Suppresses release of Insulin, Pituitary tropic hormones, gastrin and secretin.</td>
<td>Raises</td>
</tr>
<tr>
<td>Glucagon</td>
<td>Pancreatic α cells</td>
<td>1) Enhances release of glucose from glycogen; 2) Enhances synthesis of glucose from amino acids or fatty acids.</td>
<td>Raises</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Adrenal medulla</td>
<td>1) Enhances release of glucose from glycogen; 2) Enhances release of fatty acids from adipose tissue.</td>
<td>Raises</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Adrenal cortex</td>
<td>1) Enhances gluconeogenesis; 2) Antagonizes Insulin.</td>
<td>Raises</td>
</tr>
<tr>
<td>ACTH</td>
<td>Anterior pituitary</td>
<td>1) Enhances release of cortisol; 2) Enhances release of fatty acids from adipose tissue.</td>
<td>Raises</td>
</tr>
<tr>
<td>Growth Hormone</td>
<td>Anterior pituitary</td>
<td>Antagonizes Insulin</td>
<td>Raises</td>
</tr>
<tr>
<td>Thyroxine</td>
<td>Thyroid</td>
<td>1) Enhances release of glucose from glycogen; 2) Enhances absorption of sugars from intestine</td>
<td>Raises</td>
</tr>
</tbody>
</table>
Role of GIT in blood glucose regulation:

An understanding of the role of the gastrointestinal system in glucose homeostasis came initially from the observation that enteral nutrition provided a stronger insulinotropic stimulus than did intravenous administration of isoglycemic glucose.
In 1932, La Barre purified the glucose lowering element from intestinal extract, this element called incretin (INtestine seCRETtion INsulin).
<table>
<thead>
<tr>
<th>Anatomical localization</th>
<th>Name and abbreviation</th>
<th>Effects on insulin secretion under experimental conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach endocrine cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G cells</td>
<td>Gastrin</td>
<td>Stimulates</td>
</tr>
<tr>
<td>D cells</td>
<td>Somatostatin</td>
<td>Inhibits</td>
</tr>
<tr>
<td>A cells</td>
<td>Glucagon</td>
<td>Stimulates</td>
</tr>
<tr>
<td>X cells</td>
<td>Ghrelin</td>
<td>Inhibits</td>
</tr>
<tr>
<td>Proximal intestinal endocrine cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S cells</td>
<td>Secretin</td>
<td>Stimulates</td>
</tr>
<tr>
<td>I cells</td>
<td>Cholecystokinin (CCK)</td>
<td>Stimulates</td>
</tr>
<tr>
<td>K cells</td>
<td>Gastric inhibitory polypeptide (GIP)</td>
<td>Stimulates</td>
</tr>
<tr>
<td>Distal intestinal endocrine cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L cells</td>
<td>Glucagon-like peptide-I (GLP-I)</td>
<td>Stimulates</td>
</tr>
<tr>
<td>PYY cells</td>
<td>Peptide YY (PYY)</td>
<td>Inhibits</td>
</tr>
<tr>
<td>Gastrointestinal nerve terminals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasoactive intestinal polypeptide (VIP)</td>
<td></td>
<td>Stimulates</td>
</tr>
<tr>
<td>Galanin</td>
<td></td>
<td>Inhibits</td>
</tr>
<tr>
<td>Gastrin-releasing peptide (GRP)</td>
<td></td>
<td>Stimulates</td>
</tr>
<tr>
<td>Neuropeptide Y (NPY)</td>
<td></td>
<td>Inhibits</td>
</tr>
<tr>
<td>Calcitonin gene-related peptide (CGRP)</td>
<td></td>
<td>Inhibits</td>
</tr>
<tr>
<td>Pituitary adenylate cyclase activating polypeptide (PACAP)</td>
<td></td>
<td>Stimulates</td>
</tr>
</tbody>
</table>
The incretin effect:–

- Defined as the β cell secretory response evoked by factors other than glucose itself, which represented by:

\[
\text{Incretin effect (%) = } 100 \times \frac{\int SR_{oral} - \int SR_{iv}}{\int SR_{oral}}
\]
Incretin hormones:

Gut hormones released in response to nutrient ingestion, which potentiate the glucose induced insulin response.
Two criteria were defined to identify a substance as an incretine in enteroinsular axis:

I. The substance must be released in response to nutrients, particular CHO in GIT.

II. When administered at physiological concentration the insulinotropic action must be glucose concentration dependent.
Glucose dependent insulinotropic peptide (GIP)

GIP is released by K cells in the duodenum and proximal jejunum, locations that are ideal for detecting changes in nutrient status.

Secreted during meals in response to nutrient ingestion, especially CHO and fat.
proGIP

42 amino acids

PC1/3

Posttranslational cleavage by PC1/3 in endocrine K cells

GIP

\[ 1 \text{YAEGTFISDYSIAMD} \text{KIHQQDFV} \text{WNLLA} \text{Q} \text{KKNDW} \text{KHNITQ} \]
GIP exerts its actions through G protein-coupled receptor, which widely expressed in the pancreas, stomach, small intestine, adipose tissue, adrenal cortex, lung, pituitary gland, heart, testis, vascular endothelium, bone, and brain.
Glucagon like peptide-1 (GLP-1):

- Released from L cells in distal part of small intestine, colon and rectum, pancreatic alpha cells, and in brain (hypothalamus, thalamus, medulla oblongata, dorsal and ventral part of medullary reticular formation).

- Ingestion of fat, especially monounsaturated long chain fatty acids, stimulates GLP-1 release.
GLP-1: \text{HAEGTFTSDVSSYLEGQAAKFIAWLVKGR}

Posttranslational cleavage by PC1/3 in endocrine L cells

Proglucagon

GRPP, Glucagon, IP-1, GLP-1, IP-2, GLP-2

30 amino acids, 33 amino acids
• Release of GLP-1 occur in two peaks:

- The first one 15-30 minutes after food ingestion (before food reach to L-cells).
- The second peak within 60 minutes later (food reach to L-cells).
Factors affecting GIP and GLP-1 secretion:

I. Nutrient intake, composition and absorption.

II. Rate of nutrient entry into the small intestine which determined by gastric emptying.

III. Mechanical factors, such as distension.
Gut sensibility

When a gut taste cell detects sweet, it triggers a cascade of molecular events, a simplified view of which is shown here. Gustducin activation can spur production of molecules, such as GLP-1, that tell neighboring cells to absorb more glucose. Messages sent via the bloodstream tell the pancreas to produce insulin. Other molecules can hit nerve cells, which can relay signals locally and to the brain.
Effects of GLP-1 on β cell mass:

GLP-1 promotes the proliferation and neogenesis of pancreatic β cells, and reduces β cell apoptosis.
GLP-1 also activates a transcriptional programme that is critical for cell survival.

PDX1, FOXO1 and IRS2 have been identified as downstream targets for GLP-1-dependent cytoprotection of β cells.

GLP-1, also reduces the expression of pro apoptotic genes and prevents glucotoxicity and lipotoxicity through a mechanism involving PKB/Akt.
Bone formation and bone resorption are related to GIP (Glucose-dependent Insulinotropic Polypeptide) in the intestine. GIP influences the brain, pancreas, and adipose tissue. Specific actions include:

- **Brain**: Progenitor cell proliferation
- **Intestine**: GIP secretion and actions
- **Adipose tissue**: Lipogenesis
- **Pancreas**: Insulin secretion, insulin biosynthesis, β-cell proliferation, β-cell apoptosis

These interactions highlight the role of GIP in maintaining metabolic balance.
GLP-1 or Exenatide (or GIP) 

GLP-1R (or GIPR) 

GLucose 

GLUT2 

GLucose 

TCA cycle 

Mitochondria 

Epac 

PKA 

cAMP 

IP3 

Ca2+ 

[Ca2+]i 

Insulin secretion 

ATP ↑ 

ADP ↓ 

KATP channel 

K+ 

KATP channel 

K+ 

Depolarization 

L-type Ca2+ channel 

Ca2+ 

Kv channel 

K+ 

K+ 

Ca2+ 

L-type Ca2+ channel 

Ca2+ 

ψ 

ψ 

RyR
GLP-1(7-36)NH₂ → H-A
Exendin-4 → H-A + GLP-1(9-36)NH₂
GIP(1-42) – intact GIP

\( \text{NH}_2-\text{YAEFTSFISDYLMDKIHQQDFVNW} \)

COOH-QTINHWDNKKGKQALL

cleavage site

DPP IV

GIP(3-42) – truncated GIP

\( \text{NH}_2-\text{EGTFISDYLMDKIHQQDFVNW} \)

COOH-QTINHWDNKKGKQALL
10–15% of secreted amount leaves liver

LIVER

25% reaches liver

DPP-IV breakdown

VILLUS

L-cell

100% secreted
Test meal

Plasma GIP [pmol/l]

Time [min]

- Total GIP
- Intact GIP

$p < 0.0001$
Incretin effect (+)

Incretin effect (-)

Small intestine

Nutrients

K cells

L cells

Secretion

GLP(1-42)

GLP-1(7-37)

GLP-1(7-36)NH₂

Inactivation

DPP-4

GLP(3-42)

GLP-1(9-37)

GLP-1(9-36)NH₂

Renal excretion

$t_{1/2}$

4-5 min

2-3 min
Incretin effect in type 2 diabetes mellitus:

GIP and GLP-1 are the most important incretin hormones, it is possible to analyze the nature of the incretin defect in patients with type 2 diabetes.
Control Subjects
(n=8)

Incretin Effect

Time, min

IR Insulin, mU/L

Oral glucose load

Intravenous (IV) glucose infusion

0 20 40 60 80

0 0.1 0.2 0.3 0.4 0.5 0.6
Patients With Type 2 Diabetes (n=14)

The incretin effect is diminished in type 2 diabetes.
# Summary of the main characteristics of GIP and GLP-1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>GIP</th>
<th>GLP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptide</td>
<td>42 amino acids</td>
<td>30 amino acids</td>
</tr>
<tr>
<td>Released from</td>
<td>K cells - duodenum</td>
<td>L cells - ileum and colon</td>
</tr>
<tr>
<td>Active form</td>
<td>Single bioactive form</td>
<td>Two bioactive forms: (7-37) and (7-36)amid</td>
</tr>
<tr>
<td>Inactivated by</td>
<td>DPP-IV</td>
<td>DPP-IV</td>
</tr>
</tbody>
</table>

## Physiological actions

<table>
<thead>
<tr>
<th></th>
<th>GIP</th>
<th>GLP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin secretion</td>
<td>Stimulated</td>
<td>Stimulated</td>
</tr>
<tr>
<td>Insulin biosynthesis</td>
<td>-</td>
<td>Stimulated</td>
</tr>
<tr>
<td>Beta cell proliferation</td>
<td>Promoted</td>
<td>Promoted</td>
</tr>
<tr>
<td>Glucagon secretion</td>
<td>-</td>
<td>Inhibited</td>
</tr>
<tr>
<td>Food intake</td>
<td>-</td>
<td>Reduced</td>
</tr>
<tr>
<td>Gastrointestinal motiliy</td>
<td>-</td>
<td>Participates in the ileal brake</td>
</tr>
<tr>
<td>Cardiac function</td>
<td>Inhibition</td>
<td>Improvement</td>
</tr>
<tr>
<td>Bone resorption</td>
<td></td>
<td>Inhibition</td>
</tr>
</tbody>
</table>

## In type 2 diabetes

<table>
<thead>
<tr>
<th></th>
<th>GIP</th>
<th>GLP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secretion</td>
<td>Normal</td>
<td>Reduced</td>
</tr>
<tr>
<td>Response</td>
<td>Impaired</td>
<td>Preserved</td>
</tr>
</tbody>
</table>
## The multiple anti-diabetic actions of GLP-1

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Actions of GLP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired β-cell function</td>
<td>• ↑ Insulin secretion (glucose-dependent) and biosynthesis</td>
</tr>
<tr>
<td></td>
<td>• Improves β-cell function (i.e. glucose sensitivity, proinsulin:insulin ratio, HOMA-β)</td>
</tr>
<tr>
<td></td>
<td>• Upregulates genes that are essential for β-cell function (e.g. GLUT 2 and glucokinase)</td>
</tr>
<tr>
<td>Reduced β-cell mass</td>
<td>• ↑ β-cell proliferation and differentiation&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• ↓ β-cell apoptosis&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• ↑ β-cell mass&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Glucagon hypersecretion</td>
<td>• ↓ Glucagon secretion (glucose-dependent)</td>
</tr>
<tr>
<td>Over-eating, obesity</td>
<td>• ↓ Gastric emptying, ↑ satiety, ↓ appetite, which leads to ↓ food intake and body weight</td>
</tr>
<tr>
<td>Macrovascular complications</td>
<td>• Beneficial cardiovascular effects</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>• Increases insulin sensitivity&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Two strategies have been pursued to exploit the beneficial actions of the hormone:

I. Development of stable activators of the GLP–1 receptor (so-called incretin or GLP–1 mimetics)

II. Inhibitors of DPP–4 (i.e. incretin enhancer)

Sitagliptin and Vildagliptin
<table>
<thead>
<tr>
<th>GLP-1</th>
<th>Exenatide</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Glucose-dependent insulin secretion</td>
<td>✓</td>
</tr>
<tr>
<td>↓ Glucagon secretion</td>
<td>✓</td>
</tr>
<tr>
<td>↓ Hepatic glucose output</td>
<td>✓</td>
</tr>
<tr>
<td>Regulates gastric emptying</td>
<td>✓</td>
</tr>
<tr>
<td>↓ Rate of nutrient absorption</td>
<td>✓</td>
</tr>
<tr>
<td>↓ Food intake</td>
<td>✓</td>
</tr>
<tr>
<td>↓ Plasma glucose acutely to near-normal levels</td>
<td>✓</td>
</tr>
<tr>
<td>Resistant to DPP-IV degradation</td>
<td></td>
</tr>
<tr>
<td>Duration in plasma after SC injection</td>
<td>Short</td>
</tr>
</tbody>
</table>
GIP antagonist

Hyperphagia (high fat diet)

Elevated GIP (K-cell hyperplasia)

GIP receptors

Actions on adipose tissue

Increased fat stores

Obesity

Insulin resistance

Glucose intolerance

Hyperglycaemia

GIP receptors

Hyperinsulinaemia (beta-cell hyperplasia)
Ghrelin and blood glucose:

- Ghrelin is a 28-amino-acid peptide that displays a strong (GH) releasing activity through the activation of the growth hormone secretagogue receptor (GHSR).
- 60%–70% of ghrelin is secreted by oxyntic glands of the gastric epithelium.
UNACYLATED HUMAN GHRELIN

$\text{NH}_2 - \text{GSSFLSPEHQRVVQRKESKKPPAKLQPR} - \text{COOH}$

$\text{O} + \text{O} = \text{C}-(\text{CH}_2)_{6/8} \cdot \text{CH}_3$

N-Octanoic acid (C8) (or C(10) or C(6))

$\text{O} = \text{C}-(\text{CH}_2)_{4/6/8} \cdot \text{CH}_3$

GOAT

$\text{H}_2\text{O}$

ACYLATED HUMAN GHRELIN

$\text{NH}_2 - \text{GSSFLSPEHQRVVQRKESKKPPAKLQPR} - \text{COOH}$
• **Ghrelin and blood glucose:**

✓ Decrease insulin secretion.
✓ Increase GIT motility.
✓ Increase secretion of ACTH, GH, and cortisol.
✓ Increase food intake.
✓ Up regulation of gluconogenesis and suppress glycogen synthesis in liver cells.
Somatostatin:–

polypeptide consisting of 14 amino acids (SOM14), a second biologically active, amino-
terminally extended form of 28 residues was discovered and called (SOM–28).
Cholycystokinin:–

- Secreted primarily from I cells within the duodenal and jejunal mucosa.
- Its action mediated by two types of receptors CCK-1 (CCK-A) & CCK-2 (CCK-B).
- Act as hormone and neurotransmitter.
CCK and blood glucose:

- Decrease gastric empty.
- Suppress appetite.
- Stimulate $\beta$ cell proliferation.
- Decrease liver glucose output.
- Powerful stimulant for insulin secretion.
Peptide tyrosine tyrosine (PYY):—

✓ 36 a.a peptide, released after food ingestion from L cells in the ileum, colon and rectum & pancreas and remains elevated for up to 6 hours after feeding.

✓ Inhibits glucose-stimulated insulin production but not basal insulin production.
Peptide YY and blood glucose:

- Inhibits gastric acid secretion.
- Inhibits gastric emptying.
- Increase absorption from intestine.
- Suppress appetite and reduce food intake.
- Suppress insulin secretion.
- Increase insulin sensitivity.
Oxyntomodulin:

✓ OXM is a 37-amino-acid intestinal peptide member of the family of proglucagon-derived gut peptides.

✓ Identical to glucagon, but with an 8 amino acid extension on the C-terminus.

✓ L-cells of the small intestine, pancreas and brain.
PROGLUCAGON

GRPP  GLUCAGON  SP1  GLP-1  SP2  GLP-2

PROCESSING IN THE GUT/BRAIN

GLICENTIN  GLP-1  GLP2

GRPP  OXM
Oxyntomodulin and blood glucose:

- OXM promotes insulin release via GLP-1 receptor.
- Delay gastric empty.
- Decrease intestinal motility.
- Suppress appetite.
Motilin:

✓ Increase gastric empty.
✓ Increase absorption of substrate which stimulate insulin release and release of incretins.
Summary

- Glucose homeostasis is tightly controlled by the interaction of pancreatic and gut hormones by gastro–entero–insular axis.
- The incretin effect refers to the phenomenon of oral glucose eliciting a higher insulin response than iv glucose at identical plasma glucose profiles.
• It is conveyed by the two insulinotropic incretin hormones: (GLP–1) and (GIP).

• T2DM has been shown to be characterized by an almost abolished incretin effect.

• GLP–1 enhancer or mimetic used as treatment for diabetic patients.
THANK YOU

By

Mona Gaber