The Role of Glucose and GLP-1 in the Gut-Brain and Brain-Periphery Axes in Homeostasis
An overview of how glucose and GLP-1 act in the periphery and via the brain to mediate regulation of glucose homeostasis

1. Gut-brain axis
Glucose absorption activates the hypothalamus via afferent fibres of the vagus nerve
Systemic glucose and GLP-1 can also directly activate regions in the brainstem and hypothalamus

2. Peripheral actions
Glucose and GLP-1 act directly in peripheral tissues to modulate the release of insulin and glucagon

3. Brain-periphery axis
Afferent and direct signals in the brain are relayed to peripheral tissues via autonomic neurons to control glucose uptake, storage and utilisation

Cabou C and Burcelin R. Rev Diabet Stud 2011;8:418–31
Historically, glucose and GLP-1 were thought to only provide control of homeostasis via peripheral actions, e.g. direct regulation of the \( \alpha \)- and \( \beta \)-cells of the pancreatic islets. However, in addition to peripheral regulation, glucose and GLP-1 regulate homeostasis in a brain-mediated manner through afferent nerve signalling and direct activation in the brainstem and hypothalamus.

1. **Glucose** is transported via GLUT2 and **GLP-1** binds to its receptor on pancreatic \( \beta \)-cells.

2. Glucose transport and GLP-1 binding act synergistically to close ATP-sensitive \( K^+ \) channels leading to membrane polarisation.

3. Membrane polarisation elevates cytoplasmic concentrations of \( Ca^{2+} \).

4. \( Ca^{2+} \) stimulates the exocytosis of insulin-containing granules.

**Glucagon** is produced by pancreatic \( \alpha \)-cells in response to low blood glucose.

\[ \text{GI tract} \rightarrow \text{Glucose} \rightarrow \text{Liver} \rightarrow \text{Blood glucose} \]

\[ \text{Blood glucose} \rightarrow \text{Liver} \rightarrow \text{Glucose} \rightarrow \text{GI tract} \]

**Image adapted from Holst JJ. Physiol Rev 2007;87:1409–39 with kind permission from APS.**

Herman MA and Kahn BB. J Clin Invest 2006;116:1767–75
The Gut-Brain Axis
Glucose, protein and fat provide direct and indirect signals to the brain to induce satiety

1. Glucose sensing
   Glucose absorbed in the gastrointestinal tract enters the hepatoportal vein

2. Vagal nerve firing
   GLUT2-dependent hepatoportal glucose sensors increase vagal nerve firing

3. Protein sensing
   Protein induces opioid receptor-mediated intestinal gluconeogenesis leading to glucose sensing in the hepatoportal vein

2. Mithieux G. Diab Obes Metab 2014;16:56–60
In response to nutrient-sensing, the gastrointestinal tract secretes a variety of hormone peptides of which GLP-1 is the best characterised.

- **Stomach**: Ghrelin, Leptin, GRP, NMB
- **Duodenum**: CCK
- **Jejunum**: APO AIV
- **Colon**: GLP-1, Oxyntomodulin, PYY
- **Ileum**: GLP-1, Oxyntomodulin, PYY

GLP-1 is produced primarily by L cells in the ileum and colon. Nutrients stimulate GLP-1 secretion by:
- Direct contact in distal intestine
- Indirect neurohumoral mechanism

APO AIV: apolipoprotein A-IV; CCK: cholecystokinin; GRP: gastrin-releasing peptide; NMB: neuromedin B; PYY: peptide YY

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GLP-1 mediates its effects on the gut-brain axis via GLP-1 receptors expressed on vagal nerve terminals in the portal vein and on enteric neurons

GLP-1 receptor expression in the portal vein
Synaptophysin staining shows the portal vein contains a dense network of neural fibres and nerve terminals (B)
GLP-1 receptor staining is observed in the portal vein (A) and co-localises with synaptophysin at nerve terminals (C)

GLP-1 receptor expression in nodose ganglia
D and F: autofluorescence of nodose neurons
E and G: GLP-1 receptor staining is observed in nodose ganglia

GLP-1 receptor expression is also observed in enteric neuron structures surrounding the portal vein

Gut-glucose induced GLP-1 signalling is relayed to the brainstem where it is accompanied by increased c-Fos expression in the NTS.

Following intragastric glucose infusion, c-Fos–positive cells in the NTS of the brainstem increase significantly. In contrast, c-Fos–positive cells in the ARC, VMH and DMN hypothalamic nuclei are reduced, suggesting glucose-induced signalling in the brainstem is mediated in part by c-Fos.

AP: area postrema; ARC: arcuate; CC: central canal; DMN: dorsomedian; NTS: nucleus tractus solitarii; VMH: ventromedian hypothalamus

Enteric GLP-1 signals received in the brainstem are transmitted to a number of hypothalamic nuclei via GLP-1-producing neurons found largely in the NTS.

glp1r fluorescence is seen in the AP of the brainstem. The NTS and AP also contain neurons synthesising GLP-1.

High density glp1r fluorescence is also seen in the ARC, VMH and PVN of the hypothalamus.

Direct Activation of the Brainstem and Hypothalamus by Glucose and GLP-1
In addition to activating vagal afferent nerves, systemic glucose can also directly activate regions in the brainstem and hypothalamus.

1. Gut-brain axis
   Glucose absorption indirectly activates the hypothalamus via afferent fibres of the vagus nerve.

2. Direct activation
   Systemic glucose is also detected directly by neurons present in the dorsal vagal complex (NTS, AP, and DMNX) and the hypothalamus.

3. Brainstem-hypothalamus
   Direct glycaemic signals in the brainstem are transmitted to the hypothalamus via the BLM or the PBN.

4. Signal integration
   Glycaemic signals are integrated in the hypothalamus to form a response to glucose change through communication to cerebral structures such as the amygdala and the cortex.

Image adapted from Marty N et al. Physiology 2007;22:241–51, with permission from APS.
Systemic GLP-1 and GLP-1 synthesised in the brain can act directly on GLP-1 receptors expressed in the brainstem and hypothalamus

GLP-1 receptors are found in the PVN, DMN and ARC hypothalamic nuclei

GLP-1 receptors are also found in the NTS and AP of the brainstem
The NTS and AP also contain neurons synthesising GLP-1

Ventricles are represented in blue. d3V: dorsal third ventricle; LV: lateral ventricle

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The Brain-Periphery Axis
Brainstem and hypothalamic neurons form a glucose-sensing network that relays signals to pancreatic islets to regulate hormone secretion.

Glucose-sensing neurons form a network that integrates glycaemic signals that are relayed to the periphery via the sympathetic and parasympathetic nervous systems.

1. **Parasympathetic activity**
   - Stimulation of insulin secretion during hyperglycaemia
   - Stimulation of glucagon secretion during hypoglycaemia
   - Stimulation of β-cell proliferation

2. **Sympathetic activity**
   - Inhibition of insulin secretion during hypoglycaemia
   - Stimulation of glucagon secretion during hypoglycaemia
   - Formation and maturation of islet architecture

The rate of gastric emptying is a critical determinant of postprandial glycaemia and is regulated by GLP-1-mediated neuronal signalling.

1. **GLP-1 secretion**
   In response to glucose and lipid, GLP-1 is released into the hepatoportal vein.

2. **Vagal nerve firing**
   GLP-1 activates termination ends from the vagus nerve to generate a neural signal towards the brainstem.

3. **GLP-1 signalling in the brain**
   Activated nuclei in the brainstem (including the AP and NTS) send axons to the hypothalamus, which releases GLP-1 and activates GLP-1 receptors.

4. **Gastric emptying**
   A new signal is sent via vagal efferent nerves which slows gastric motility and decreases appetite.

Cabou C and Burcelin R. Rev Diabet Stud 2011;8:418–31
Tong J and D'Alession D. Diabetes 2014;63:407–9
GLP-1 receptor stimulation in the brain activates autonomic regulatory neurons that increase blood pressure and heart rate

1. GLP-1 receptor stimulation
Circulating GLP-1 engages GLP-1 receptors on hypothalamic neurons and medullary catecholamine neurons

2. Sympathetic activity
The GLP-1 activated neurons have monosynaptic descending projections to the sympathetic preganglionic neurons in the IML

3. Autonomic responses
The preganglionic neurons in the IML innervate the adrenal medulla and heart to increase blood pressure and heart rate

IML: intermediolateral cell column

GLP-1 mediated neuronal signalling through the autonomic nervous system regulates metabolism in other peripheral tissues

1. White adipose tissue
   Decrease in lipid storage

2. Liver
   Increase in glucose uptake and storage

3. Muscle
   Decrease in glucose uptake and utilisation

Cabou C and Burcelin R. Rev Diabet Stud 2011;8:418–31
There are many gut-derived peptides that regulate food intake via the gut-brain and brain-periphery axes.

### Selected gastrointestinal and pancreatic peptides that regulate food intake

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Main site of synthesis</th>
<th>Receptors mediating feeding effects</th>
<th>Sites of action of peripheral peptides germane to feeding</th>
<th>Effect on food intake*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypothalamus   Hindbrain     Vagus nerve</td>
<td></td>
</tr>
<tr>
<td>CCK</td>
<td>Proximal intestinal L cells</td>
<td>CCK-1R</td>
<td>X             X             X</td>
<td>↓</td>
</tr>
<tr>
<td>GLP-1</td>
<td>Distal-intestinal L cells</td>
<td>GLP-1R</td>
<td>X?            X?            X</td>
<td>↓</td>
</tr>
<tr>
<td>Oxyntomodulin</td>
<td>Distal-intestinal L cells</td>
<td>GLP1R and other</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>PYY</td>
<td>Distal-intestinal L cells</td>
<td>Y2R</td>
<td>X             X</td>
<td></td>
</tr>
<tr>
<td>Enterostatin</td>
<td>Exocrine pancreas</td>
<td>F1-ATPase β subunit</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>APO AIV</td>
<td>Intestinal epithelial cells</td>
<td>Unknown</td>
<td>X             X</td>
<td></td>
</tr>
<tr>
<td>PP</td>
<td>Pancreatic F cells</td>
<td>Y4R, Y5R</td>
<td>X             X</td>
<td></td>
</tr>
<tr>
<td>Amylin</td>
<td>Pancreatic β Cells</td>
<td>CTRs, RAMPs</td>
<td>X             X</td>
<td></td>
</tr>
<tr>
<td>GRP and NMB</td>
<td>Gastric myenteric neurons</td>
<td>GRPR</td>
<td>X             X</td>
<td></td>
</tr>
<tr>
<td>Gastric leptin</td>
<td>Gastric chief and P cells</td>
<td>Leptin receptor</td>
<td>?             ?             X</td>
<td>↓</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>Gastric X/A-like cells</td>
<td>Ghrelin receptor</td>
<td>X             X             X</td>
<td>↑</td>
</tr>
</tbody>
</table>

CTRs: calcitonin receptors; RAMPs: receptor activity-modifying proteins; GRPR: GRP receptor.

X? indicates that it is unclear whether physiologically relevant quantities of GLP-1 from the gut evade DPP4-mediated degradation in blood to activate GLP-1 receptors in the brain, although these receptors might interact with CNS GLP-1 to regulate food intake. ? Indicates that it seems very unlikely that gastric leptin interacts in a physiologically meaningful way with leptin receptors in the hypothalamus or hindbrain, which are important targets of leptin secreted from adipocytes.

*Effect of peripheral peptides on food intake. In some cases, central administration yields opposite results.
The Gut-Brain and Brain-Periphery Axes and T2DM
Gastric emptying is a critical determinant of postprandial glycaemia and is frequently disordered in patients with diabetes due to multiple mechanisms.

- Glycation products formed due to increased reactive oxygen species can lead to loss of nNOS, impaired neurotransmission and delayed gastric emptying.
- Increased oxidative stress and a lack of anti-oxidant enzymes results in loss of ICC and delayed gastric emptying.
- Autonomic neuropathy leads to disordered motility and function of the stomach.
- Smooth muscle atrophy leads to loss of IGF-1, a survival factor for ICC.

ICC: interstitial cells of Cajal; nNOS: neuronal nitric oxide synthase.
The ability of GLP-1 to delay gastric emptying is retained in patients with T2DM – this effect is lessened with prolonged exposure to GLP-1 due to tachyphylaxis.

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Diabetes is associated with delayed or rapid gastric emptying, reflecting the heterogeneous nature of the underlying pathophysiology.

The rate of gastric emptying and factors associated with gastric emptying (e.g., weight loss, insulin therapy, neuropathy) were determined for a database of patients with diabetes in whom gastrointestinal transit was assessed by scintigraphy.

In a multivariable analysis of factors associated with gastric emptying disturbances, significant weight loss was a risk factor for delayed gastric emptying and neuropathy was a risk factor for rapid gastric emptying.
Summary

• Glucose and GLP-1 regulate glucose homeostasis via:
  – Direct action in the periphery
  – Afferent nerve signalling and direct activation of neurons in the brainstem and hypothalamus

• Activated nuclei in the brainstem (including the AP and NTS) send axons to the hypothalamus releasing GLP-1 and activating GLP-1 receptors expressed in hypothalamic nuclei

• Glucose- and GLP-1-sensing neurons form a network that integrates glycaemic signals that are then relayed to the periphery via the sympathetic and parasympathetic nervous systems

• Functions such as insulin expression, gastric emptying, blood pressure, heart rate and glucose utilisation are regulated by the signalling of the gut-brain and brain-periphery axes