Intermediary Metabolism

- GLUCOSE AND ENDOCRINE PANCREAS
  - Introduction to the pancreas, its cell types, its hormones, its functional organization, its venous output to liver and its regulation
  - Overview of intermediary metabolism and enzyme sites of major actions of insulin and glucagon
  - Pancreatic hormones, insulin, glucagon, SS and PPY. Their structure, synthesis, related peptides, secretion, regulation, receptors and effects. Effect of exercise on insulin and on its counter-regulatory hormones
  - Regulation of pancreatic hormones, Diabetes Mellitus, hypoglycemia, fasting, NIDDM

Intermediary Metabolism

GLUCOCORTICOIDS & GLUCOSE CONTROL

- Introduction to steroids in general: synthesis, regulation, mechanisms of action, development, physiology and related - diseases
- Adrenal gland: anatomy, histology, hormones, effects, feedback. Cortisol secretion, receptors, mechanism of action and effects
- Cortisol: effects on glucose metabolism, anti-inflammatory action, regulation, synthetic cortisol, the stress response
- Cortisol related pathologies: Addison’s disease and Cushing’s syndrome
Intermediary Metabolism Control

Question #06: Control of intermediary metabolism

Your first draft report for this topic is due on Wed Oct 26. The question for this week is as follows:
Select a homoeostatic event and / or physiological system involving the regulation of intermediary metabolism basic processes (e.g. glycogenesis, gluconeogenesis, lipolysis) as your structure, in which you can show the importance of structure / function relationship, levels of organization, and feedback control. Your answer must follow the outline presented in the introduction (sub-questions a, b, c, d, see above).

a) Name the structure and the function on which your overall answer will be based? Be as specific as you can in delimiting the boundaries of your example (the most important part of your answer, since the following b, c, & d sub-questions are based on your answer to this first sub-question, a).

b) Why do you think that your structure and your function are related? Support your contention based on 3 lines of evidence on the chemistry, physics, anatomy or physiology involved in your example.

c) Which are the levels of organization involved in your example? Cite events occurring at its main level of organization and indicate how they relate to the whole body homoeostatic level.

d) Which are the main feedback mechanisms involved in your example (cite at least two)? Expand on one of them and indicate an absolute requirement for that feedback to be operational.
Plasma levels of glucose and insulin in relation to meal intake, and the time course of blood glucose related to the origin of glucose under fasting conditions.

Quantitative turnover of substrates in the basal state after fasting for 24 hours. The opposite direction of plasma insulin and glucagon define metabolic state.
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Some associations to remember for an endocrine regulatory viewpoint. Remember hormones act on enzymes and channels.
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An overview of the factors affecting insulin signalling

An overview of blood glucose stimulation of insulin secretion and effect
Intermediary Metabolism Control

An overview of blood glucose stimulation of insulin secretion and effect. Insulin’s main effect is on Glu-4 transporters.
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The effect of insulin on the enzymes glycogen synthetase and 6 – phosphofructokinase (PFK), two of the main metabolic switches.

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Glucagon secreted by the pancreatic alpha-cells increase blood glucose levels, acting through a cAMP mediated mechanism.
Main actions of glucagon on metabolic pathways and the effect of a meal or arginine infusion on blood glucose, insulin & glucagon

<table>
<thead>
<tr>
<th>Organ</th>
<th>Net effect</th>
<th>Chief mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>glycogenolysis</td>
<td>glycogen phosphorylase (AMP-dependent)</td>
</tr>
<tr>
<td></td>
<td>gluconeogenesis</td>
<td>glucose, transportation, glucose-6-phosphate, glucose-6-phosphatase, glucose-6-phosphatase (phosphorylation)</td>
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<tr>
<td></td>
<td>glycolysis</td>
<td>glycogen synthase, glycogen synthase, glycogen synthase (phosphorylation)</td>
</tr>
<tr>
<td></td>
<td>ketogenesis</td>
<td>substrate delivery, releasing inhibitory effect of adenylate cyclase inhibition, allowing mitochondrial transfer and FA oxidation</td>
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</tbody>
</table>

A good example of “pushing the regulatory feedback envelope” in endocrinology is Diabetes Mellitus (both type 1 and type 2)
Pathologies of the endocrine pancreas

<table>
<thead>
<tr>
<th>Type I (insulin-dependent diabetes mellitus, IDDM)</th>
<th>[16]</th>
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</thead>
<tbody>
<tr>
<td>Insulin resistance [1, 3, 14, 51]</td>
<td></td>
</tr>
<tr>
<td>Pre-receptor resistance</td>
<td></td>
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<tr>
<td>Antibodies against insulin</td>
<td></td>
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<tr>
<td>Mutant insulin structures</td>
<td></td>
</tr>
<tr>
<td>Defect in primary structure of insulin β chain at one or more positions</td>
<td></td>
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<tr>
<td>Familial hyperinsulinemia</td>
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<tr>
<td>B-C proinsulin mutation at the cleavage site between the B chain and the connecting (C) peptide</td>
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<tr>
<td>Receptor resistance</td>
<td></td>
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<tr>
<td>Type A: Decrease in insulin receptor number and/or affinity for the hormone</td>
<td></td>
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<tr>
<td>Point mutation in insulin receptor gene prevents processing of the receptor precursor</td>
<td></td>
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<tr>
<td>Impaired expression of receptor tyrosine kinase activity [47]</td>
<td></td>
</tr>
<tr>
<td>Point mutation blocks insertion of mature receptor into plasma membrane</td>
<td></td>
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<tr>
<td>Type B: Receptor blocked by circulating antibodies to the receptor</td>
<td></td>
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<tr>
<td>Leprechaunaniun</td>
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<tr>
<td>An autosomal recessively inherited disorder of insulin function that leads to severe intrauterine growth retardation, characteristic dysmorphic features and a disturbed glucose homeostasis. The process underlying this disease is a structural defect in the insulin receptor</td>
<td></td>
</tr>
<tr>
<td>Post-receptor resistance</td>
<td></td>
</tr>
<tr>
<td>Decreased capacity of pancreatic β cells to compensate for the underlying insulin resistance by increased secretion of insulin [51]</td>
<td></td>
</tr>
<tr>
<td>Possible underexpression (down-regulation) of β-cell glucose transporters (therefore failure to recognize and respond to hyperglycemia)</td>
<td></td>
</tr>
<tr>
<td>Autoantibodies to the GLUT2 glucose transporter of β-cells [24]</td>
<td></td>
</tr>
<tr>
<td>Mutation of the glucokinase gene may prevent uptake and metabolism of glucose necessary for the mechanism of insulin secretion. May be responsible for a young onset type II diabetes (MODY) [5, 25]</td>
<td></td>
</tr>
</tbody>
</table>

Inlet cell tumors:

- Insulinoma: Excess insulin secretion from a β-cell pancreatic tumor (severe hypoglycemia)
- Glucagonoma syndrome: Excess glucagon secretion from an α-cell pancreatic tumor
- Somatostatinaoma: Excess somatostatin secretion from D-cell pancreatic tumor

Hypoglycemic disorders:

- Hypoglycagomina (isolated glucagon deficiency). Possibly due to autosomal recessive inheritance
- Hyperinsulinemia (β-cell tumor)
- Antibodies (stimulatory) to the insulin receptor (increased glucose uptake by cells)

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Intermediary Metabolism Control

**HPA axis and its “story lines”**

**Regulation of adrenocorticotropic hormone secretion**

- Corticosterone
-norepinephrine
- ACTH
- Glucocorticoid
- Hypothalamus
- Adrenal

**Hypothalamic - pituitary - adrenal axis (HPA axis) is control predominantly by cortisol negative feedback**
The main stimulus for ACTH secretion is hypothalamic CRH acting through AC and PLC mediated mechanisms. ACTH increases Pregnenolone through cAMP.

The secretion of ACTH and adrenal steroids to plasma has a circadian rhythm. Secretion of these ligands is also affected by stress, such as insulin injection.
The main metabolic effect of cortisol on metabolism is gluconeogenesis

Intermediary Metabolism Control

Question #96: Control of intermediary metabolism
Your first draft report for this topic is due on Wed Oct 26. The question for this week is as follows:
Select a homeostatic event and/or physiological system involving the regulation of intermediary metabolism basic processes (e.g., glycolysis, gluconeogenesis, lipolysis) as your structure, in which you can show the importance of structure/function relationship, levels of organization, and feedback control. Your answer must follow the outline presented in the introduction (sub-questions a, b, c, d, e, see above).

a) Name the structure and the function on which your overall answer will be based? Be as specific as you can in delimiting the boundaries of your example (the most important part of your answer, since the following b, c, & d sub-questions are based on your answer to this first sub-question, a).

b) Why do you think that your structure and your function are related? Support your contention based on 3 lines of evidence on the chemistry, physics, anatomy or physiology involved in your example.

c) Which are the levels of organization involved in your example? Cite events occurring at its main level of organization and indicate how they relate to the whole body homeostatic level.

d) Which are the main feedback mechanisms involved in your example (cite at least two)? Expand on one of them and indicate an absolute requirement for that feedback to be operational.
Intermediary Metabolism Control

- **struct**ure - Which, increase or decrease?
- **func**tion

(a) Structure - Increase or decrease?

(b) How do you know?

(c) Parts to total?

(d) Two feedbacks and an absolute requirement?

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Next week question

**Question #07: Growth and blood pressure regulation**

Your first draft report for this topic is due on Wed Nov 02. The question for this week is as follows:

Select a homeostatic event and/or physiological system involving growth OR blood pressure regulation as your structure, in which you can show the importance of structure/function relationship, levels of organization, and feedback control. Your answer must follow the outline presented in the introduction (sub-questions a, b, c, d, see above).

- **a)** Name the structure and the function on which your overall answer will be based? Be as specific as you can in delimiting the boundaries of your example (the most important part of your answer, since the following b, c, & d sub-questions are based on your answer to this first sub-question, a).
- **b)** Why do you think that your structure and your function are related? Support your contention based on 3 lines of evidence on the chemistry, physics, anatomy or physiology involved in your example.
- **c)** Which are the levels of organization involved in your example? Cite events occurring at its main level of organization and indicate how they relate to the whole body homeostatic level.
- **d)** Which are the main feedback mechanisms involved in your example (cite at least two)? Expand on one of them and indicate an absolute requirement for that feedback to be operational.