Endocrinology – glucose homeostasis

The pancreas

- Remember the pancreas is also exocrine.
- The pancreatic **islets** contain the following cells:

Islet cell type	Proportion	Hormone	Hormone action
α	20–30%	**glucagon**	**hyperglycaemia**
β	60–80%	**insulin**	**hypoglycaemic**
δ or D	≤ 8%	somatostatin	inhibits insulin and glucagon secretion
PP	variable	pancreatic polypeptide	? appetite

Insulin

Nature

- 51-amino acid polypeptide, made of two chains (A & B) connected by disulphide bridges.
- Synthesised from proinsulin by removal of the connecting (C) peptide. Proinsulin is itself made from preproinsulin.
- Acts on the insulin receptor, a cell-surface glycoprotein ($M_r \sim 340\ 000$). This receptor shows a maximum response with <10% occupancy. It can react with other agents (e.g. somatomedins, epidermal growth factor, nerve growth factor). The receptor shows "negative cooperativity" – affinity decreases with increasing concentrations of bound hormone.
- Receptors exhibit **downregulation:** continuous presence of high [insulin] reduces the number of insulin receptors on target cells (and the converse is also true).
- The receptor is a transmembrane **tyrosine kinase,** i.e. when activated it phosphorylates tyrosine residues of intra-cellular proteins. One of the proteins it phosphorylates is itself (*autophosphorylation*).

Functions

- Insulin is a **hormone of plenty.** It enhances the conversion of circulating pools of glucose, amino acids and FFAs into stored glycogen, protein and adipose tissue.
- **On carbohydrate metabolism,** it has two main functions. First, it **reduces the rate of release of glucose from the liver.** It does this by inhibiting glycogenolysis, by stimulating glucose uptake / glycolysis / glycogen synthesis, and by indirectly inhibiting gluconeogenesis via inhibition of fatty acid mobilization from adipose tissue. Second, it **increases the rate of uptake of glucose into all insulin-sensitive tissues,** notably muscle, adipose tissue and the ventromedial nucleus of the hypothalamus (the "satiety centre"). It does this directly, by stimulating glucose transport across the plasma membrane, and indirectly, by reducing plasma FFA levels.
- **On lipid metabolism,** it reduces the rate of release of glycerol/FFAs from adipose tissue, stimulates fatty acid synthesis and the conversion of FFAs to triglycerides in the liver.
- **On protein metabolism,** it stimulates uptake of amino acids into liver and muscle, stimulates protein biosynthesis and reduces the release of amino acids from muscle.
- **On ion transport,** it increases the accumulation of K^+ and Mg^{2+} in muscle and adipose tissue.
- **On growth and development.** It is particularly important in fetal development. Remember also that somatomedins (IGFs) have some activity at insulin receptors.

Control

- **Metabolites.** Glucose stimulates secretion, both directly and via the CNS and autonomic nerves. Amino acids also stimulate secretion (though they also increase glucagon release).
- **Hormones.** Gastrointestinal hormones stimulate secretion (gastrin, secretin, CCK…). Adrenaline, noradrenaline and somatostatin inhibit insulin release.
- **Nervous.** Parasympathetic activity stimulates release; sympathetic nervous stimulation of β cells inhibits insulin secretion.
- **Drugs.** Secretion is stimulated by sulphonylureas, for example.
- Secretion measured in international units (IUs). Basal secretion rate 1 IU/hour, total daily secretion 50 IU, pancreatic store 200–250 IU.
- Not all tissues experience the same level of insulin: thanks to the hepatic portal system, it reaches the liver in high concentration. 50% of insulin is removed in passage through the liver.
- Prolonged stimulation of β cells leads to hypertrophy, exhaustion, vacuolation and death. They are not replaced. Therefore any stimulus to prolonged hyperglycaemia is potentially diabetogenic.

Glucagon

Nature

- A 29-amino acid polypeptide.
- Acts via a G-protein-coupled receptor that stimulates adenylate cyclase.

Functions

- Acts primarily on the liver, where it stimulates glycogenolysis and gluconeogenesis and thus **increases hepatic glucose output.** Glucagon also stimulates **ketogenesis,** providing an alternative fuel for those tissues that can use it and sparing glucose for those that cannot do without.
- Also causes **lipolysis** in adipose tissue (which provides FFAs and glycerol for hepatic gluconeogenesis).
- Vital to defend blood glucose levels under conditions of prolonged fasting, exercise or in the neonatal period.
- An important part of the endocrine response to a high protein meal, because insulin alone could precipitate hypoglycaemia. The presence of both allows amino acid utilisation while maintaining normal glucose levels. Note the "anticipatory" response of both these hormones.

Control

- **Metabolites.** Hypoglycaemia is the most important trigger to secretion. Amino acids also stimulate glucagon release.
- **Hormonal/nervous.** Adrenaline and sympathetic activity stimulate glucagon secretion, while parasympathetic activity has the opposite effect. Somatostatin inhibits glucagon secretion.
- Advanced point. Pancreatic microcirculation is such that β cells are perfused first, then α cells, then D cells. The primary glucose sensor is in β cells. Insulin suppresses glucagon secretion, while glucagon stimulates insulin secretion. Somatostatin inhibits both α and β cells. If the β cells die, then not only is insulin lost but glucagon secretion is *increased*.

Overview

There is one glucose-lowering hormone – insulin – but many physiological antagonists. Hormonal control of glucose homeostasis involves

insulin	thyroid hormones
glucagon	gastrointestinal hormones
adrenaline & noradrenaline	growth hormone
cortisol	testosterone
ketones (both a messenger and a fuel)	…

A simplified summary (lifted from a previous lecture handout):

"Hormone"	Action on carbohydrate metabolism	Action on protein metabolism	Action on fat metabolism
insulin	hypoglycaemia ↑ glucose uptake by cells ↓ hepatic glucose output	↑ protein synthesis ↑ amino acid uptake by cells	↓ plasma FFAs Inhibits hormone-sensitive lipase Stimulates fat synthesis
glucagon	hyperglycaemia ↑ hepatic glucose output stimulates gluconeogenesis	–	↑ plasma FFAs ↑ lipolysis
adrenaline	hyperglycaemia ↑ hepatic glucose output ↓ insulin secretion ↑ glucagon secretion	–	↑ plasma FFAs ↑ lipolysis
GH	hyperglycaemia ↓ glucose uptake by muscle and adipose tissue	↑ protein synthesis ↑ amino acid uptake	↑ plasma FFAs ↑ lipolysis
cortisol	hyperglycaemia	stimulates deamination of amino acids	↑ plasma FFAs ↑ lipolysis
T_3	↑ use of all energy substrates inc. glucose	↑ protein degradation	↑ lipolysis
ketones	↓ glucose utilisation by brain (also muscle, kidney, mammary gland etc.)	↓ protein degradation ↓ gluconeogenesis	↓ lipolysis

You should know how hormones levels and metabolism changes during starvation (Part 1A biochemistry revisited). Consider the *postabsorptive phase* (glucose → stores), *early starvation* (begins 6h after a meal, lasts 18h; glycogen stores supply the brain with glucose while fatty acid stores supply other organs); *intermediate starvation* (24h after a meal until ~23 days; glycogen exhausted, protein is broken down to make glucose, some use of ketones), *prolonged starvation* (from ~24 days since last meal; protein is conserved and lipolysis predominates as tissues adapt to use FAs and ketones).

Diabetes mellitus (DM)

First, distinguish diabetes mellitus (disorder of sugar metabolism) from **diabetes insipidus (DI)**, caused by ADH deficiency and resulting in a polydipsic patient who produces large quantities of dilute urine.

Diabetes mellitus comes in two forms.

Insulin-dependent diabetes mellitus (IDDM), also known as *type I* or *juvenile-onset* DM. Accounts for 10–20% of cases. Due to severe, absolute lack of insulin, because the pancreatic β cell mass has been reduced. Patients are dependent upon insulin therapy for survival. Pathogenesis is by autoimmune destruction of islet β cells (*insulitis*).[1] Association with certain HLA-D (MHC class II) alleles.[2]

Non-insulin dependent diabetes mellitus (NIDDM), also known as *type II* or *adult-onset* DM. Accounts for 80–90% of cases. Much less is known about it. Genetic factors are even more important than for IDDM. Obesity and overeating predispose. NIDDM is characterised by (a) insulin secretion that is insufficient for the glucose load; (b) insulin resistance in peripheral tissues. There is a spectrum of disease: between normality and frank diabetes there is a condition called **impaired glucose tolerance (IGT)** which is basically a mild version of NIDDM. Severe forms may need insulin therapy, but milder forms can be treated by dietary control and oral hypoglycaemic drugs.

Diabetic ketoacidosis (DKA)

A complication of IDDM (*very* rare in type II diabetes). Results from severe insulin deficiency, coupled with absolute or relative increases in glucagon.

Insulin deficiency causes hyperglycaemia, which causes polyphagia and glycosuria. Glycosuria produces polyuria, which cases volume depletion (and polydipsia). In addition, insulin deficiency causes increased lipolysis, which increases FFA levels. This results in more FFA oxidation in the liver – accelerated by glucagon – resulting in the formation of ketone bodies. If ketones are formed more rapidly than they can be used, ketonaemia and ketonuria occur. If the urinary excretion of ketones is compromised by dehydration, the plasma H^+ ion concentration rises and *systemic metabolic ketoacidosis* and coma result.

DM is known as "starvation in the midst of plenty" – glucose is all around, but tissues aren't using it.

Symptoms include polydipsia, nausea, vomiting, respiratory difficulties. Signs include an odour of ketones, dehydration and coma. Glucose levels will be very high. A medical emergency.

Hyperosmolar non-ketotic coma (HONK)

In type II diabetes, the fasting hyperglycaemia may be accompanied by polyuria, polydipsia and polyphagia, but ketoacidosis is rare. Nevertheless, severe dehydration may occur, leading to coma.

Complications of diabetes

Apart from the emergencies, much diabetic morbidity is caused by retinopathy, cataract formation and glaucoma (→blindness), nephropathy, atherosclerosis (→heart attacks, strokes) and neuropathy (→numb feet!). The hyperglycaemia also encourages certain infections. Good control of glucose levels helps to prevent all these complications.
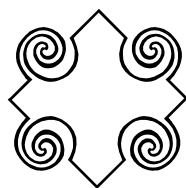
That's it for endocrinology!

Postscript – grammatical whinge

I've just noticed that your current lecture handout gets "its" and "it's" wrong. Never do this in an exam; it makes you look illiterate.

"It is", "it has" can be *abbreviated* to "it's". Because it's an abbreviation, you use an apostrophe. (*It's a beautiful day; it's got a ruffled collar.*)

In the sense of "belonging to it", "its" is a word in its own right. (*Its role as an anti-hypercalcaemic agent is doubtful; ... by controlling its exchange with calcium...*) The more common mistake is to put an apostrophe here, which is what your lecturer has done. People assume incorrectly that because you use an apostrophe to denote possession with names (*Rob's bike*), you need to use one here.

My apologies in advance if you knew this.

---

[1] N.B. Insulin is so named because it comes from the islets (Latin *insula* = island).

[2] You should know why this is common in autoimmune disease!