Imperial College Healthcare NHS
NHS Trust

The Endocrine Pancreas

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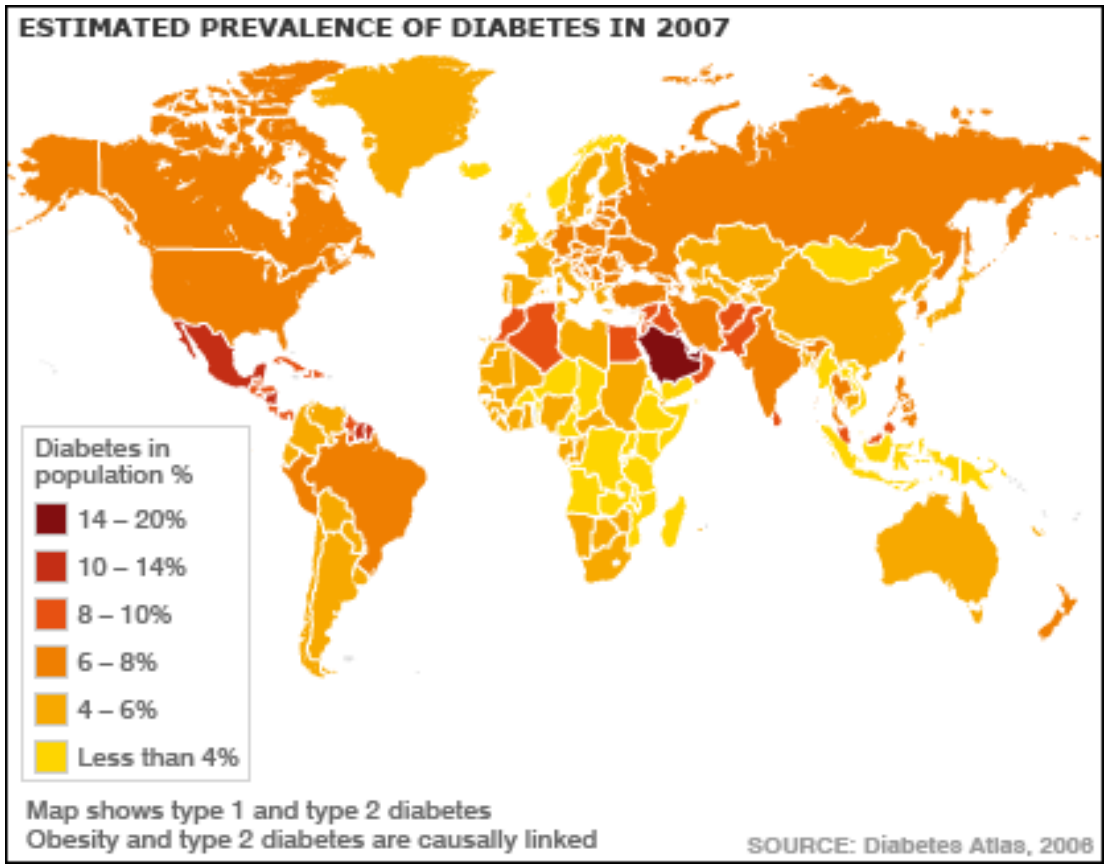
Worldwide, there are 170 million people with diabetes mellitus



- This prevalence will double before 2030
- 2.7 million with diabetes mellitus in UK
- 3.2 million deaths annually directly attributable to diabetes
- Commonest cause of end stage renal failure, blindness and non-traumatic amputations

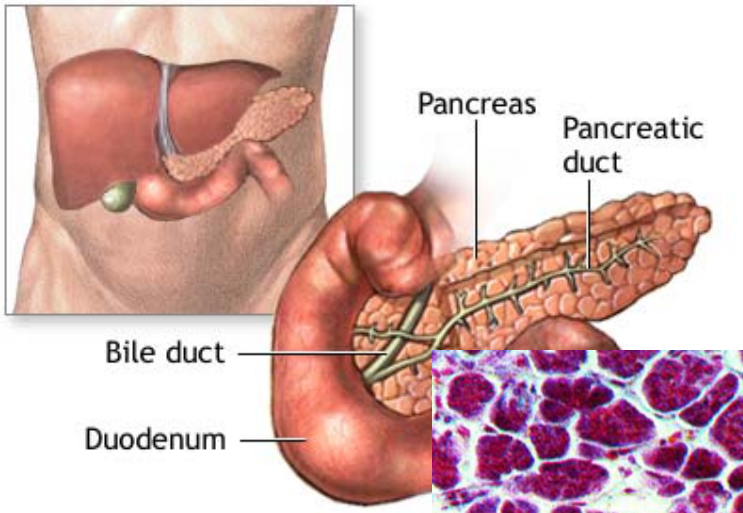
Aim of lecture

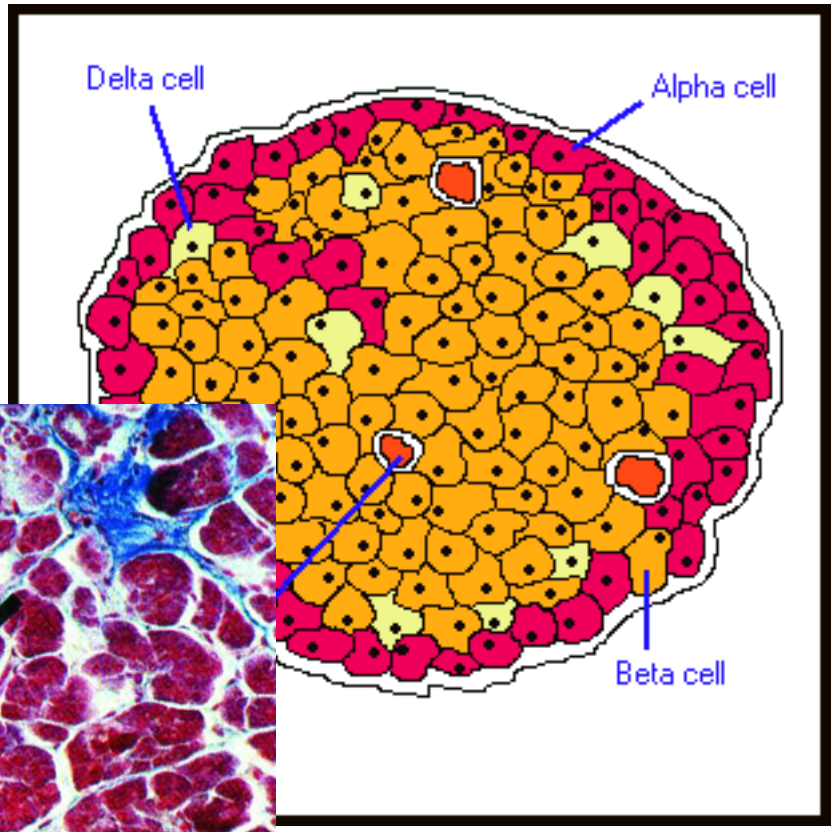
To explain the endocrine pancreas and how it regulates carbohydrate, lipid and protein metabolism

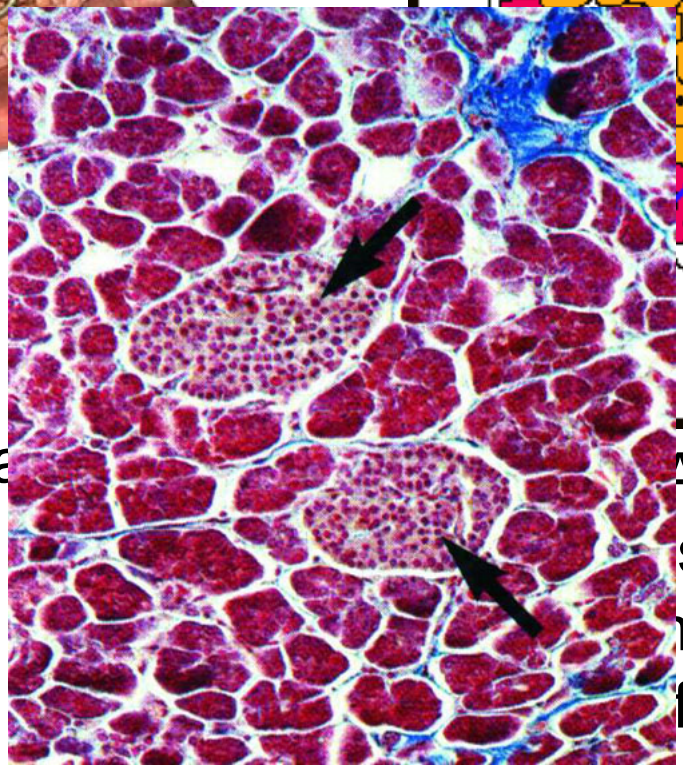
Learning objectives

1. Know the anatomy, embryology and physiology of the endocrine pancreas
2. Describe glucose sensing by the beta cell
3. Be able to describe the principal actions of insulin and glucagon on metabolism
4. Be able to describe the synthesis, storage and regulation of insulin and glucagon secretion
5. Discuss the insulin receptor and its function
6. Be able to integrate the actions of insulin and glucagon on intermediary metabolism

Pancreas - Anatomy





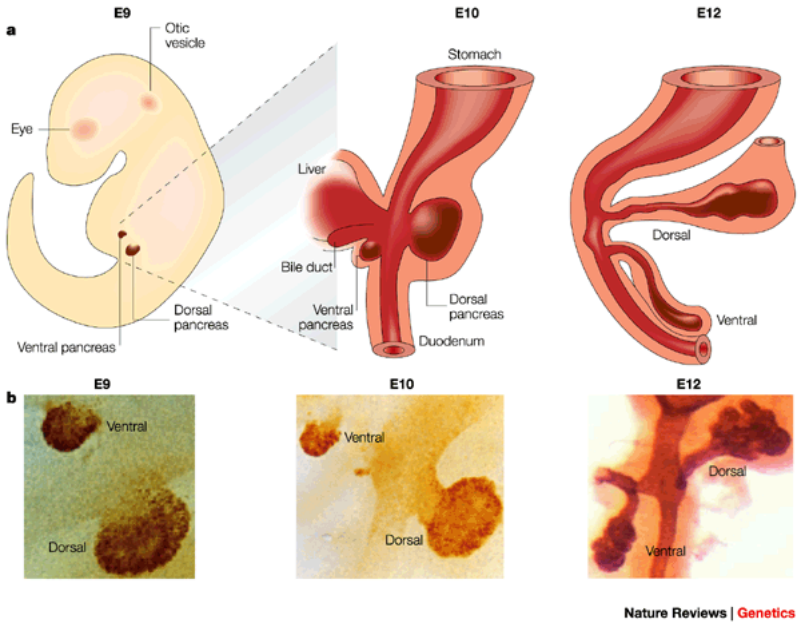


β cell - insulin
α cell - glucagon
δ cell - somatosta

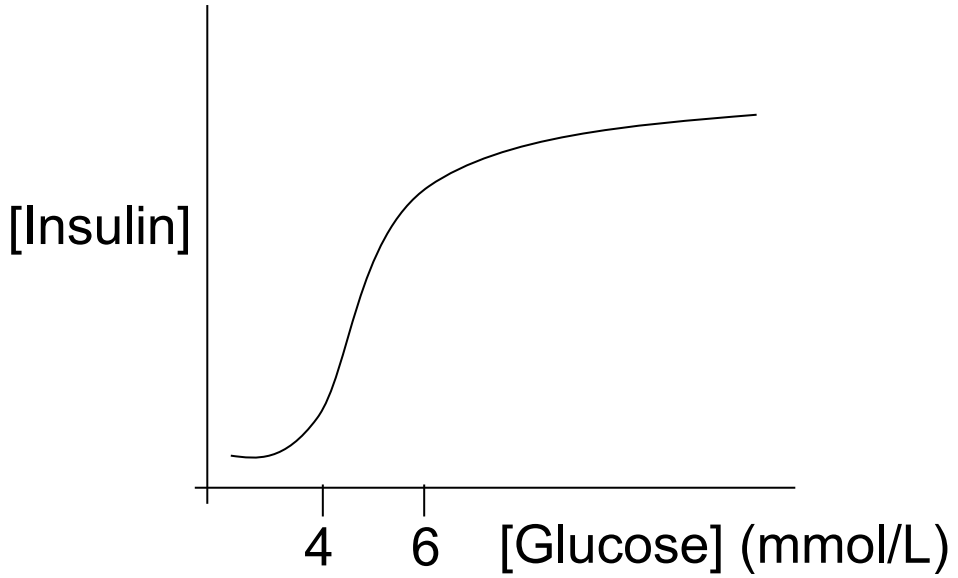
Autonomic innervation
slets = 2% of pancreatic
ass, but receive 15%
f perfusion

Pancreas - Embryology

- Develops from two buds from the primitive gut
- Buds grow, branch and fuse
- Islet cells differentiate from cells adjacent to buds
- Endocrine function from 10–15 weeks



Pancreas - Physiology



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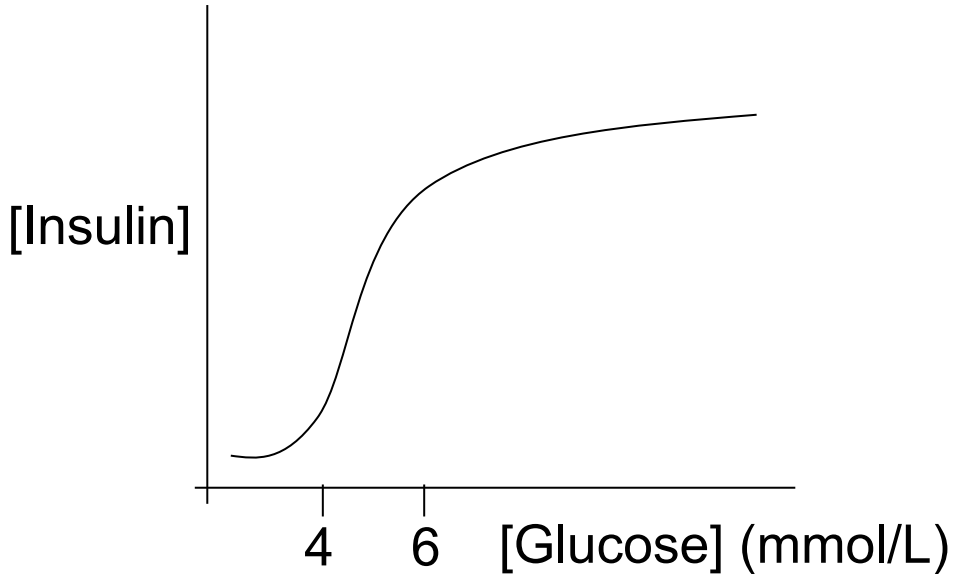

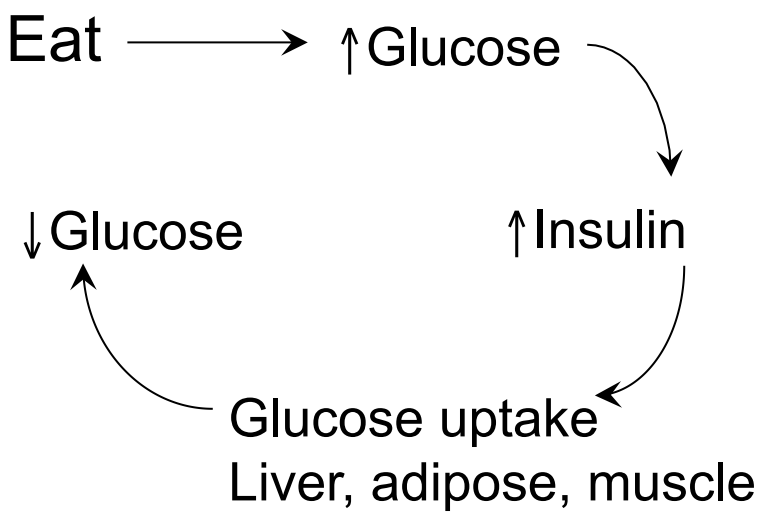

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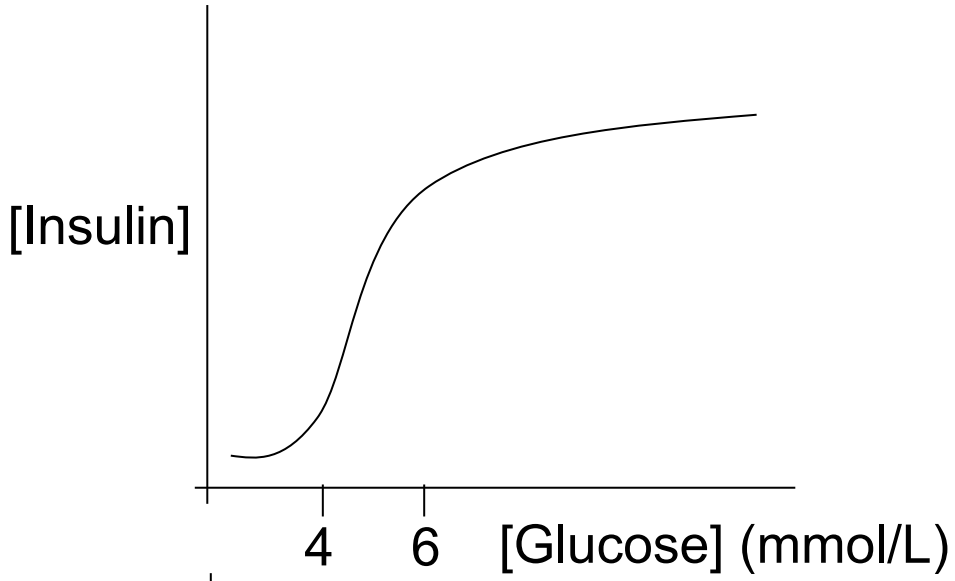

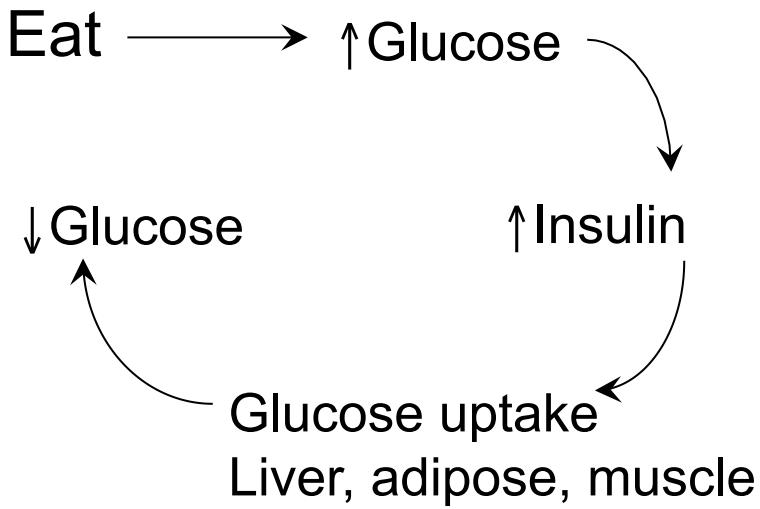

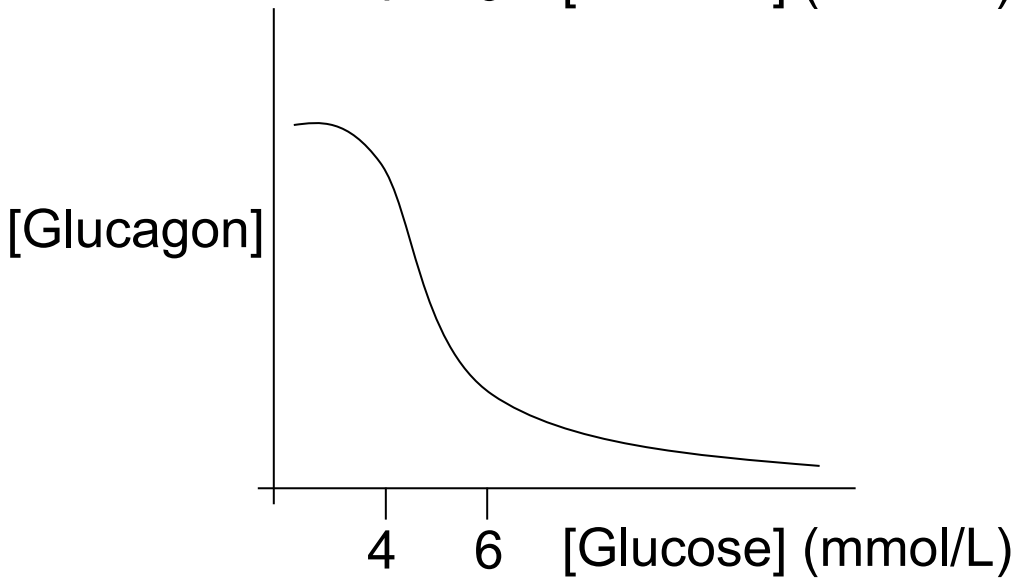

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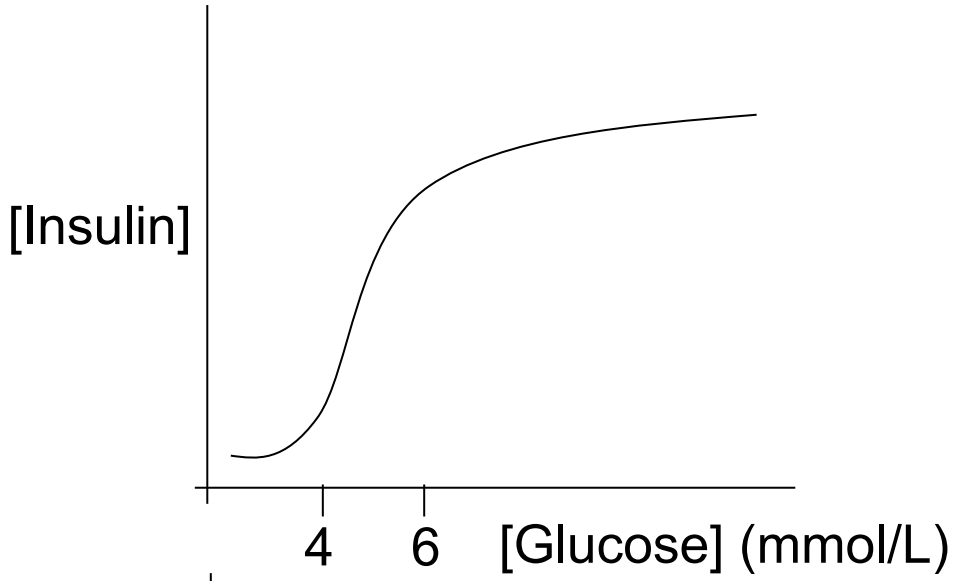

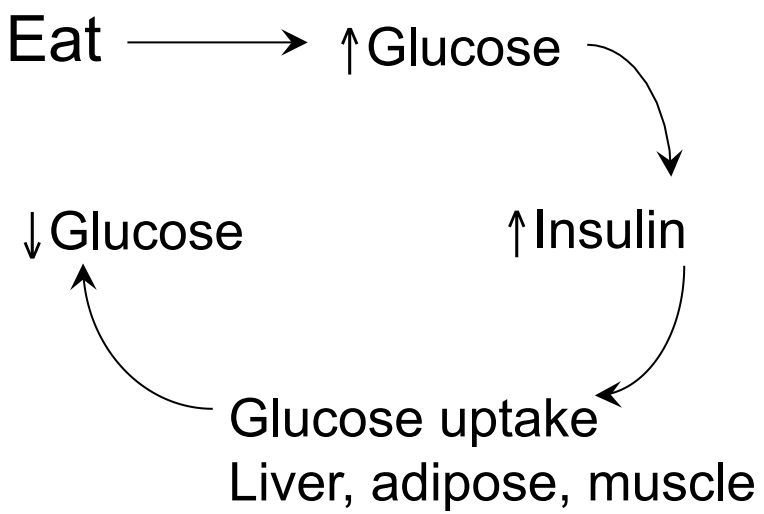

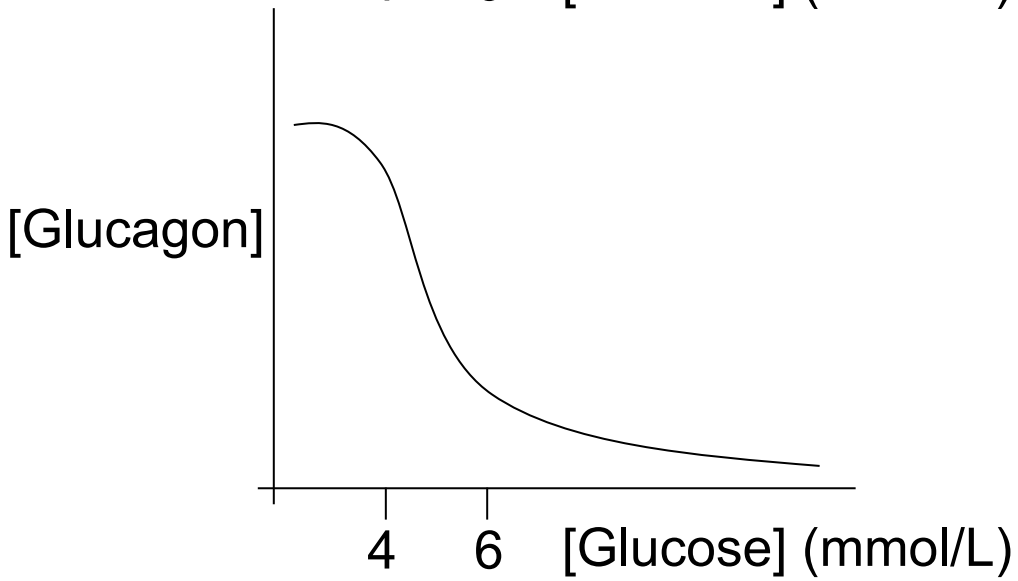

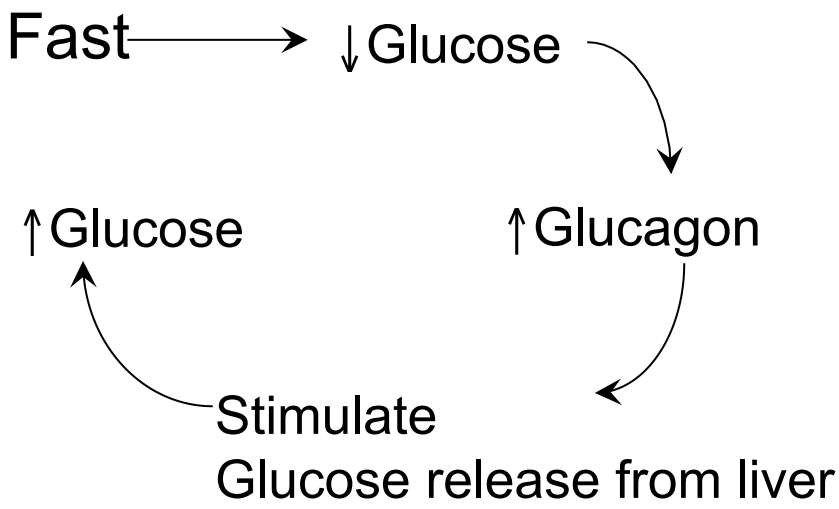

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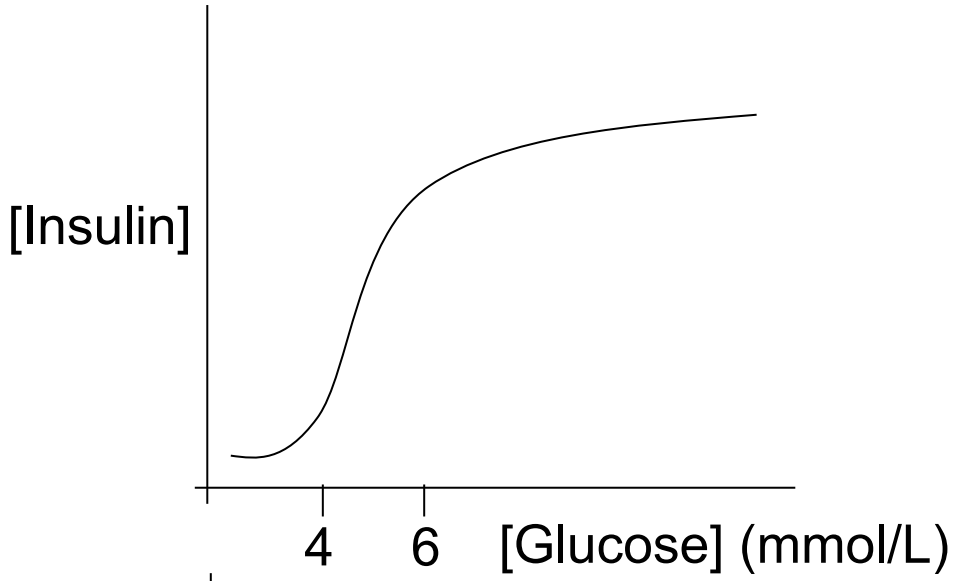
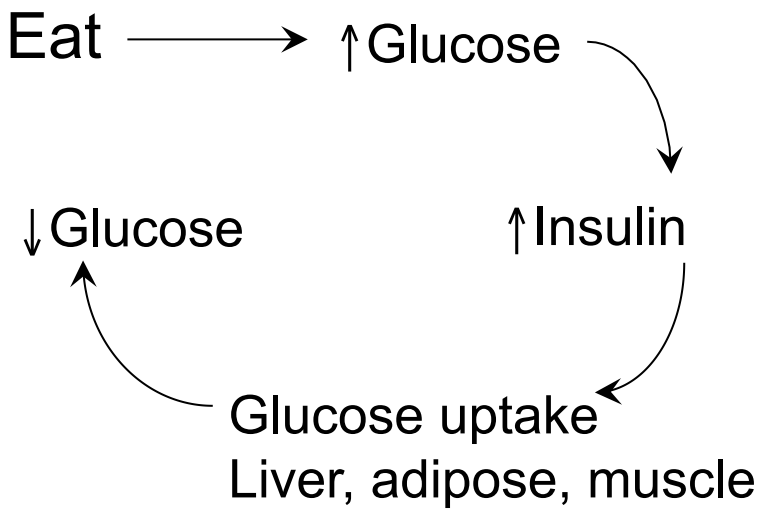
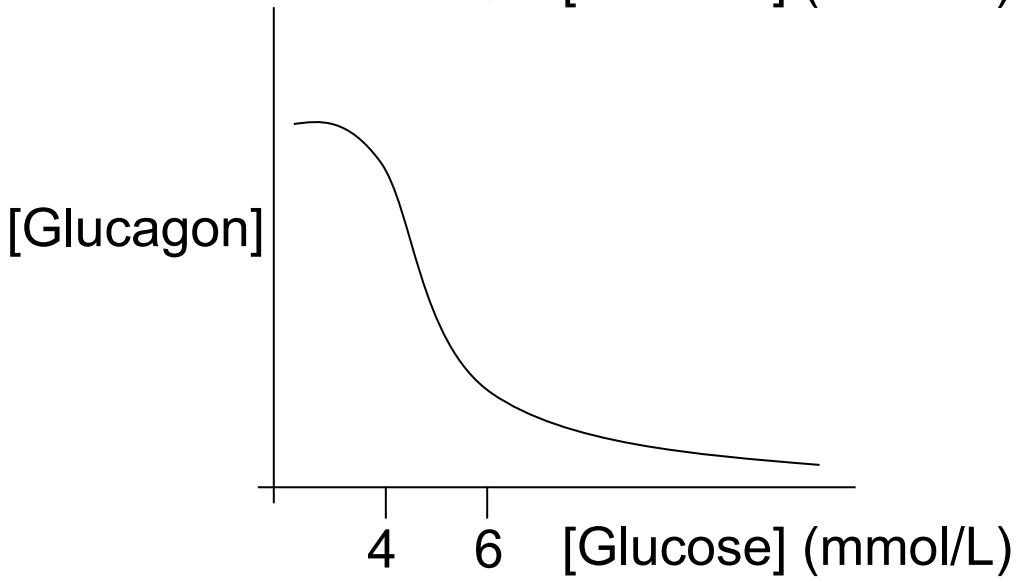
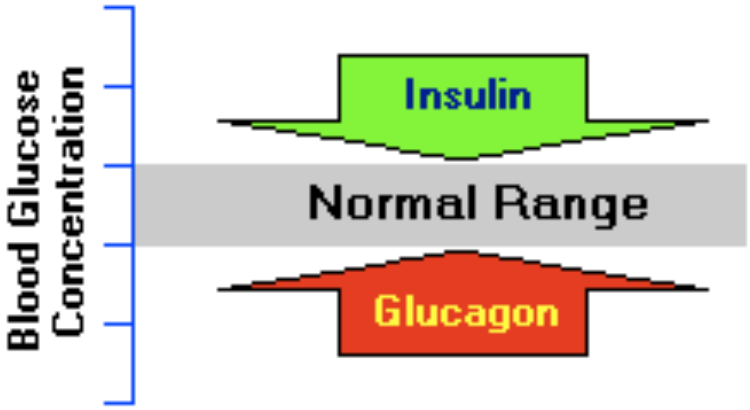


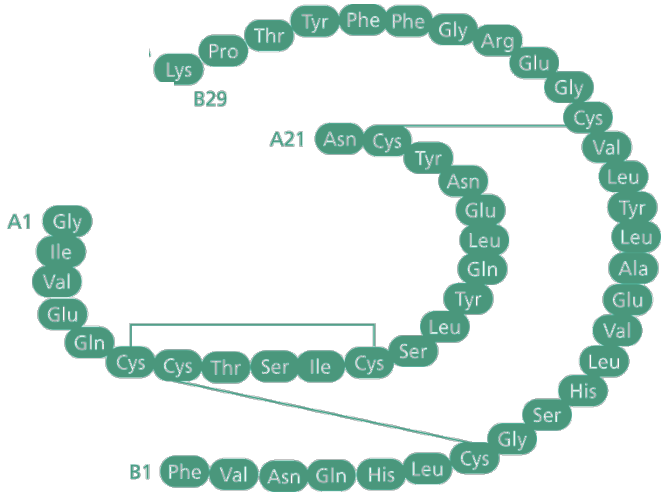






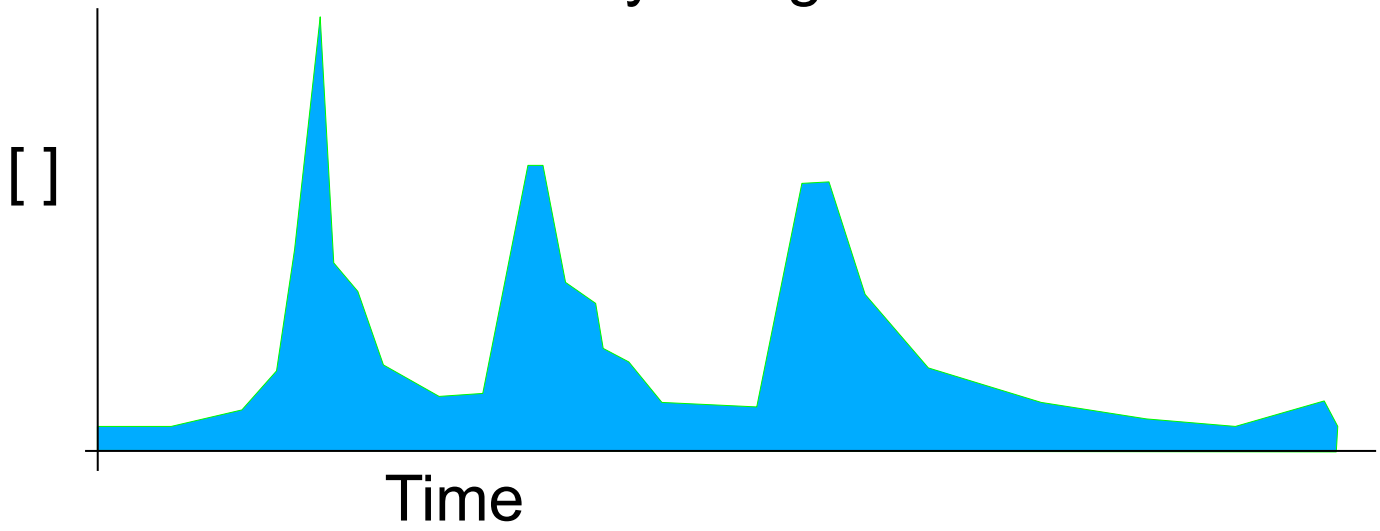
Banting/Best/Collip Isolate Insulin in 1920

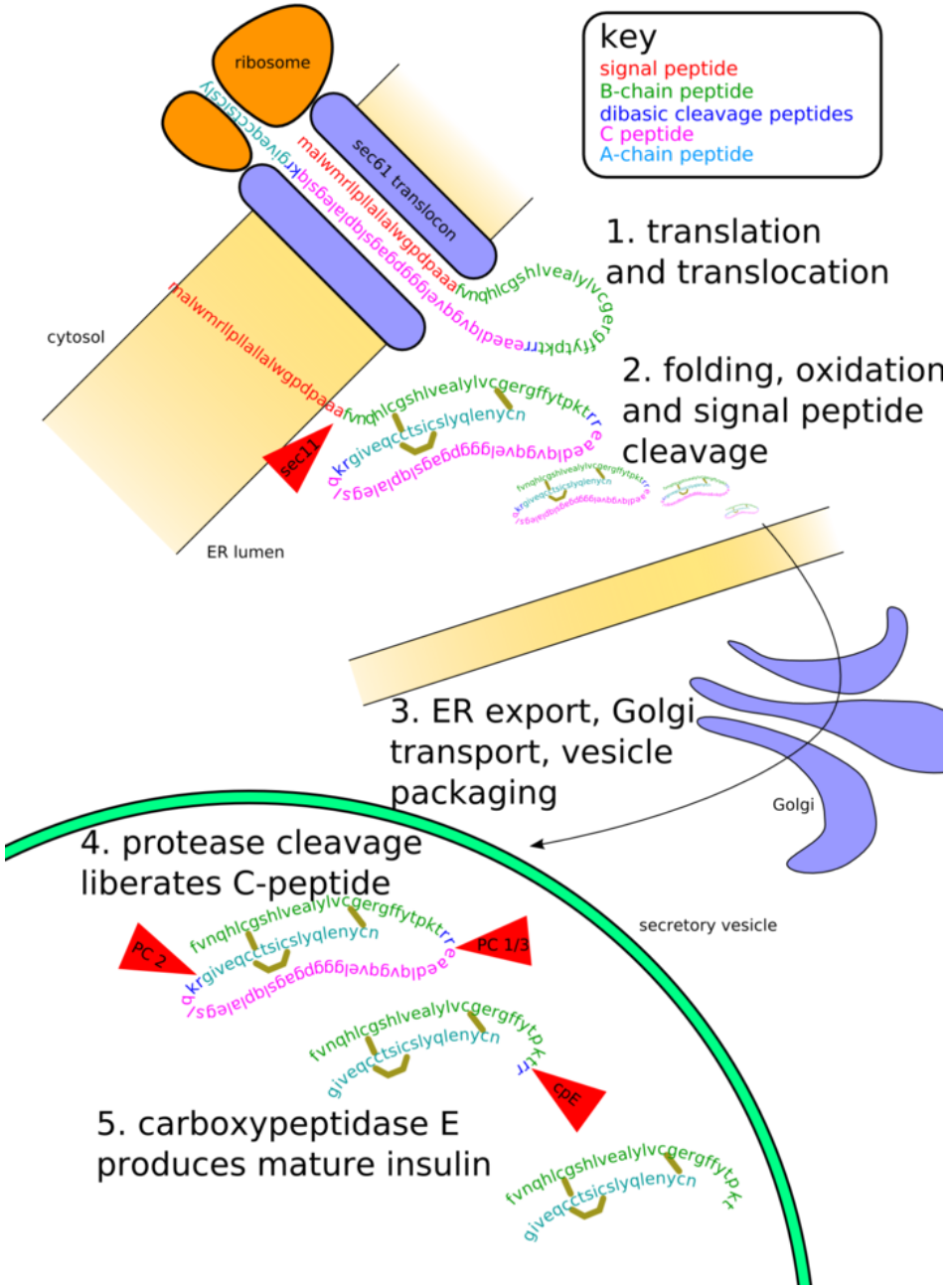
Insulin Synthesis and Secretion



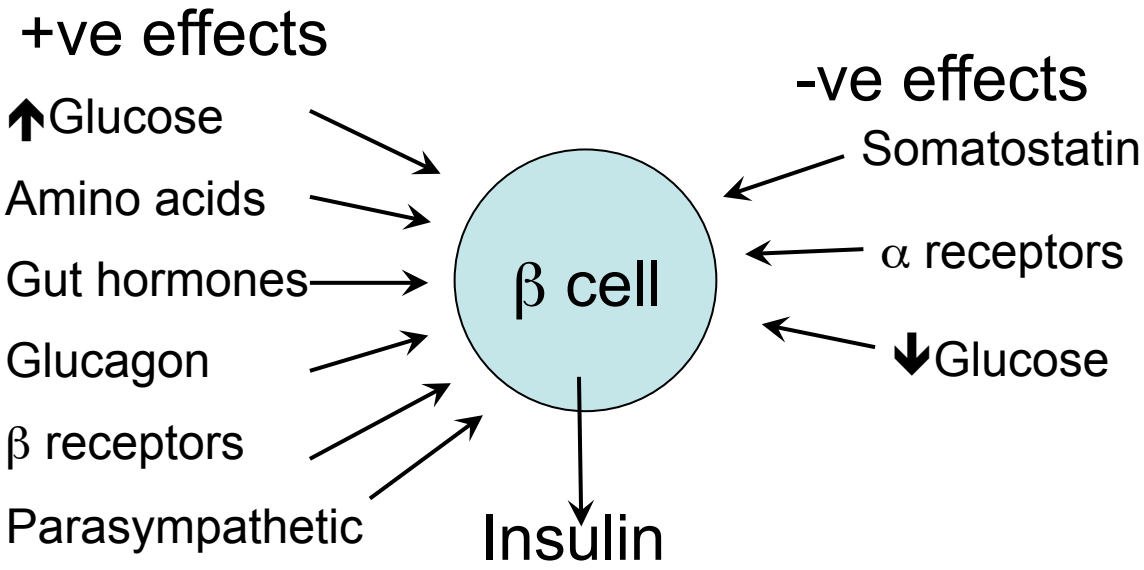
- 50 AA peptide, 3 intramolecular disulphide bridges, 5808 kDa
- Synthesised as preproinsulin
- Peptidases cleave C-peptide off
- Half life of insulin in the circulation = 6 minutes

Physiological Insulin Profile:

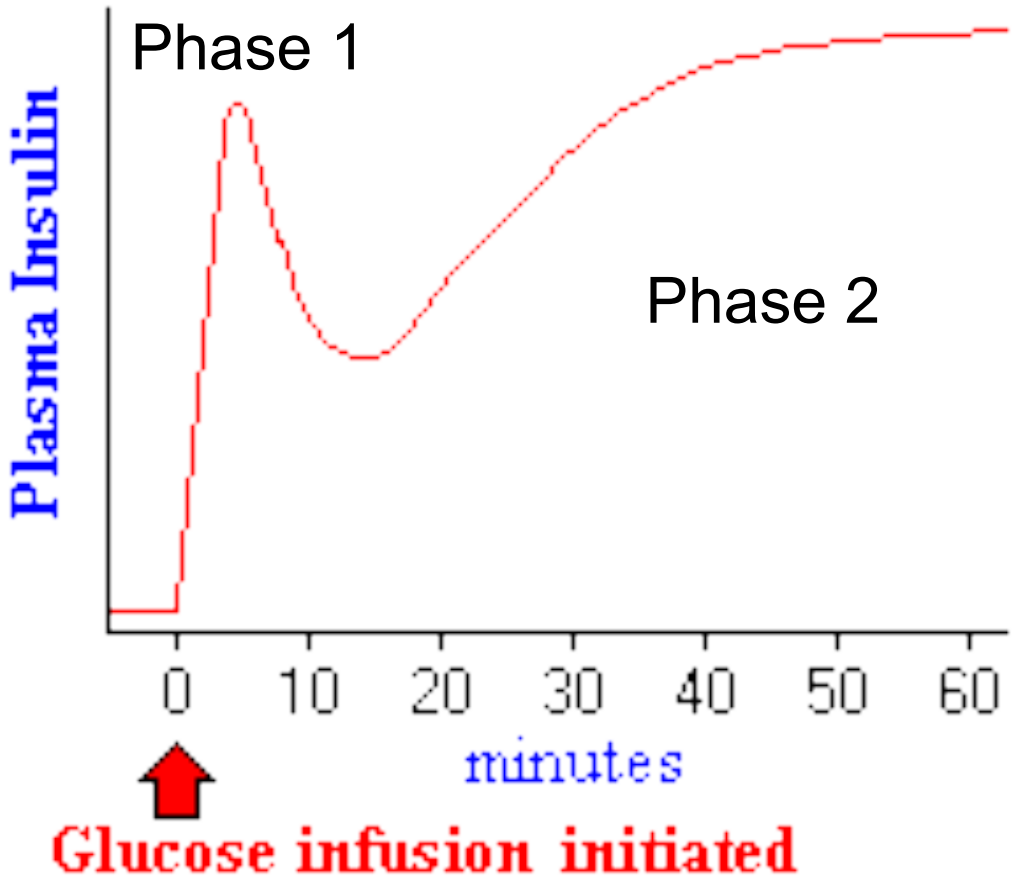



key
signal peptide
B-chain peptide
dibasic cleavage peptides
C peptide
A-chain peptide
ribosome
sec61 translocon
cytosol
ER lumen
1. translation and translocation
2. folding, oxidation and signal peptide cleavage
sec11
3. ER export, Golgi transport, vesicle packaging
Golgi
secretory vesicle
4. protease cleavage liberates C-peptide
PC 2
PC 1/3
5. carboxypeptidase E produces mature insulin
cpE

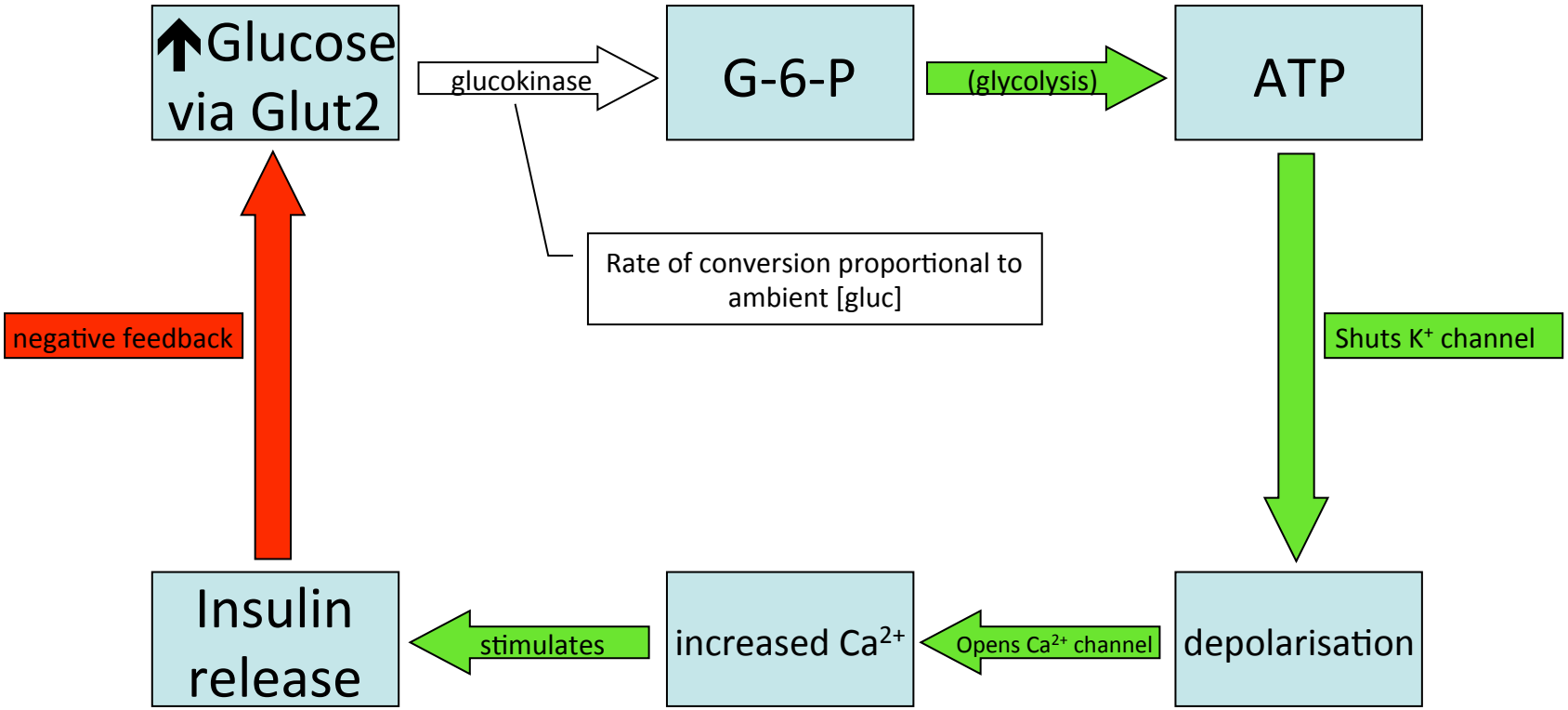
Insulin Release



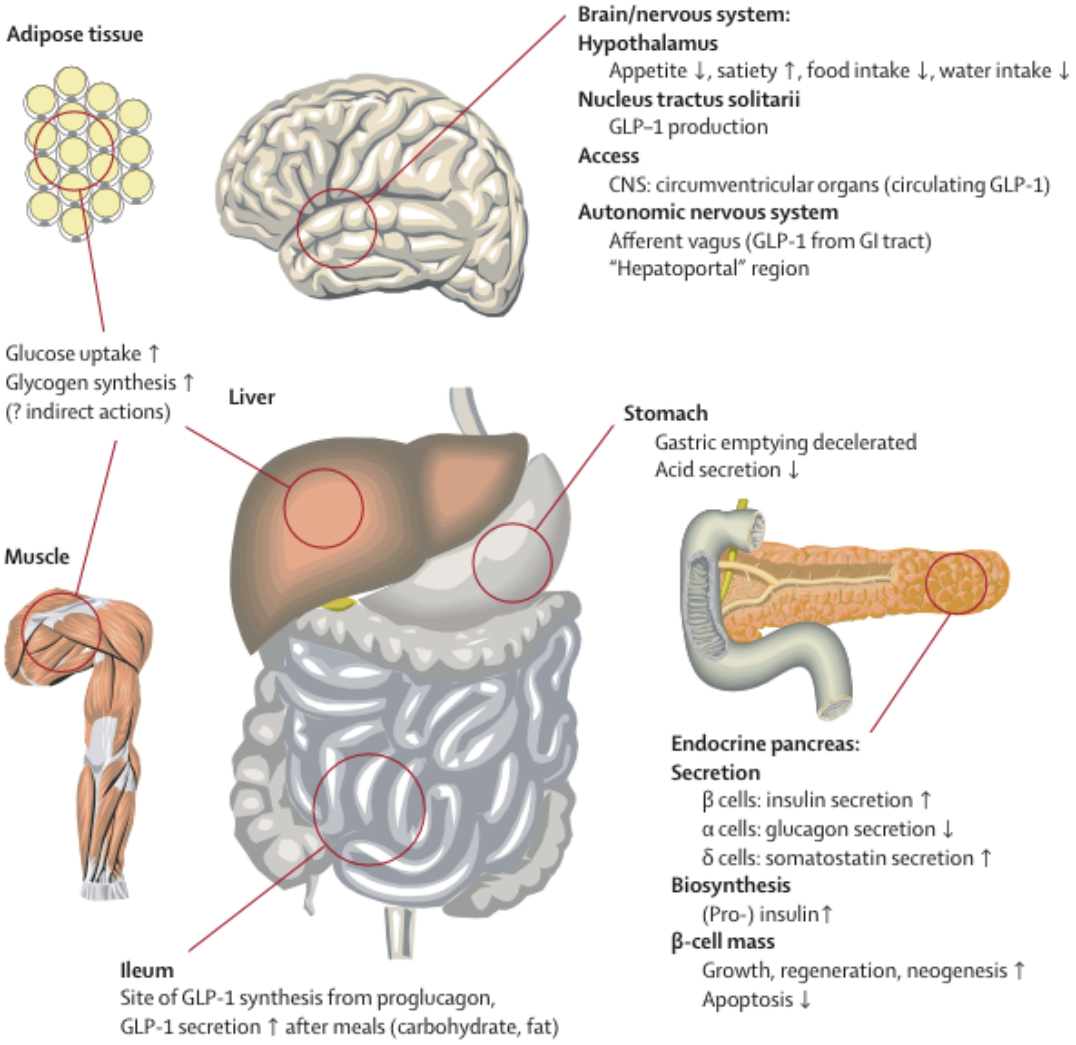
Biphasic insulin release



Glucose sensor in beta cells

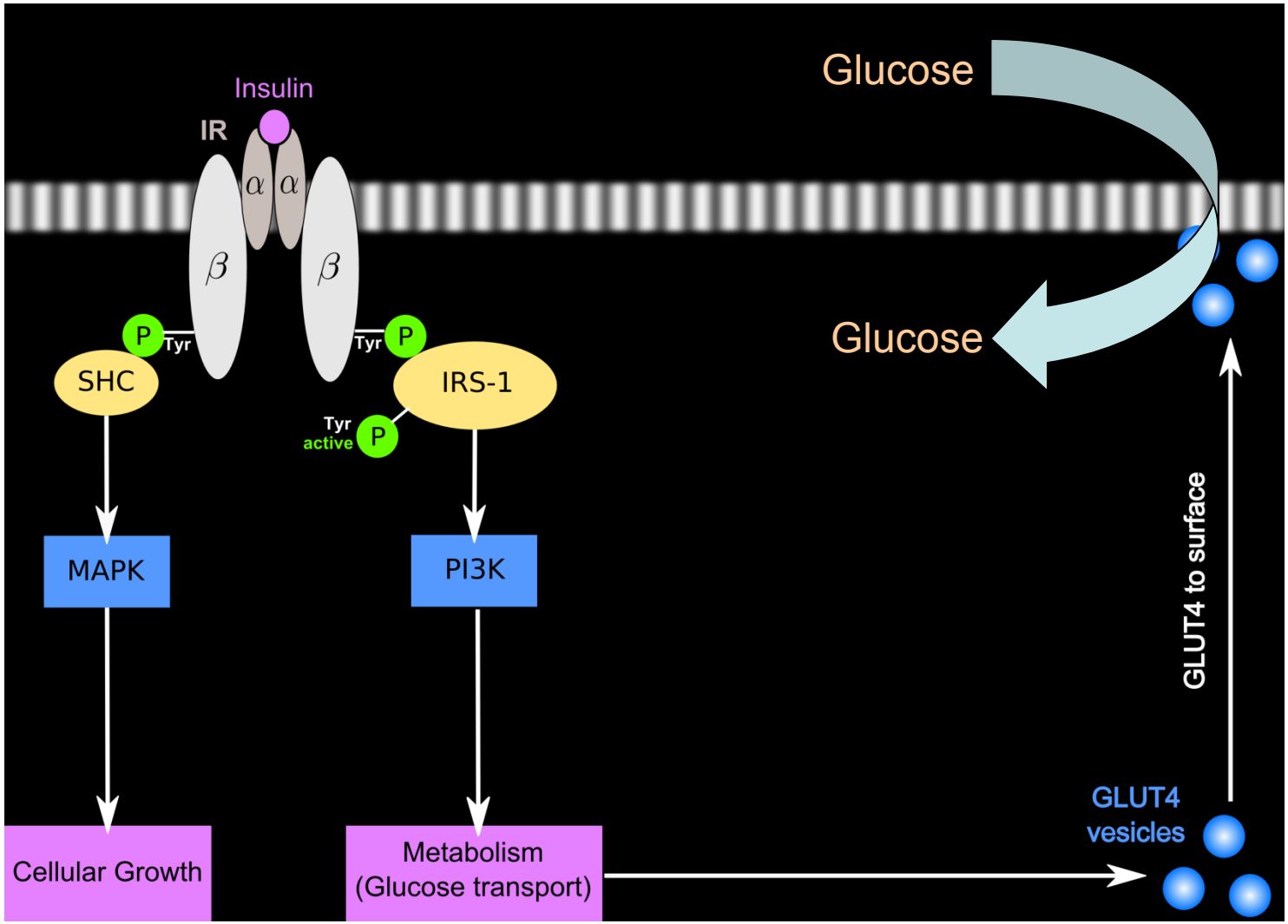


Glucagon-like peptide 1 (GLP-1) is an incretin



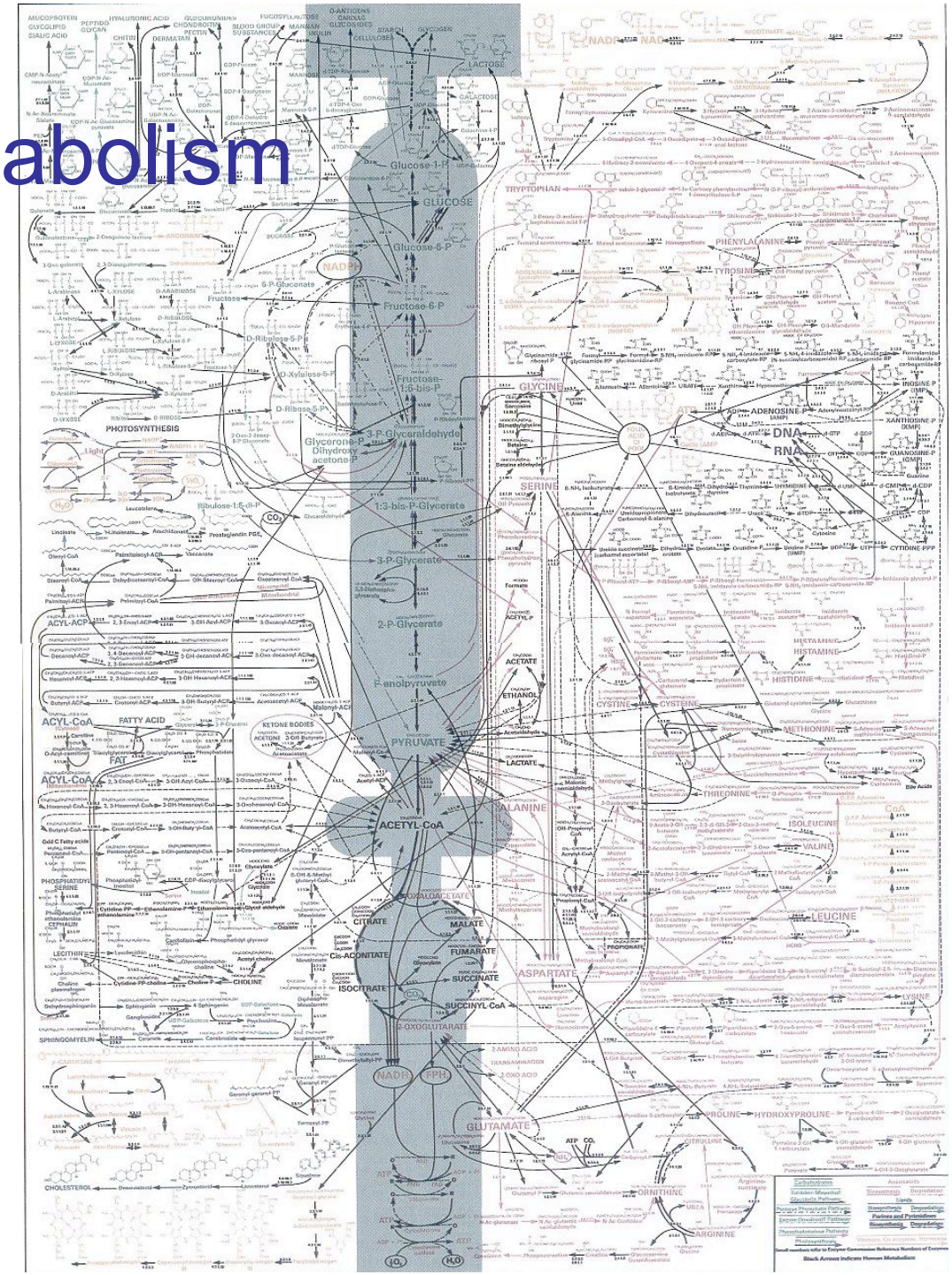
- Stimulates Insulin secretion
- Inhibits Glucagon secretion
- Inhibits Gastric emptying
- Inhibits Appetite
- Stimulates Nausea

Molecular Basis of Insulin Action

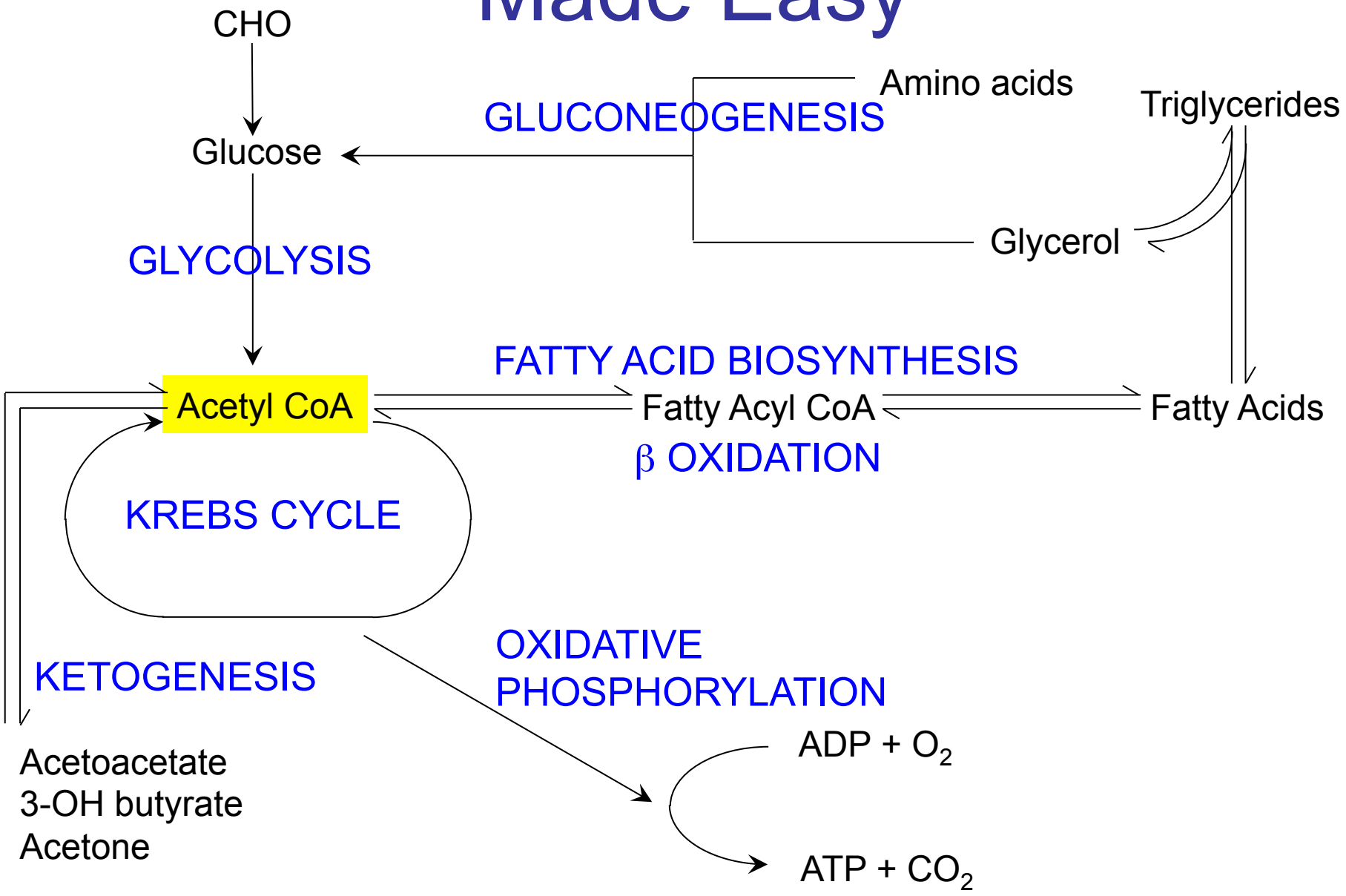


Intermediary Metabolism

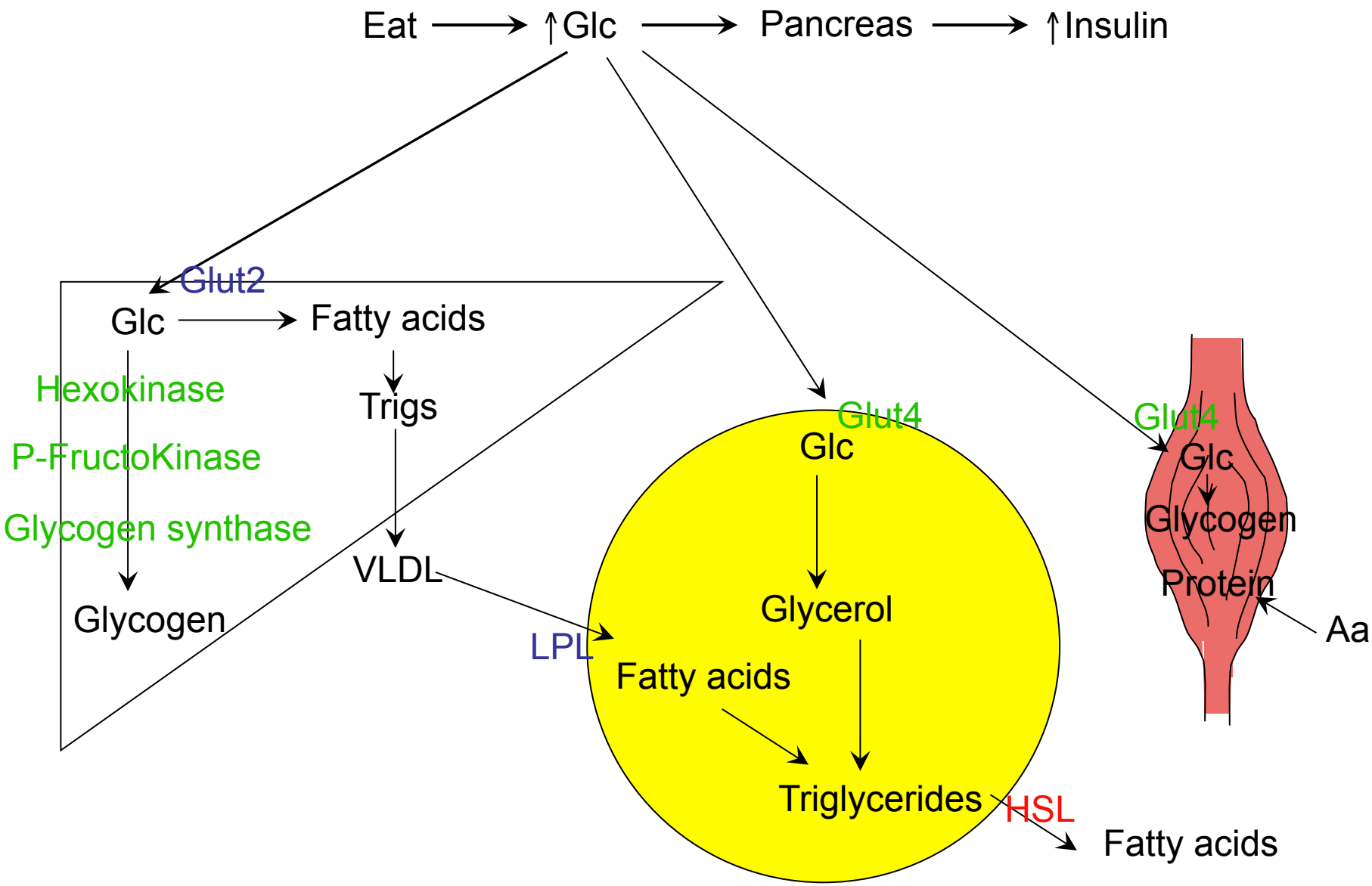
All reactions concerned with storing and generating metabolic energy. Using that energy in cellular processes



Intermediary Metabolism Made Easy



Insulin & Intermediary Metabolism

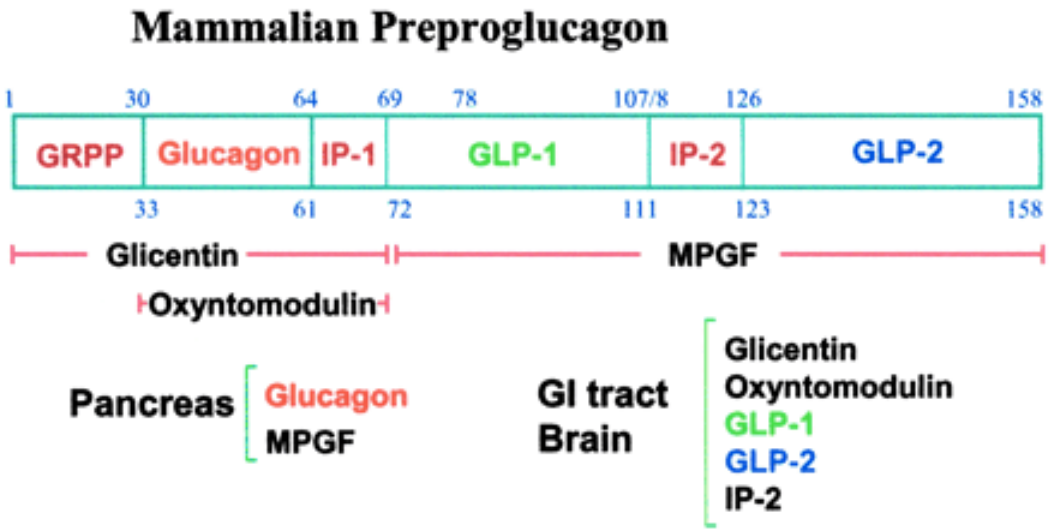


Actions of Insulin

- Carbohydrate
  - Glucose uptake
  - Glycogenesis
  - Inhibit glycogenolysis
  - Inhibit gluconeogenesis
- Lipid
  - Inhibit HSL
  - Hepatic fatty acid synthesis
  - Suppress ketone body production
- Protein
  - Aa uptake
  - Anabolic
- Others
  - K^+ uptake
  - H_2O retention

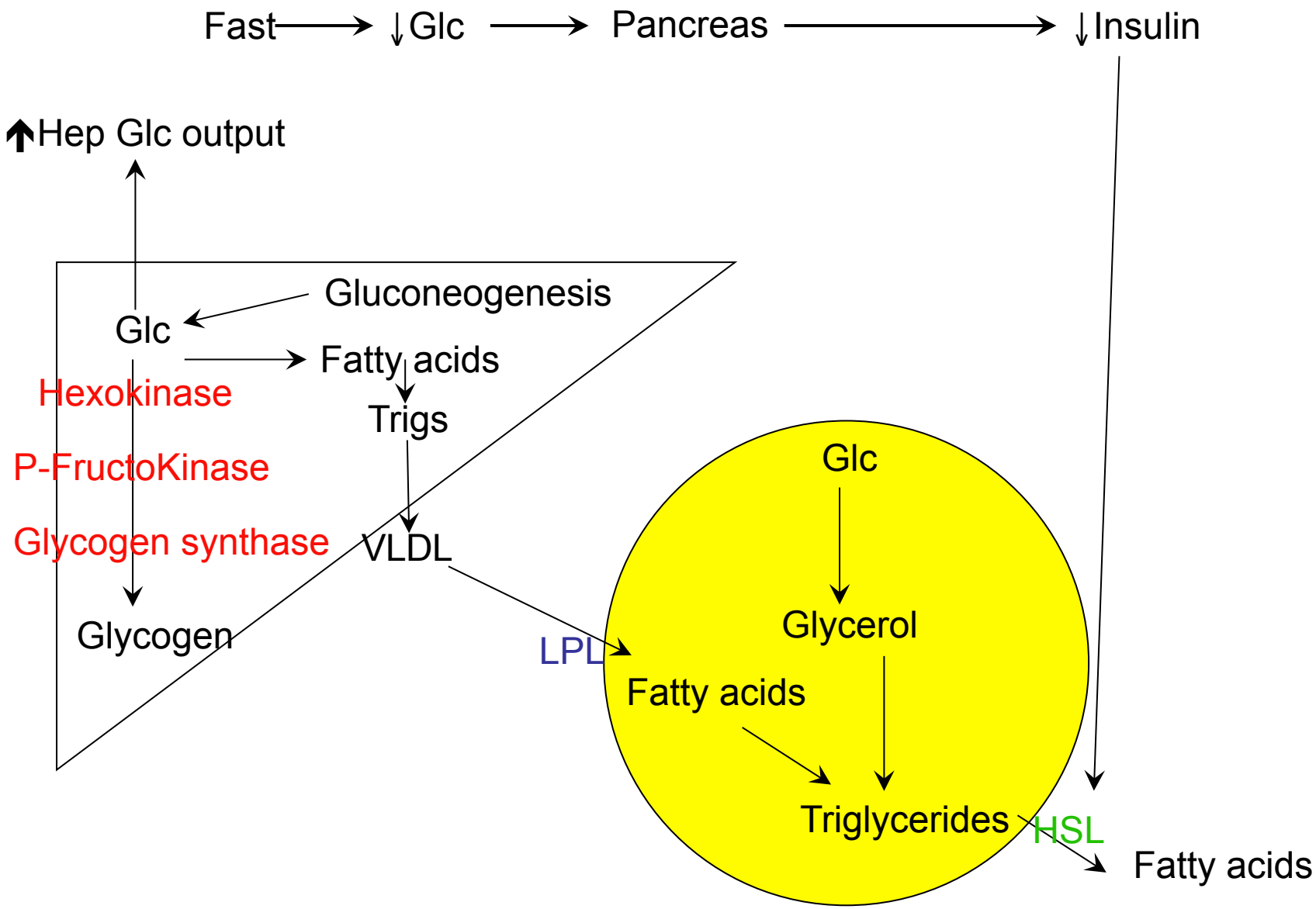
Glucagon

- 29 Aa peptide hormone from alpha cells
- Synthesised from preproglucagon

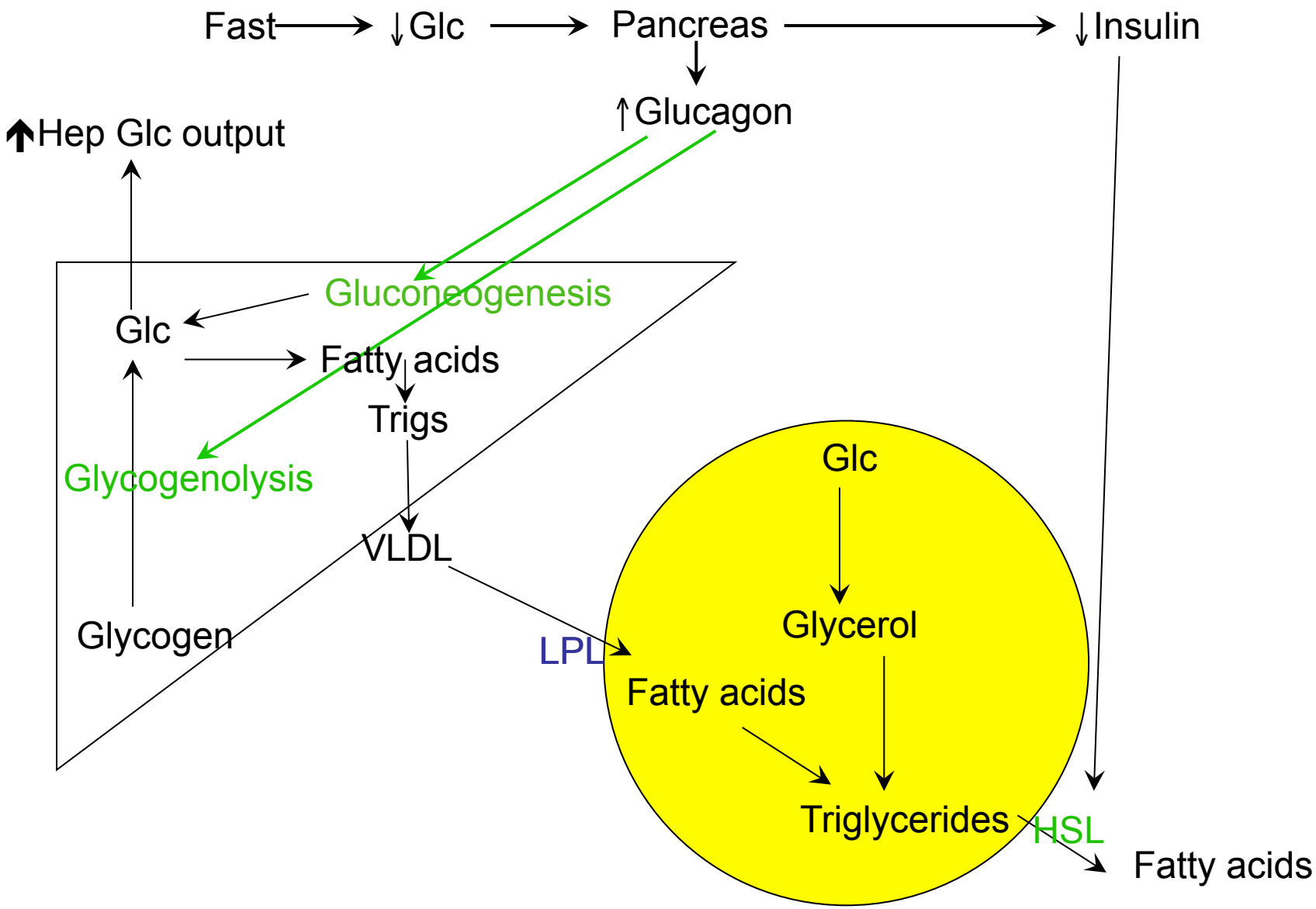


- Released in response to low blood glucose
- Stimulates glycogenolysis and gluconeogenesis
- Disordered secretion also occurs in diabetes mellitus

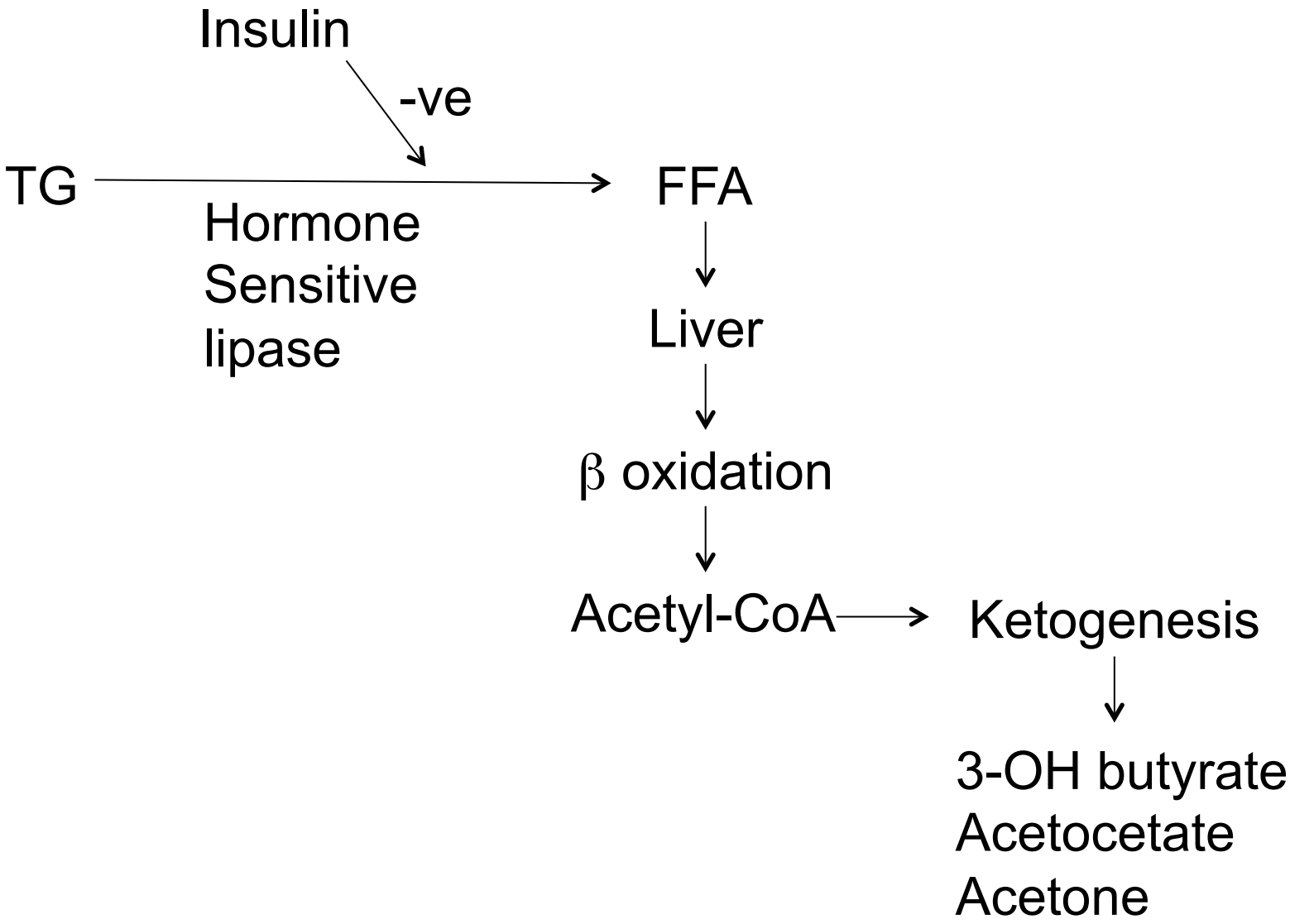
Insulin & Intermediary Metabolism



GCG & Intermediary Metabolism



Ketogenesis



N.B.

- Islets do secrete other hormones
  - Pancreatic Polypeptide
  - Vasoactive Intestinal Polypeptide
  - Ghrelin
  - Gastrin
  - Somatostatin
- Rarely functional endocrine tumours of the pancreas release these hormones
- This can occur in genetic diseases such as multiple endocrine neoplasia type 1

Summary

- The endocrine pancreas mainly secretes insulin (β cells) and glucagon (α cells)
- They have opposing effects on blood glucose (insulin↓, glucagon↑)
- Insulin controls much more than just carbohydrate metabolism (lipids and protein, K)
- The principal insulin-responsive tissues are liver, adipose and muscle
- Diabetes mellitus, the commonest endocrinopathy is caused by a lack of insulin action and excessive glucagon
- Neuroendocrine tumours of the pancreas are rare but important (especially at Hammersmith Hospital!)