EAT TO LIVE: THE ROLE OF THE PANCREAS

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THE ROLE OF THE PANCREAS

- Exocrine pancreas
- Endocrine pancreas

THE ROLE OF THE PANCREAS

- EXOCRINE PANCREAS
  - **Digestive enzymes**
  - **Sodium bicarbonate**

EAT TO LIVE: THE ROLE OF THE PANCREAS

- Digestive enzymes
  - Trypsin, chymotrypsin and carboxypeptidase
  - Pancreatic amylase
  - Pancreatic lipase, cholesterol esterase, phospholipase
- Bicarbonate ions

EAT TO LIVE: THE ROLE OF THE PANCREAS

- Regulation of exocrine pancreatic secretion

- **1. Acetylcholine**
- **2. Cholecystokinin (CCK)**
- **3. Secretin**

THE PANCREAS

- *Clinical correlation*
  - *Acute pancreatitis*
  - *Exocrine pancreatic insufficiency*
  - *Endocrine pancreatic insufficiency*

THE ROLE OF THE PANCREAS

- ENDOCRINE PANCREAS
  - **Insulin**
  - **Glucagon**
  - **Somatostatin**
  - **Pancreatic polypeptide**
  - **Amylin**
  - **Uncoupling protein 2**

EAT TO LIVE: THE ROLE OF THE PANCREAS

- Insulin
  - Hypoglycemic hormone
  - Beta cells
  - Two chain polypeptide
  - Receptor interactions
  - Intracellular interactions
  - Transporters
  - *Clinical correlation*

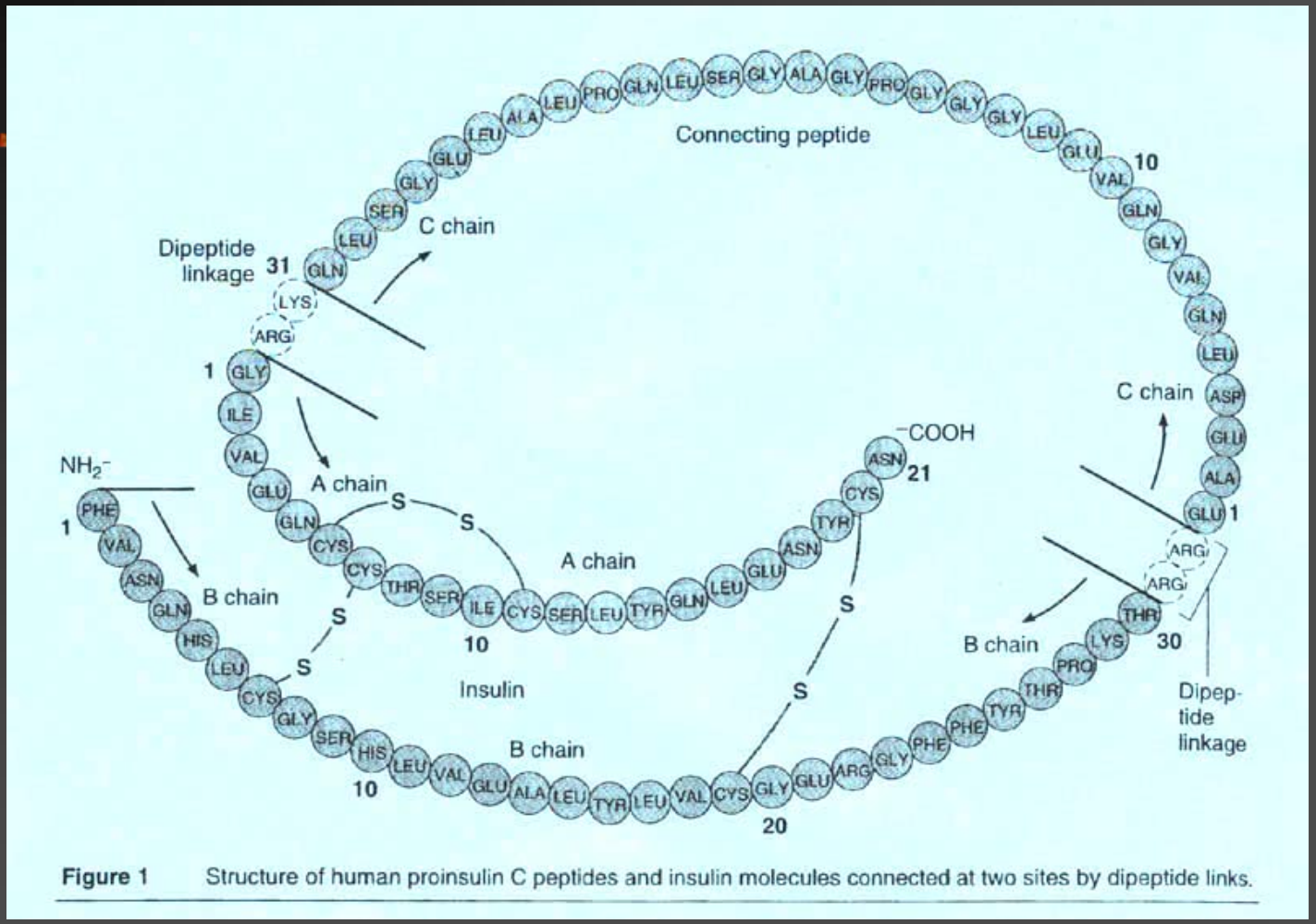
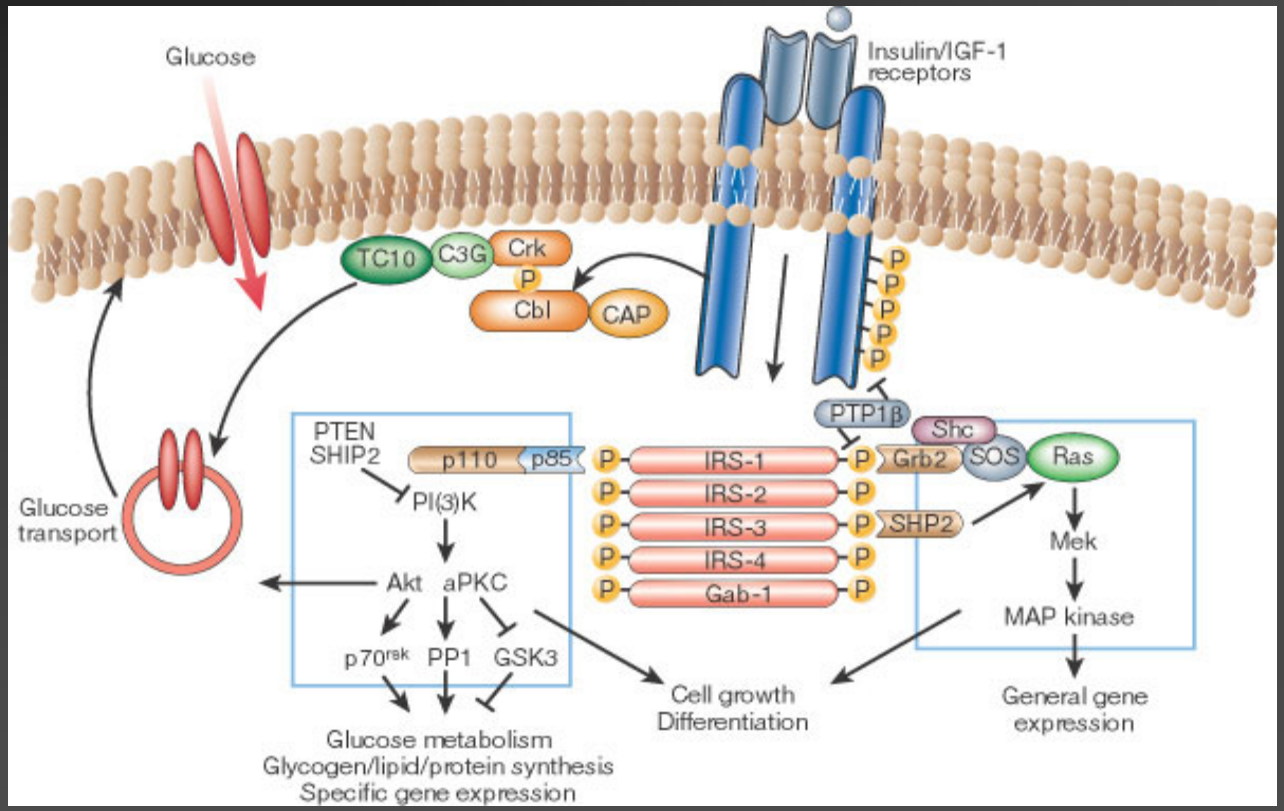


Figure 1 Structure of human proinsulin C peptides and insulin molecules connected at two sites by dipeptide links.

INSULIN MECHANISM OF ACTION

- Insulin binds to its transmembrane receptor.
- β subunits of the receptor become phosphorylated; receptor has intrinsic tyrosine kinase activity.
- Intracellular proteins are activated/inactivated—IRS-1, IRS-2 and seven PI-3-kinases; GLUT-4, transferrin, LDL-R, IGF-2-R move to the cell surface.
- Cell membrane permeability increases: glucose, K^+, amino acids, PO_4

INSULIN Signaling



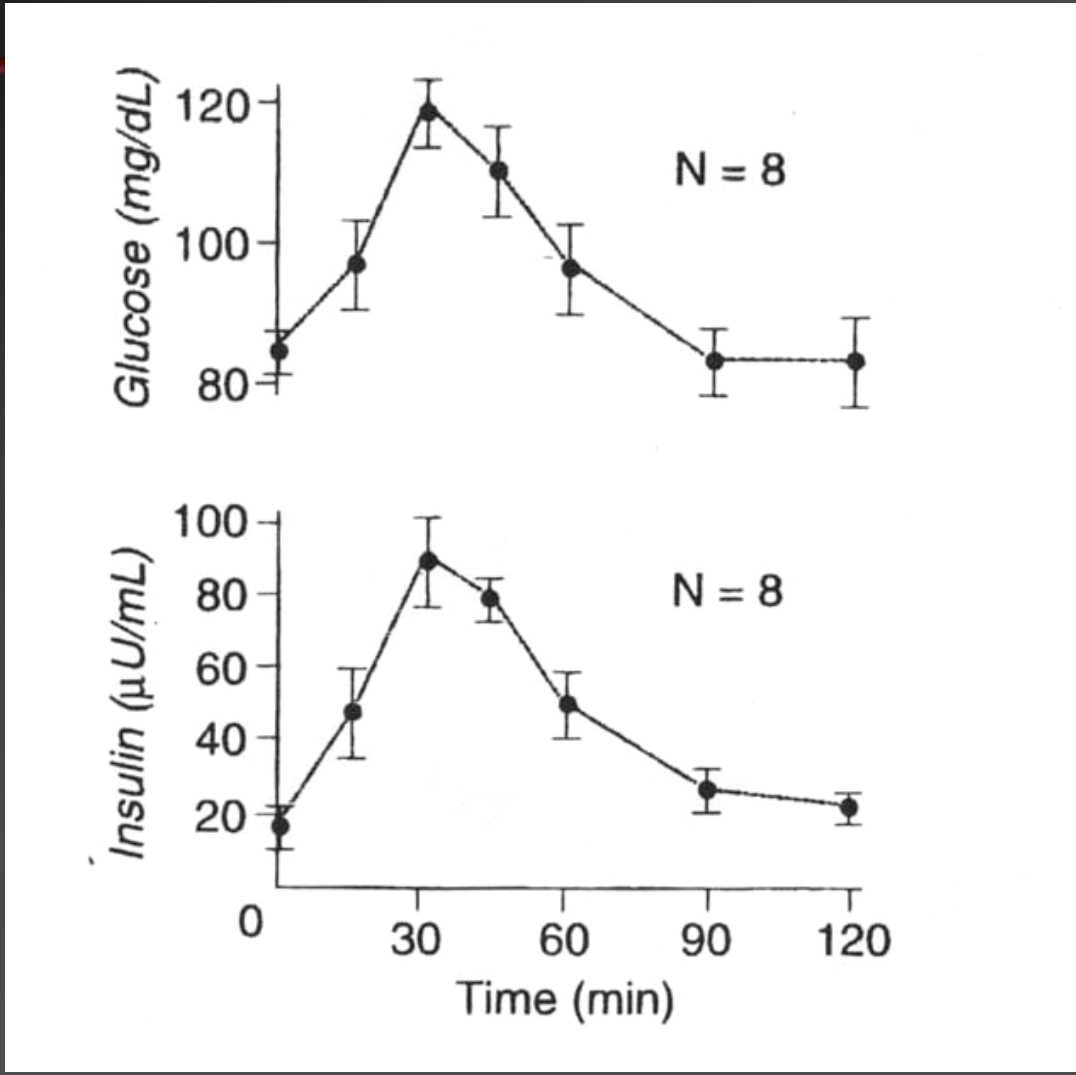
INSULIN MECHANISM OF ACTION

- Delayed effects include gene activation or deactivation, upregulation or downregulation of mRNA and protein synthesis.
- *Insulin receptor interactions are altered in insulin resistance syndromes and Type 2 diabetes mellitus.*
- *Insulin-receptor binding is also altered by obesity, high carbohydrate diet, fasting or exercise.*

INSULIN

- Insulin Release
  - In a 24 hour period, 50% of the insulin secreted is basal and 50% is stimulated.
  - The main stimulator is glucose.
  - Amino acids also stimulate insulin release, especially lysine, arginine and leucine. This effect is augmented by glucose.

CONTROL OF INSULIN SECRETION



CONTROL OF INSULIN SECRETION

Glucose interacts with the GLUT2 transporter on the pancreatic beta cell.

Glucose $\xrightarrow[\text{RLS}]{\text{hexokinase}}$ G-6-P

Increased metabolism of glucose $\xrightarrow{*}$ ATP $\rightarrow$ blockade of ATP-dependent K channels $\rightarrow$ membrane depolarization $\rightarrow \uparrow$ cytosolic Ca++ $\rightarrow \uparrow$ insulin secretion.

- * $\uparrow$NADH with oxidation of glyceraldehyde-3-P
- $\uparrow$Pyruvate $\rightarrow$ TCA cycle $\rightarrow$ respiratory chain

CONTROL OF INSULIN SECRETION

- Insulin secretion is also increased by intestinal polypeptide hormones
- GLP-1 (glucagon like peptide) 7-37 and 7-36, derived from proglucagon in the small intestine is the major physiological gut factor.
- Glucose-dependent insulinotropic peptide (GIP)
- Cholecystokinin
- And by pancreatic glucagon.
- Insulin secretion is decreased by pancreatic somatostatin-14, made in the delta cells of the pancreas, and by intestinal somatostatin-28.

CONTROL OF INSULIN SECRETION

Insulin secretion is also increased by

- growth hormone (acromegaly)#
- glucocorticoids (Cushings')#
- prolactin (lactation)
- placental lactogen (pregnancy)
- sex steroids

#: helps get newly formed glucose into cells

THE ROLE OF INSULIN

Summary of feedback mechanism for regulation of insulin secretion

↑ blood glucose

↓

↑ insulin

↓

↑ transport of glucose into cells, ↓ gluconeogenesis, ↓ glycogenolysis

↓

↓ blood glucose

↓

↓ insulin

THE ROLE OF INSULIN

- Metabolic Effects of Insulin
  - main effect is to promote storage of nutrients
  - paracrine effects—main one is to decrease glucagon secretion
  - carbohydrate metabolism
  - lipid metabolism
  - protein metabolism and growth

THE ROLE OF INSULIN

- Carbohydrate metabolism
  - increases uptake of glucose
  - promotes glycogen storage
    - Stimulates glucokinase
  - inhibits gluconeogenesis
  - inhibits hepatic glycogenolysis
    - Inactivates liver phophorylase

SOURCES OF GLUCOSE

- Glucose is derived from 3 sources
  - Intestinal absorption of dietary carbohydrates
  - Glycogen breakdown in liver and to a lesser degree in the kidney. Only liver and kidney have glucose-6-phosphatase. Liver stores 25-138 grams of glycogen, a 3 to 8 hour supply.
  - Gluconeogenesis, the formation of glucose from precursors including lactate and pyruvate, amino acids (especially alanine and glutamine, and to a lesser degree, from glycerol

FASTING STATES

- Short fast
  - utilize free glucose (15-20%)
  - break down glycogen (75%)
- Overnight fast
  - glycogen breakdown (75%)
  - gluconeogenesis (25%)
- Prolonged fast
  - Only 10 grams or less of liver glycogen remains.
  - Gluconeogenesis becomes sole source of glucose; muscle protein is degraded for amino acids.
  - Lipolysis generates ketones for additional fuel.

THE ROLE OF INSULIN

- Lipid Metabolism
  - Insulin promotes fatty acid synthesis
    - stimulates formation of α-glycerol phosphate
    - α-glycerol phosphate + FA CoA = TG
    - TG are incorporated into VLDL and transported to adipose tissues for storage.
  - Insulin inhibits hormone-sensitive lipase, thus decreasing fat utilization.

THE ROLE OF INSULIN

- Protein Metabolism and Growth
  - increases transport of amino acids
  - increases mRNA translation and new proteins, a direct effect on ribosomes
  - increases transcription of selected genes, especially enzymes for nutrient storage
  - inhibits protein catabolism
  - acts synergistically with growth hormone

THE ROLE OF THE PANCREAS

- Lack of insulin
  - Occurs between meals, and in diabetes.
  - Transport of glucose and amino acids decreases, leading to hyperglycemia.
  - Hormone sensitive lipase is activated, causing TG hydrolysis and FFA release.
  - ↑ FFA conversion in liver → PL and cholesterol → lipoproteinemia, FFA breakdown leads to ketosis and acidosis.

What causes insulin resistance?

- Decreases in receptor concentration and kinase activity,
- changes in concentration and phosphorylation of IRS-1 and -2,
- decreases in PI3-kinase activity,
- decreases in glucose transporter translocation,
- changes in the activity of intracellular enzymes.

THE ROLE OF THE PANCREAS

Other pancreatic hormones

- Somatostatin
  - 14 amino acid paracrine factor
  - Potent inhibitor of glucagon release
  - Stimili: glucose, arginine, GI hormones
- Pancreatic polypeptide
  - 36 amino acids, synthersized in the PP or F cells, secreted in response to food
- Glucagon
- Amylin
- UCP2

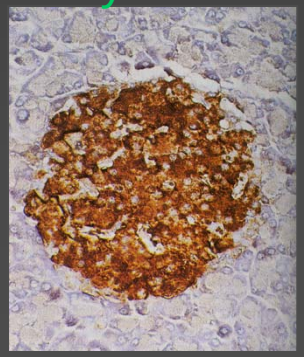
UCP2

- Inhibitor of insulin secretion made in pancreatic islet cells.
- Levels are increased in obese, diabetic, insulin-resistant mice (ob/ob).
- Variations in expression predict development of DM in healthy middle-aged men.
- Inhibition of UCP2 expression reverses diet-induced DM by effects on both insulin secretion and action.
- The PPAR (peroxisome proliferators-activated receptors) subtypes mediate to a large extent the transcriptional regulation of the UCP genes.

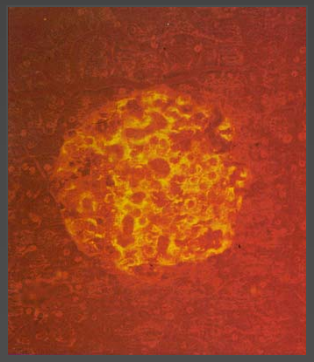
Amylin the Hormone

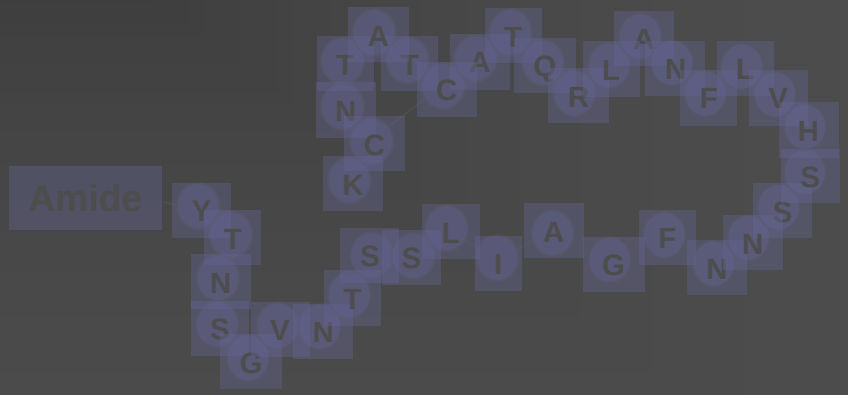
- Reported in 1987
- 37-amino acid peptide
- Co-located and co-secreted with insulin from pancreatic β-cells
- Islet levels are increased and serum levels are decreased in diabetes

Amylin



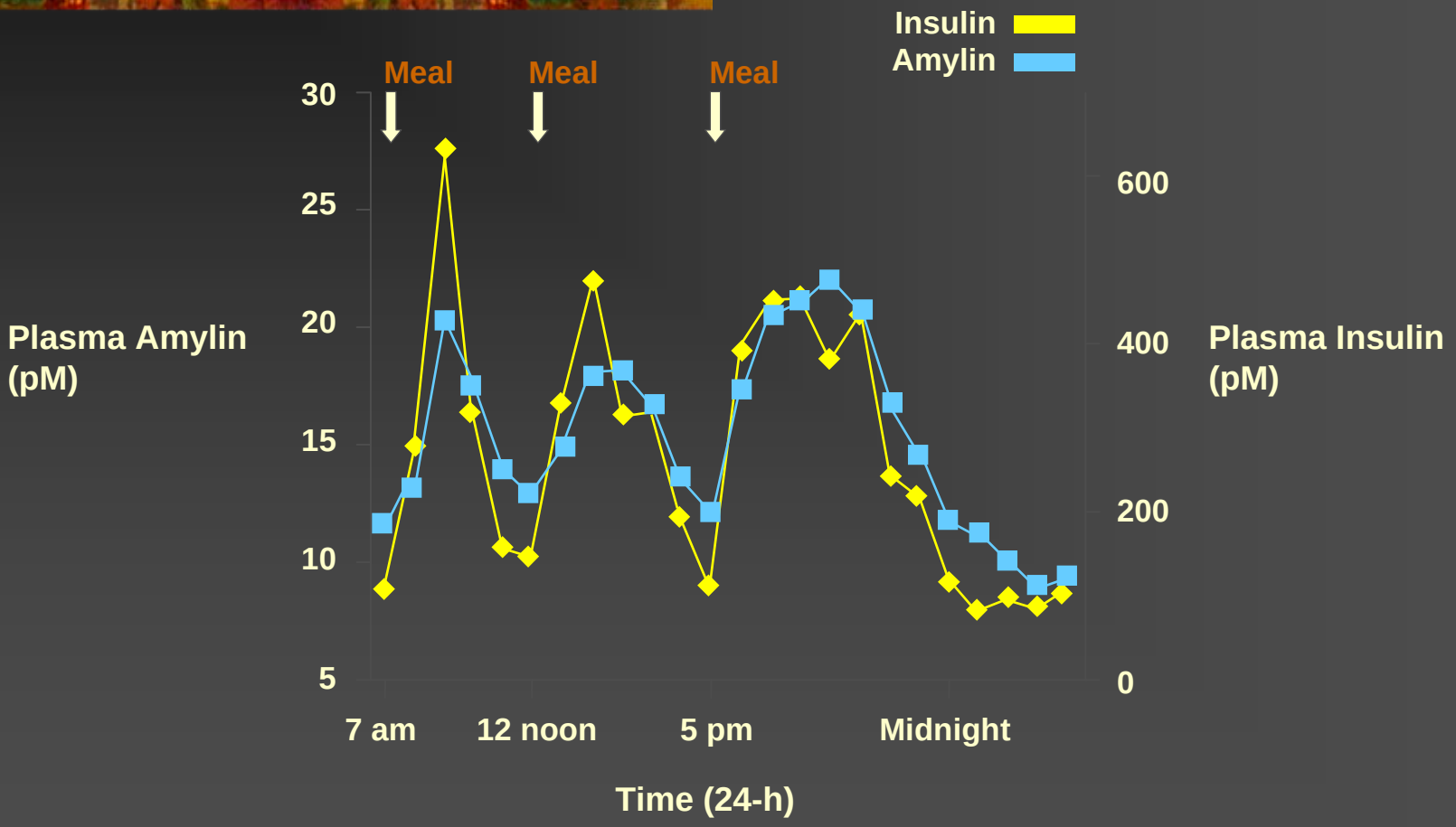
Insulin





Unger RH, Foster DW. *Williams Textbook of Endocrinology (8th edition)* 1992; 1273-1275

Amylin the Hormone: Co-Secreted With Insulin



Data from Kruger D, et al. *Diabetes Educ* 1999; 25:389-398

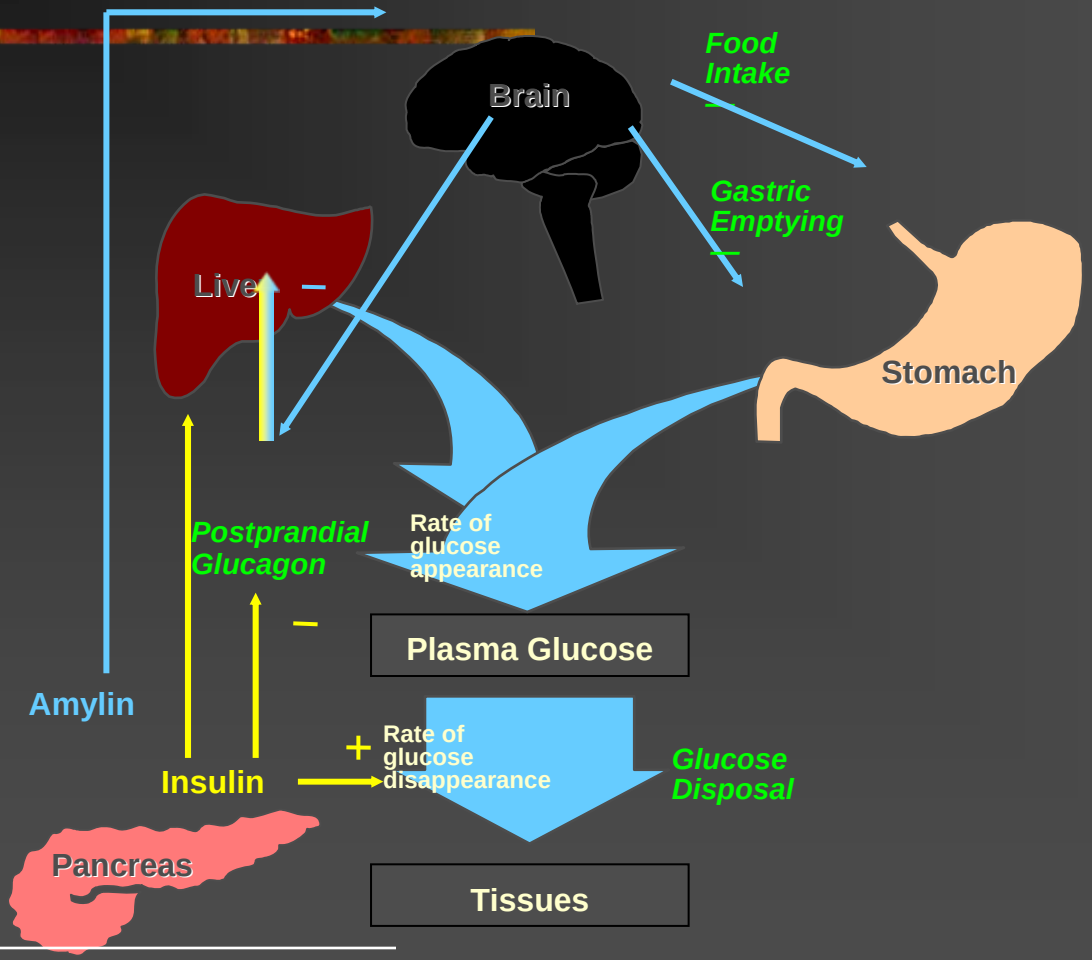
Effect of Amylin on Postprandial Glucose Excursions

In animal models, amylin has been shown to:

- Suppress postprandial glucagon secretion
  - glucagon is an important determinant of hepatic glucose production
- Regulate gastric emptying
  - regulates rate of gastric emptying from stomach to small intestine
  - rate of gastric emptying is an important determinant of early glucose excursion postprandially
- Reduce food intake and body weight

Gedulin B, et al. *Metabolism* 1997; 46:67-70
Young A, et al. *Diabetologia* 1995; 38:642-648
Rushing PA, et al. *Endocrinology* 2000; 141:850-853

Insulin and Amylin Are Complementary Partner Hormones



Model derived from animal studies

Edelman SV, et al. *Diabetes Technol Ther* 2002; 4:175-189

Incretins

- Glucagon like peptide-1 (GLP-1) and glucose dependent insulinotropic peptide (GIP) are gut derived stimulators of insulin release (L cells and K cells).
- GLP-1 also inhibits glucagon secretion, delays gastric emptying, and enhances satiety, thereby reducing caloric intake.

Incretins

- GLP-1 also stimulates beta-cell proliferation and inhibits beta-cell apoptosis, resulting in increased pancreatic beta-cell mass.
- GIP also promotes beta-cell proliferation and survival.
- The insulinotropic effect of GIP is blunted or lost in T2DM.
- There is a decrease in endogenous GLP-1 secretion in T2DM, but the response to exogenous GLP-1 is retained.

Adipocyte Factors

- Leptin
- Tumor necrosis factor alpha (TNF alpha)
- Adiponectin
- Resistin

Leptin

- Leptin is produced in adipose cells
- It decreases appetite and food intake
- It increases sympathetic activity and metabolic rate
- It decreases insulin secretion
- It reduces fat storage

TNF alpha

Decreases insulin sensitivity.

Increase in FFA leads to increased expression from adipose tissue in obesity.

Increased serum levels of TNF alpha have been correlated with insulin resistance.

Adiponectin

- Deficiency of adiponectin, a adipocyte-derived hormone, plays a role in insulin resistance and subsequent development of T2DM.
- Adiponectin is downregulated in obesity.
- In adiponectin KO mice, plasma and adipocyte concentrations of TNF alpha increase, resulting in severe diet-induced insulin resistance.

Resistin

- Decreases insulin-mediated glucose uptake by adipocytes.
- Secreted by adipocytes in diet-induced or genetic obesity in mice.
- May be a hormone that links obesity to diabetes.

THE COUNTER REGULATORY HORMONES

- Early response
  - glucagon
  - epinephrine
- Delayed response
  - cortisol
  - growth hormone

THE COUNTER REGULATORY HORMONES

- Glucagon
  - Acts to increase blood glucose
  - Secreted by alpha cells of the pancreas
  - Chemical structure
    - 29 amino acids derived from 160 aa proglucagon precursor
    - GLP-1, the most potent known insulin secretagogue, is made in the intestine by alternative processing of the same precursor
  - Intracellular actions

THE ROLE OF GLUCAGON

- Metabolic Effects of Glucagon
  - increases hepatic glycogenolysis *
  - increases gluconeogenesis
  - increases amino acid transport
  - increases fatty acid metabolism (ketogenesis)

GLUCAGON SECRETION

- Stimulation of glucagon secretion
  - blood glucose < 70 mg/dL
  - high levels of circulating amino acids especially arginine and alanine
  - s and ps nerve stimulation
  - catecholamines
  - CCK, gastrin and GIP
  - glucocorticoids

Response to Decreasing Glucose Concentrations

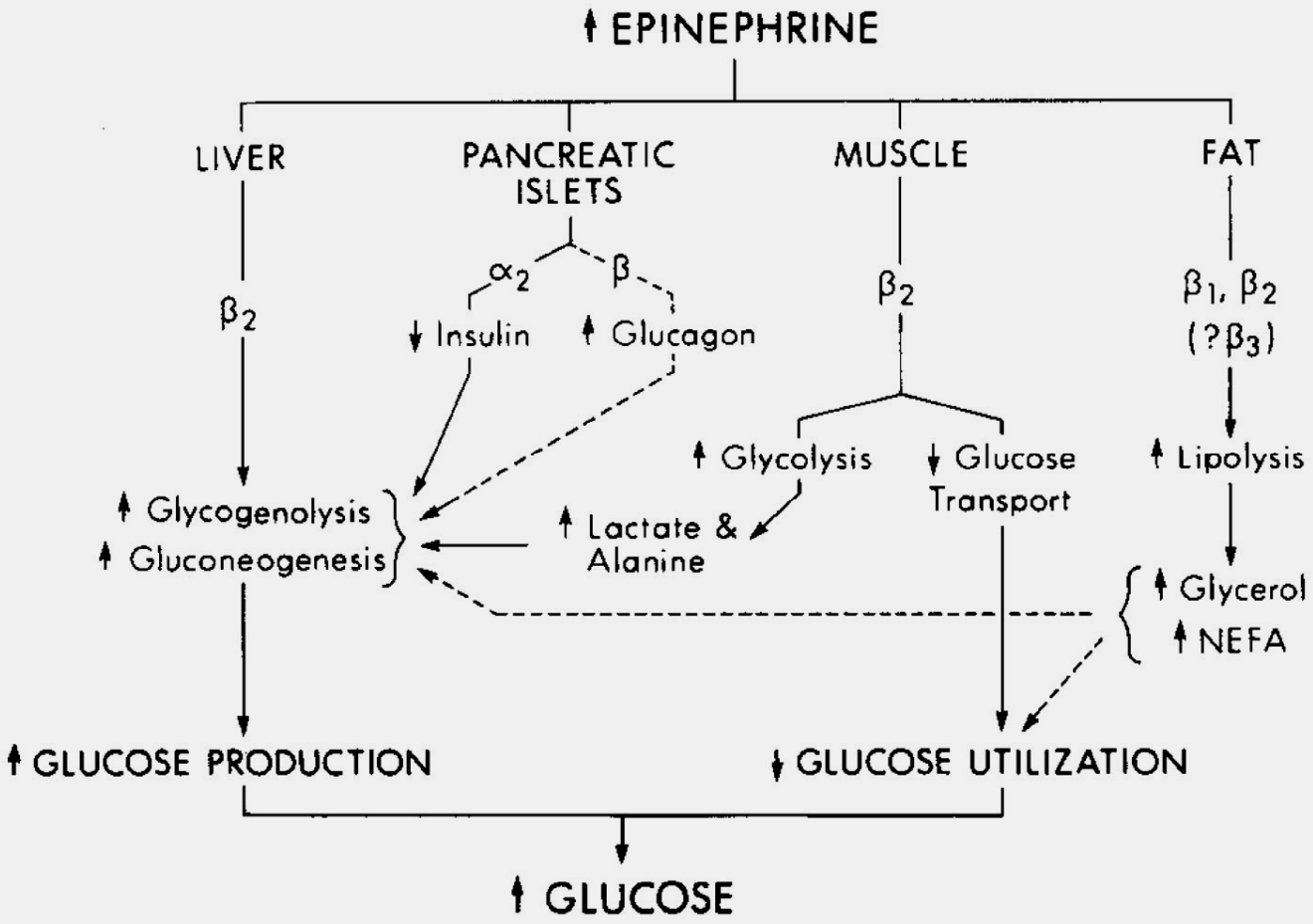
Response	Glycemic Threshold	Physiological Effects	Role in Counterreg.
↓ insulin	80-85 mg/dL	↑ R_a (↓ R_d)	Primary First defense
↑ glucagon	65-70	↑ R_a	Primary 2nd defense
↑epinephrine	65-70	↑ R_a ↓ R_d	Critical 3rd defense
↑ cortisol, ↑ GH	65-70	↑ R_a ↓ R_d	Not critical
↑ Food ingestion	50-55	↑ Exogenous glucose	< 50, Cognitive change halts

Ra-rate of glucose appearance; Rd-rate of glucose disappearance

ROLE OF EPINEPHRINE

- Epinephrine is the second early response hyperglycemic hormone.
- This effect is mediated through the hypothalamus in response to low blood glucose (VMN and others).
- Stimulation of sympathetic neurons causes release of epinephrine from adrenal medulla .
- Epinephrine causes glycogen breakdown, gluconeogenesis, and glucose release from the liver.
- It also stimulates glycolysis in muscle, lipolysis in adipose tissue, decreases insulin secretion and increases glucagon secretion.

Hyperglycemic Effect of Epinephrine



ROLE OF CORTISOL AND GH

- These are long term hyperglycemic hormones; activation takes hours to days.
- Cortisol and GH act to decrease glucose utilization in most cells of the body.
- Effects on these hormones are mediated through the CNS.

Liver and Kidney

- Major source of net endogenous glucose production by gluconeogenesis and glycogenolysis when glucose is low, and of glycogen synthesis when glucose is high.
- Can oxidize glucose for energy and convert it to fat which can be incorporated into VLDL for transport.

Muscle

- Can convert glucose to glycogen.
- Can convert glucose to pyruvate through glycolysis which can be further metabolized to lactate or transaminated to alanine or channeled into the TCA cycle.
- In the fasting state, can utilize FA for fuel and mobilize amino acids by proteolysis for transport to the liver for gluconeogenesis.
- Can break down glycogen, but cannot liberate free glucose into the circulation.

Adipose Tissue (AKA fat)

- Can store glucose by conversion to fatty acids and combine these with VLDL to make triglycerides.
- In the fasting state can use fatty acids for fuel by beta oxidation.

Brain

- Converts glucose to CO_2 and H_2O.
- Can use ketones during starvation.
- Is not capable of gluconeogenesis.
- Has no glycogen stores.

Clinical Correlations

- Why is glucose regulation so important?
- What are the CNS manifestations of hypoglycemia?
- What states alter the threshold for these manifestations?

Sources

- Insulin structure. DG Gardner and D Shoback, Basic and Clinical Endocrinology, 8th ed., Lange Medical Books/McGraw Hill, 2007, page 665.
- Insulin signaling. AR Saltiel and CR Kahn. Insulin signalling and the regulation of glucose and lipid metabolism. Nature 414:799-806, 2001, Fig. 2.
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