# ENDOCRINE PANCREAS: METABOLIC INTERACTIONS

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# THE ROLE OF THE PANCREAS

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

# Adipocyte Factors

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

# GI Tract Factors

- Incretins
- Cholecystokinin

# EAT TO LIVE: THE ROLE OF THE PANCREAS

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

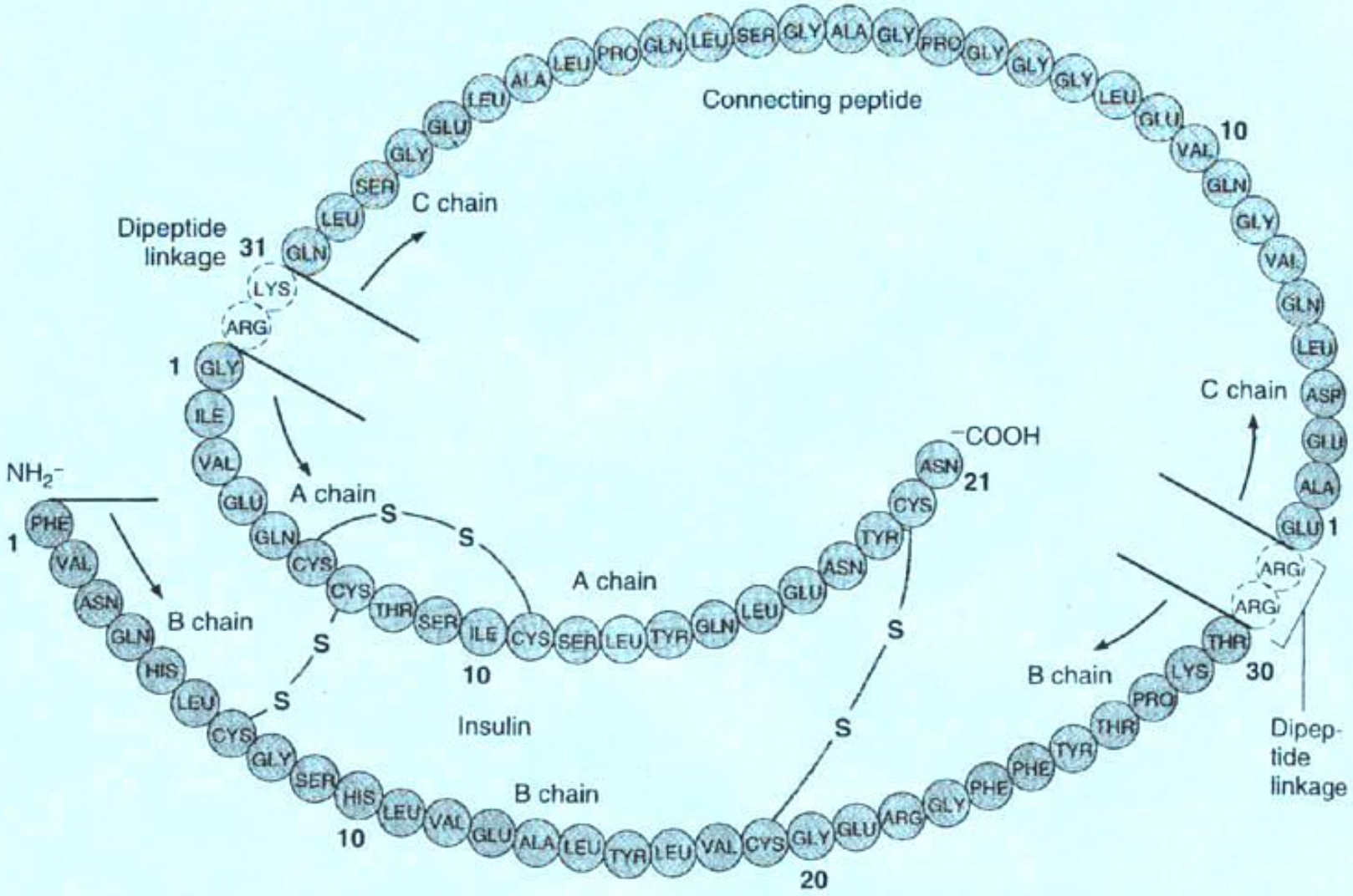
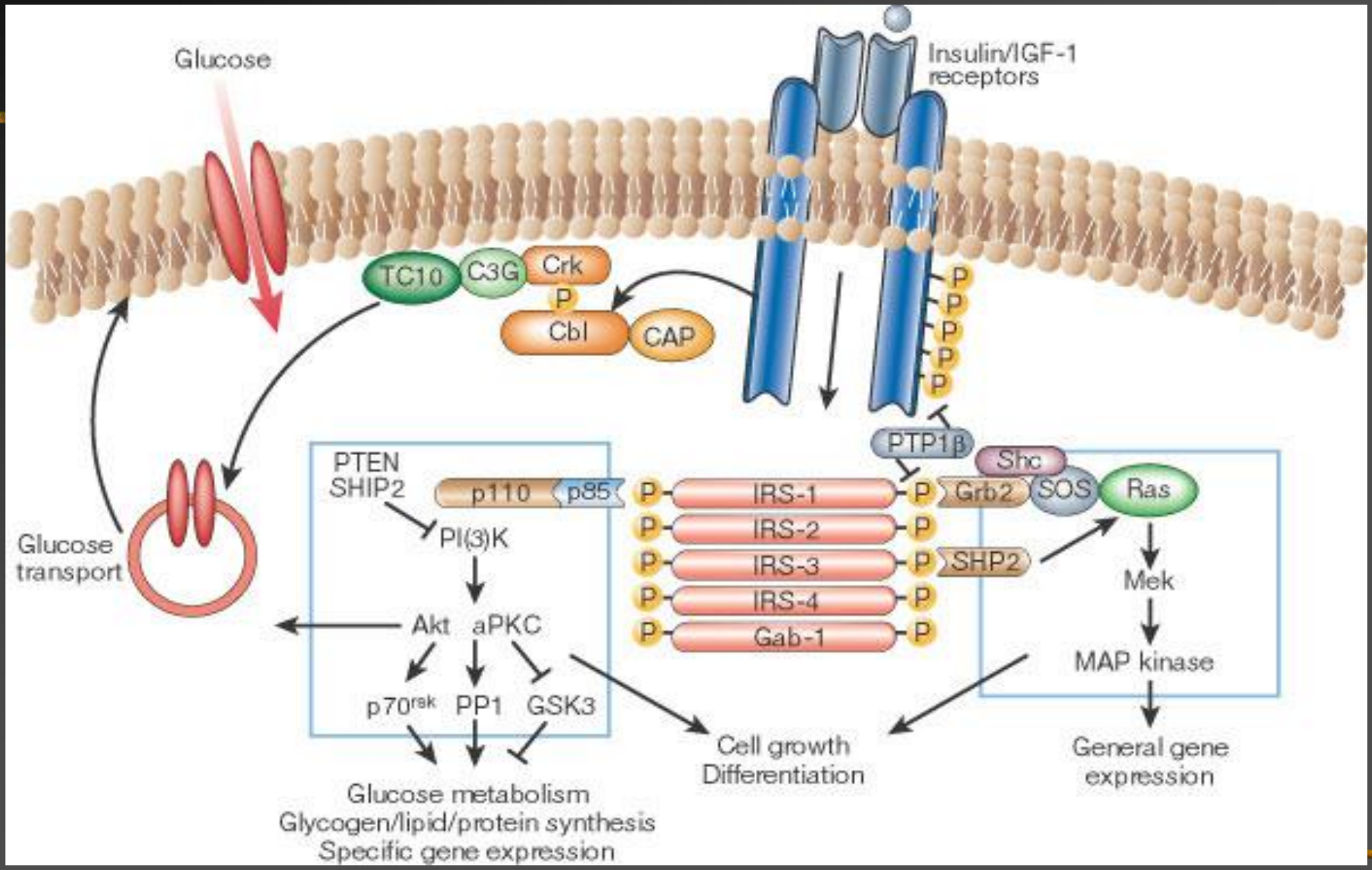



**Figure 1** Structure of human proinsulin C peptides and insulin molecules connected at two sites by dipeptide links.

# 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



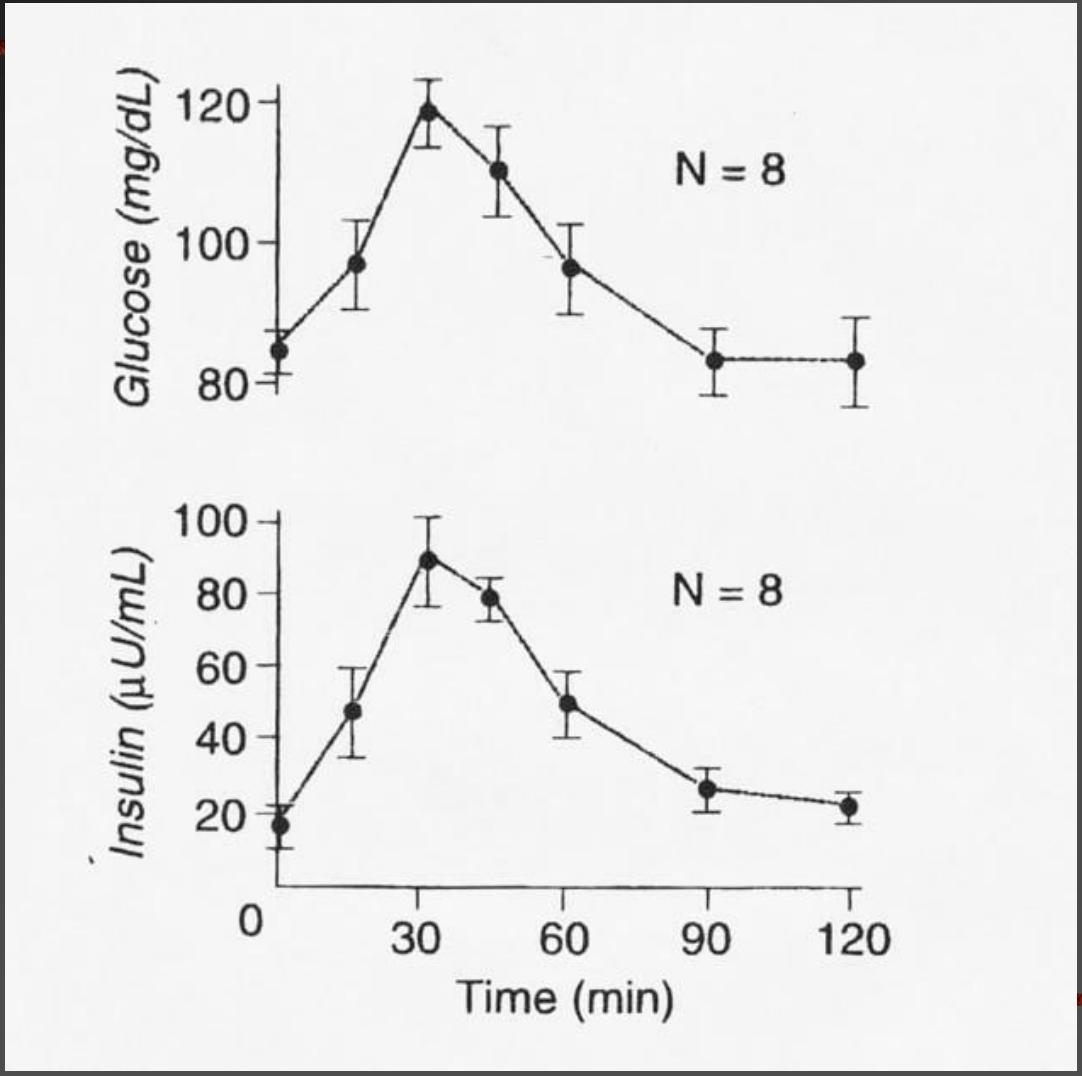
# INSULIN MECHANISM OF ACTION

- 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

#:but insulin resistance may also be present

# 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 $\alpha$-glycerol phosphate
    - $\alpha$-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.

# Mechanisms of 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

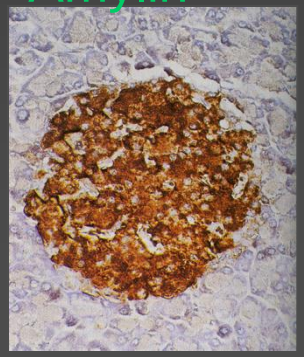
Other pancreatic hormones

- 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

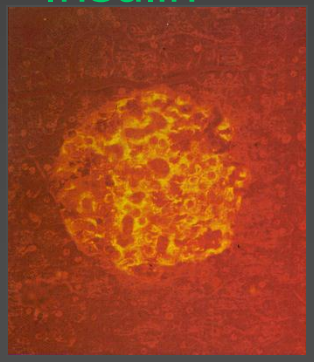
# Amylin the Hormone

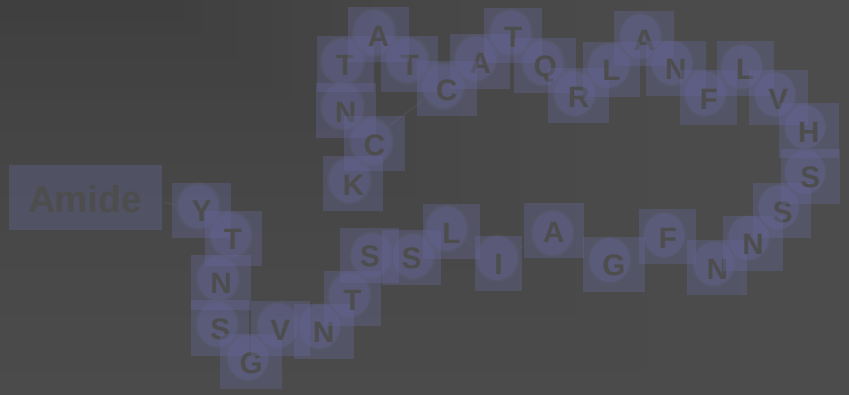
- Reported in 1987
- 37-amino acid peptide
- Co-located and co-secreted with insulin from pancreatic β-cells
- Islet levels are increased and serum levels are decreased in diabetes

Amylin



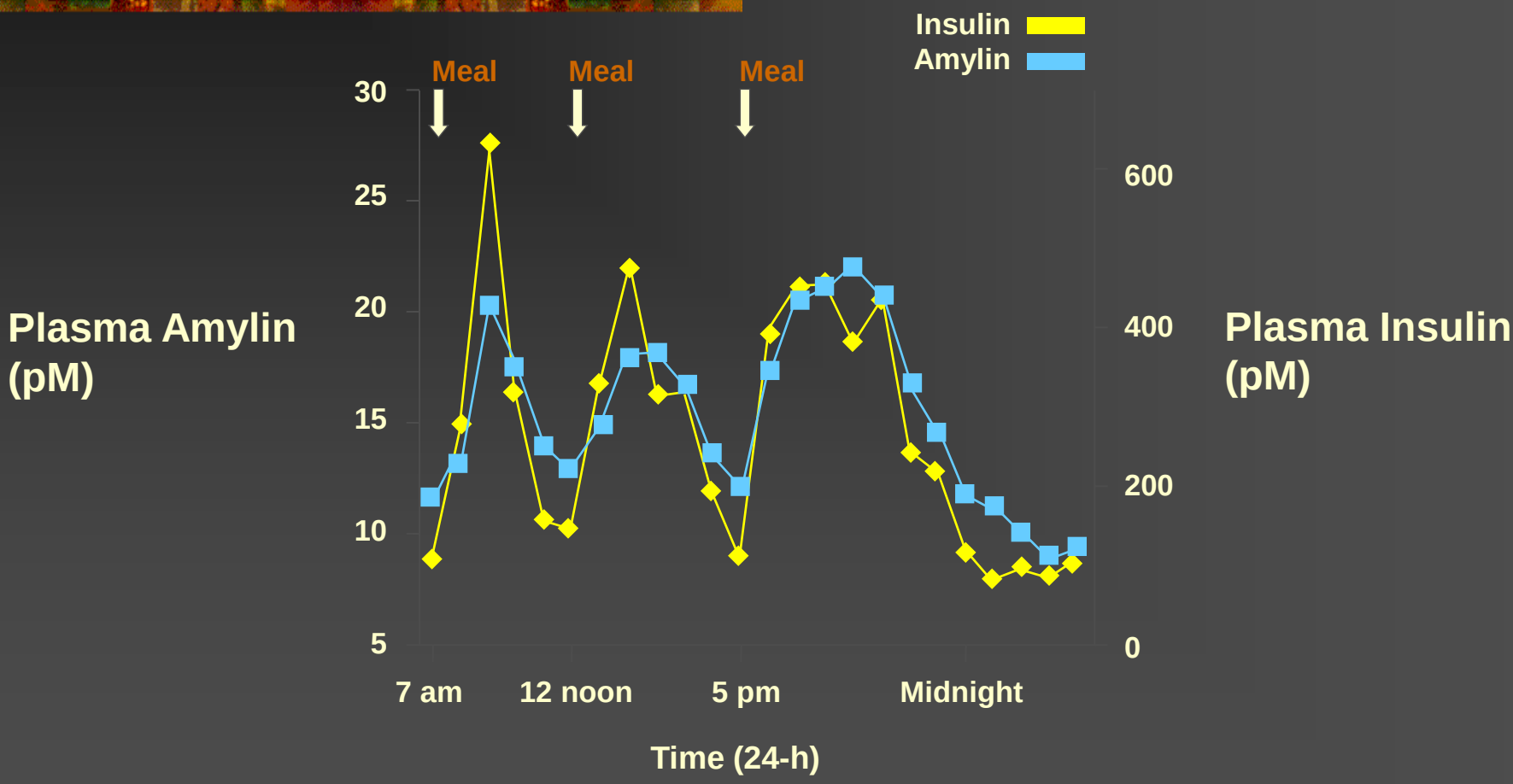
Insulin






**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

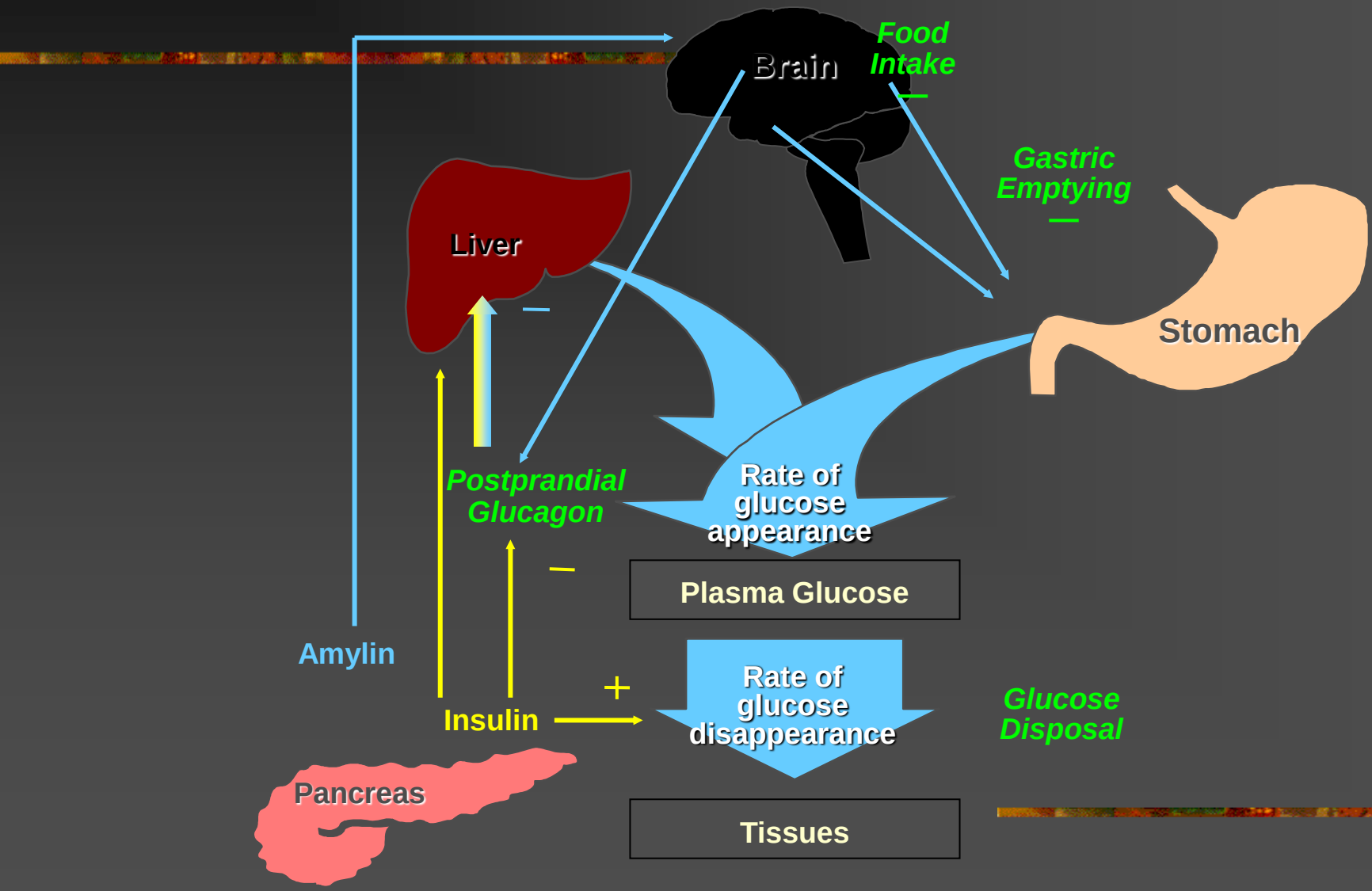
# Effect of Amylin on Postprandial Glucose Excursions

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



# 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.

# 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 another 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

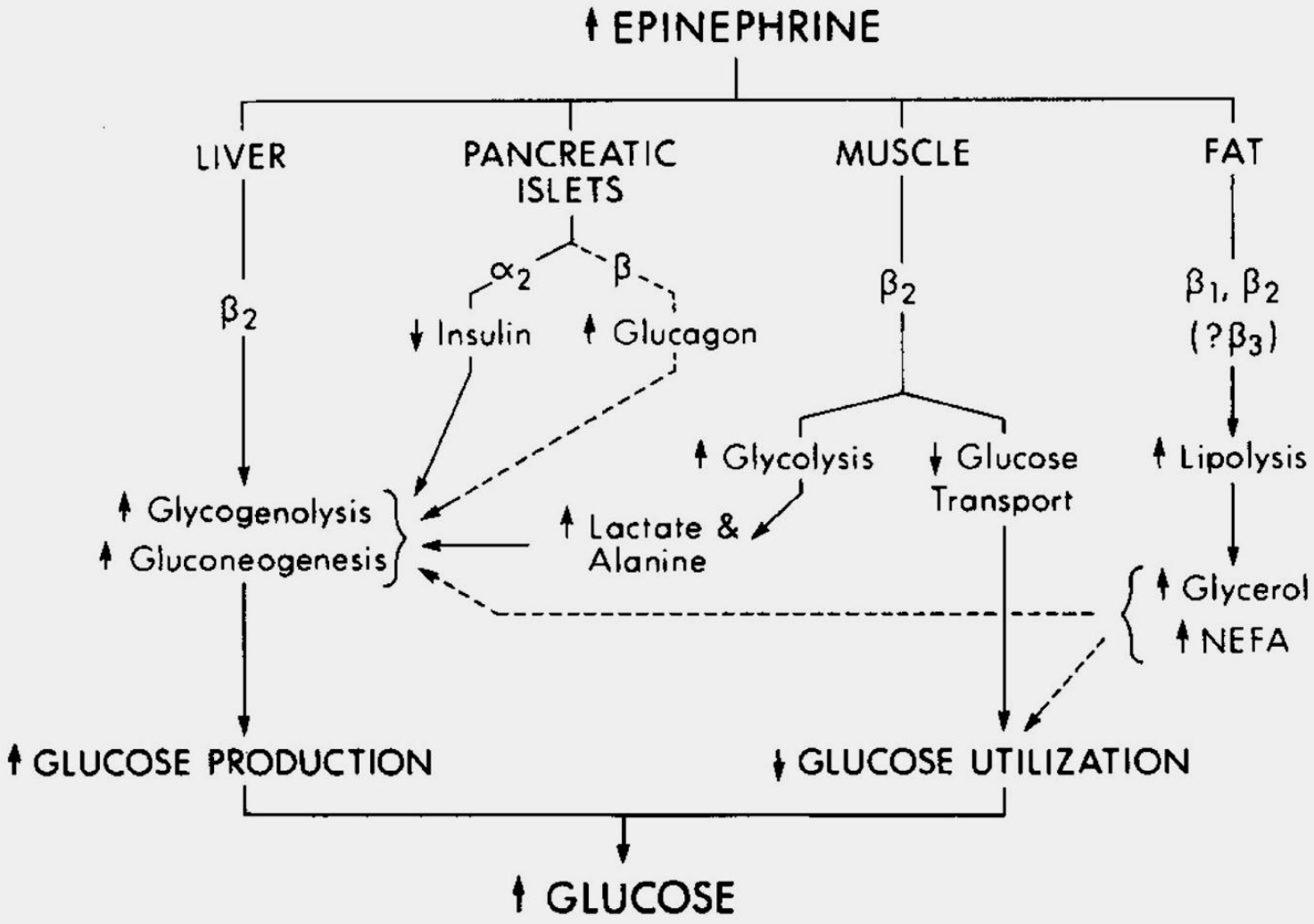
| Response | Glycemic Threshold | Physiological Effects | Role in Counterreg. |
|---|---|---|---|
| ↓ insulin | 80-85 mg/dL | ↑ $R_a$ (↓ $R_d$) | Primary<br>First defense |
| ↑ glucagon | 65-70 | ↑ $R_a$ | Primary<br>2nd defense |
| ↑epinephrine | 65-70 | ↑ $R_a$ ↓ $R_d$ | Critical<br>3rd defense |
| ↑ cortisol,<br>↑ 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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