The Mechanisms of Diabetes

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Diabetes Mellitus

- Results from the failure of insulin to exert its normal metabolic effects
  - Type 1 Diabetes
    - Death of beta-cells leading to decreased insulin production
  - Type 2 Diabetes
    - Failure of insulin to have its effect on tissues – Occurs from Insulin RESISTANCE
- The result
  - Damage to the “8-Organ-Model” of Diabetes
    - Brain, Eyes, Heart, Kidney, Blood Vessels, Pancreas, Neurons, Feet

Type 2 Diabetes Mellitus

- Dr. O thinks of Type 2 diabetes like this:
  - Results from CHRONIC ENERGY SURPLUS leading to OVERWHELMED metabolic signaling
    - From various Proteins, Carbohydrates, and Fat
  - This metabolic disease is then driven by insulin RESISTANCE, with chronic inflammation acting as a major upstream amplifier and perpetuator.

- So let's look at Metabolic Syndrome and Diabetes through a similar lens
  - Nutrient Handling → Pathology
  - Endocrine Disruption
  - Damage to Organs and Resulting Pathology
  - Pharmacology

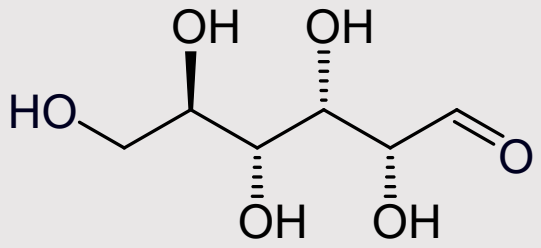
Nutrient Handling

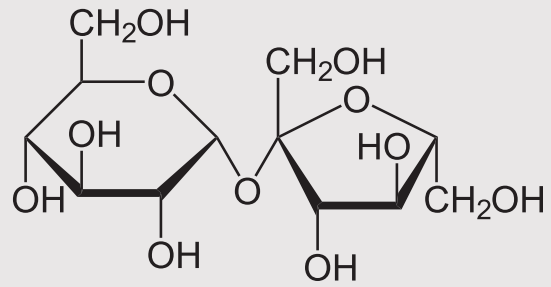
Nutrient Handling

- We eat food to intake energy
  - Carbohydrates → Glucose
  - Proteins → Amino Acids
  - Fats → Free Fatty Acids (FFA)
- All of these will enter the bloodstream, signal to our body that we now have a nutrient abundance and demand our body to handle them.
  - But the handling of these nutrients will depend on the **QUALITY** of the nutrient you just consumed.
- **Not all nutrients are processed the same way.**
  - The metabolic response depends on:
    - **Structural complexity**
    - **Speed of absorption**
    - **Type of cellular signaling activated**
- The problem isn't energy — it's energy delivered too fast, too often, and in the wrong form.

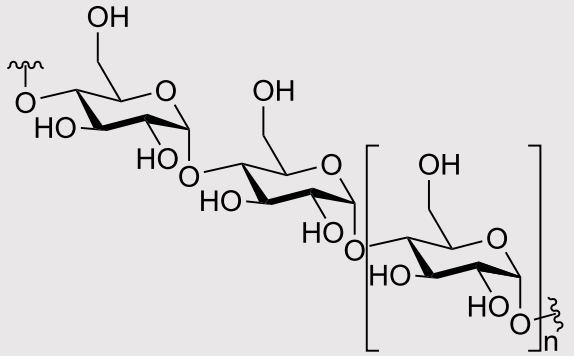
Nutrient Handling – Carbohydrates

- Carbohydrates are handled on how quick glucose is delivered to the blood
- Simple, refined, low fiber sugars
  - Monosaccarides
  - Disaccarides
  - Refined Starches





- Complex, large, intact, fiber containing sugars
  - Oligosaccarides
  - Polysaccarides



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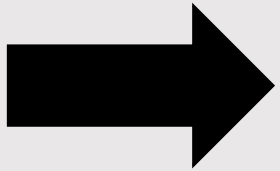
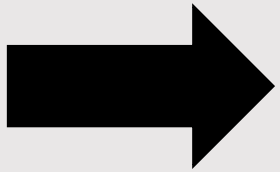


Rapidly absorbed by the intestine
Sharp Glucose Rise

- Complex, large, intact, fiber containing sugars
  - Oligosaccharides
  - Polysaccharides



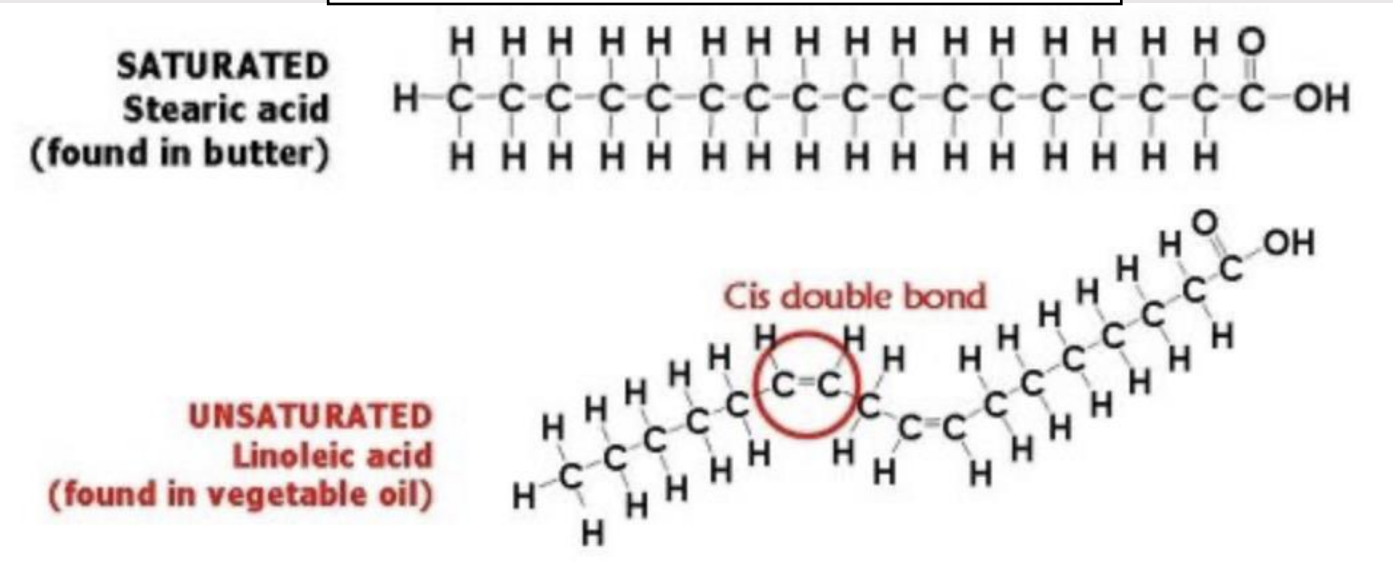
Require enzymatic breakdown before absorption
Gradual Glucose Rise

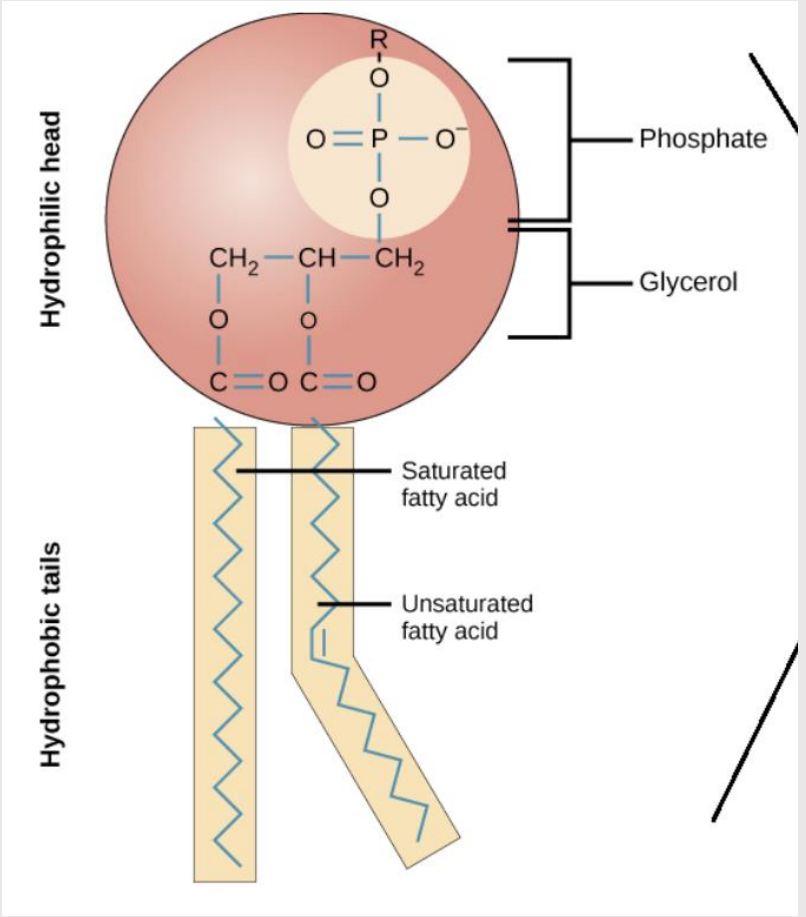
- **Carbohydrates are not harmful because they are sugar**
  - **They are harmful when glucose is delivered too fast.**

Nutrient Handling – Fats

- The normal cell membrane in all cells are made up of:
  - Hydrophilic phosphate and glycerol
  - Lipophilic Tail
    - Saturated Fats
    - Unsaturated Fats

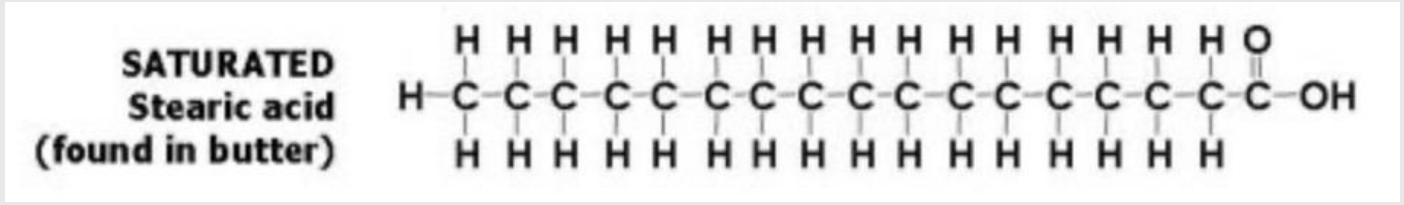
We need a delicate balance of both



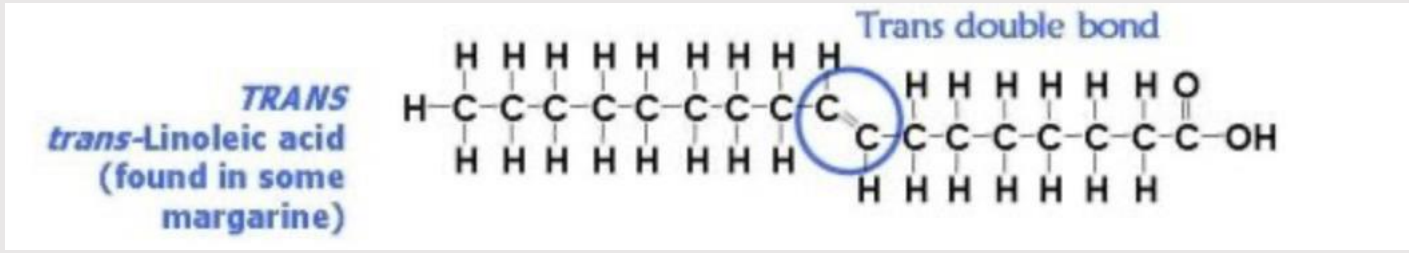


Nutrient Handling – Low Quality Fats

- Fats are handled based on their **carbon structure** and how they were **processed**
- Saturated Fats
  - Structure -- Rigid, straight hydrocarbon chains
  - Concern
    - Pack very tightly together in cell membranes, decreasing the fluid nature of cell membranes
      - "Think of your cell membranes being the consistency of butter rather than oil"
    - These cell recognizes the abnormality and releases toxic mediators

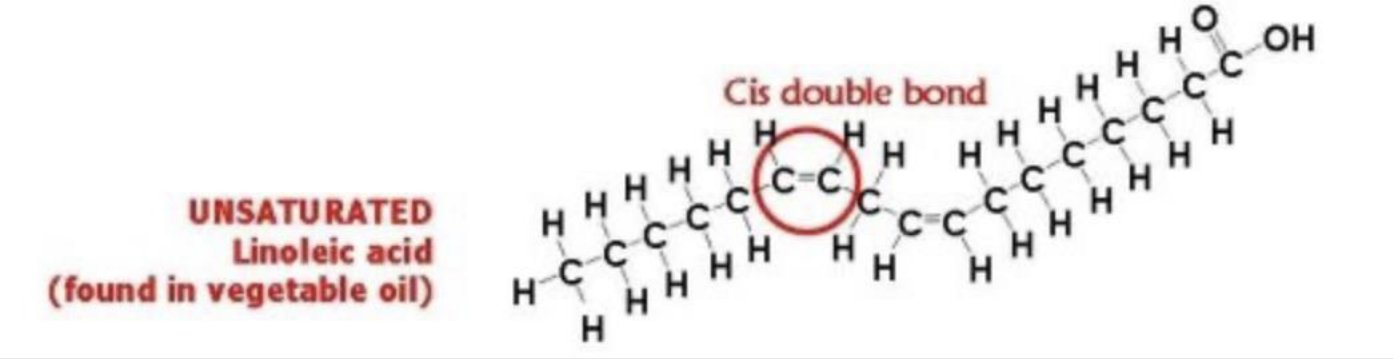


- Trans Fats
  - Structure -- Rigid, artificial trans-double bonds. Mimics saturated fats
  - Concern
    - Packs very tightly in cell membranes, decreasing fluid nature of cell membranes.
    - However, Not naturally metabolized due to trans-double bond

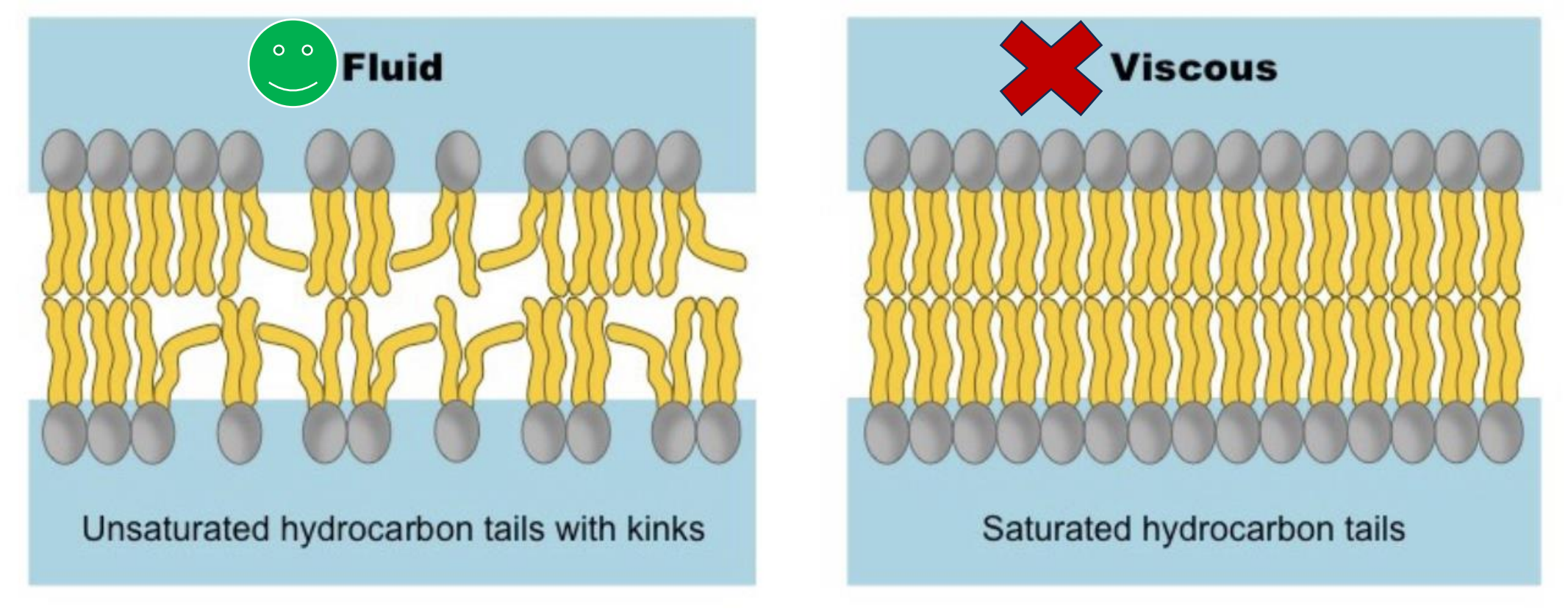


Nutrient Handling – High Quality Fats

- Mono-unsaturated and Poly-unsaturated fats
  - Structure: Cis-Double bonds with kinks
  - Health:
    - The kinks keep the membrane fluid with better signaling



Nutrient Handling – Summary of Fats



Lower-quality fats are harmful because they physically alter cell membranes and generate toxic lipid signals that block insulin signaling

Nutrient Handling – Proteins

- Proteins in the diet are broken down into various amounts of our 20 available Amino-Acids

Essential Amino Acids
(Must be obtained from Diet)

1. Histidine
2. Isoleucine
3. Leucine
4. Lysine
5. Methionine
6. Phenylalanine
7. Threonine
8. Tryptophan
9. Valine

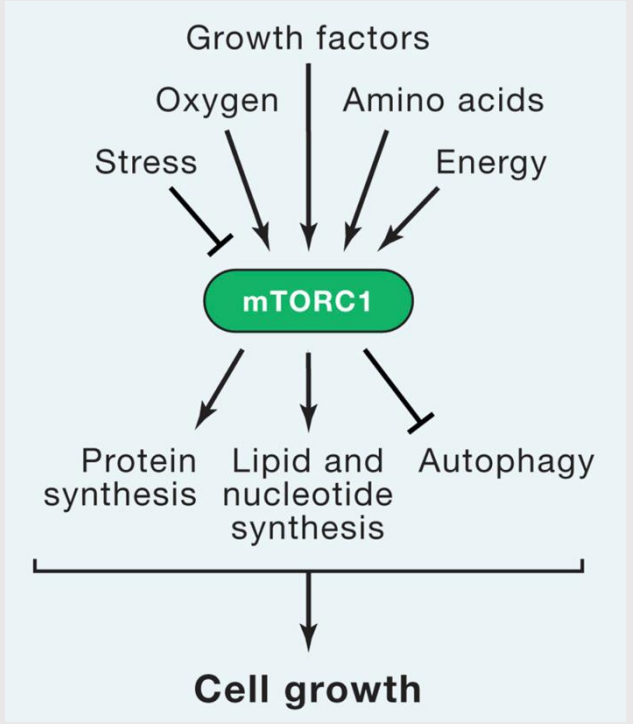
Non-Essential Amino Acids
(Can be synthesized by the body)

10. Alanine
11. Asparagine
12. Aspartic acid (Aspartate)
13. Glutamic acid (Glutamate)
14. Glutamine
15. Glycine
16. Proline
17. Serine
18. Tyrosine
19. Cysteine
20. Arginine

Nutrient Handling – Proteins

Two Major Roles of Amino Acids

1. **Serve as the Primary Building Blocks for**
   - Proteins, crucial for building and repairing tissues, making enzymes and hormones, and supporting immune function, but they also have vital roles in energy production, neurotransmitter synthesis (like serotonin, dopamine, epinephrine)
2. **Regulating Metabolism**
   - **Branched Chain Amino Acids (BCAAs)**
     - Isoleucine, Leucine, Valine
       - Signal **nutrient abundance**
       - Promote **protein synthesis**
       - Activate **mTOR in MUSCLE**



Storage of Energy ⟷ Use of Energy

Increased Insulin Receptors

Decreased Insulin Receptors

Nutrient Handling – Proteins

- **Branched Chain Amino Acids (BCAAs)**
  - Tend to be at elevated levels in:
    - Processed Meats
    - Protein Supplements

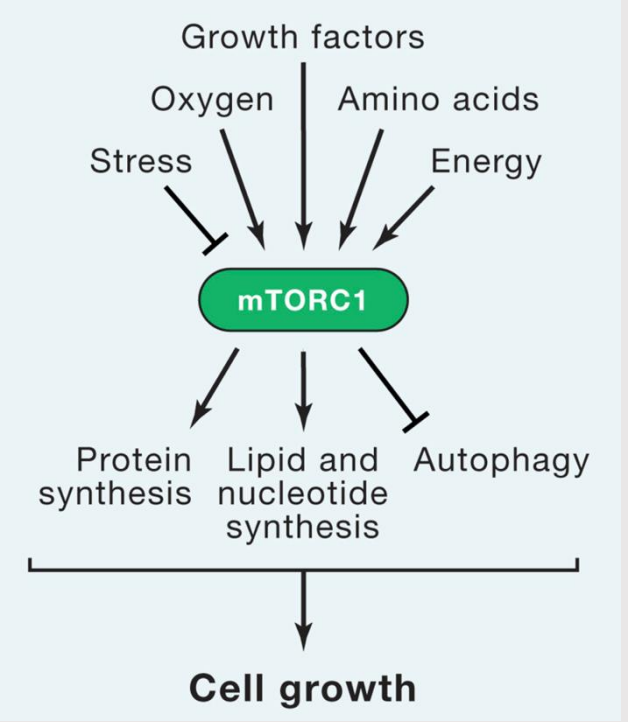
- Bottom Line:

  BCAAs are important because they tell the cell it's time to grow, and chronic growth signaling interferes with insulin signaling

Storage of Energy ⟷ Use of Energy

Increased Insulin Receptors

Decreased Insulin Receptors



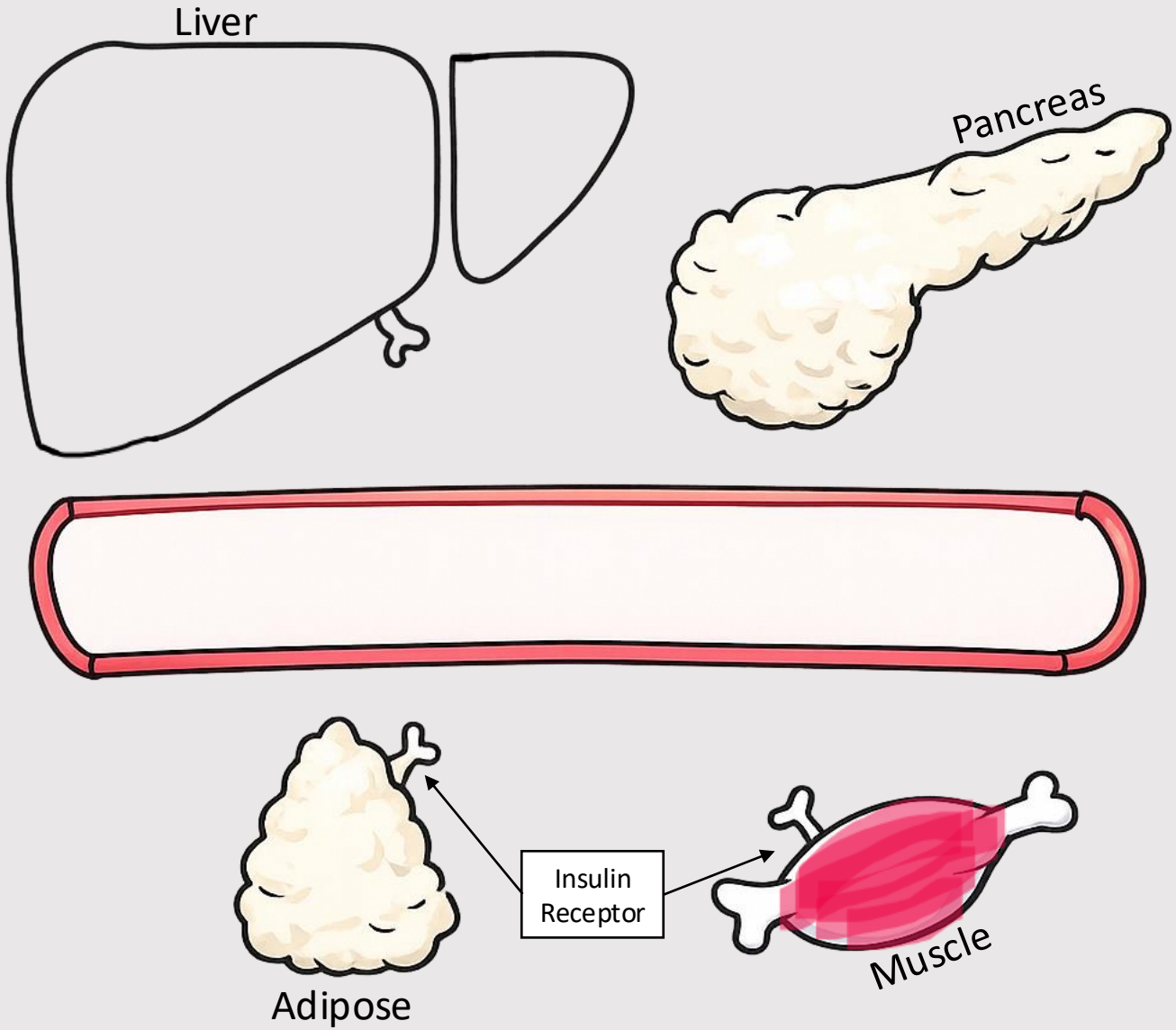
The Worst Combination for Metabolism

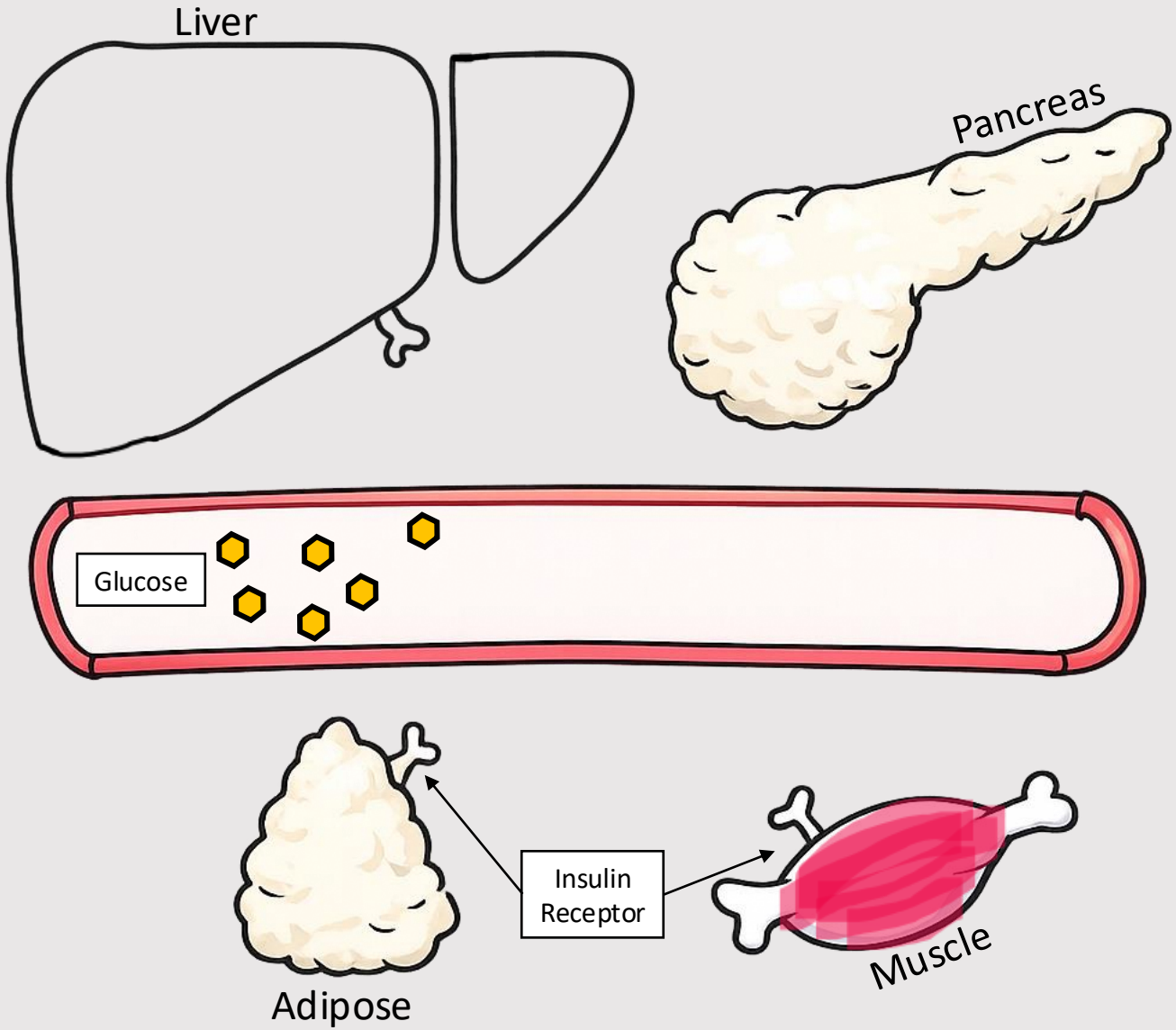
- High Fat + Refined Carbohydrates + BCAA-Rich Protein
  - Refined carbs → ↑ glucose → ↑ insulin demand
  - Bad fats → ↓ insulin signaling and ↑ inflammation (TNF / IL-6)
  - BCAAs → mTOR → Insulin resistance + hyperinsulinemia

This combination creates maximal insulin resistance while simultaneously demanding maximal insulin output.

Pizza, Burger-Fries, Fried Chicken, Donuts, Ice Cream

Endocrine Pathway


Liver
Pancreas
Insulin
Receptor
Adipose
Muscle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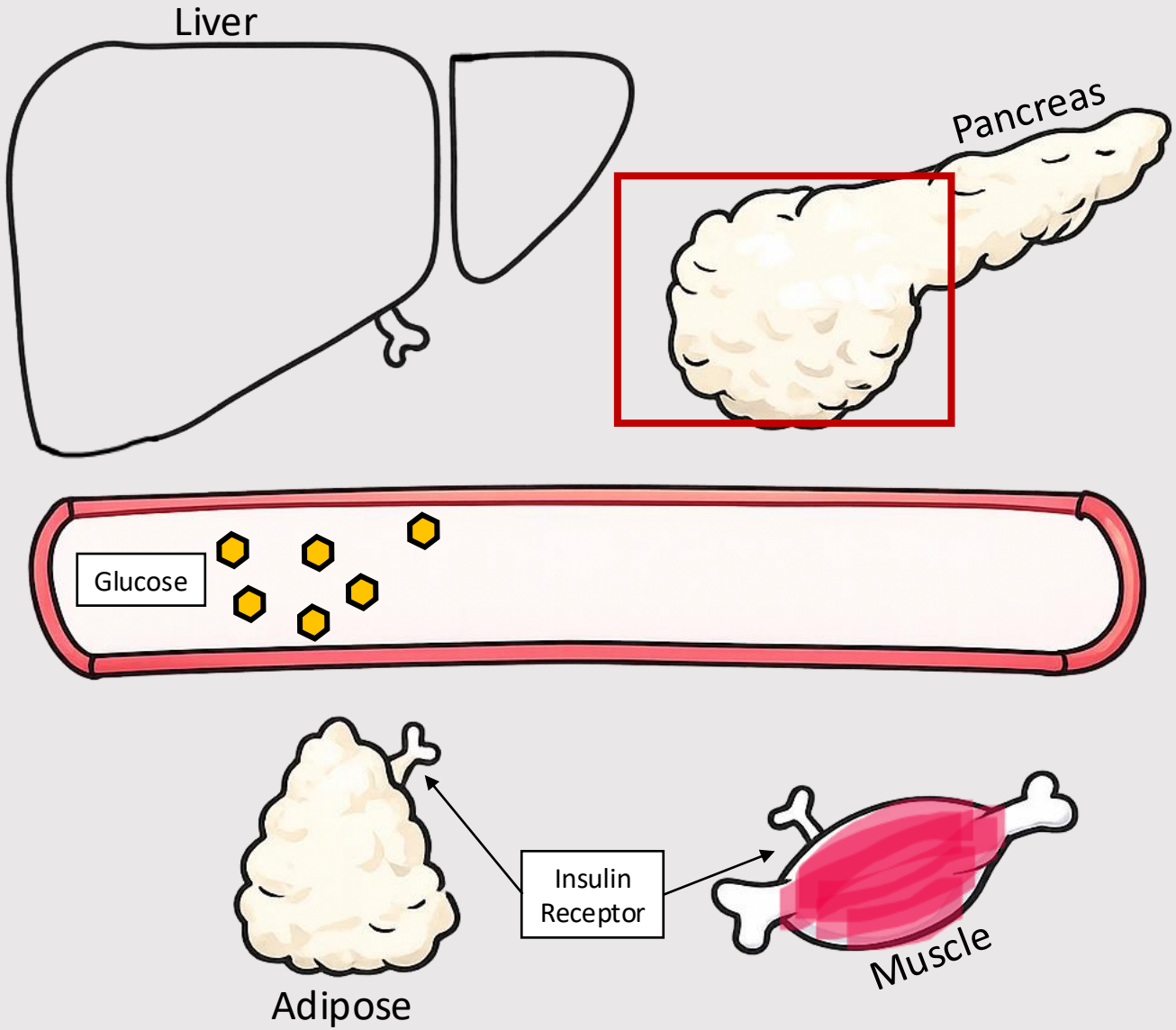
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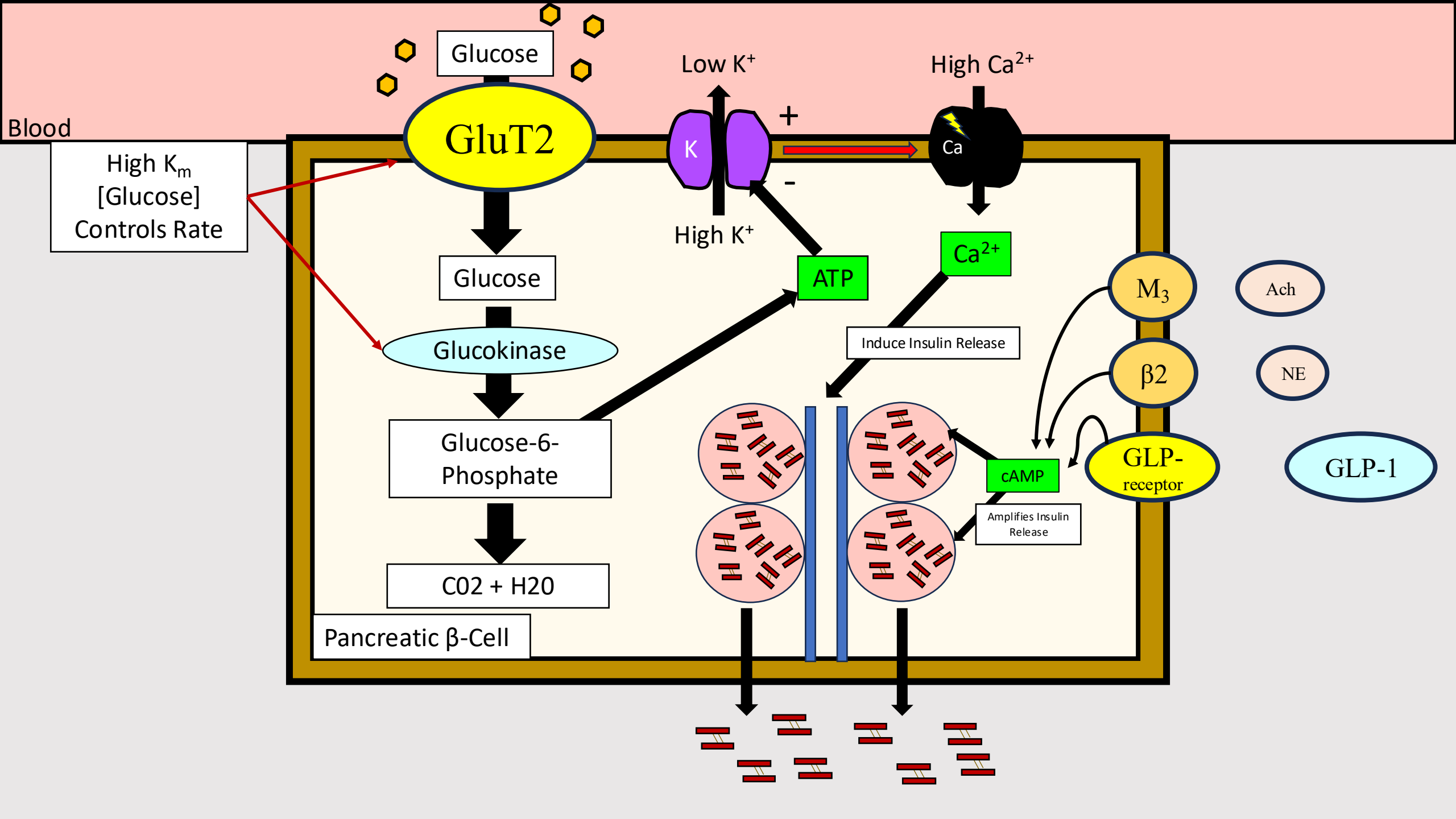
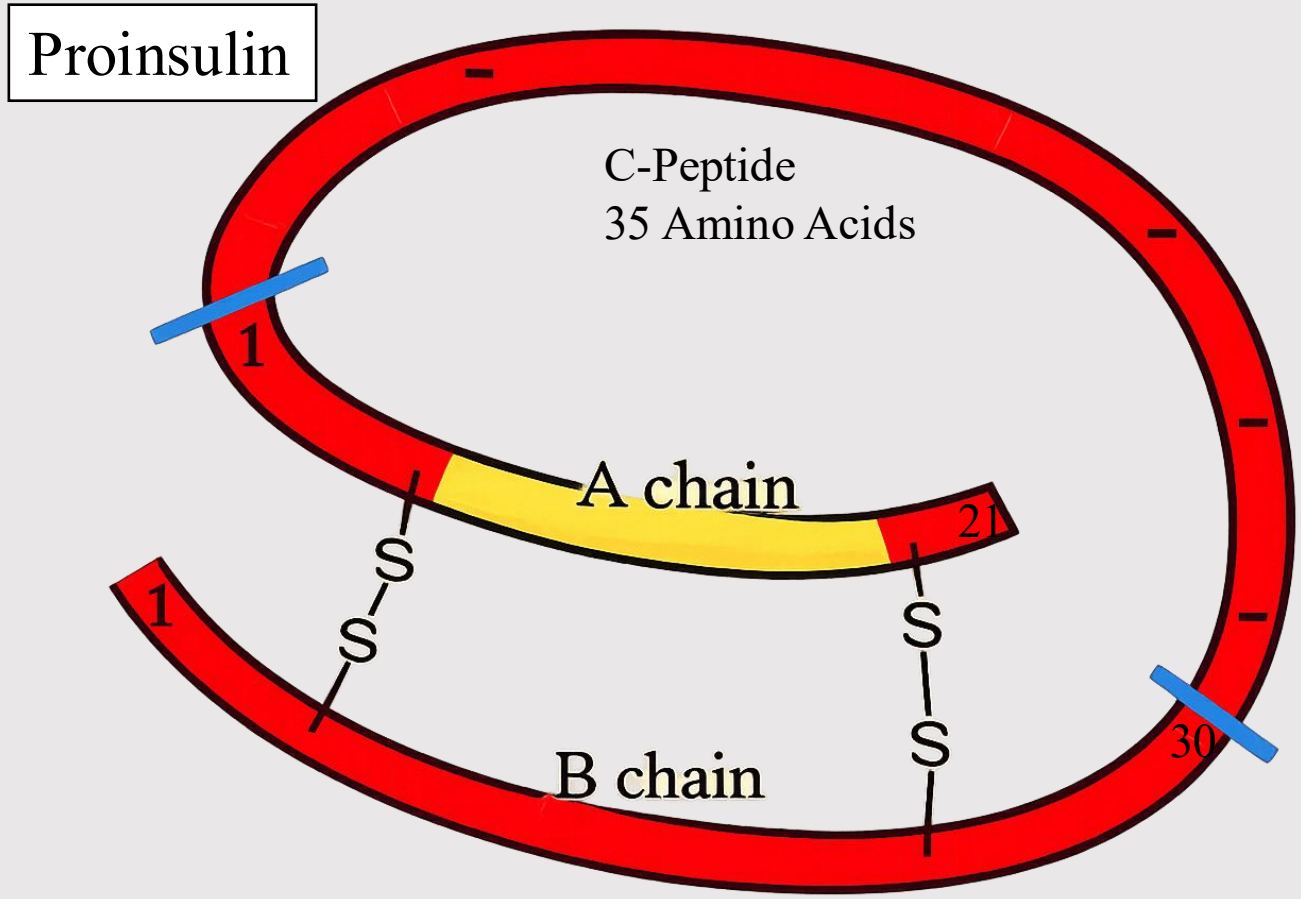

Blood
Glucose
GluT2
High K_m
[Glucose]
Controls Rate
Low K^+
High K^+
K
+
-
High Ca^{2+}
Ca
ATP
Ca^{2+}
Induce Insulin Release
Glucose
Glucokinase
Glucose-6-
Phosphate
C02 + H20
Pancreatic β-Cell
cAMP
Amplifies Insulin
Release
M_3
β2
GLP-
receptor
Ach
NE
GLP-1

Insulin

- Mature insulin has 51 amino acids
- 21 in A-chain
- 30 in B-chain



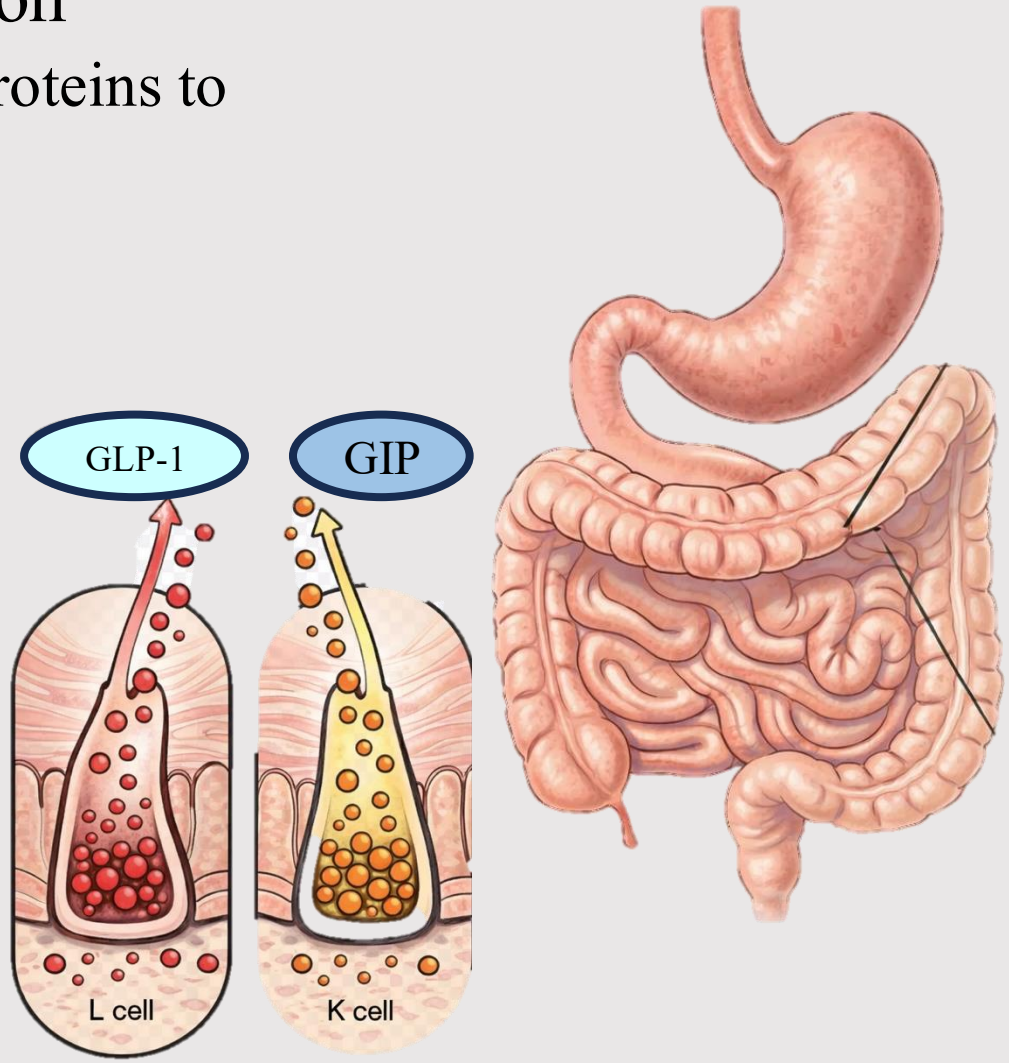
- Made as a single chain and stored in vesicles
- "**C-peptide**" is removed to yield the active hormone
- Stored as a hexameric complex containing 2 Zn^{2+} ions
- Dissociates to active monomers upon release/dilution

Secretion of Insulin

- While fasting, insulin is normally secreted at a low basal rate
- Secretion is stimulated by glucose, gut hormones (also mannose, leucine, arginine, vagus)
  - Glucose enters β-cell → elevation of ATP, GluT2 and glucokinase have high K_m so sensitive to glucose conc
  - ATP blocks K^+ channels → membrane depolarization → opening of voltage-dependent Ca^{2+} channels
  - Elevation in cytosolic Ca^{2+} triggers secretion
- Compare to the mechanisms of neurotransmitter release and contraction of smooth muscle

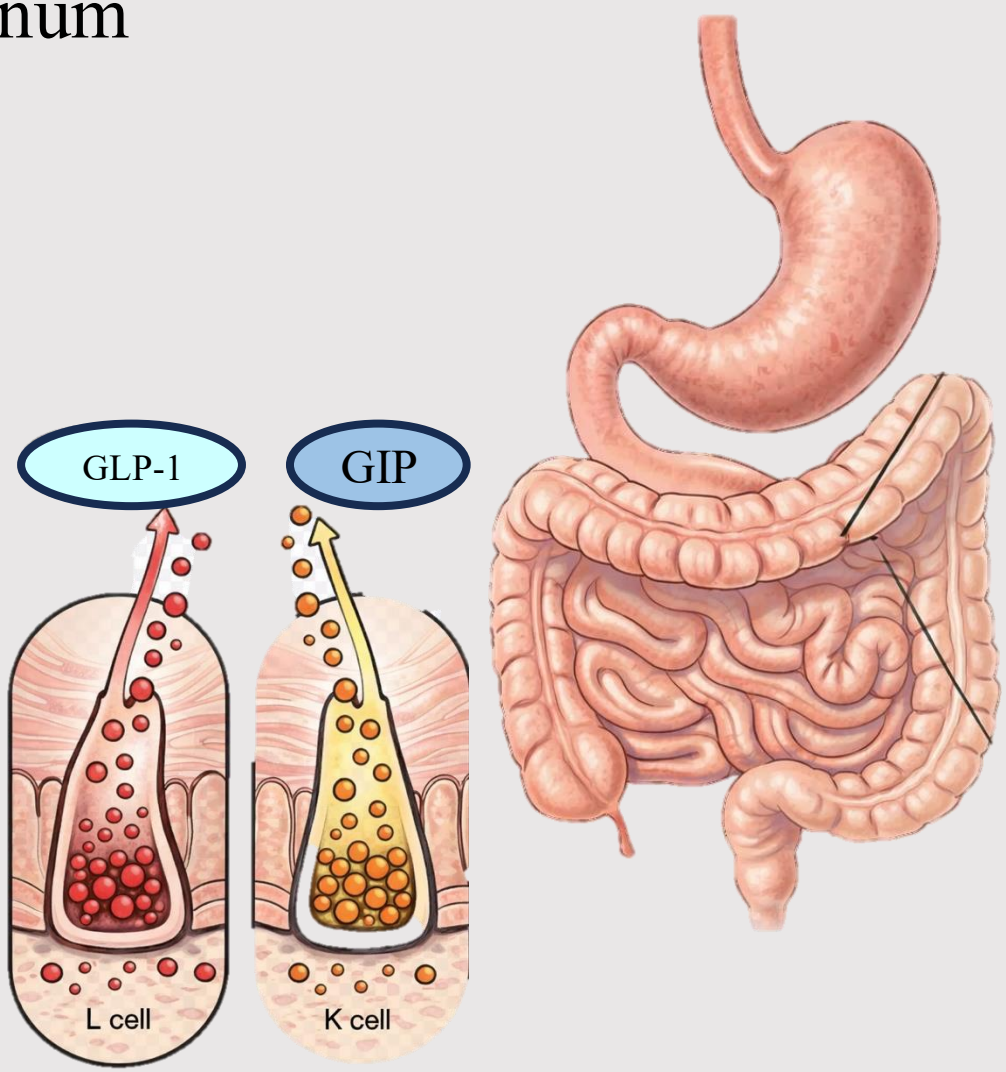
Role of GLP-1 and GIP

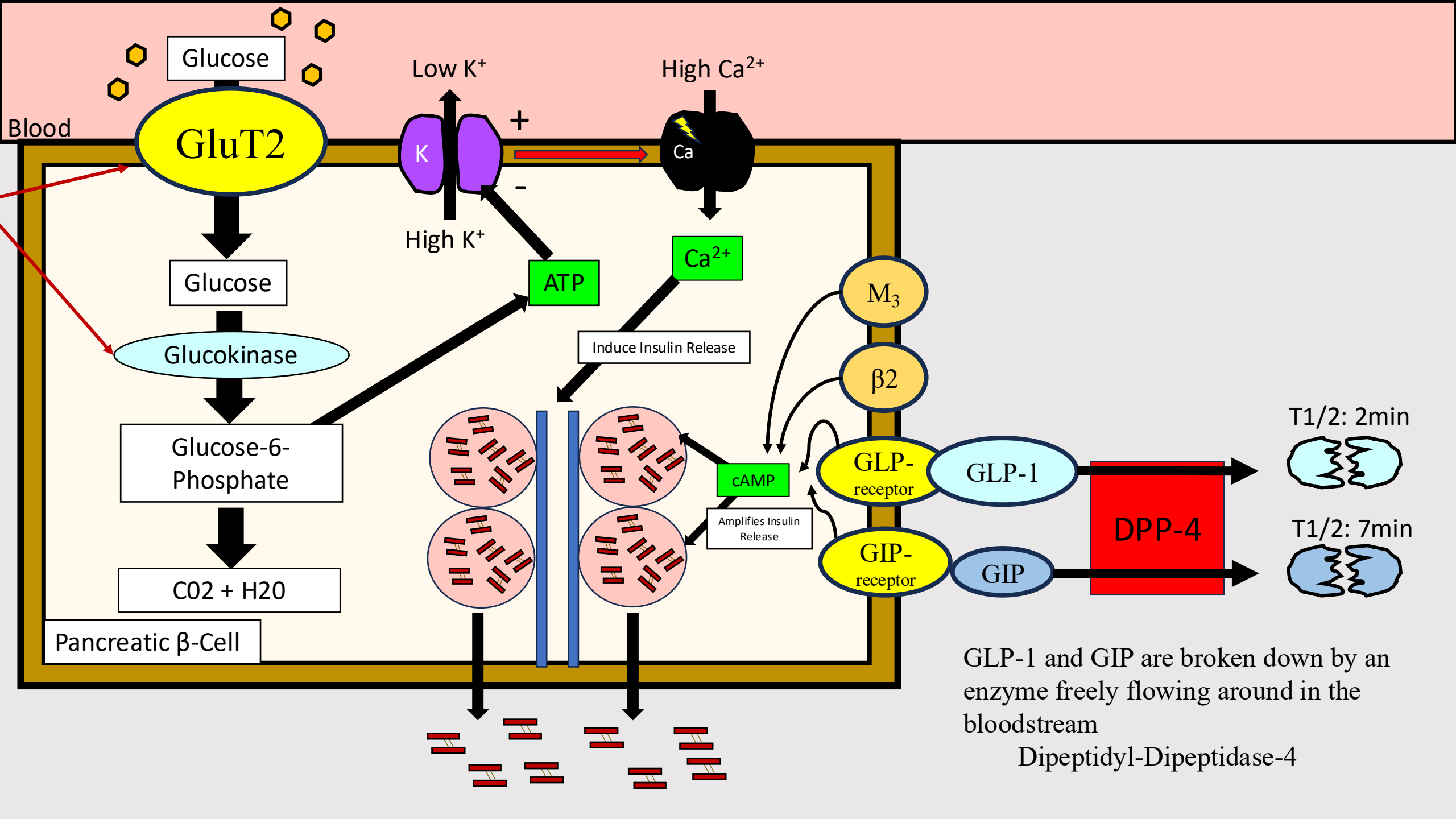
- **GLP-1 (Glucagon-Like-Peptide-1)**
  - Secreted by L-Cells in the distal ilium and colon
    - Released in response to carbohydrates, fats, and proteins to prepare the body for incoming nutrients
  - Physiologic Role
    - Amplify insulin secretion
    - Decrease glucagon secretion
    - Decrease gastric emptying
      - To slow down absorption
    - Increase satiety and decrease appetite in the CNS
  - GLP-1 $T_{1/2}$: 2 minutes (Broken down by Dipeptidyl-Dipeptidase-4 (DPP-4)
- **Optimizes insulin secretion, CNS satiety signaling, and slows gastric emptying.**



Role of GLP-1 and GIP

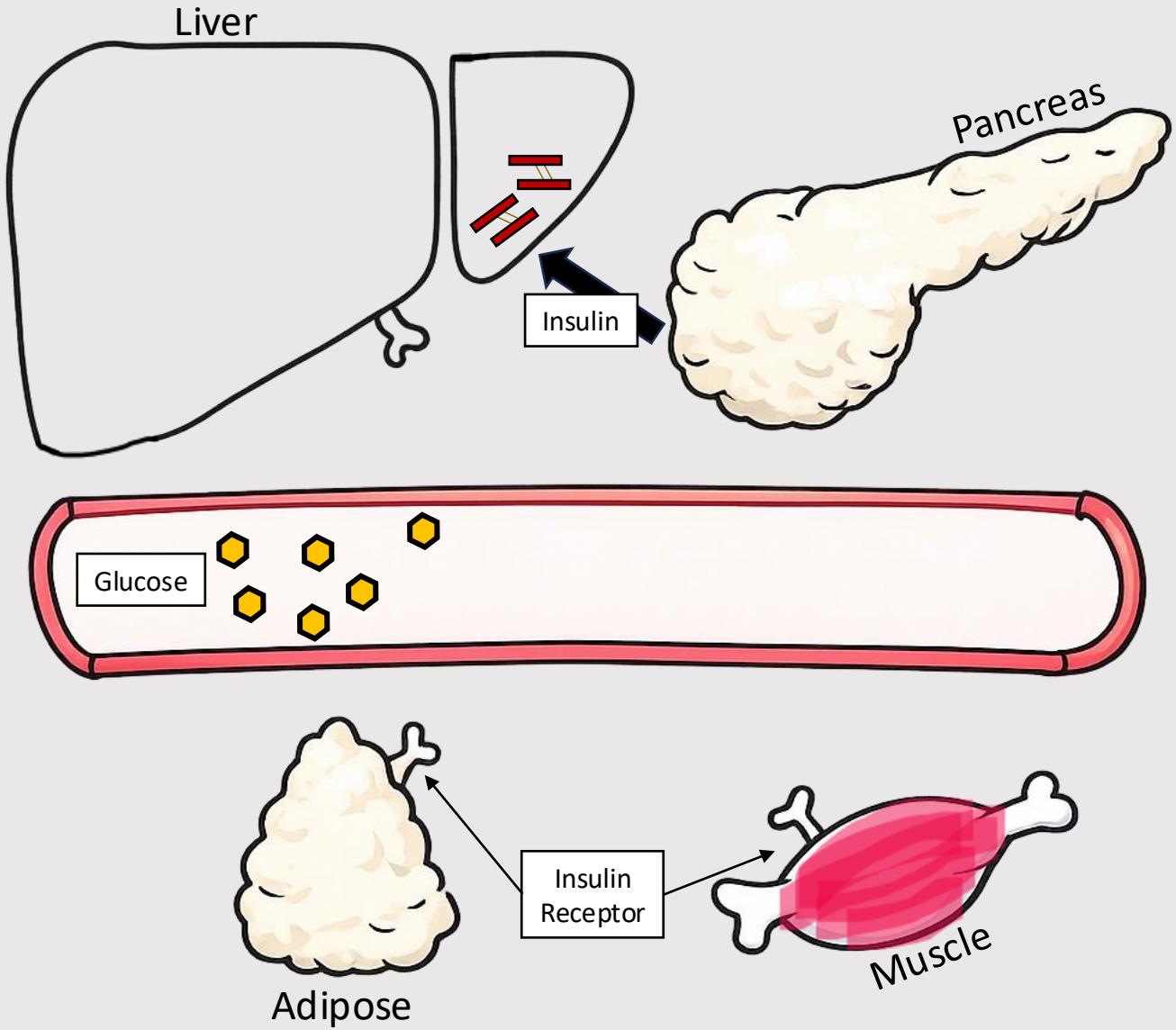
- **GIP (Gastric Inhibitory Peptide)**
  - Secreted by K-Cells in the duodenum and jejunum
    - Released in response to carbohydrates and fats to prepare the body for incoming nutrients
  - Physiologic Role
    - Amplify insulin secretion
    - Increase satiety and decrease appetite in the CNS
    - Improves insulin sensitivity in adipose
  - GIP $T_{1/2}$: 7 minutes (Broken down by Dipeptidyl-Dipeptidase-4 (DPP-4)
- **Overall optimizes insulin secretion, CNS satiety signaling, and metabolic efficiency**





GLP-1 and GIP are broken down by an enzyme freely flowing around in the bloodstream

Dipeptidyl-Dipeptidase-4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Glucose
Insulin
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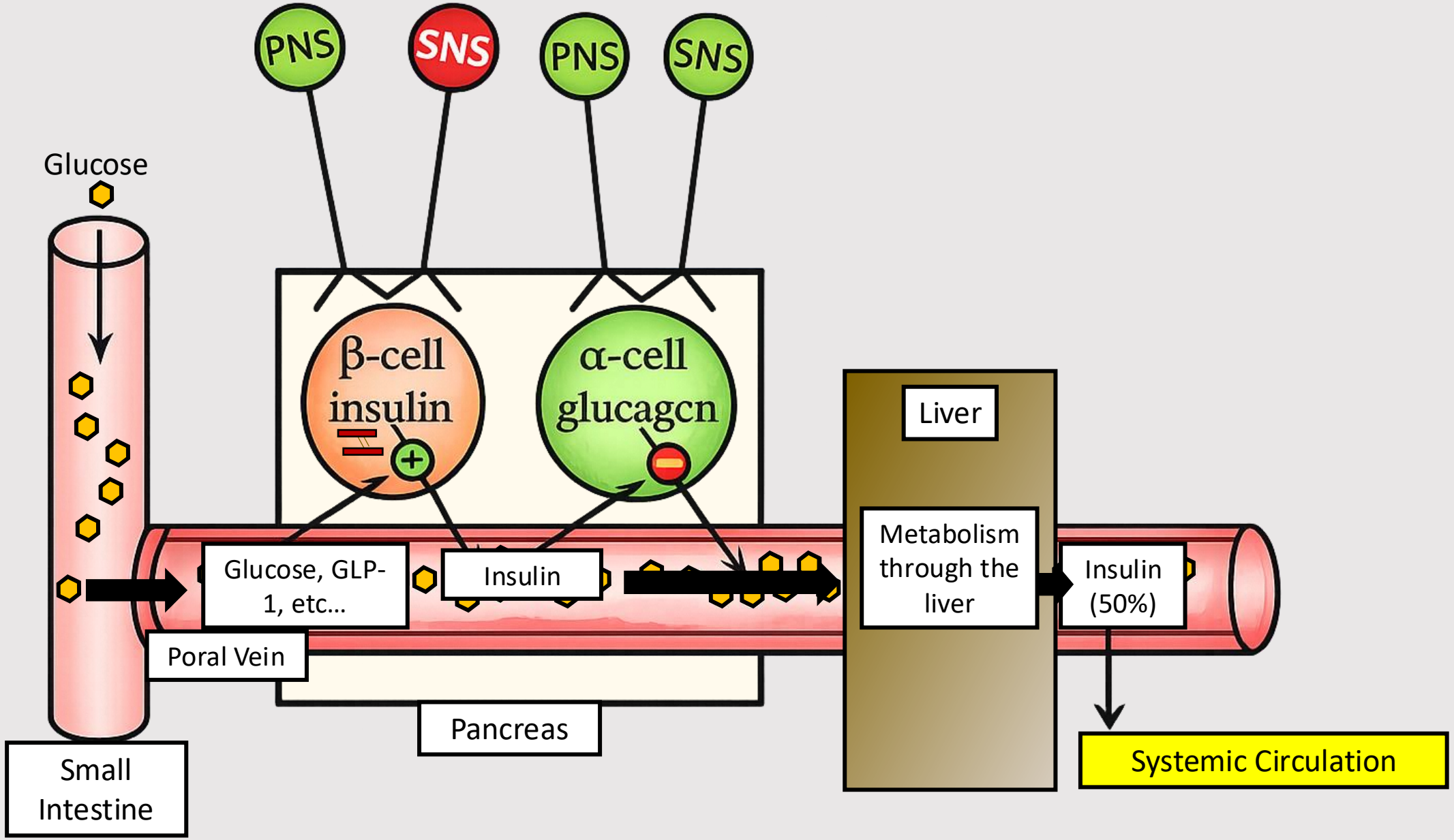
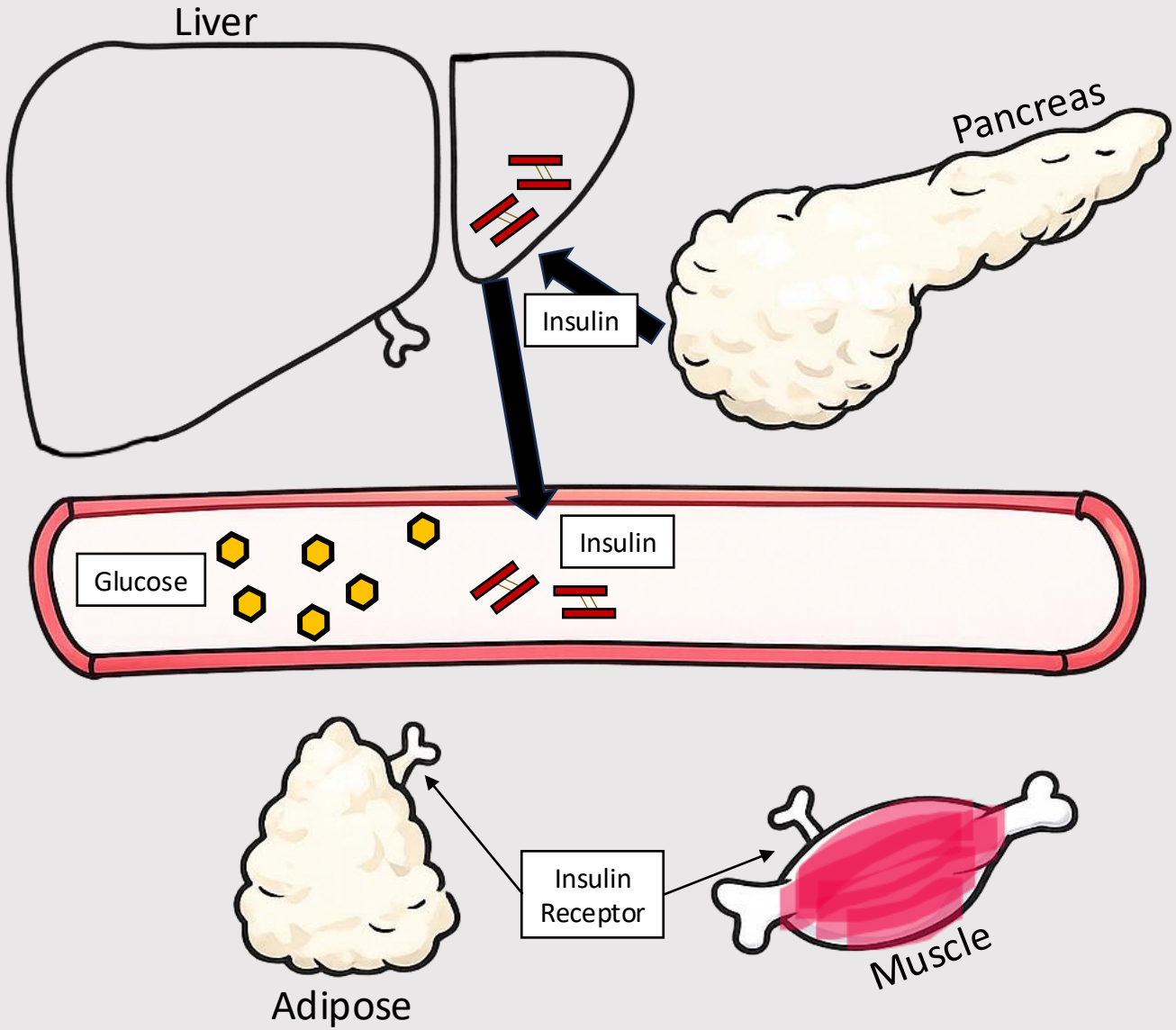
Muscle


PNS
SNS
PNS
SNS
Glucose
β-cell insulin
α-cell glucagcn
Liver
Metabolism through the liver
Glucose, GLP-1, etc…
Insulin
Insulin (50%)
Poral Vein
Pancreas
Small Intestine
Systemic Circulation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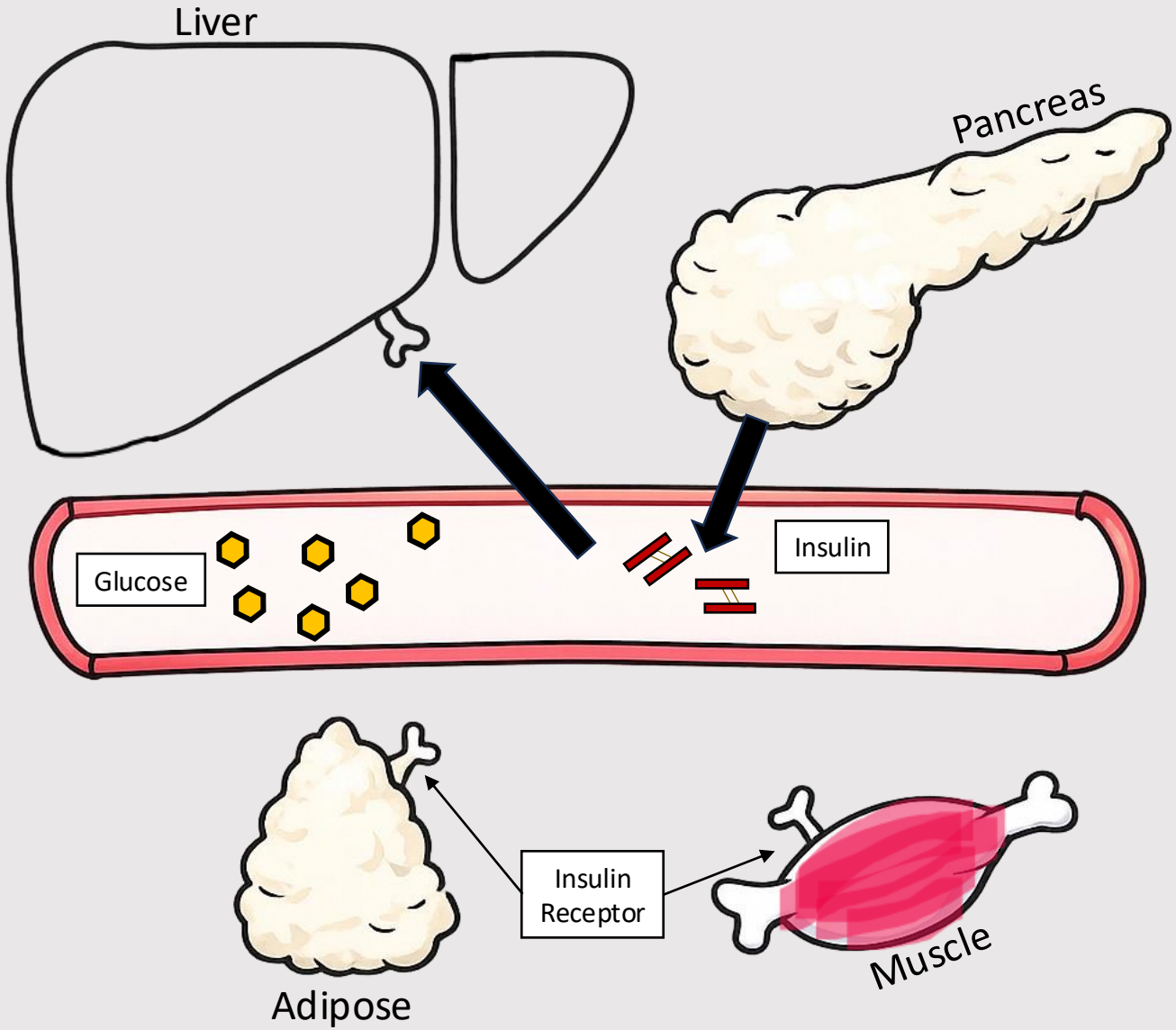
Insulin Secretion

- Insulin inactivated in liver and kidney, after internalization of insulin-receptor complex
  - Disulfide bonds cleaved by glutathione followed by proteolysis of peptides
- Remember **all the insulin** secreted by pancreas enters the hepatic portal vein
  - Liver clears 60%, (50% removed in **first pass**)
  - Kidney clears 35-40%, (filtered and then reabsorbed)
  - Percentages are reversed for subcutaneous insulin
  - Half-life of circulating insulin 3-5 min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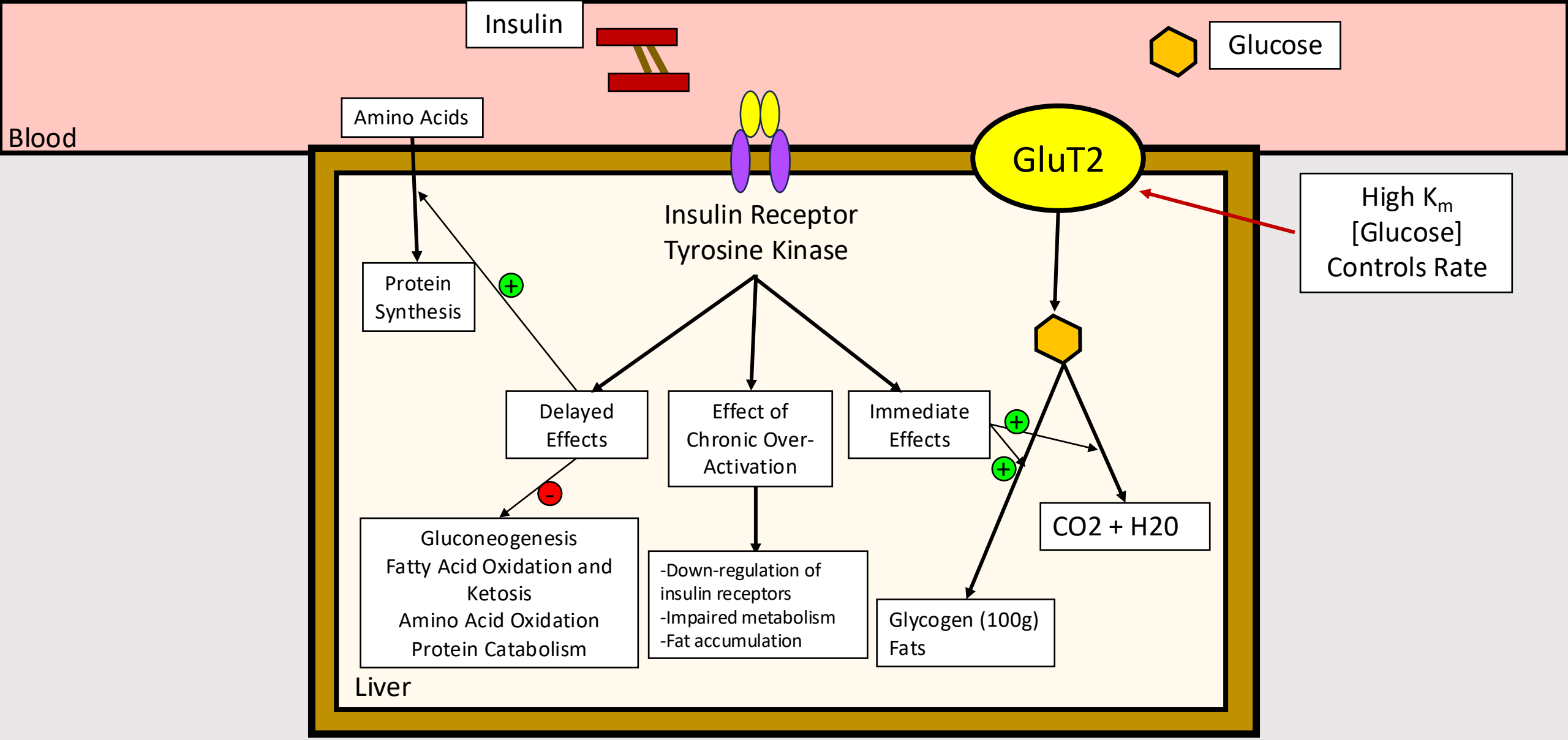


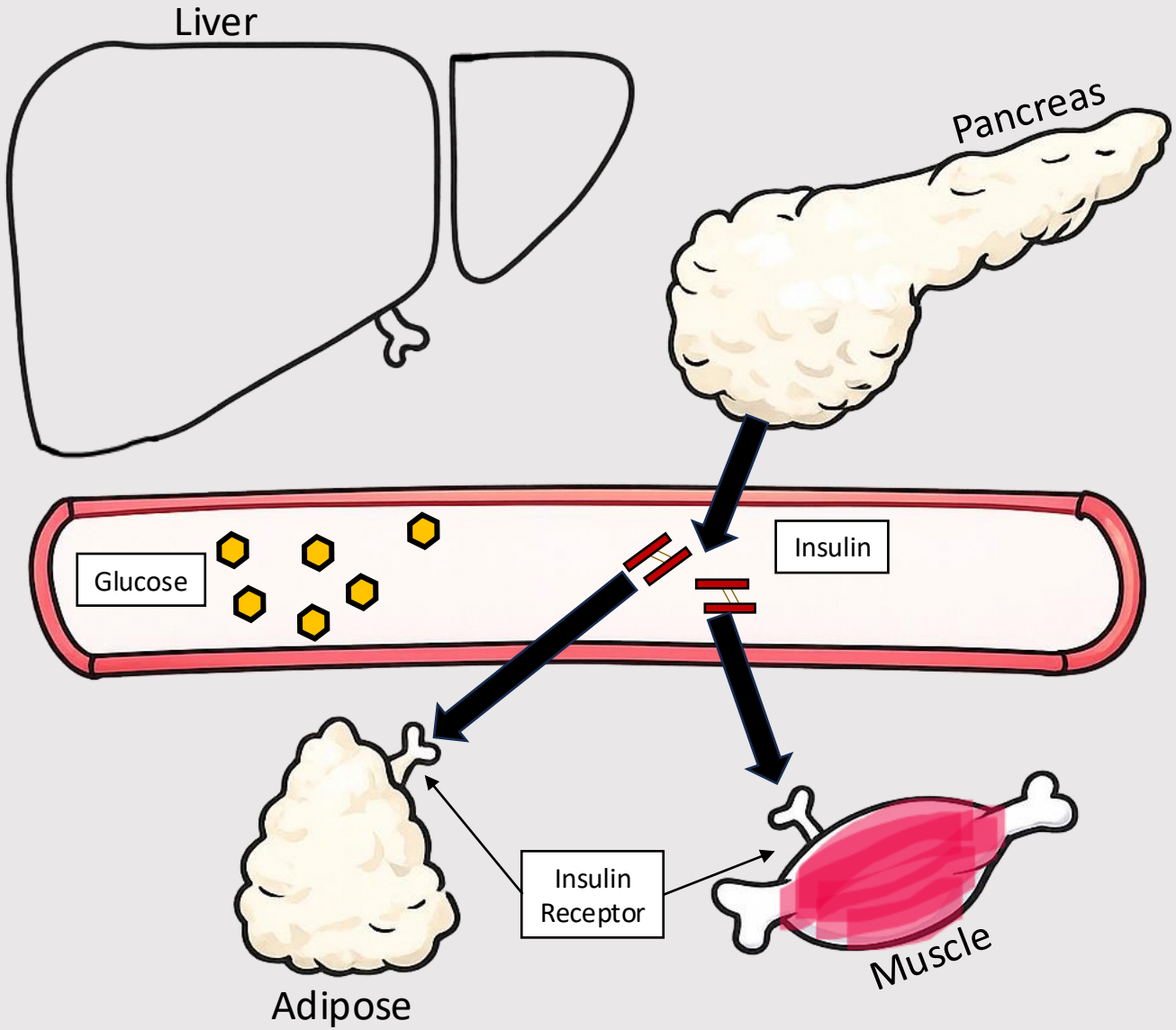
Insulin Mechanism: LIVER

Insulin: Mechanism of Action

- External membrane receptor (α subunit) - linked to internal tyrosine kinase (β subunit)
- Phosphorylation of proteins including other kinases leads to activation of glucose metabolism – leads to ***immediate*** effects
- Stimulates protein synthesis – ***delayed*** effects
- Insulin and receptors are internalized
- Excessive activation, e.g. in insulinoma, obesity, leads to down-regulation of receptors

Effects of Insulin

- **LIVER**
  - Stimulates **glycogen synthesis**, glycolysis
  - Inhibits glycogenolysis, **gluconeogenesis** (Glucose synthesis)
    - Recognize that we can get glucose from our diet OR synthesize it in the liver
  - Stimulates synthesis of Fatty Acids and Fat from excess glucose
  - Inhibits oxidation of fatty acids and amino acids and hence inhibits **ketogenesis**
  - Promotes amino acid transport and protein synthesis
  - Inhibits protein catabolism, and urea synthesis
- ***Note: Due to high K_m's of GluT2 and glucokinase, glycolysis in liver is limited by blood glucose conc. Contrast with muscle and adipose tissue.***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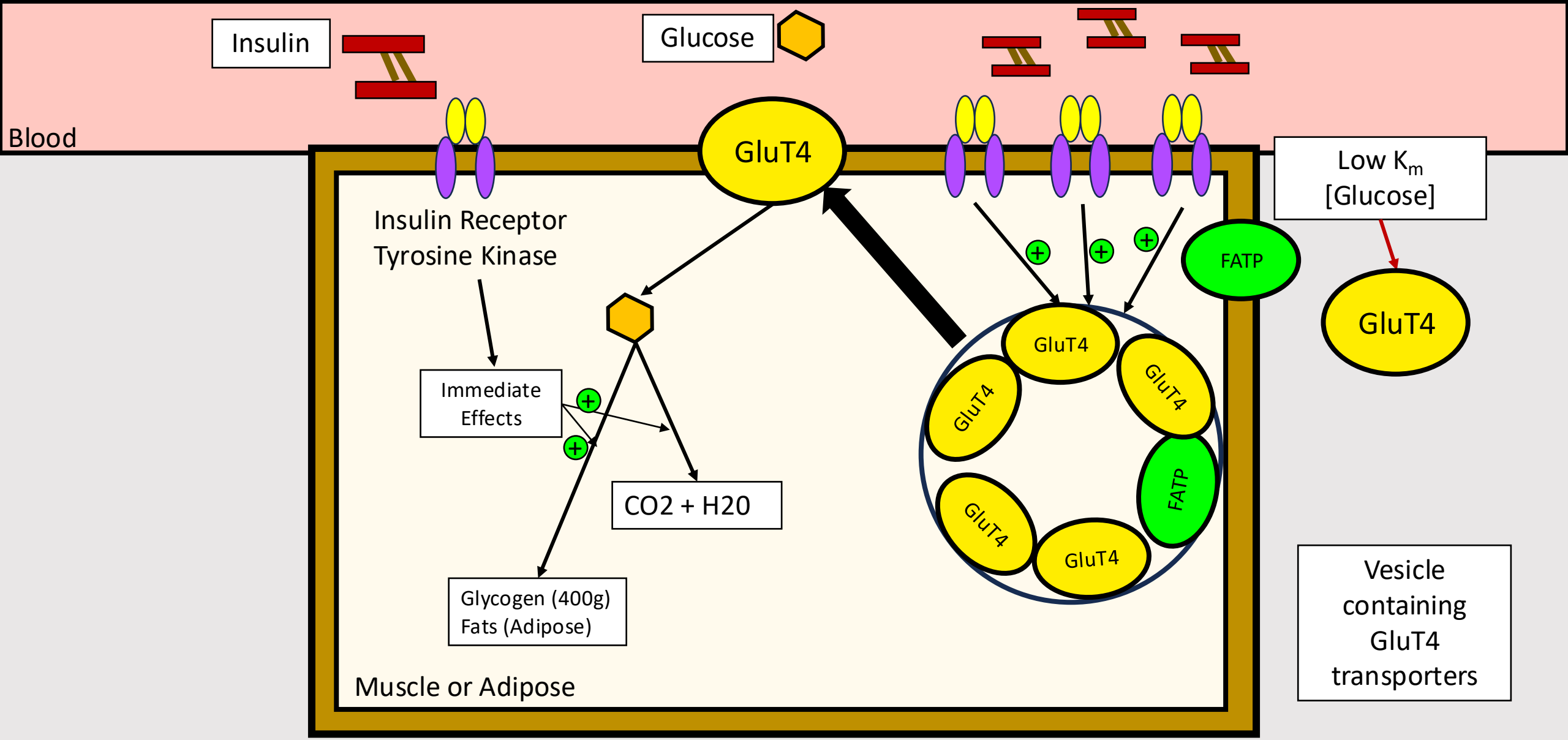
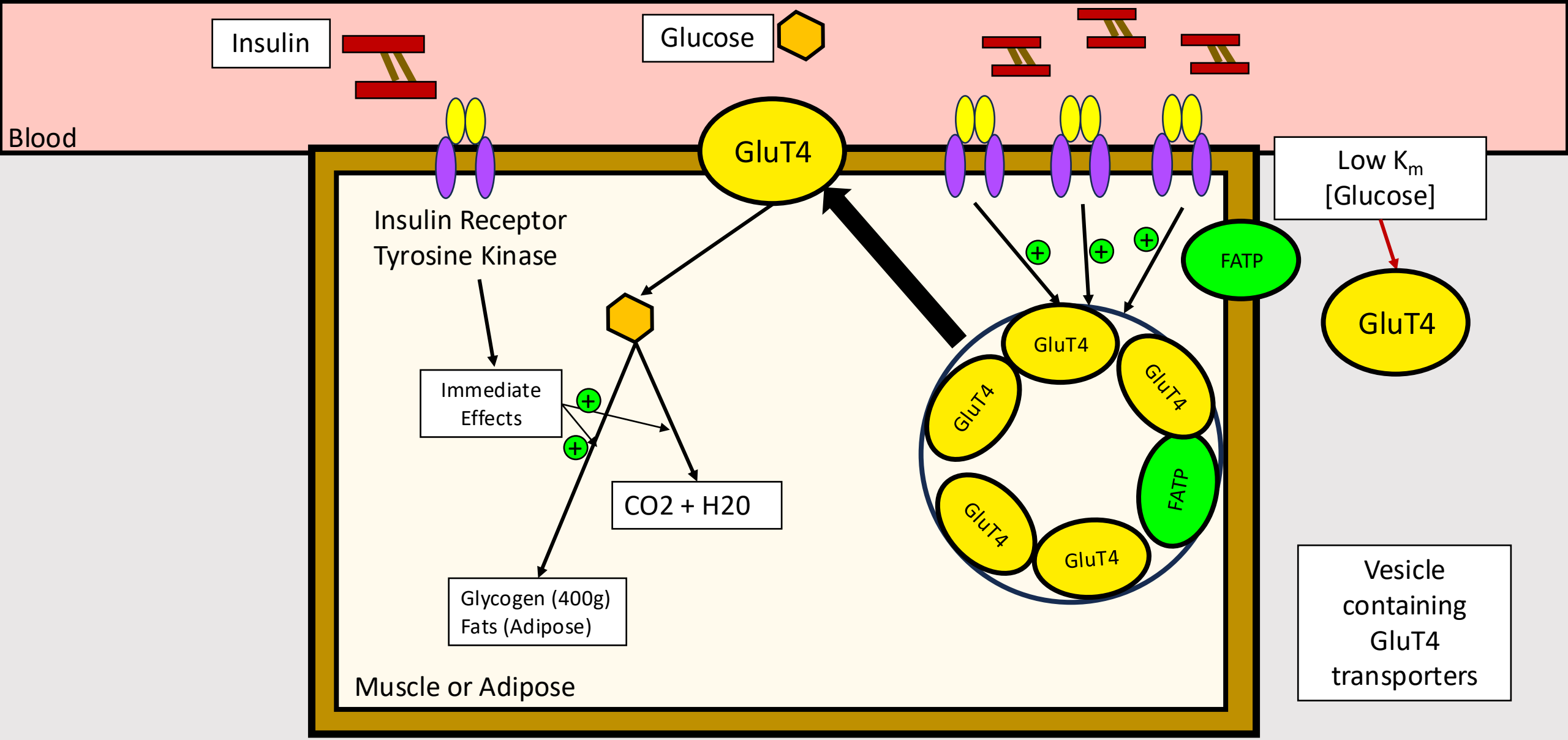
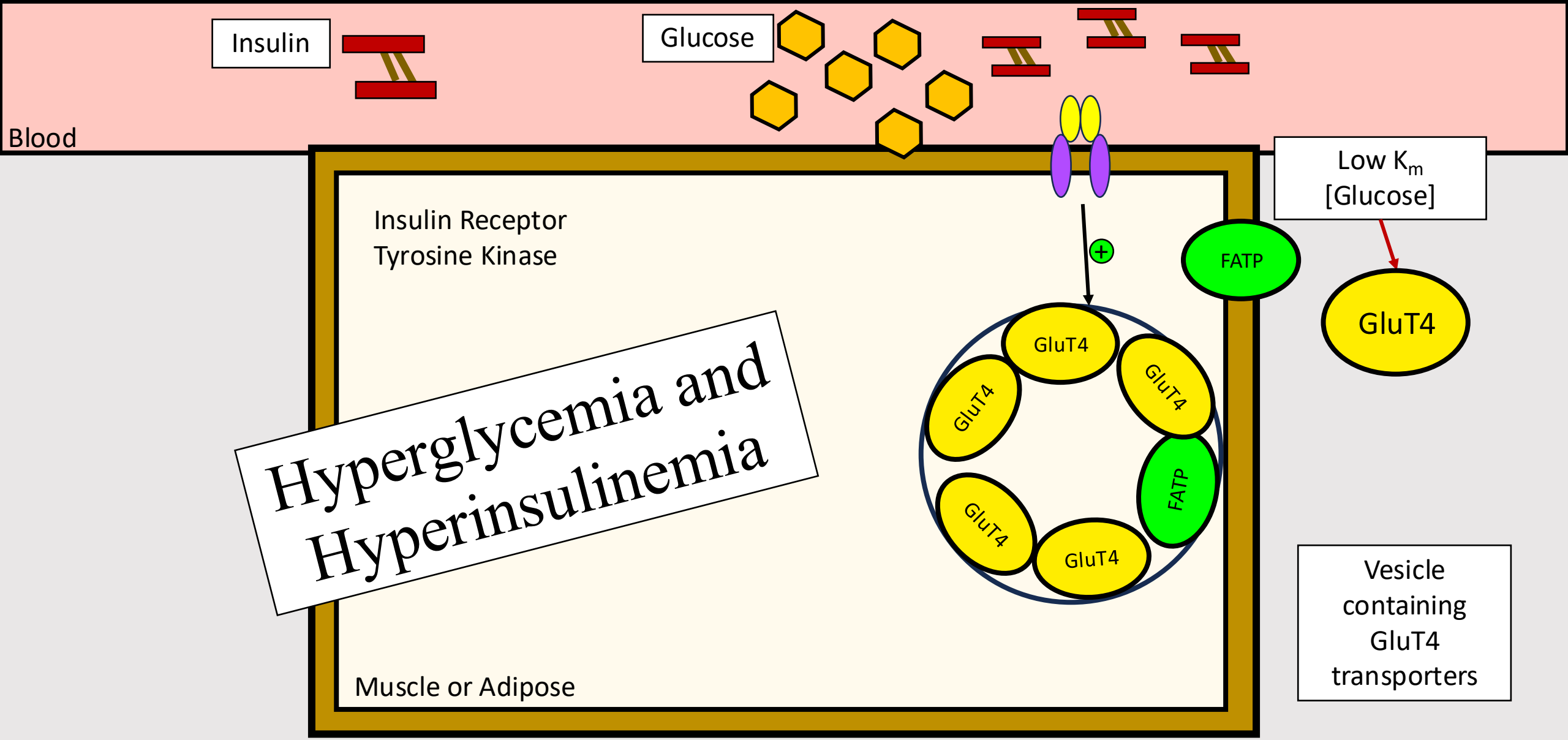


Insulin Mechanism: MUSCLE and ADIPOSE



Insulin Mechanism: MUSCLE and ADIPOSE

Consequence of overactivation of insulin receptors = Downregulation



Insulin Mechanism: MUSCLE and ADIPOSE

Consequence of overactivation of insulin receptors = Downregulation

Effects of Insulin

- **MUSCLE**
  - Promotes **glucose transport** by insertion of glucose transporters (GluT4, K_m ~5mM) and **glycogen synthesis**
    - **GluT4 is the rate limiting step of glucose uptake in adipose and muscle**
  - Promotes amino acid transport and **protein synthesis**
- **ADIPOSE TISSUE**
  - Insertion of glucose transporters (GluT4)
  - Stimulates glycolysis for conversion of glucose to fat
  - Increases rate of fatty acid import from blood (FATP)
  - Increases rate of triglyceride (fat) synthesis
  - Intracellular lipolysis↓ (HSL); endothelial lipolysis↑
- **Net effect is decreased plasma free fatty acids, increase in amounts of stored fat → weight gain**

Damage to Organs

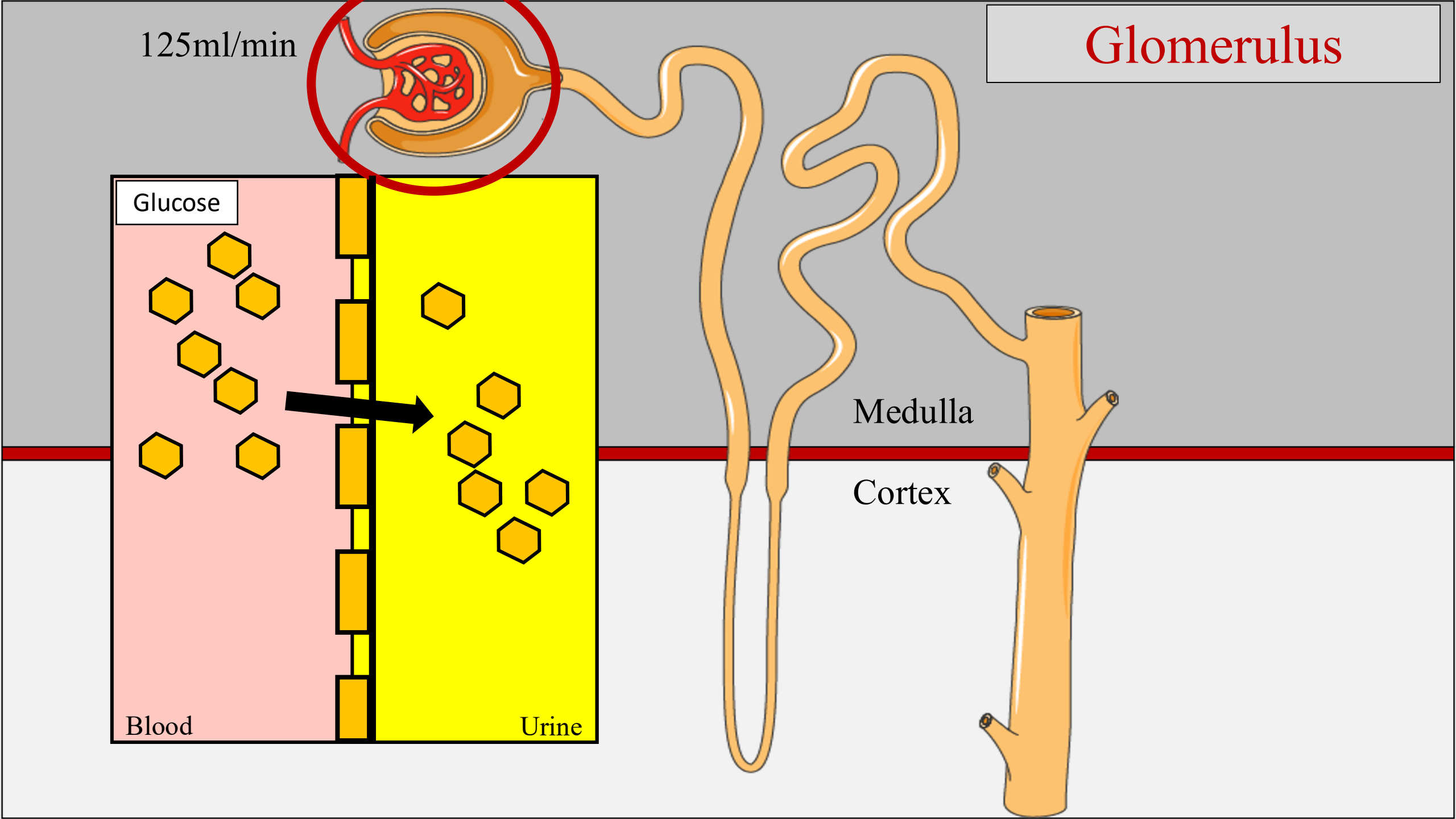
Diabetes Mellitus

- Two major classifications (1990's)
  - **Type 1**, (Insulin-dependent, "juvenile onset")
    - Affects about 0.5% adults in USA
    - **Autoimmune** destruction of insulin-secreting cells (β cells) in the *Islets of Langerhans* of the pancreas (95% of cases)
    - Not associated with obesity - often below normal weight
  - **Type 2**, (Non-insulin-dependent, "adult onset")
    - Affects about 5% (24 million) adults in USA
    - **Insulin resistance** and often associated with obesity
- **– Others: Type 1-LADA, type 1.5, type 2 + auto Ab's**

Hyperglycemic Damage

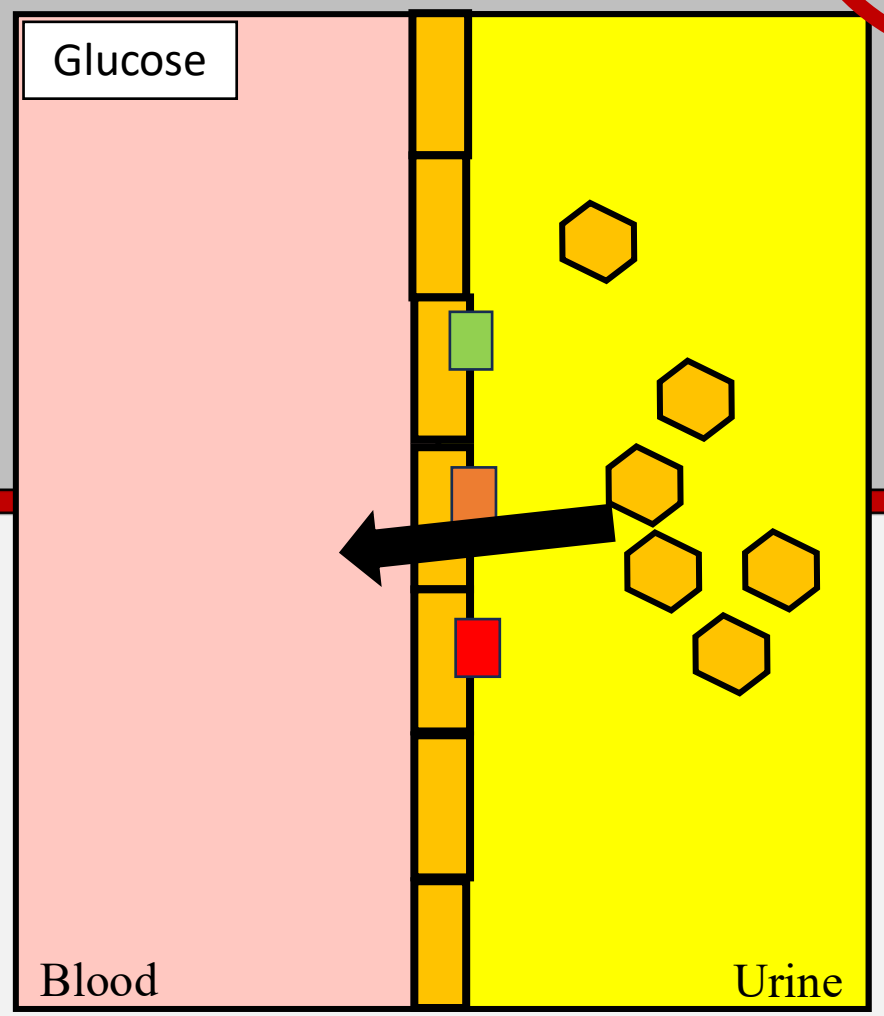
- Dr. O thinks that “Hyperglycemia damages the body by chemically modifying proteins over time, mechanically dehydrating tissues through osmotic forces, and overwhelming metabolic signaling pathways that amplify inflammation”.
- Elevated Blood Sugar Generally damages the body:
  - Acutely
    - Osmotic Diuresis → Electrolyte Disturbances
  - Chronically
    - Glycation of Proteins → Chronic Inflammation

Glomerulus



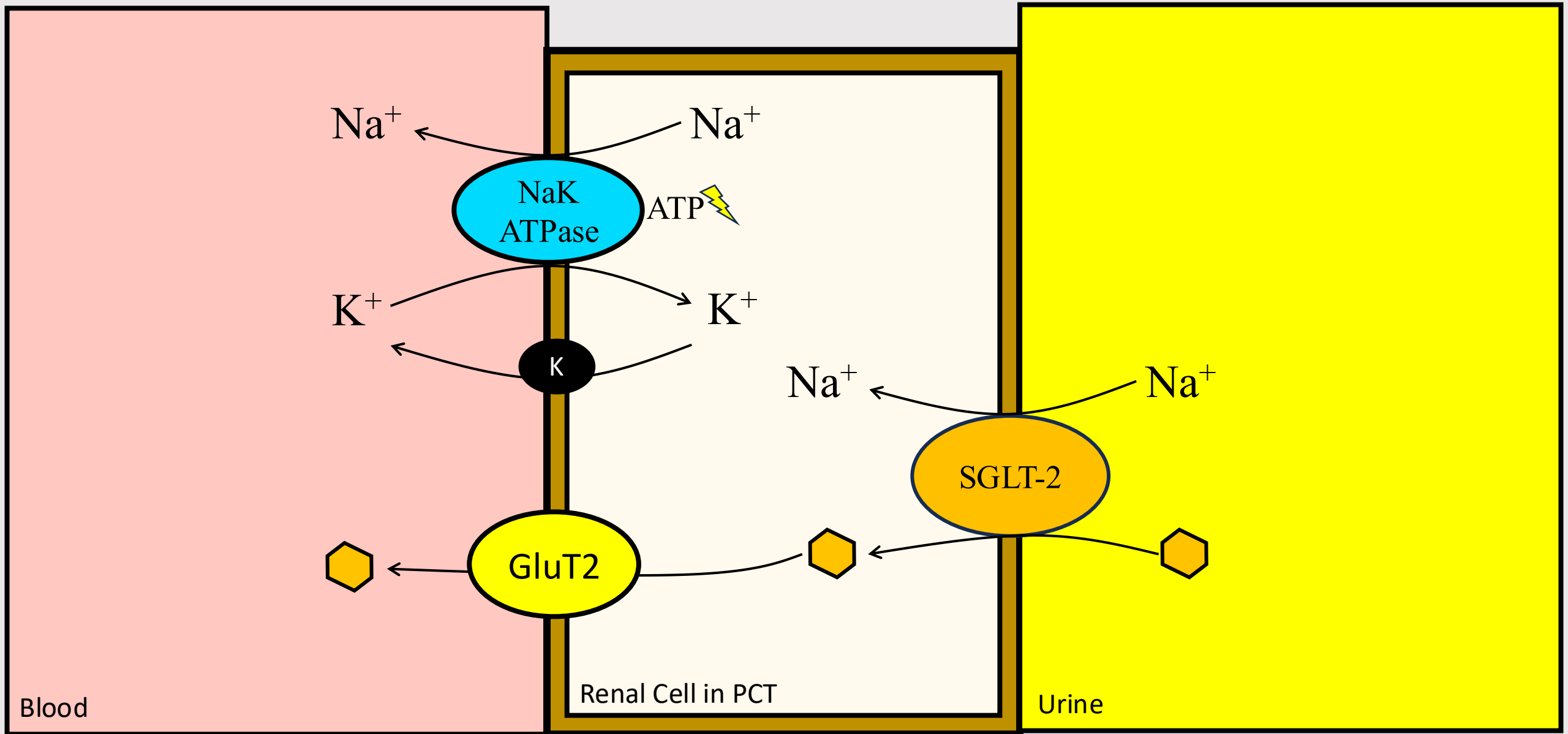
PCT

125ml/min



Reabsorption in PCT:
Water: 65%
Na: 65%
Cl: 60%
K: 65%
HCO3: 90%
Glucose: 100%
Amino Acids: 100%
P04: 80%
Ca: 65%
Mg: 20%
Urea: 50%
Proteins: 100%

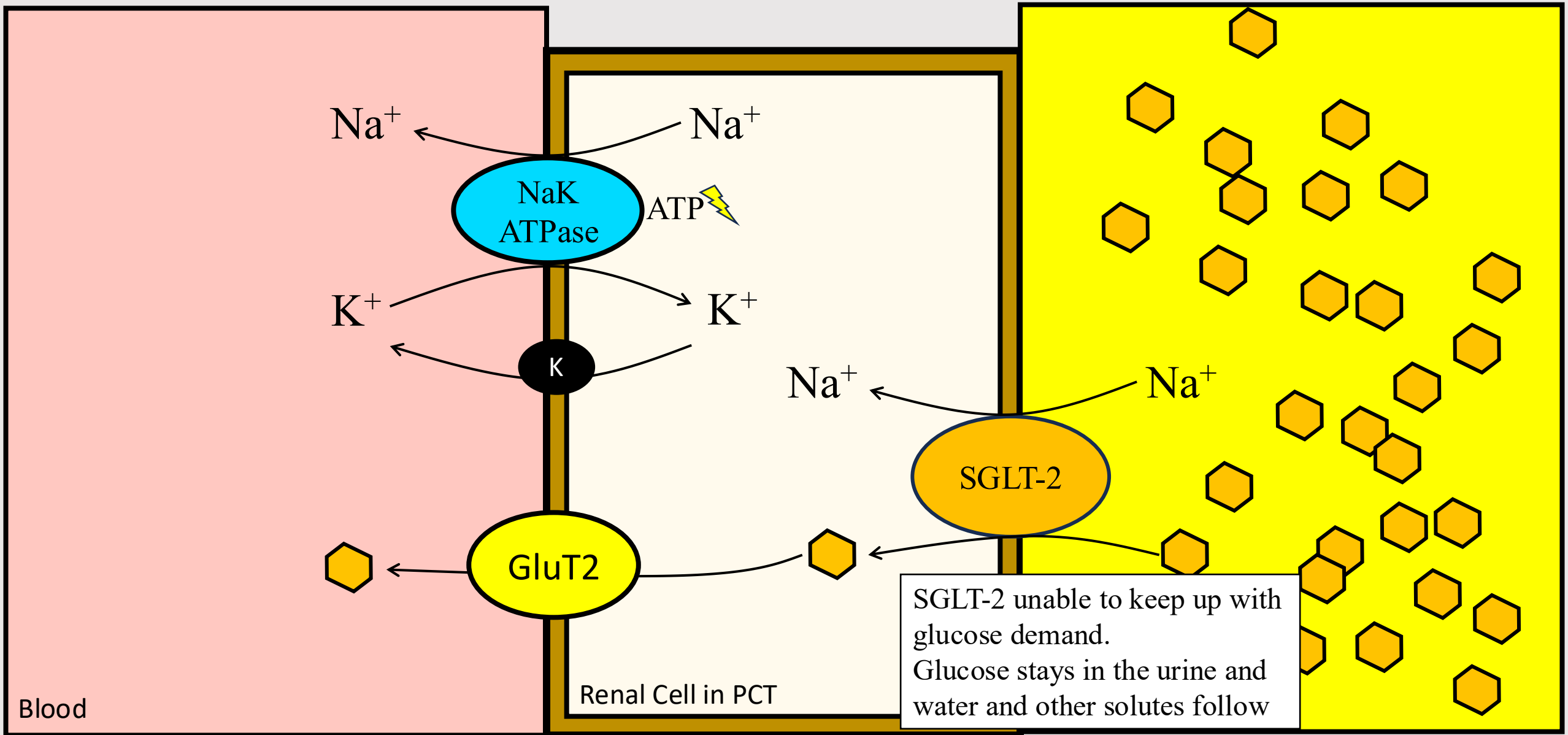
Renal Reabsorption of Glucose in the PCT



Renal Handling of Glucose

- Glucose enters urine through pores → urine → PCT
- In the PCT, glucose can be reabsorbed by a Sodium-Glucose Cotransporter-2 (SGLT-2)
  - This enzyme cotransports one Na and one Glucose together.
  - SGLT-2 is driven by the Sodium-Potassasium ATPase (NaK ATPase), which works to keep intracellular sodium low. This creates a gradient of high sodium in the urine and low sodium in the cell, allowing sodium to flow down it's concetration gradient via the SGLT-2 and transport glucose at the same time.
  - The NaK ATPase is generating a gradient, which is driven by ATP.
- GLUT-2, as also found in the liver, works to reabsorb the glucose.
  - Remember, GLUT-2 and GLUT-4 are different. GLUT-2 has a high Km, so it can take up glucose very easily.

Hyperglycemia in the PCT



Problems Associated with Elevated Blood Glucose

- **Osmotic diuresis** - when glucose conc. > 10mM
  - Na+/glucose cotransporters (SGLT2) in kidney are saturated and kidney can no longer reabsorb it all
    - Polyuria
    - Polydipsia
    - Dehydration
    - Electrolyte loss (Na^+, K^+, Mg^{2+})
    - Acute Kidney Injury
    - Confusion
    - DKA / HHS physiology

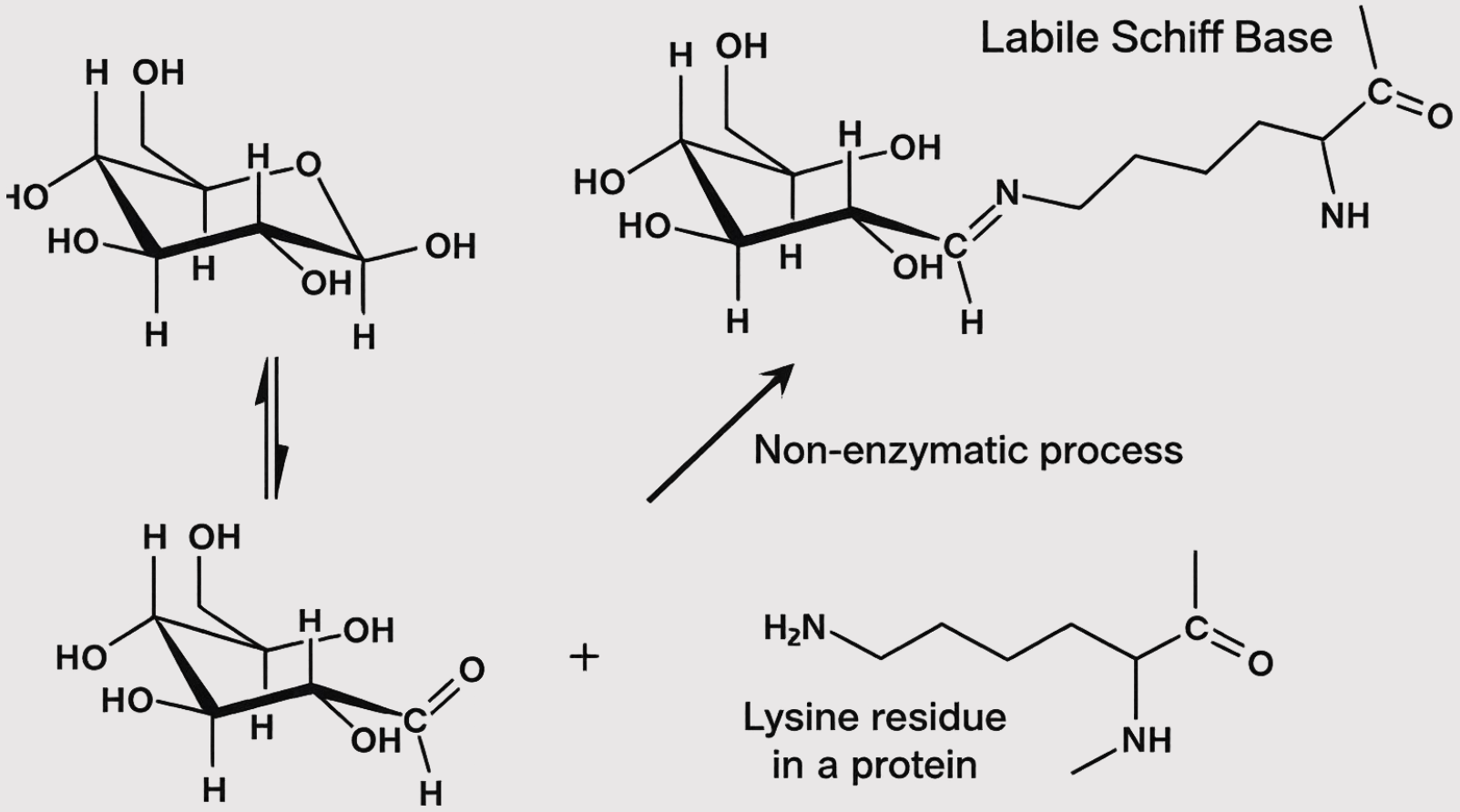
Type 1 Diabetes Mellitus

- Progressive loss of β cells leads to decrease in insulin secretion and elevation of blood glucose
  - By 30 years of age, secretion essentially ceases
  - Insulin administration necessary for survival
- Hyperglycemia leads to osmotic diuresis
- **Ketoacidosis** (DKA): v. low insulin + high glucagon leads to oxidation of fatty acids and amino acids
  - Na, K salts of ketoacids leads to diuresis, **K depletion**
  - Polyuria, polydipsia, vomiting, pH↓ → hyperventilation
- **Hyperosmolar dehydration**, shock, coma and death
  - but DKA symptoms provide early warning

Type 2 Diabetes Mellitus

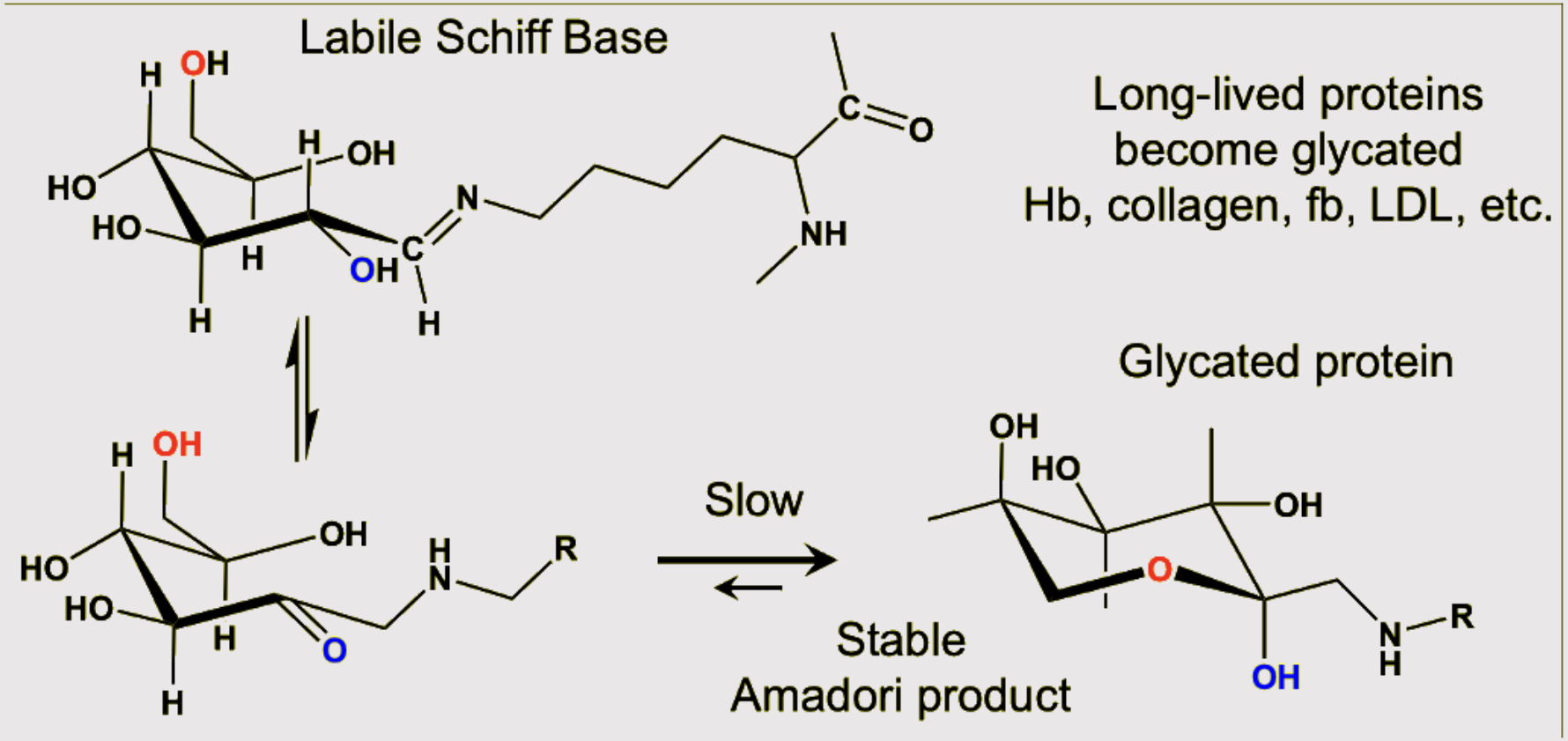
- Target cells become resistant to insulin
  - Blood glucose rises
  - Insulin secretion rises to compensate, but the concentration is less than would be found in a normal individual with the same level of glucose. ***Why?***
  - β -cells become less sensitive to glucose
- Osmotic diuresis/Polyuria
  - Dehydration "**hyperglycemic hyperosmolar state**"
  - BP↓ → HR↑, mental confusion, lethargy, coma → death in > 50% cases - few warning signs –***Why?***
  - Insulin secretion↓, but not enough to cause ketoacidosis – so, **NO** vomiting, abdominal pain, or hyperventilation

Glycation of Proteins



- Linear form of glucose (aldehyde) can react with the N-terminal α-NH2 groups or ε-NH2 groups on lysine
- **Hemoglobin**, LDL, collagen, fibronectin, crystallins

Glycation of Proteins



- Glycation of HbA to HbA_{1c} is **irreversible** - assayed every 3 months to monitor control of blood glucose –
  - Control: HbA1c <7% optimal, >10% poor
- Approved for ***diagnosis*** of diabetes by FDA(2013)

Glycation = Chronic Structural Damage

- Glucose non-enzymatically binds to proteins
- Cumulative Chemical Scarring of:
  - **Vessels** → atherosclerosis, stiffness. → Atherosclerosis, Poor wound heal
  - **Kidneys** → GBM thickening, albuminuria → Diabetic Nephropathy
  - **Nerves** → axonal & Schwann cell injury → Peripheral Neuropathy
  - **Retina** → capillary damage, ischemia → Retinopathy
  - **Skin, collagen, joints** → Charcot foot, Arthropathy