

How Do Insulins Work?

The Pharmacology of Insulin

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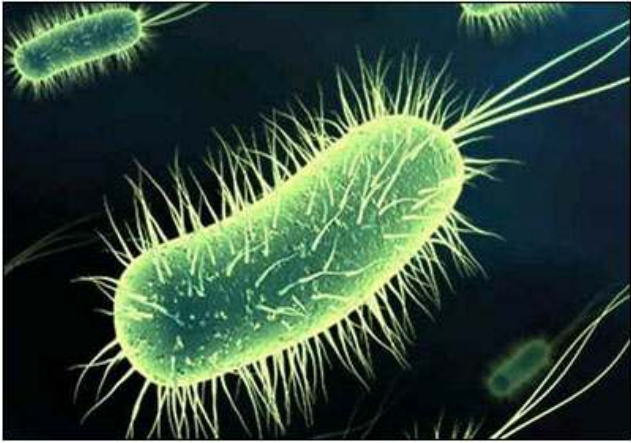
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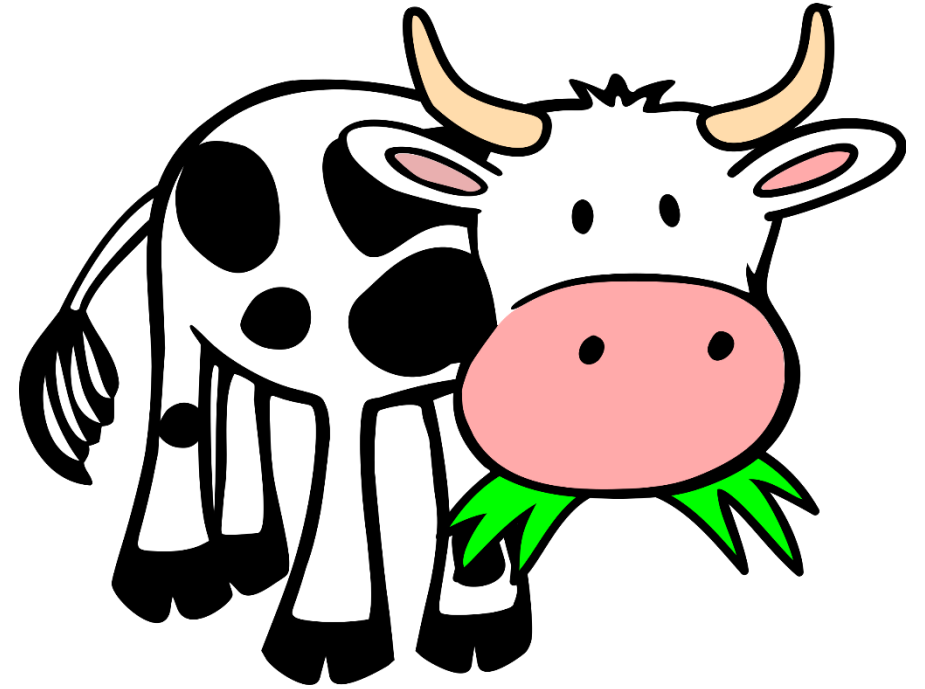
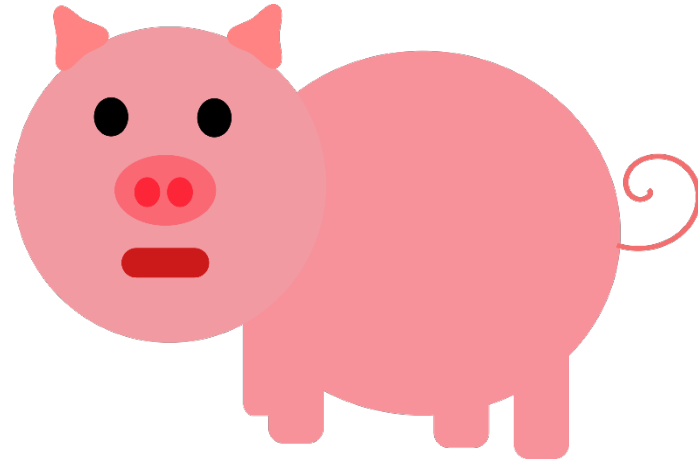
April 18, 2018

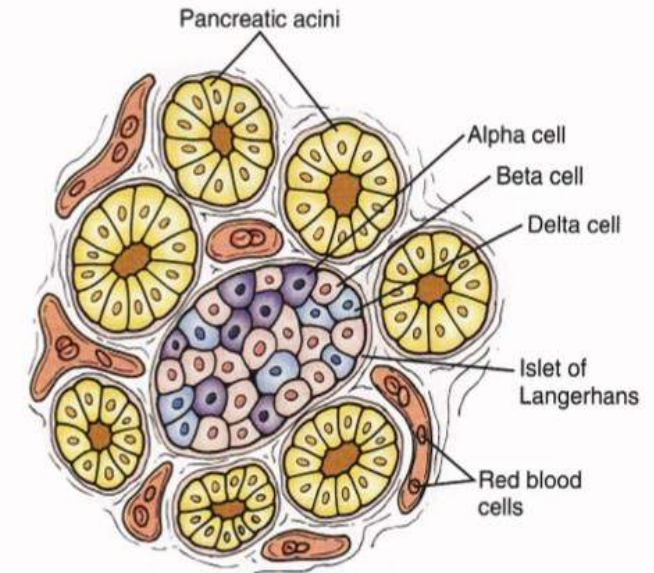
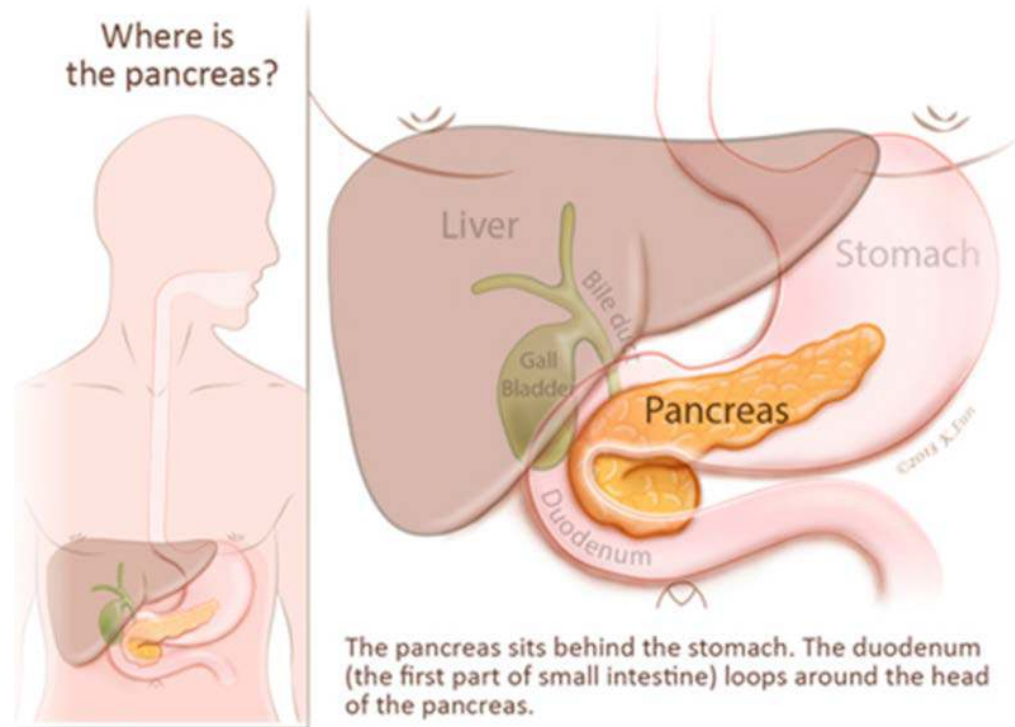
- Review insulin and its actions
- Describe differences between insulins and effects on onset and duration of action
- Discuss other reactions that occur with insulin

What do these have in common?



Escherichia Coli



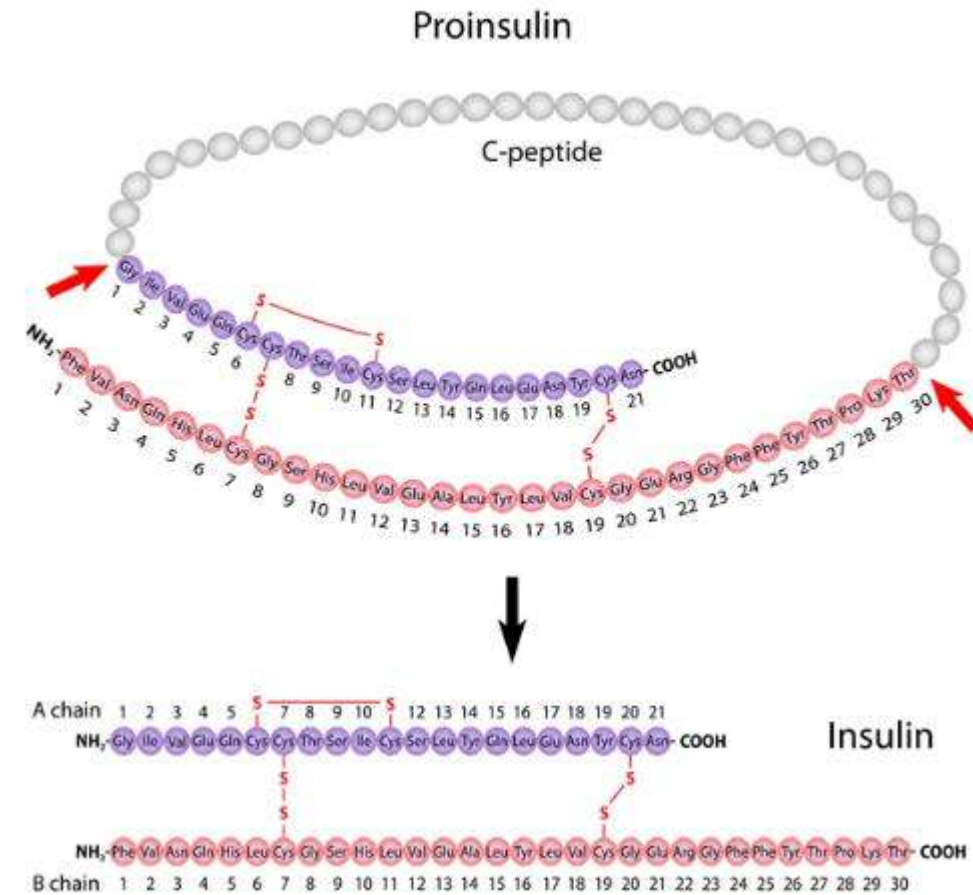
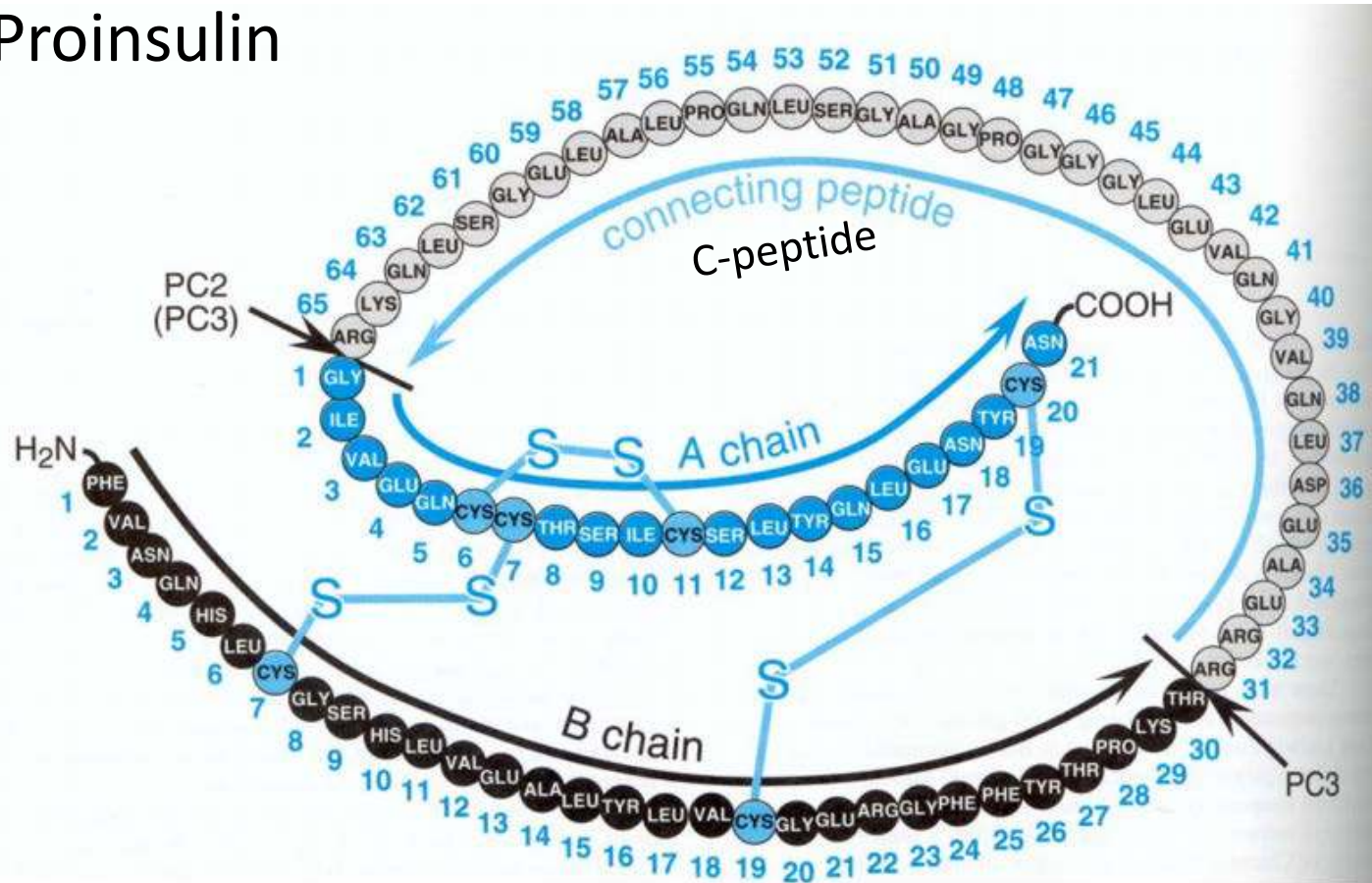


Porth, CM. Pathophysiology: concepts of altered health states. 7th ed. 2005. p. 988.

- Released from pancreatic beta cells

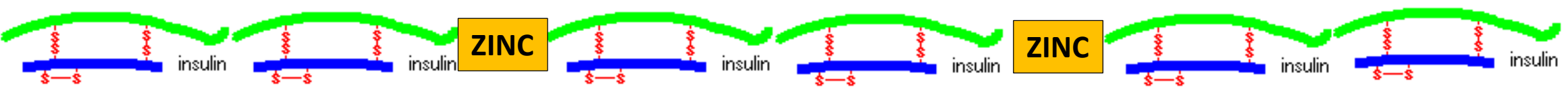
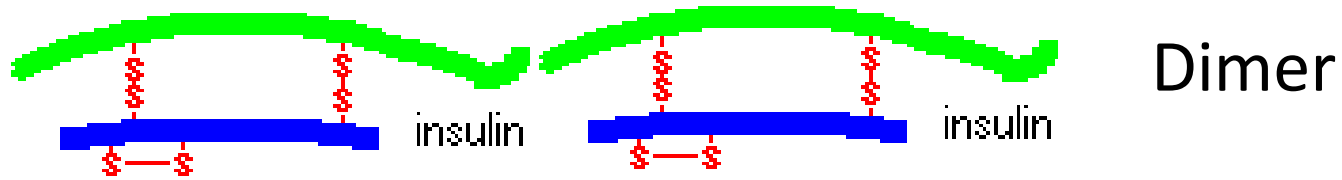
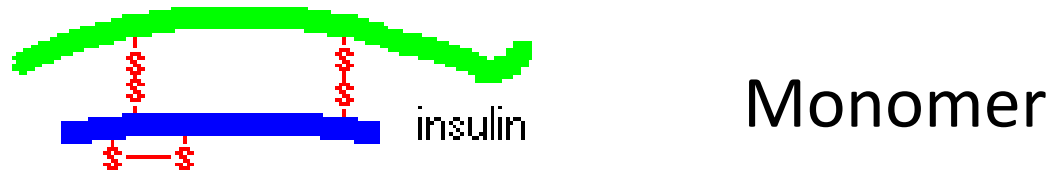
Insulin

Proinsulin

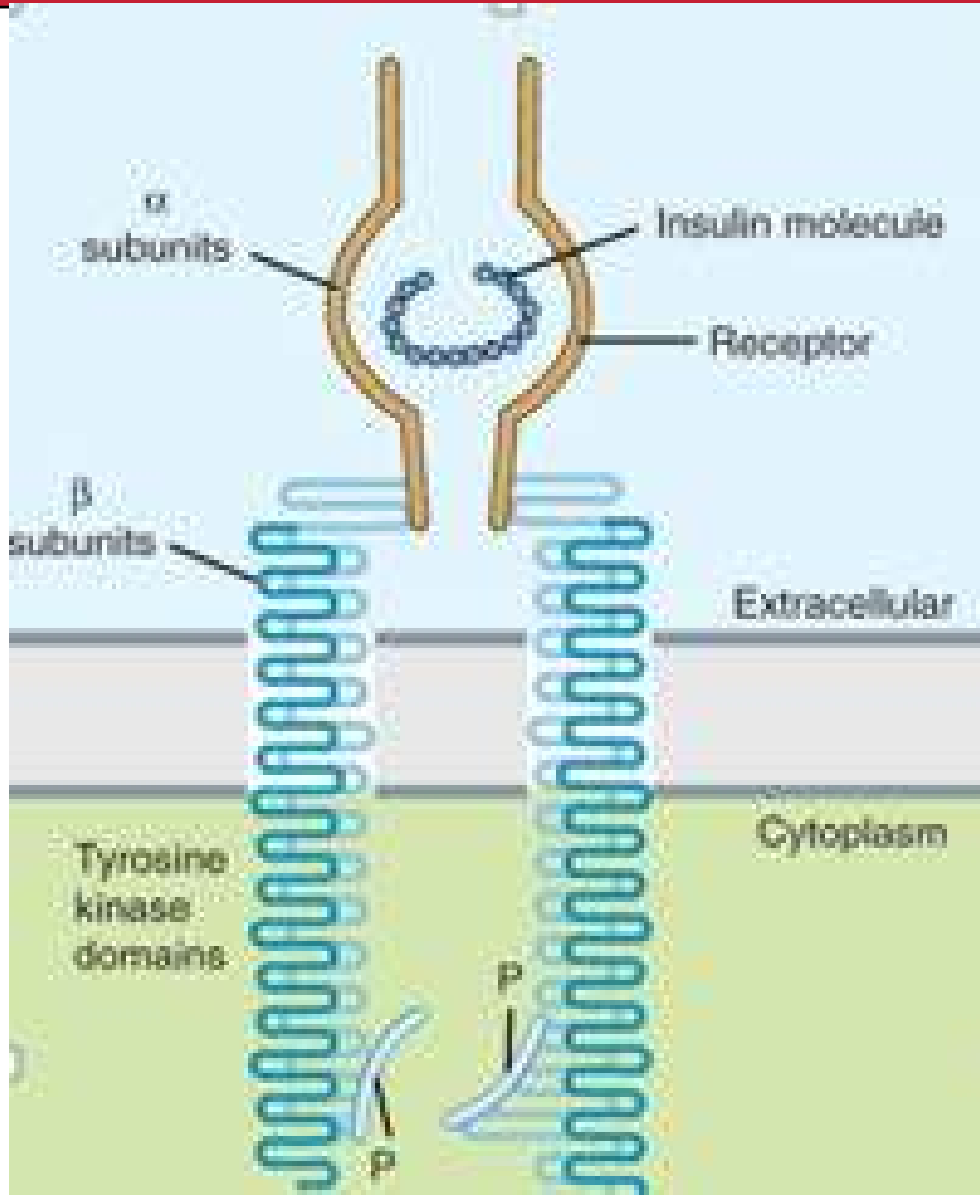


- Proinsulin cleaved to form active insulin and connecting (c) peptide

Insulin



Insulin and how it works



- 1) Glucose (muscles, liver, adipose tissue)
 - a. UPTAKE (from blood)
 - b. STORAGE
- 2) Fatty acid
 - a. In the liver: increases triglycerides synthesis
 - b. In adipose tissue: UPTAKE (from blood)
- 3) DNA synthesis → cell growth, division

- **Biosynthetic insulin: genetically engineered human insulin**
 - Exact amino acid structure as human insulin
 - Grown in non harmful bacteria (*Escherichia coli*) or yeast (*Saccharomyces cerevisiae*)
 - Examples: Regular insulin, NPH
- **Analog insulin: genetically altered human insulin**
 - Changing the form or substitute parts of human insulin
 - Grown in non harmful bacteria (*Escherichia coli*) or yeast (*Saccharomyces cerevisiae*)
 - Examples:
 - Rapid acting: Aspart, glulisine, lispro
 - Long acting: Glargine, detemir, degludec
- **Semisynthetic human insulin: transforming pork insulin to human**
 - substituting an amino acid (threonine for alanine)-the last amino acid in the beta
 - Not used in the United States

Types of insulin based on onset of action

	Insulin class	Products	Type of insulin
Prandial (Bolus)	Rapid Acting	SQ: lispro (Humalog, Admelog), aspart (Novolog, Fiasp), glulisine (Apidra)	Analog
Prandial (Bolus)	Rapid Acting	Inhalation: (Afrezza)	Biosynthetic
Prandial (Bolus)	Short acting (Regular Insulin)	Regular (Novolin R, Humulin R)	Biosynthetic

Types of insulin

	Insulin class	Products	Type of insulin
Basal	Intermediate Insulin	NPH (Novolin N, Humulin N), concentrated regular (Humulin U-500)	Biosynthetic
Basal	Long Acting	Glargine (Lantus, Basalgar), detemir (Levemir)	Analog
Basal	Ultra long acting	Degludec (Tresiba), concentrated glargine (Toujeo)	Analog

- Types: SQ: lispro (Humalog, Admelog), aspart (Novolog), glulisine (Apidra)
- One of the amino acids are replaced
 - Allows for quick disassociation into monomers → faster absorption
 - Lowest variability of absorption (5%)
- aspart (Fiasp)
 - Ultra rapid acting insulin
 - Same modified insulin molecule as aspart but has niacinamide (vitamin B3) in solution which helps with faster absorption (2.5 minutes) and amino acid (arginine hydrochloride) to stabilize the solution

Rapid acting insulins-inhaled



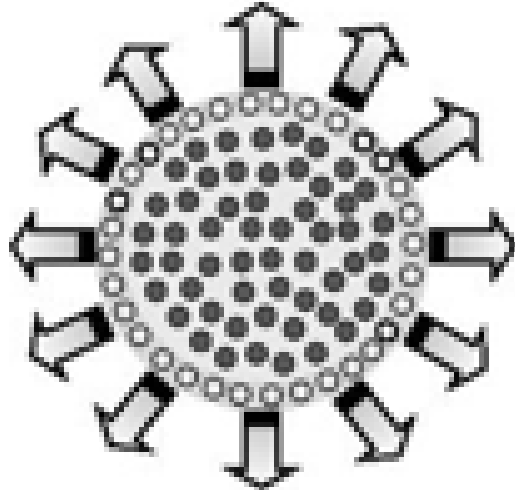
- Inhaled insulin: Afrezza
- Synthetic human insulin produced in E. Coli
- Protected by fumaryl diketopiperazine (FDKP) and polysorbate 80

- Regular insulin
 - Same structure as human insulin
 - Duration of action increases with higher doses (e.g. U 500)

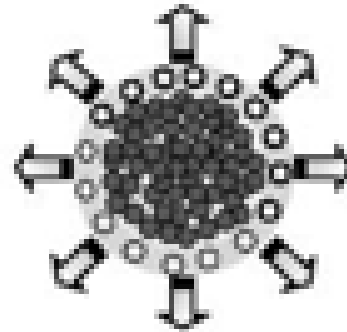
- Neutral Protamine Hagedorn (NPH)
 - Human
 - A protein called protamine (positively charged polypeptide) is added to the human regular insulin → forms a poorly soluble insulin–protamine complex
 - enzymes in the body will slowly breakdown the protein, which allows absorption of insulin → slower onset and longer duration of action
- Rapid acting insulin + protamine
 - Component of insulin aspart protamine and insulin aspart (Novolog) 70/30, insulin lispro protamine and insulin lispro (Humalog) 75/25, 50/50

- Glargine (100 units/ml)
 - 2 amino acids (arginine) added to insulin and substitution of an amino acid (glycine replaces asparagine)
 - In acidic solution for solubility
 - Precipitates once injected into the neutral pH of the body → forms hexamers → slowly dissociate into individual insulin molecules (monomers) → continuous level of circulating insulin (peakless)
 - Can't be mixed with other insulins
 - Irritation at injection site

- Glargine (300 units/ml)
 - Same modified human insulin as glargine
 - More concentrated, less volume



Glargine-100



Glargine-300

- Detemir
 - One amino acid removed and fatty acid molecule is added
 - Fatty acid molecule combines with albumin in the plasma and creates a depot in subcutaneous tissue
 - Duration of action of 24 hours at higher doses

- Degludec
 - One amino acid is removed and replaced with fatty acid
 - Longer duration of action due to
 - Forms large multihexamer chains of thousands of dihexamers → slowly dissolve in the SQ tissue
 - Fatty acid side chain binds to albumin in the plasma which is acts as a storage area

- Allergies-histamine release from tissue mast cells sensitized by anti-insulin IgE antibodies
 - local or systemic urticaria
 - Anaphylaxis-rare
 - Typically due to excipients in formulations and not due to insulin
- Immune insulin resistance
 - IgG antibody may develop to exogenous insulin injection
 - May develop but low risk for reducing insulin function
 - If leads to insulin resistance, most likely due to other autoimmune conditions (lupus erythematosus)