

# *Diabetes and Current Therapeutics*



MacMillan Group Meeting

April 4, 2012

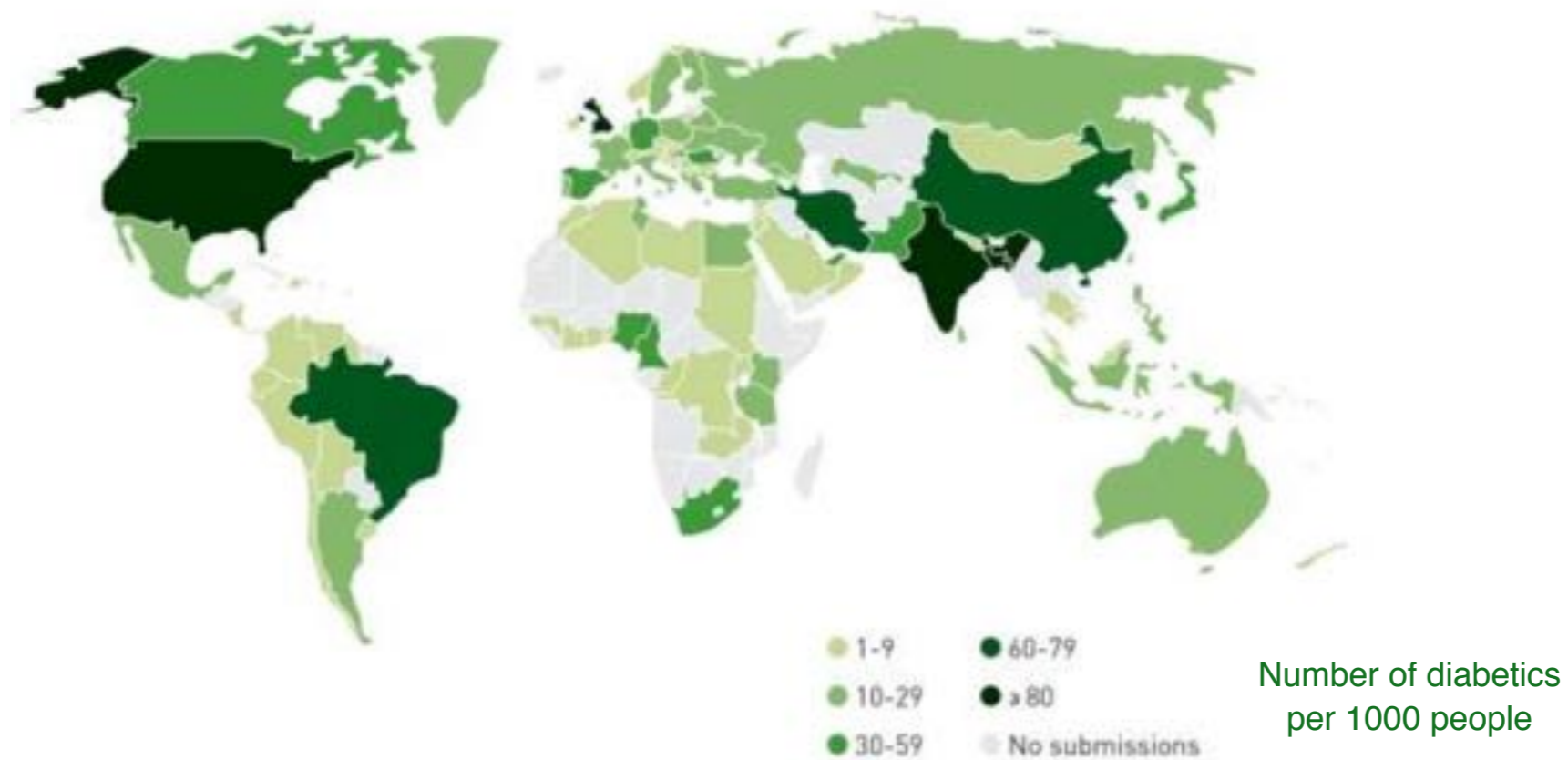
Scott Simonovich

## Definition and World Prevalence

### Diabetes mellitus

Metabolic disease in which abnormally high blood glucose levels result from poor production of insulin and/or inefficient use of insulin

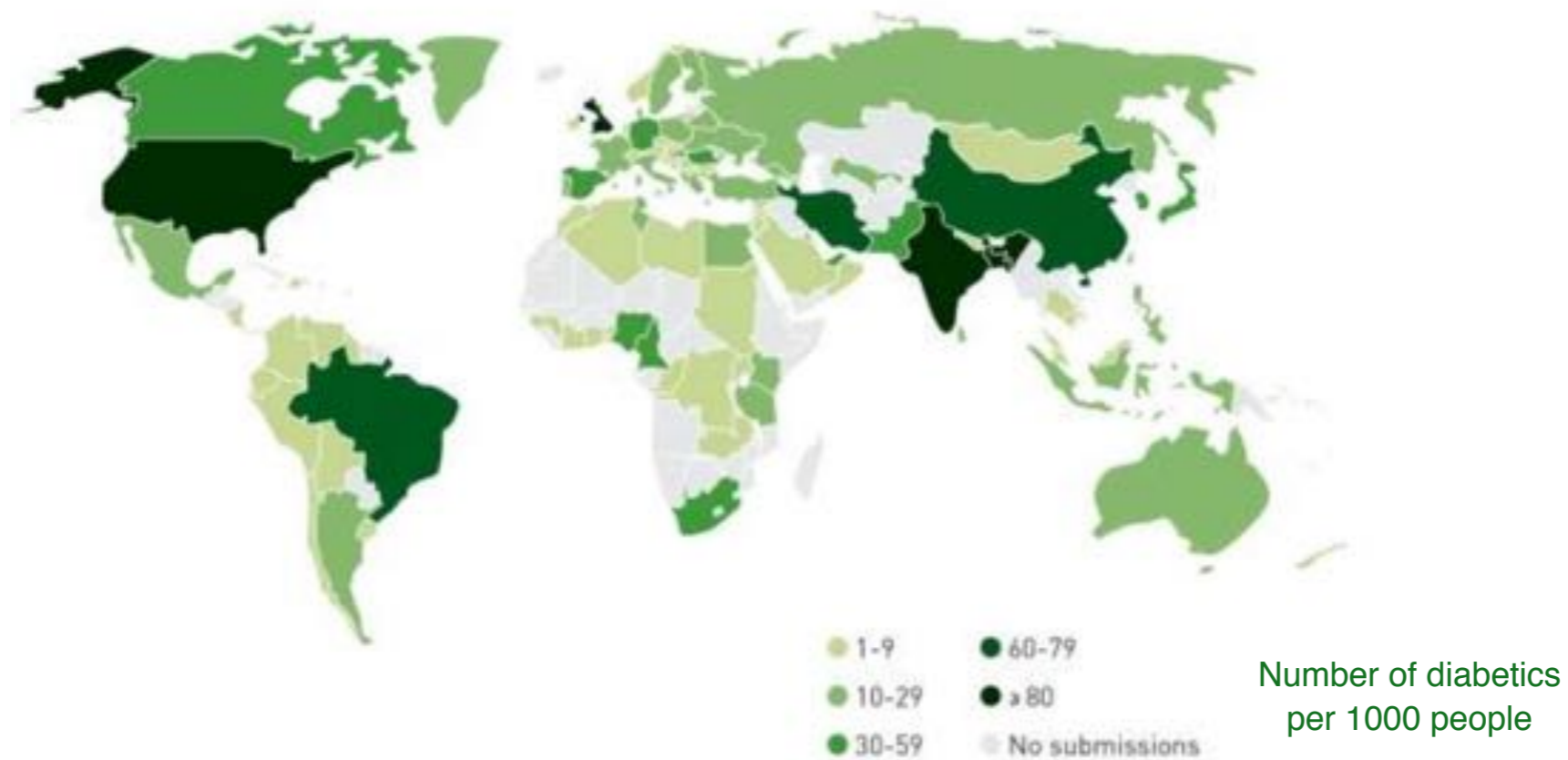
Abstract submissions to the 2011 World Diabetes Congress



## *Definition and World Prevalence*

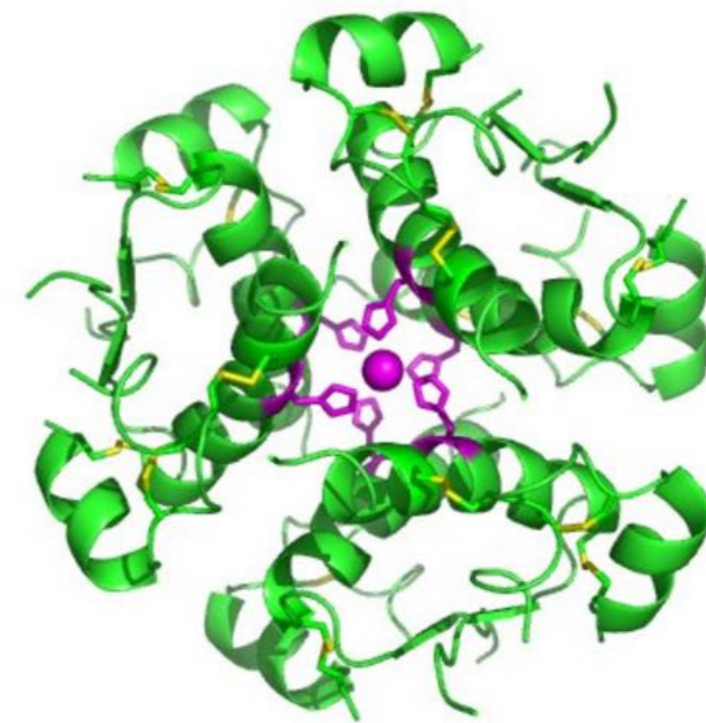
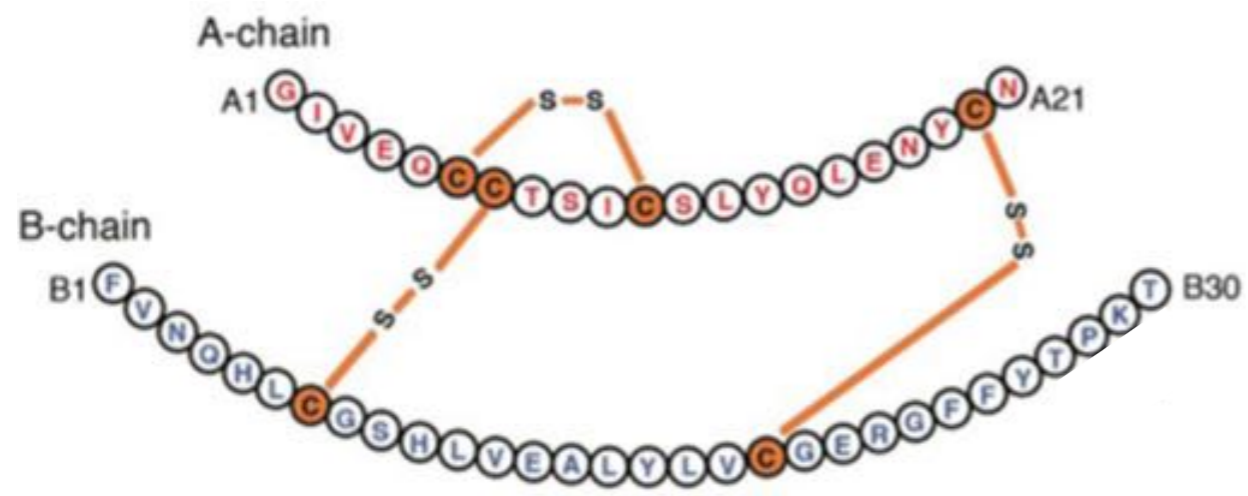
- Incidence of diabetes increasing tremendously around the world
- Less physical activity and high caloric nutrition at low cost
- Prevalence will double in the next 20 years
- Expected to be 440 million type 2 diabetics by 2030
- Increased prevalence in children and adolescents

Abstract submissions to the 2011 World Diabetes Congress



# Outline

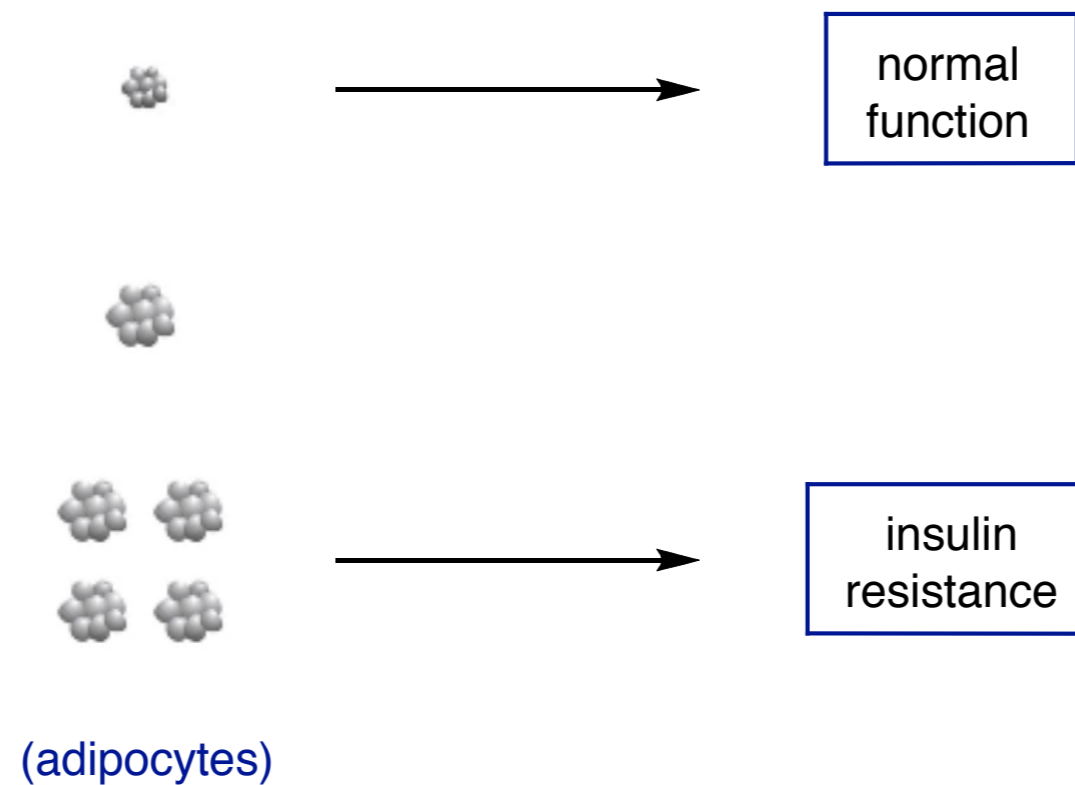
- Insulin - structure, physiology, and link to hyperglycemia



inactive insulin hexamer

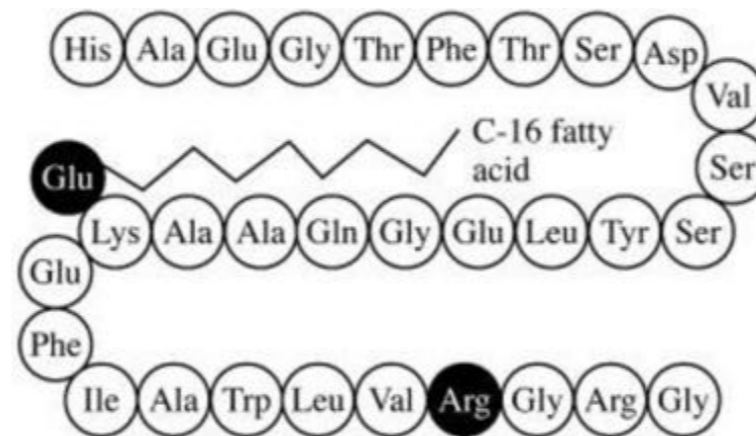
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- Insulin - structure, physiology, and link to hyperglycemia
- Diabetes - pathophysiology and environmental causes of type 2

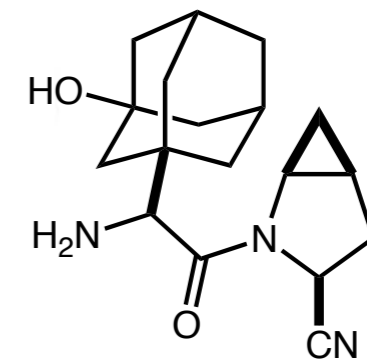


# Outline

- Insulin - structure, physiology, and link to hyperglycemia
- Diabetes - pathophysiology and environmental causes of type 2
  - Current therapeutics: Insulin analogues
    - GLP-1 agonists
    - DPP-4 inhibitors



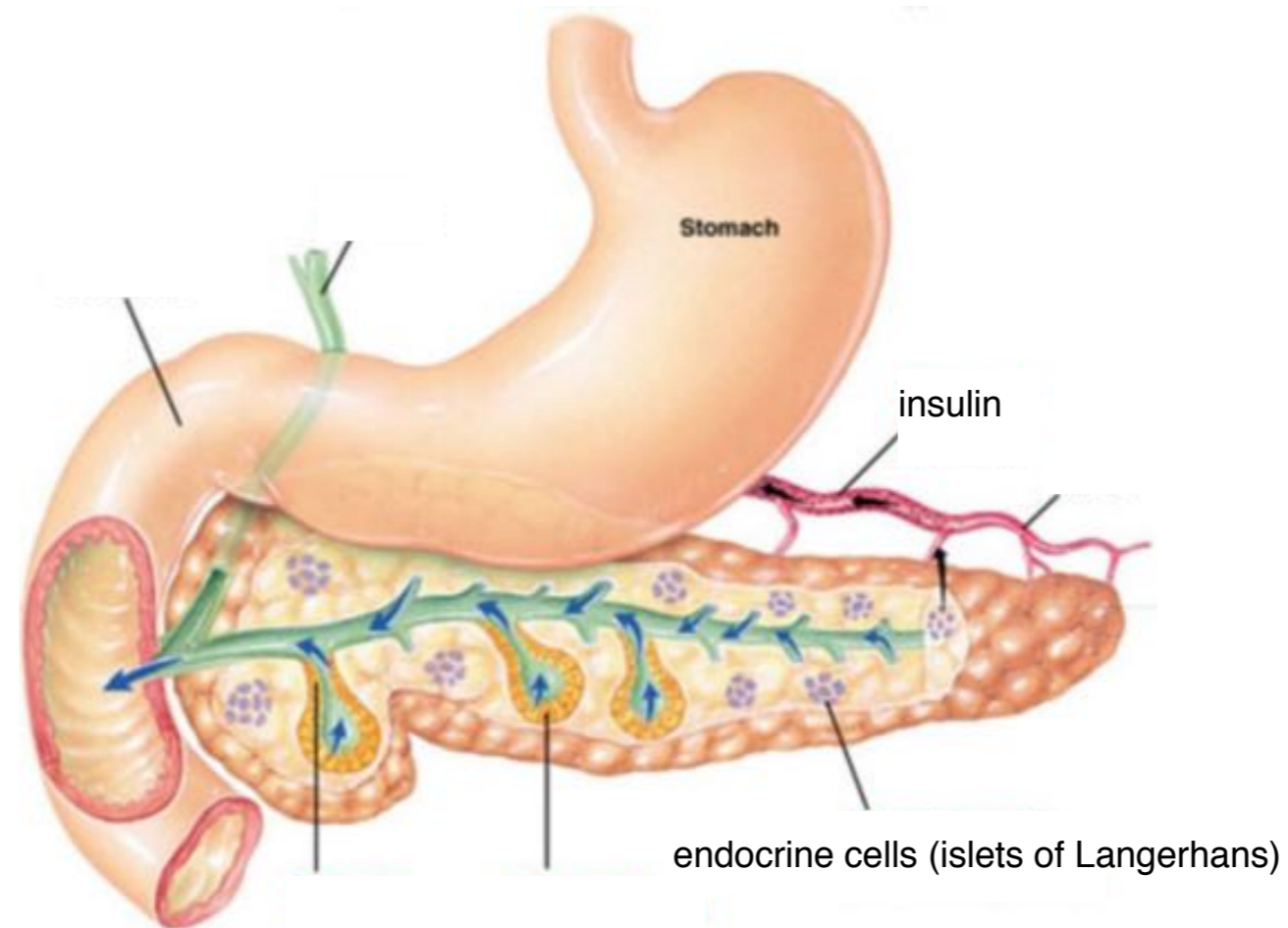
Liraglutide



Saxagliptin

## *Insulin - General Overview*

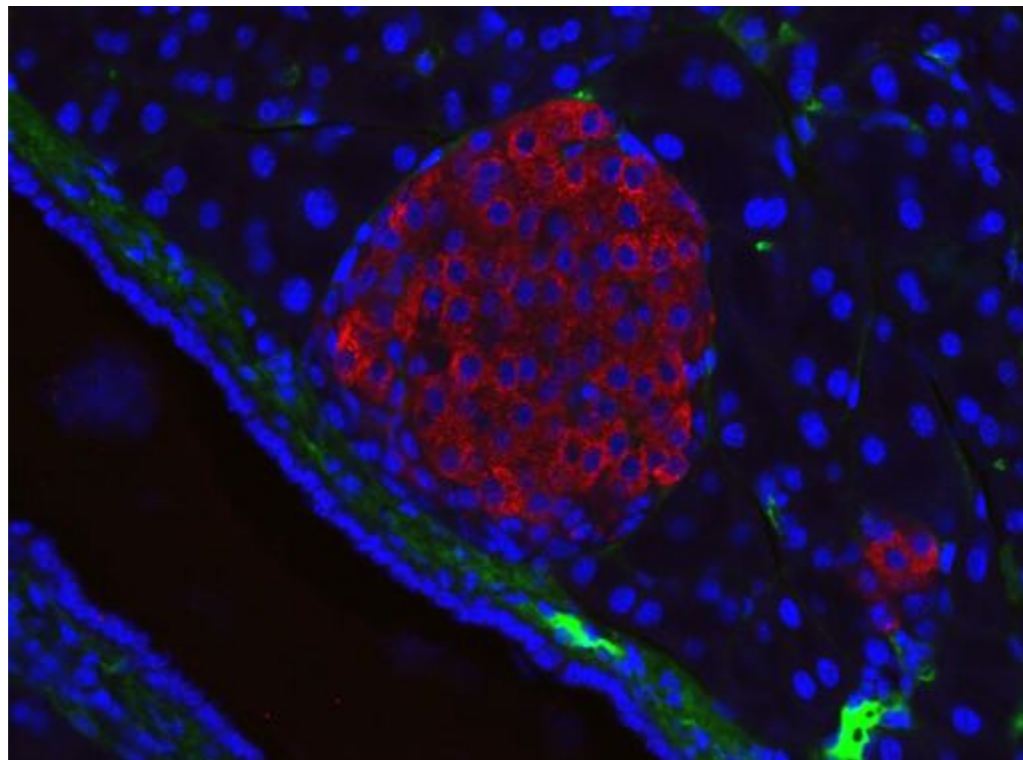
- Hormone produced by  $\beta$ -cells in pancreas (Islets of Langerhans)



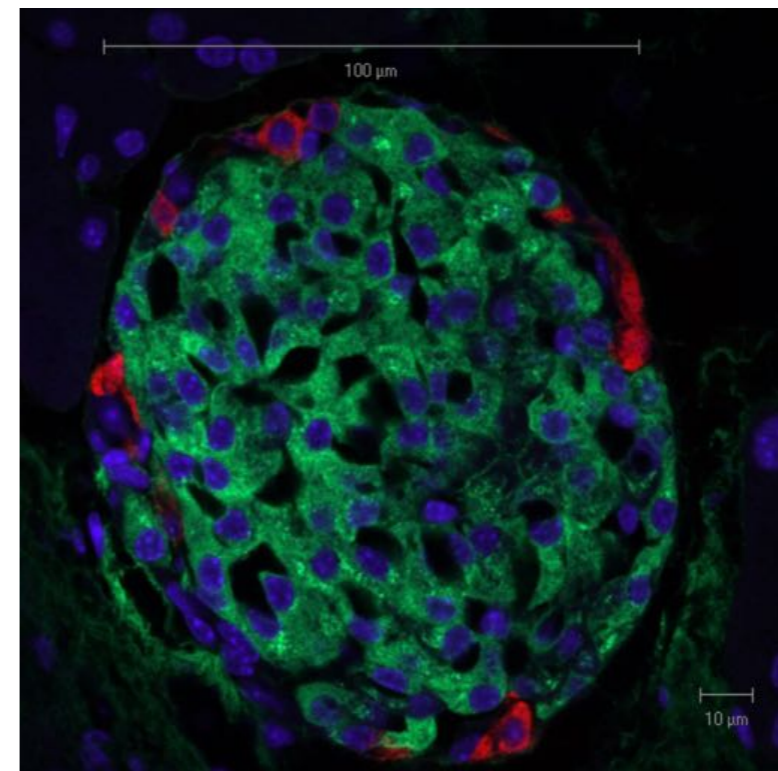


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optical microscopy image of islet  
(cell nuclei and insulin are stained)

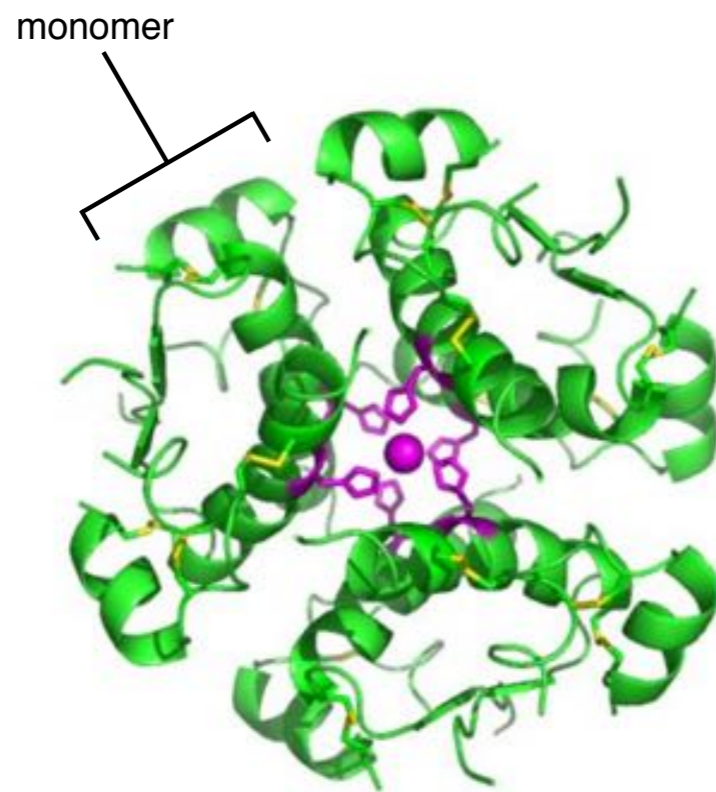


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## Insulin - General Overview

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- Stored in body as inactive hexamer, while active form is monomeric

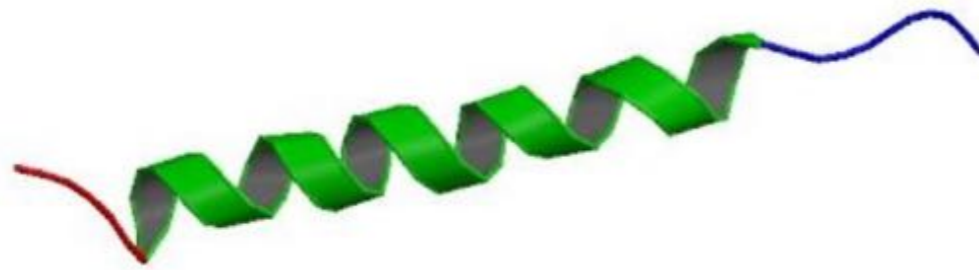


C3 symmetry in hexamer  
Histidine residues coordinate to central zinc ion



## *Insulin - General Overview*

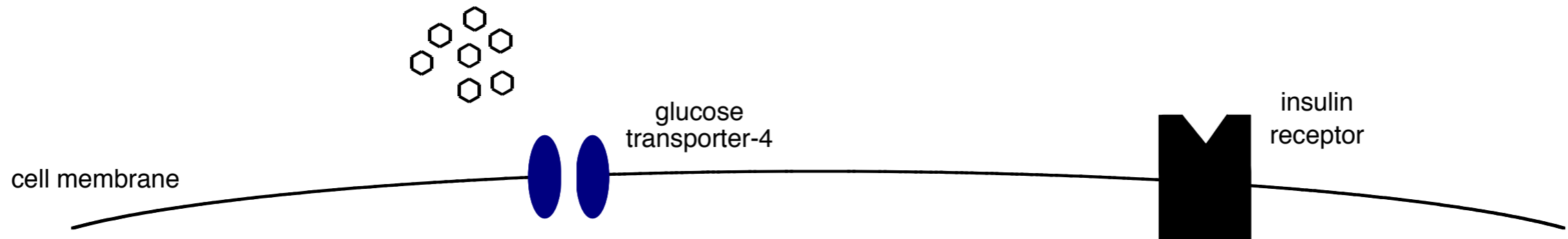
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- Stored in body as inactive hexamer, while active form is monomeric
- Central in regulating carbohydrate and fat metabolism
  - Promotes liver, muscle, and fat cells to take in glucose from blood for glycogen storage
  - Stops use of fat and glycogen as energy by inhibiting the release of glucagon



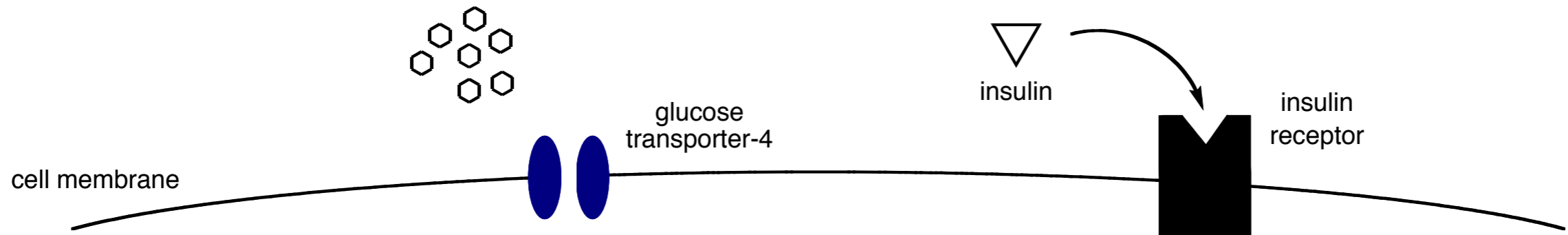
Glucagon ribbon structure (29 amino acids)

Secreted by pancreas  $\alpha$ -cells  
Promotes liver to break down glycogen  
Releases glucose into bloodstream

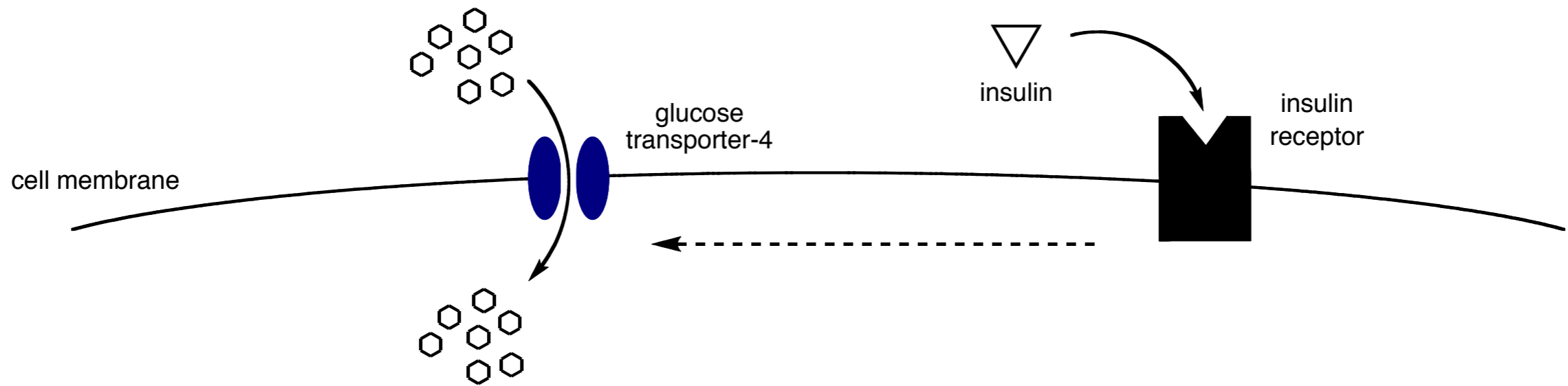
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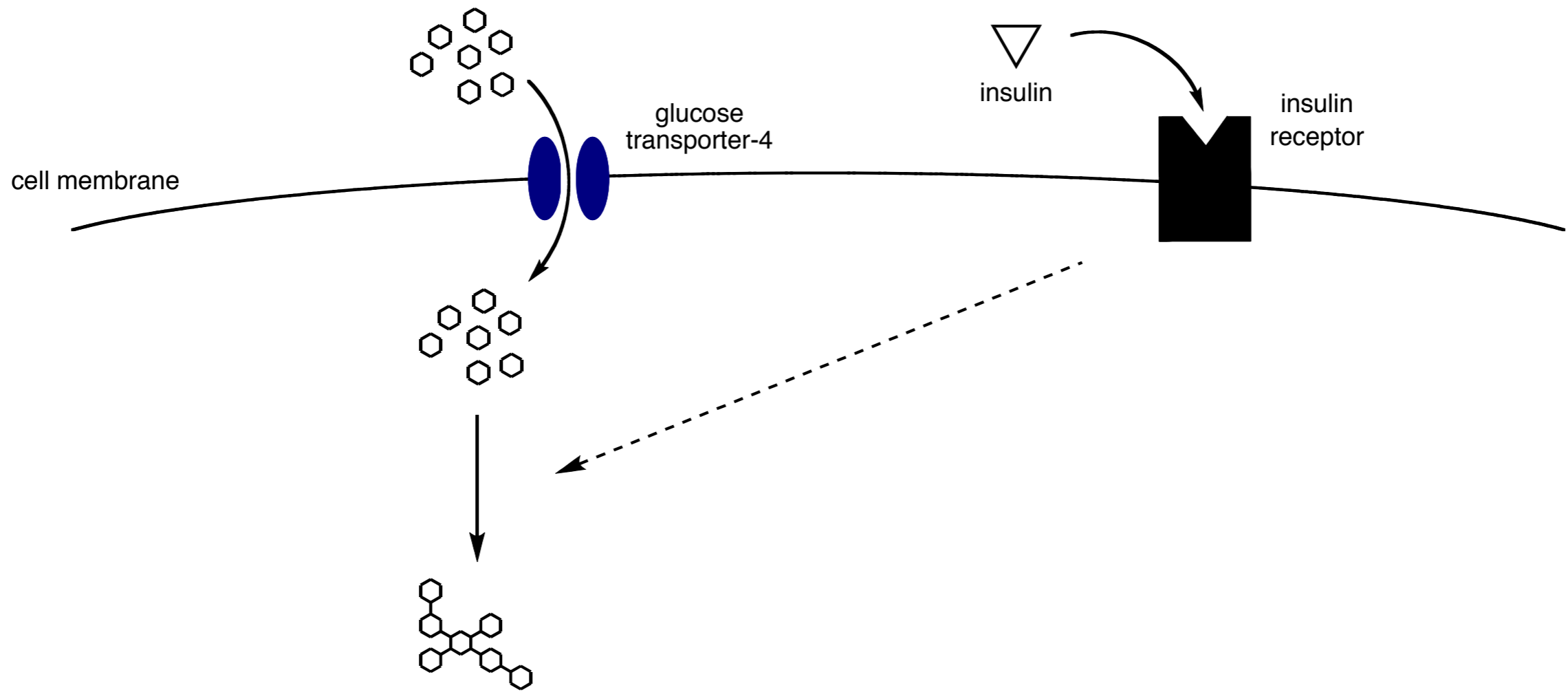


# Insulin - Several Metabolic Functions



influx of glucose from  
bloodstream into cell

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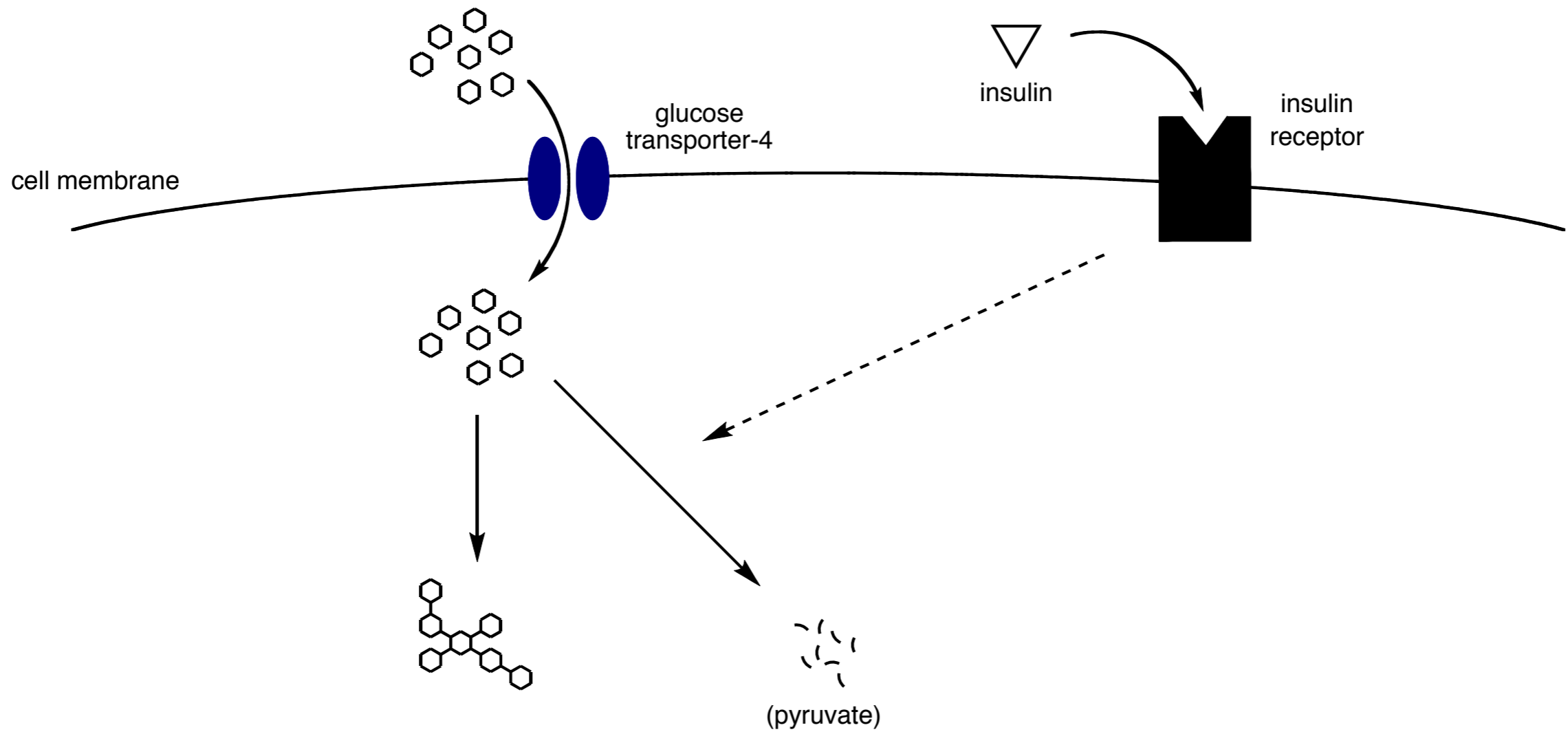


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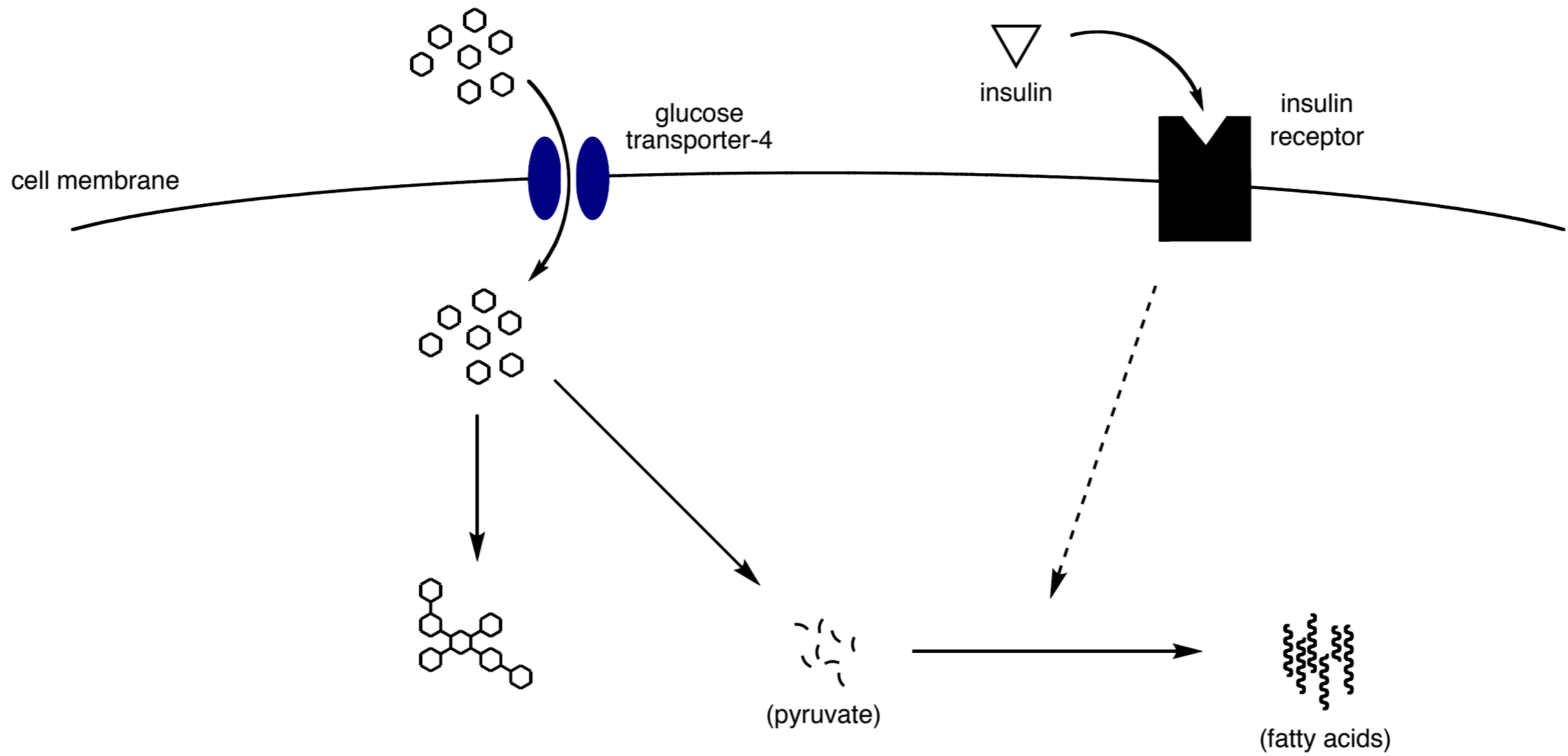


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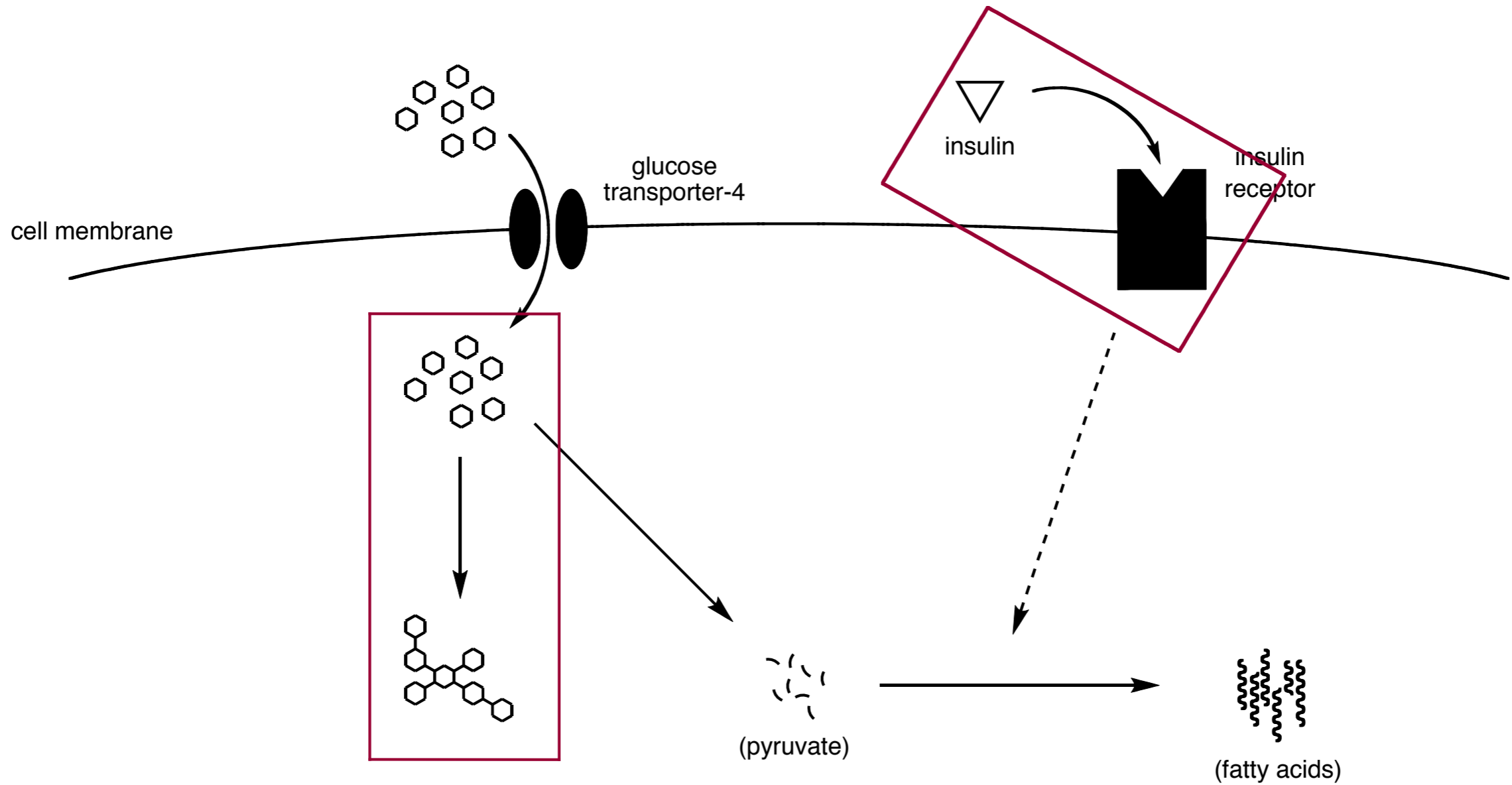
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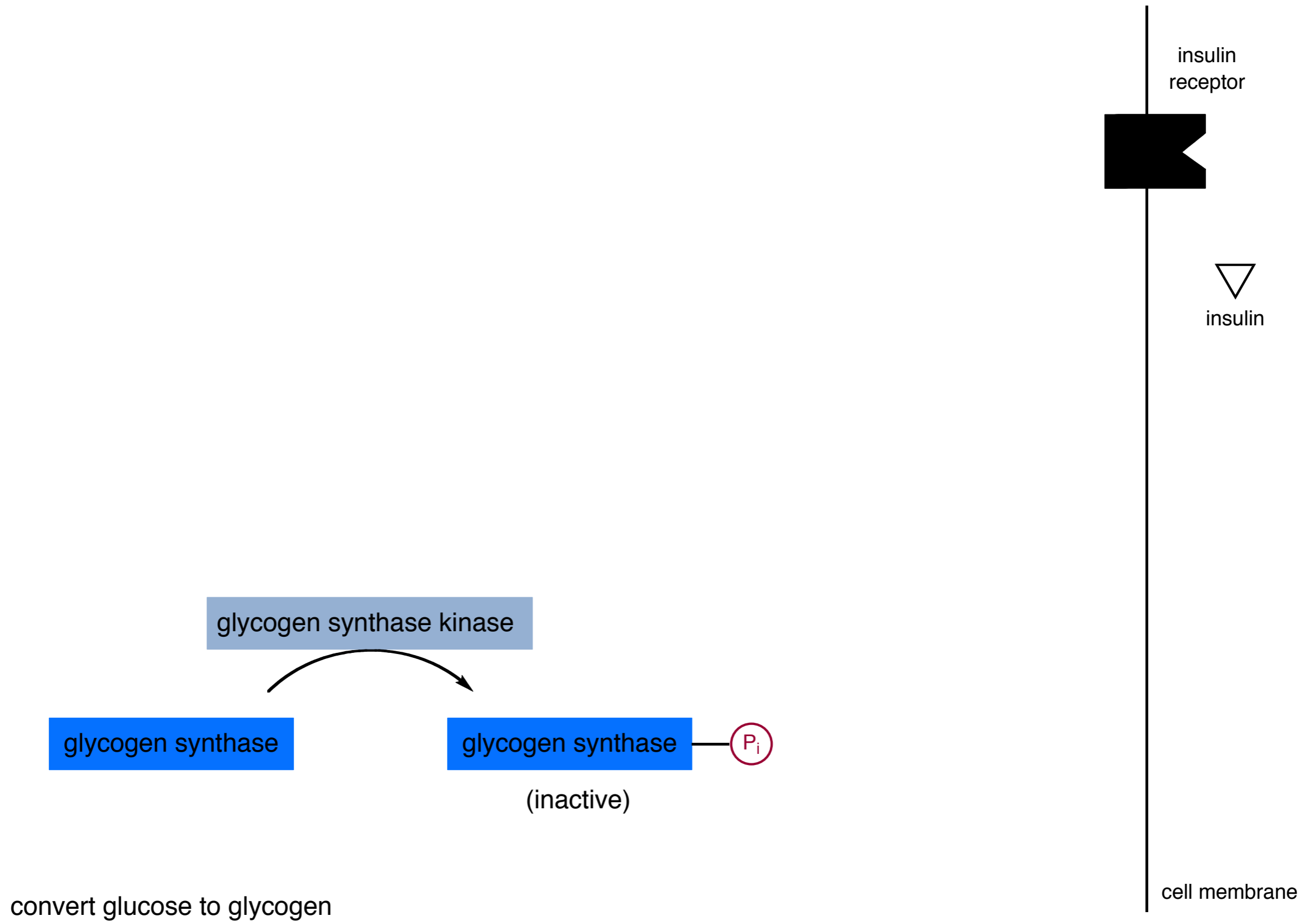
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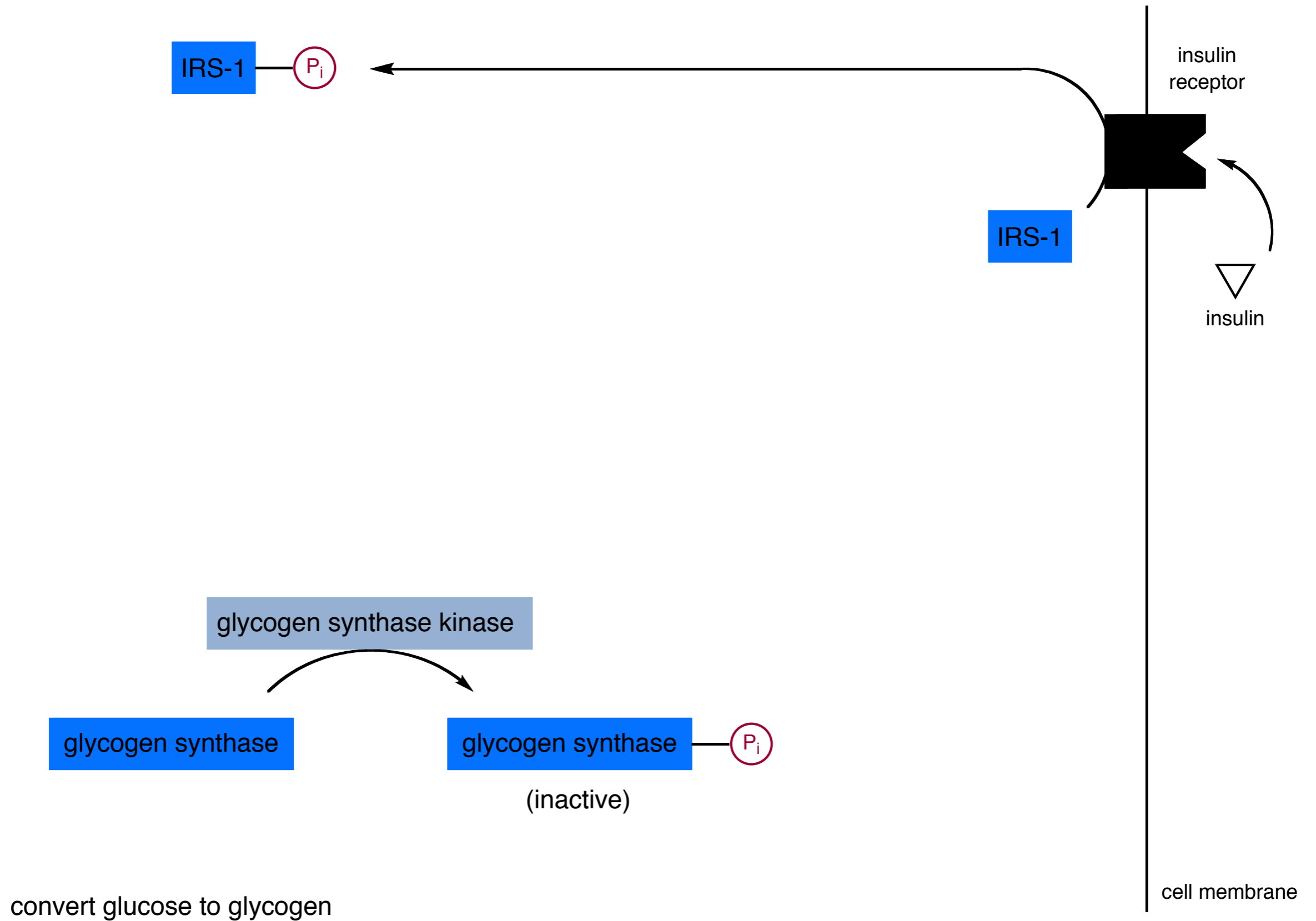
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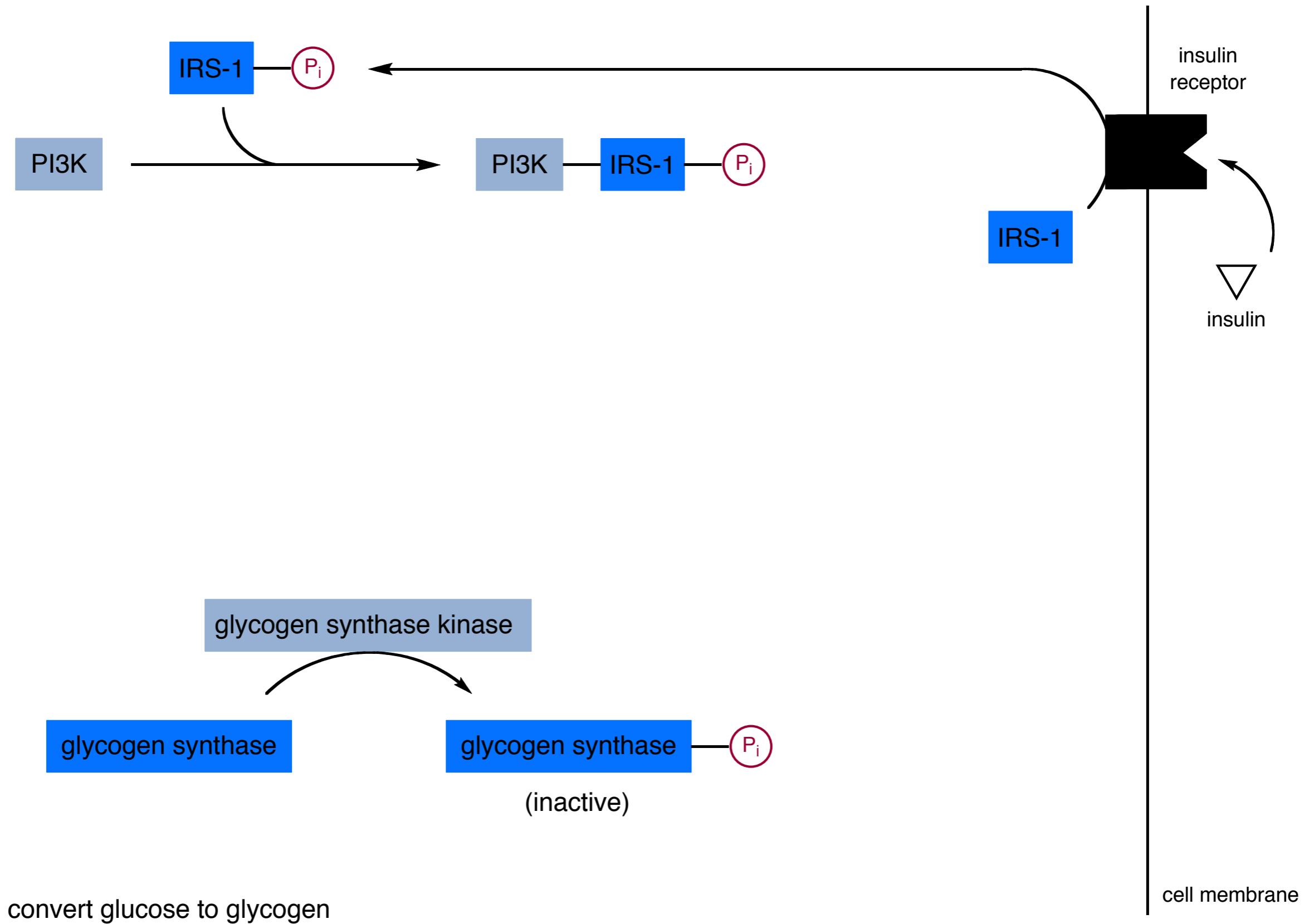
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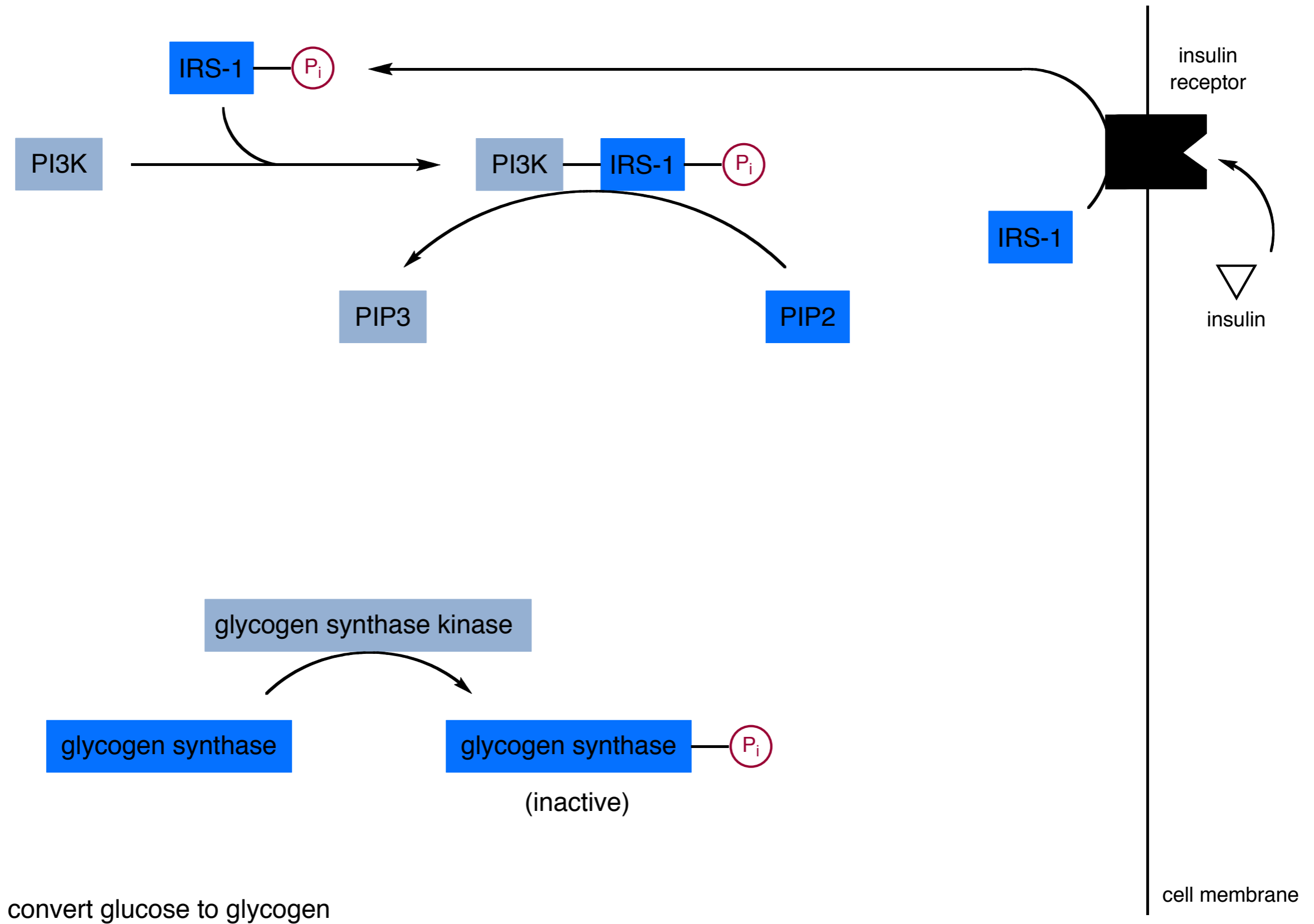


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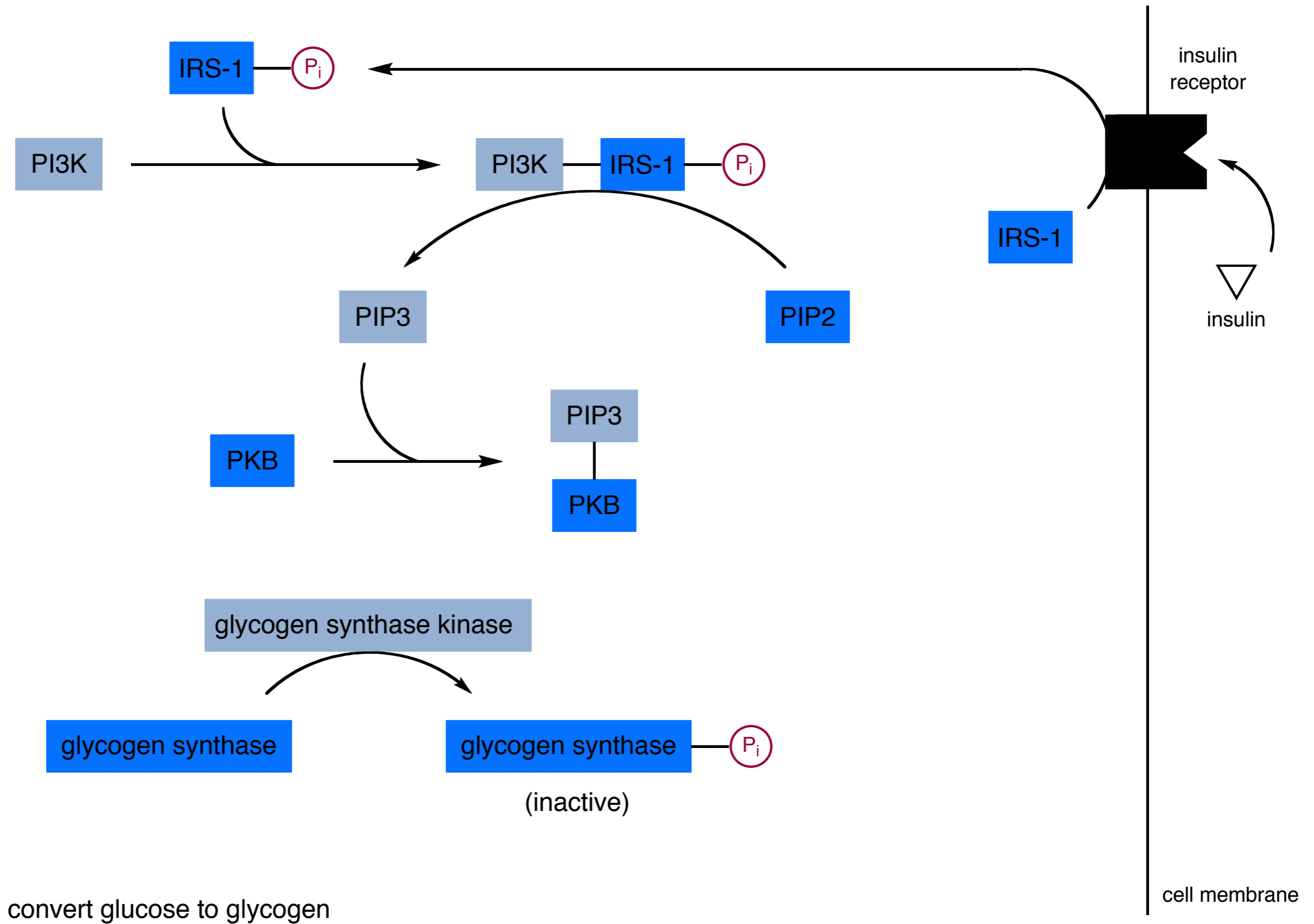




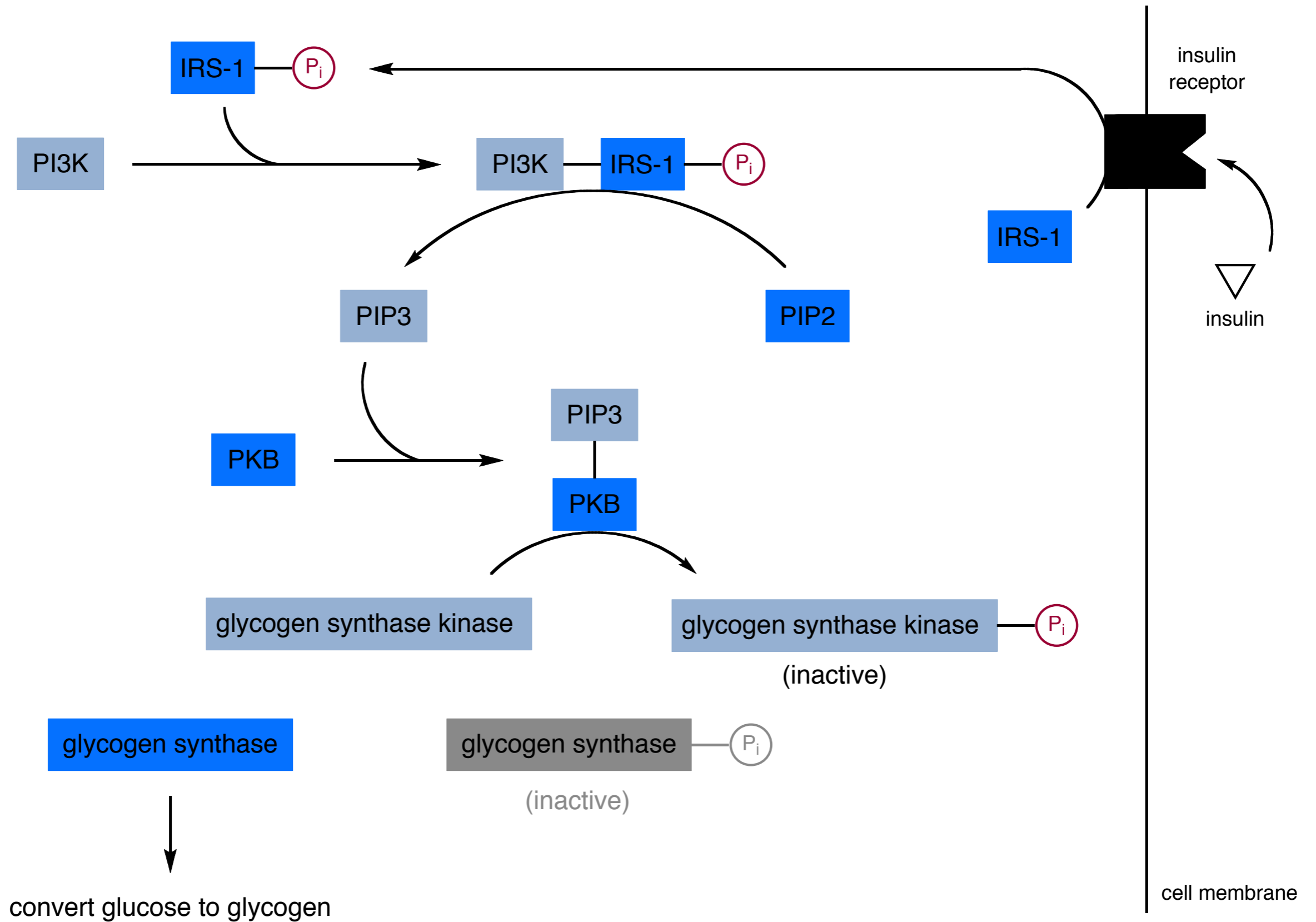
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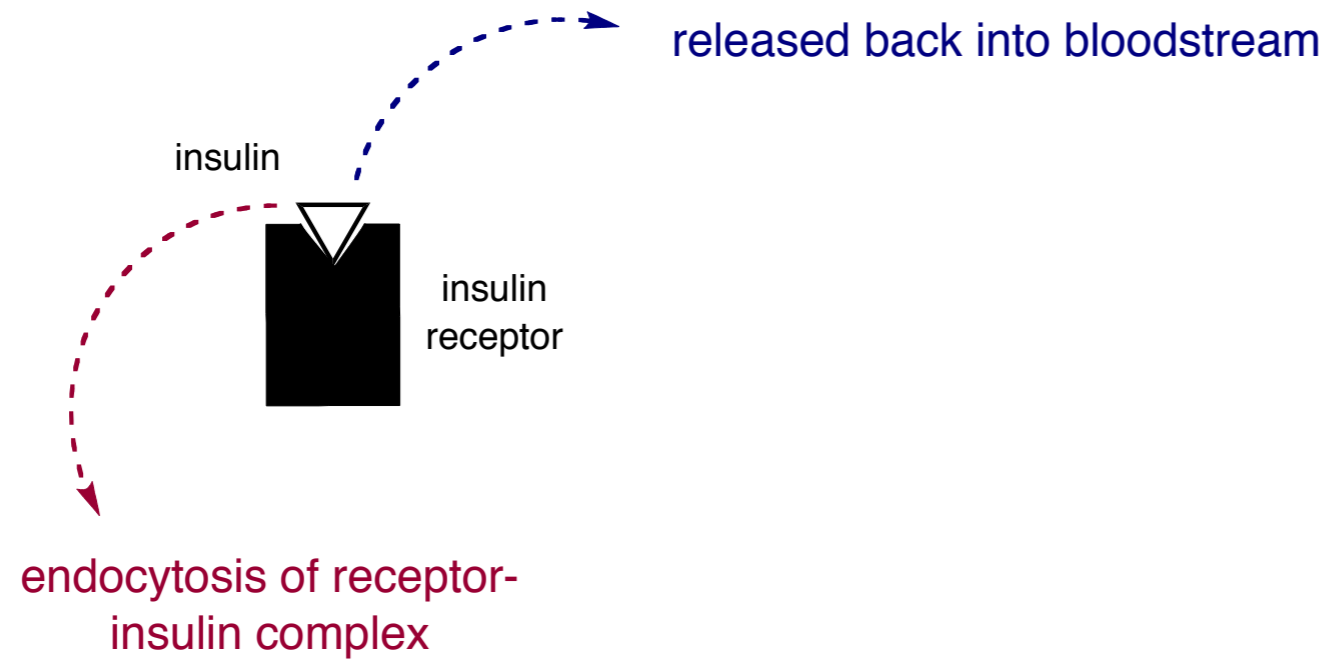
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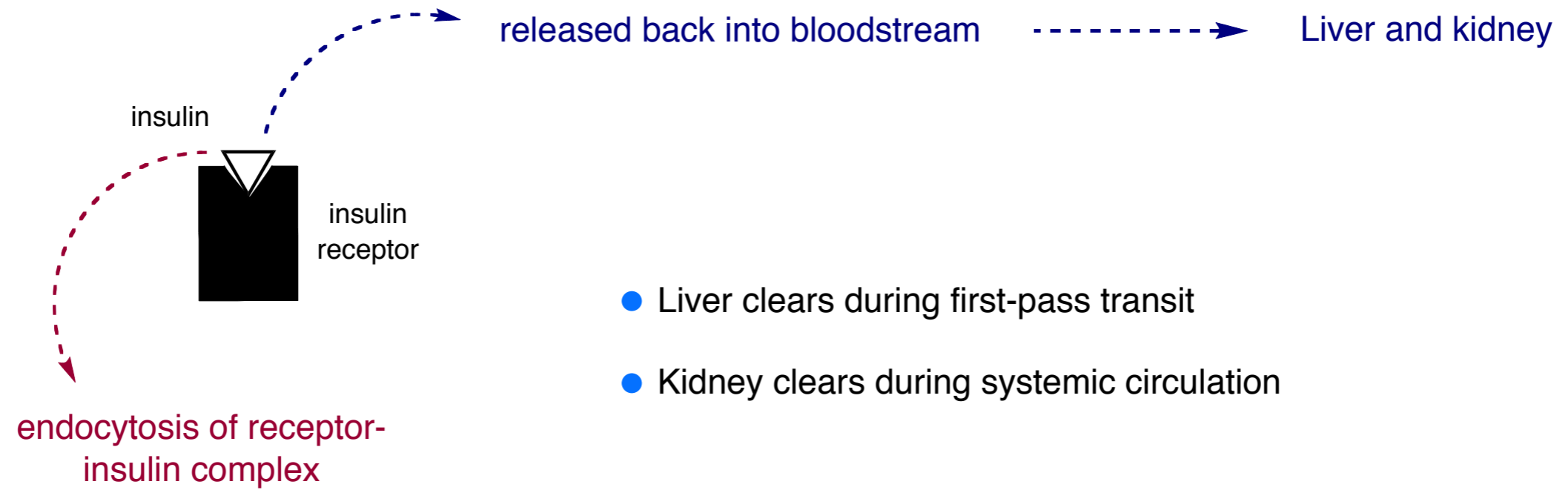
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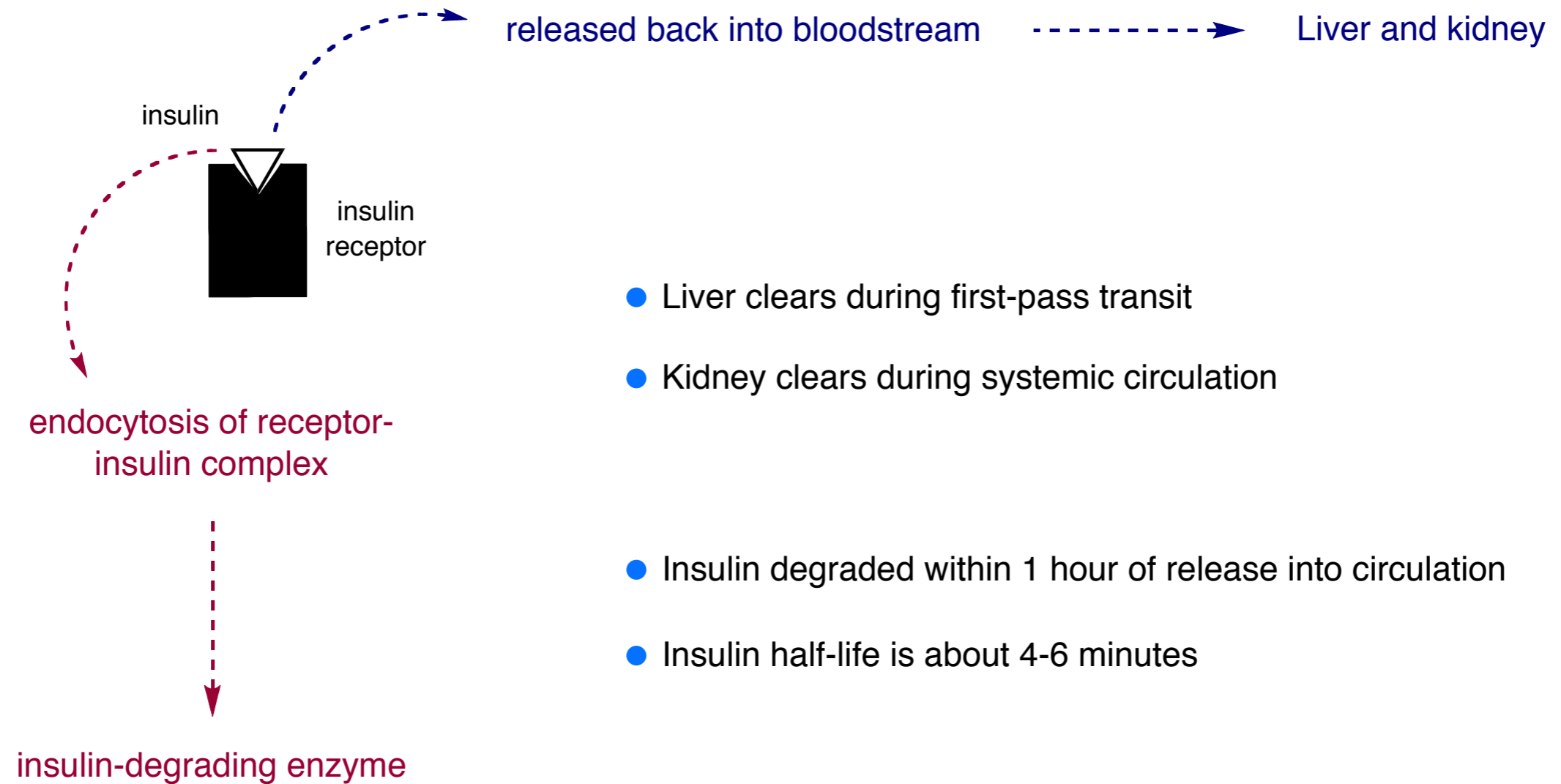
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## *What If Metabolic Homeostasis Malfunctions?*

**Glycosylated hemoglobin (HbA1c)** - identifies average blood glucose concentration over prolonged time

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- Pancreas  $\beta$ -cells have stopped producing insulin - **Type 1 Diabetes** (10% of diabetes cases)
  - Generally will be otherwise healthy
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- Muscle and fat cells show resistance to insulin signalling- **Type 2 Diabetes** (90% of diabetes cases)
  - Impaired  $\beta$ -cell function
  - Interruption of insulin signal transduction pathways
  - Heavily dependant on lifestyle and environmental factors, as well as genetic susceptibility

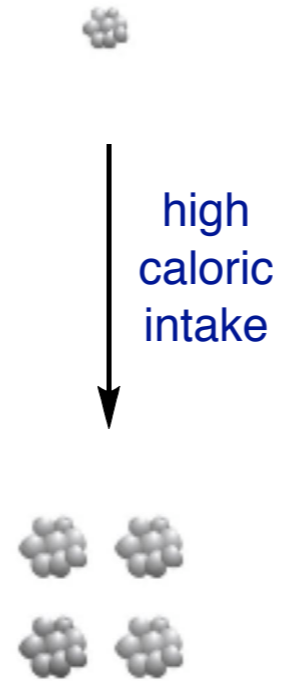
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- Glucose coats red blood cells, making circulation difficult
- Promotes clotting and cholesterol buildup in blood vessels
- Eyes, kidneys, and feet are most susceptible to damage

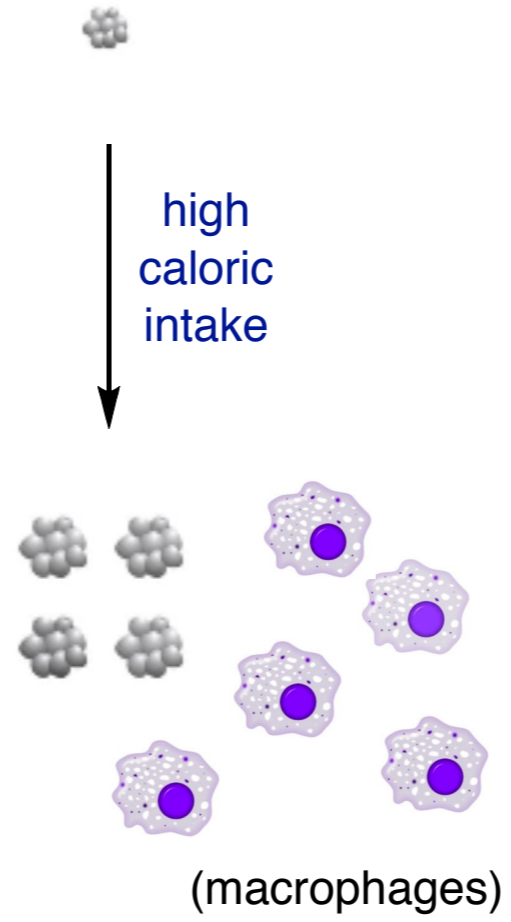
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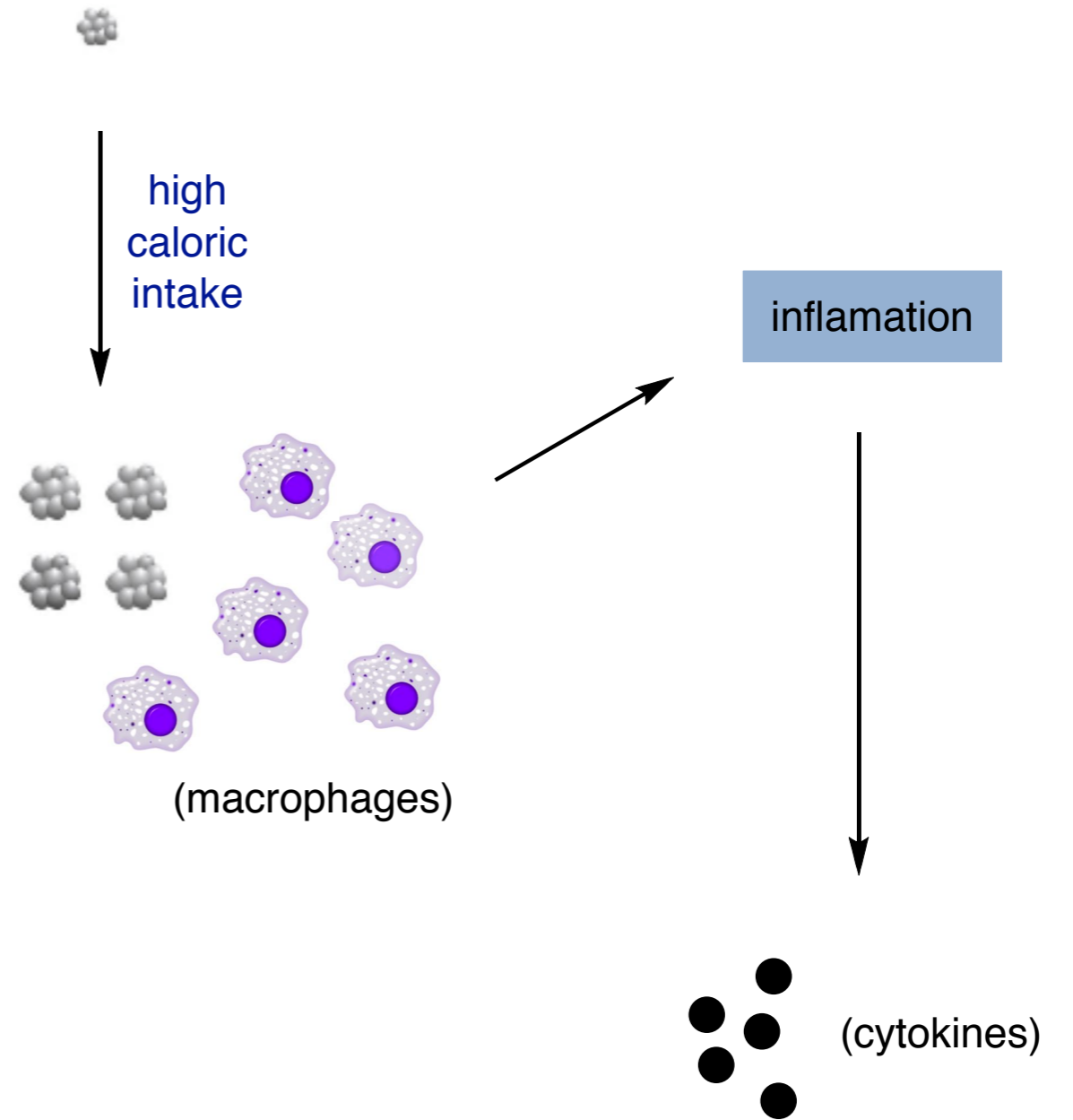
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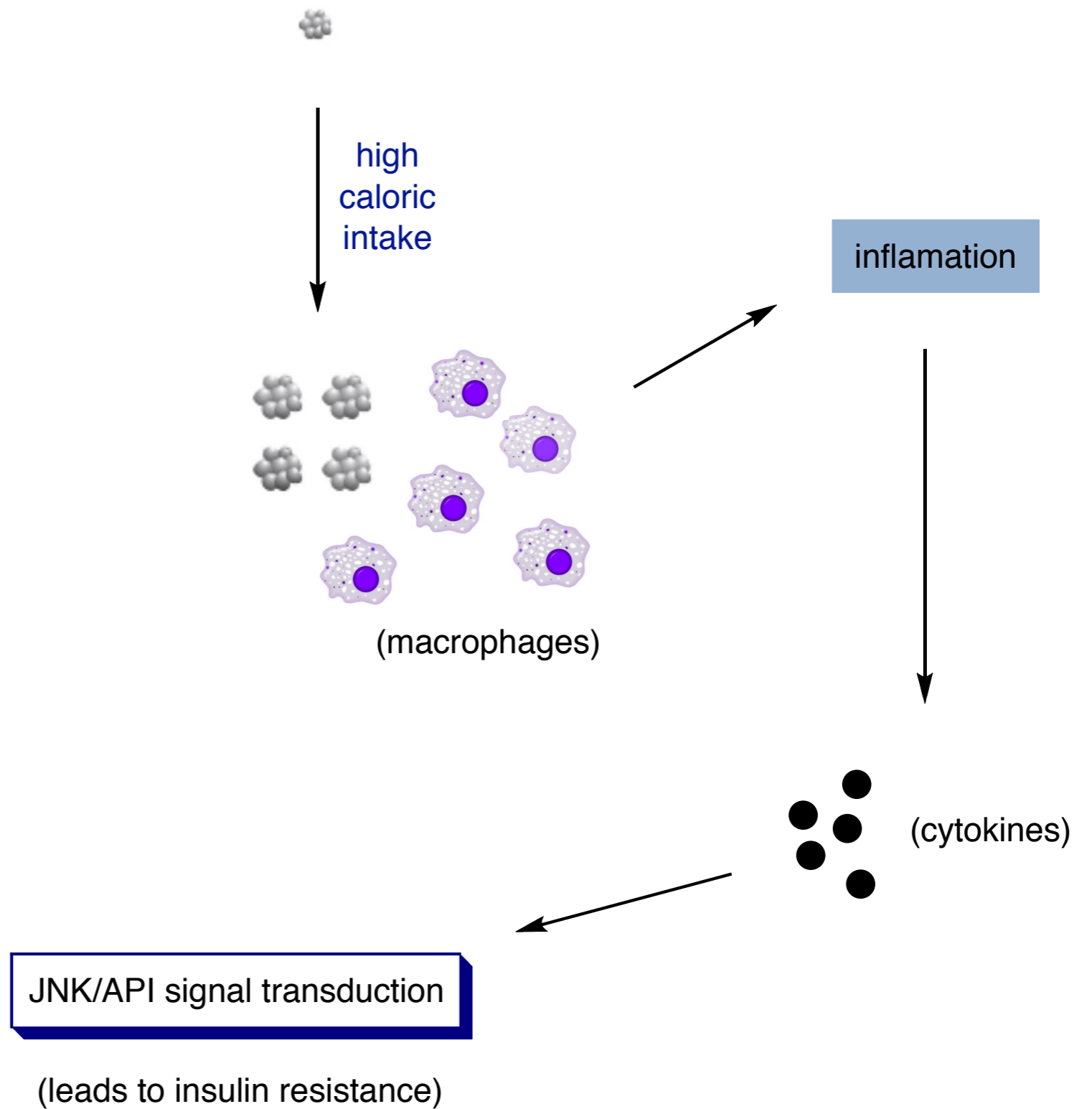


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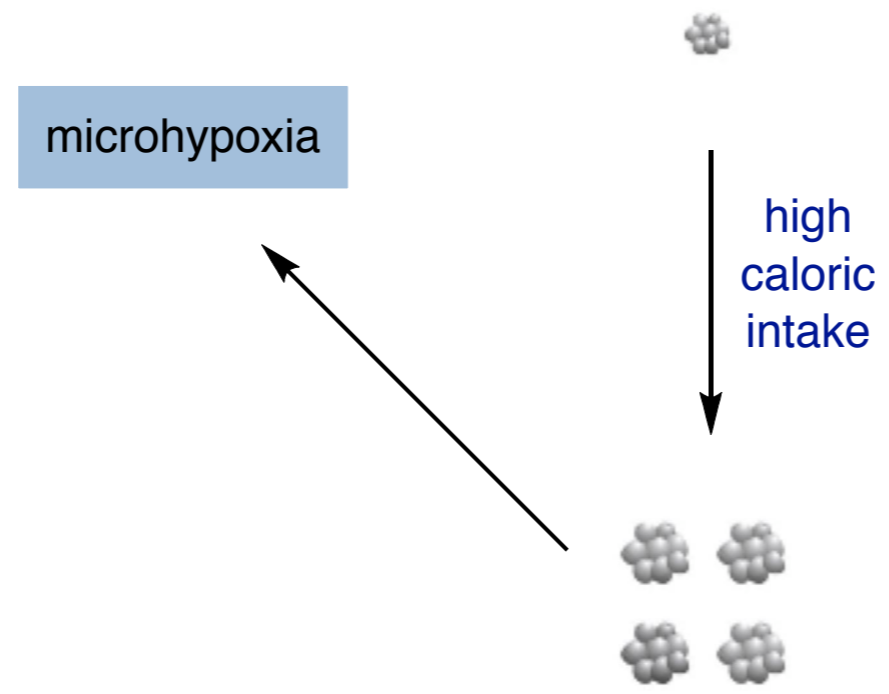




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Hypoxia - state in which tissue fails to acquire adequate oxygen supply

JNK/API signal transduction

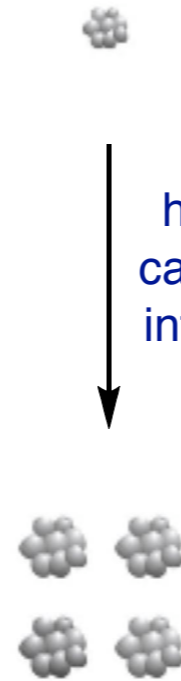
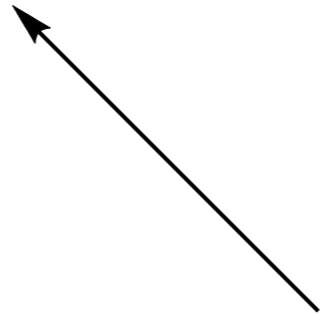
(leads to insulin resistance)

# Insulin Resistance (Type 2 Diabetes)

increase in FFA

microhypoxia

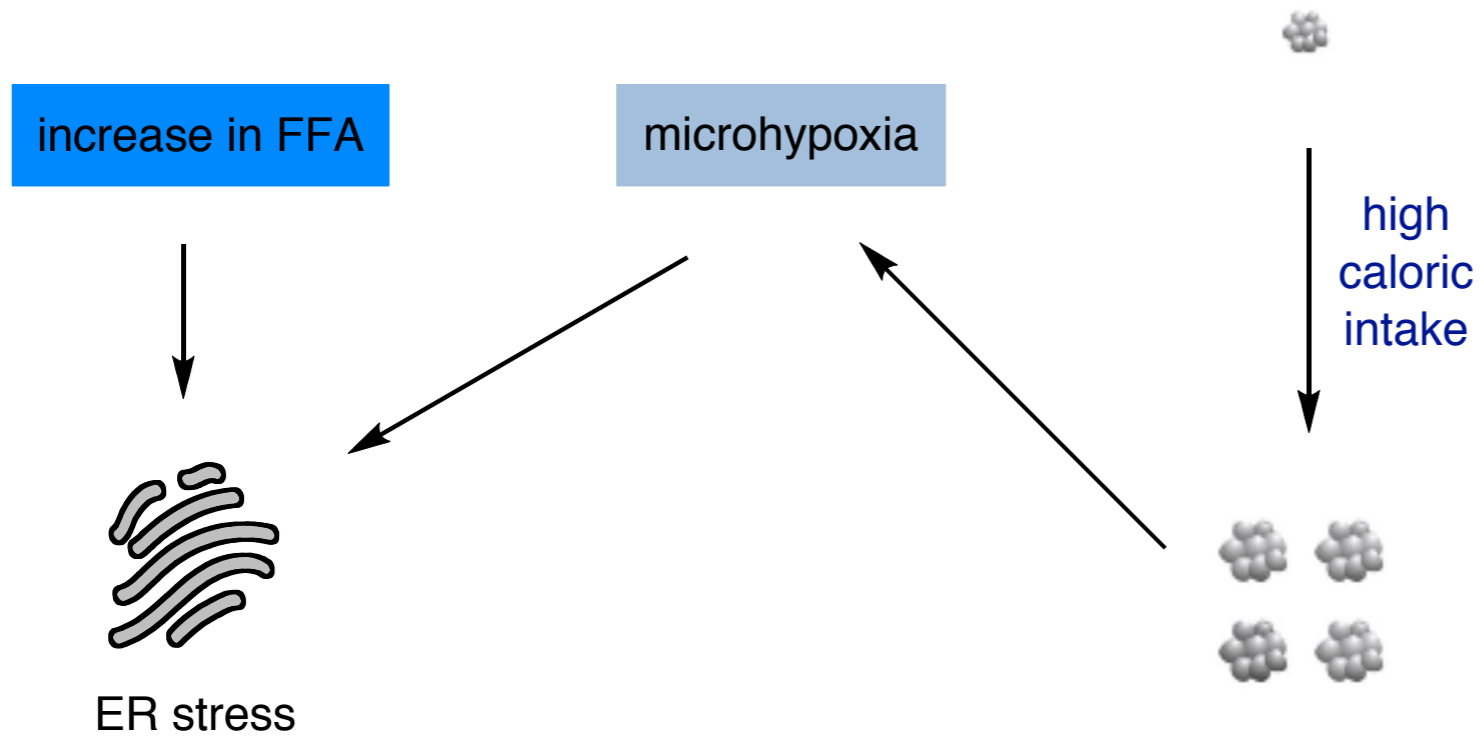
high caloric intake



JNK/API signal transduction

(leads to insulin resistance)

# Insulin Resistance (Type 2 Diabetes)

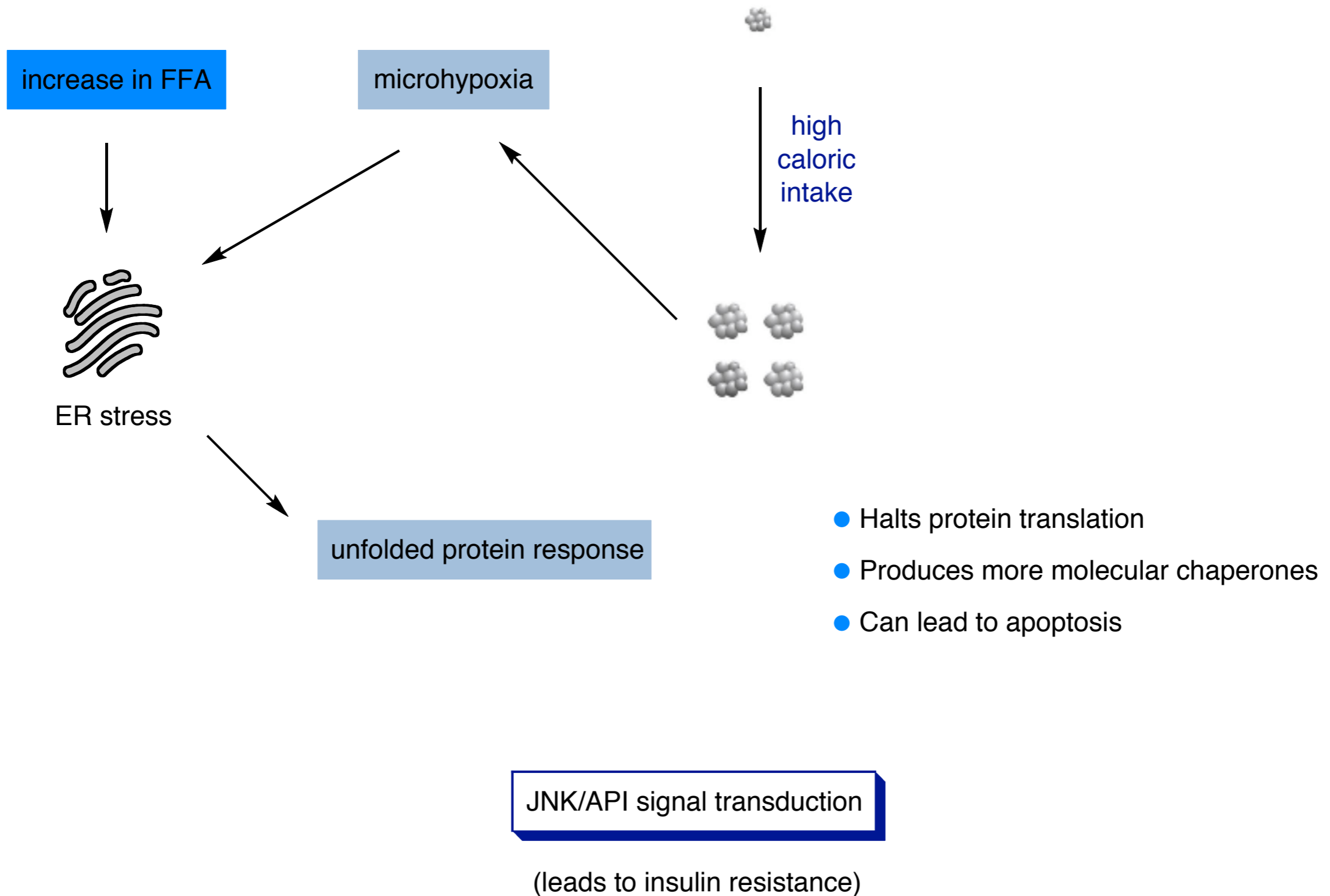


ER stress leads to increase in unfolded and/or misfolded proteins

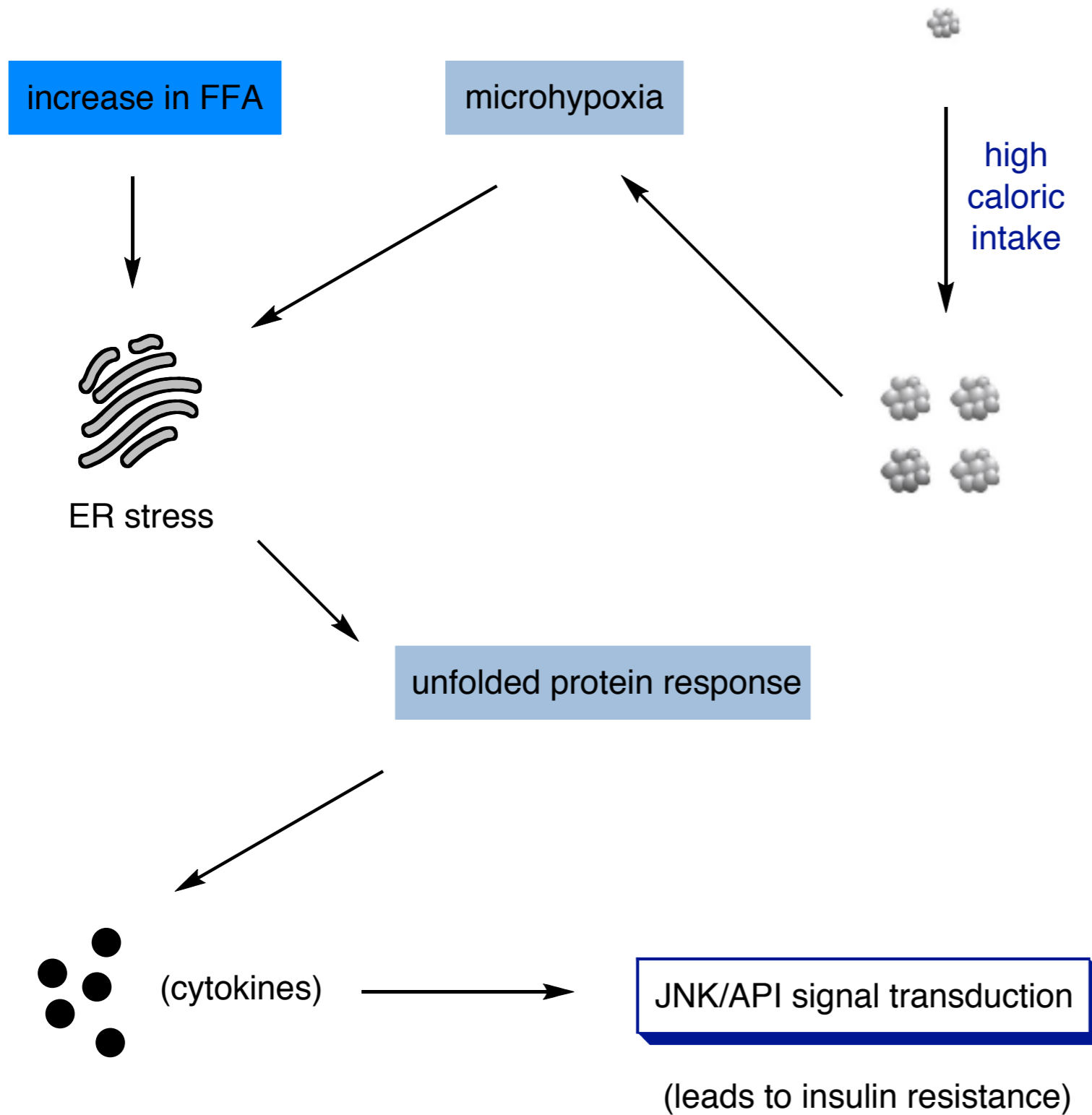
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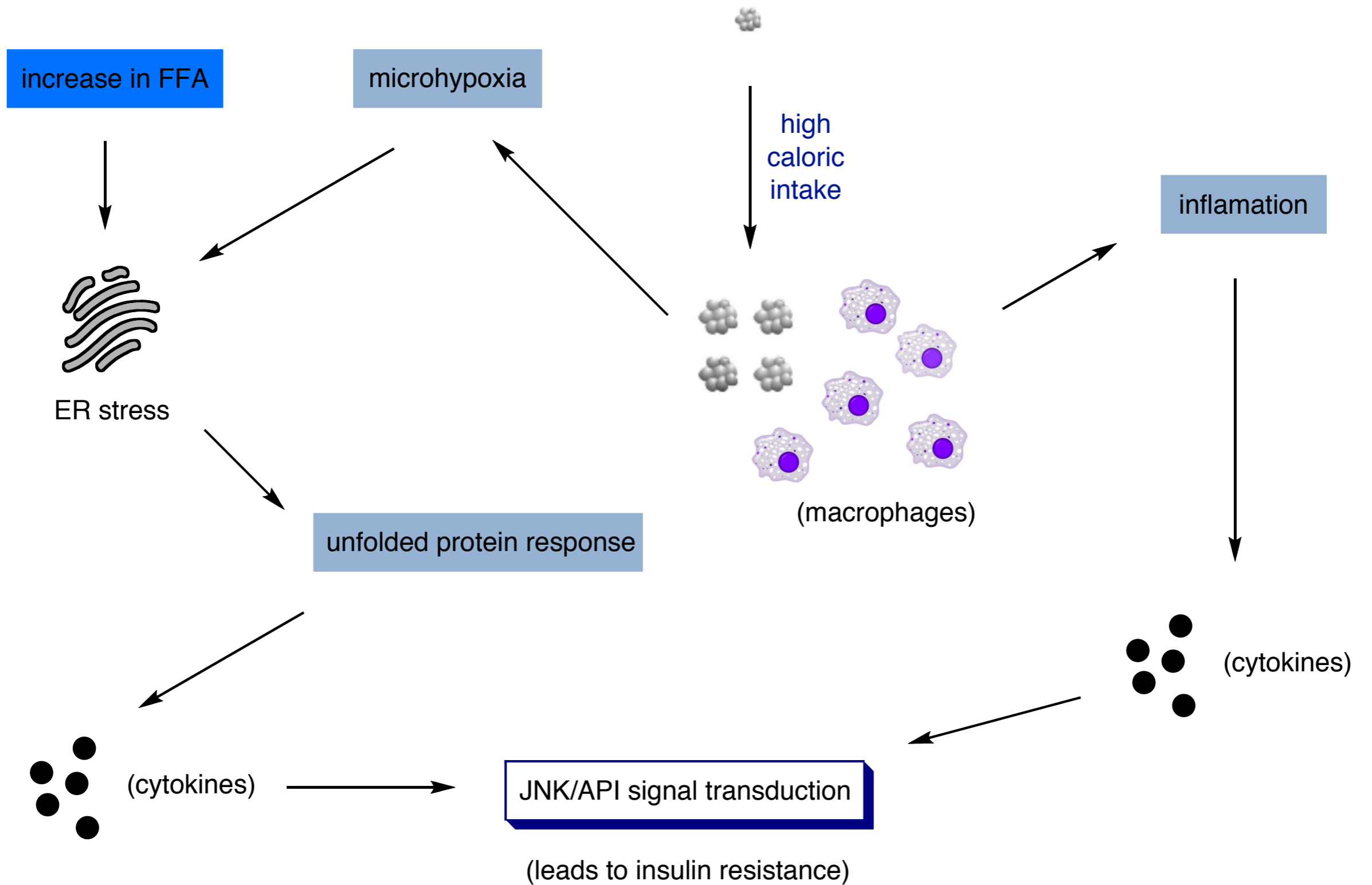
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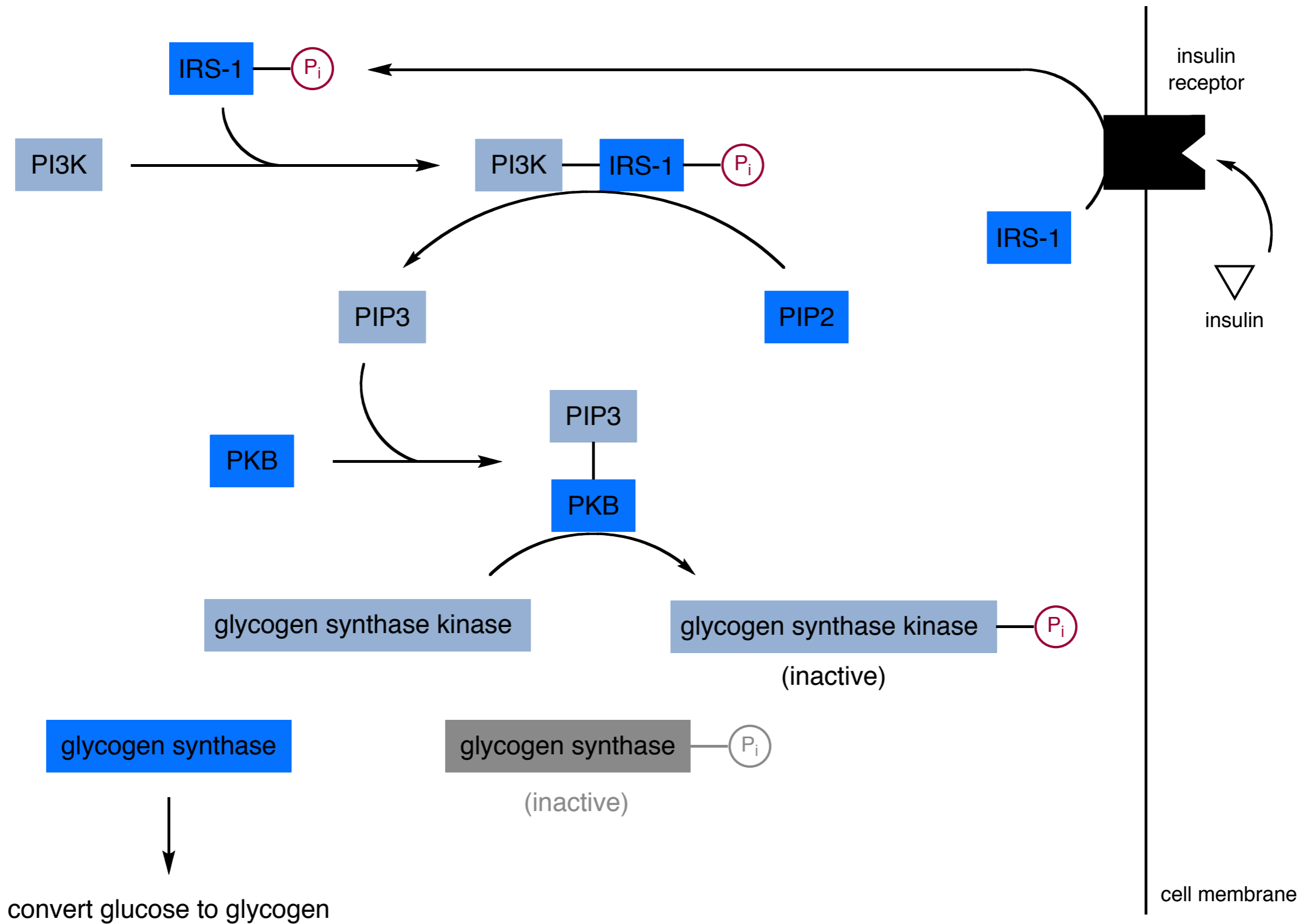
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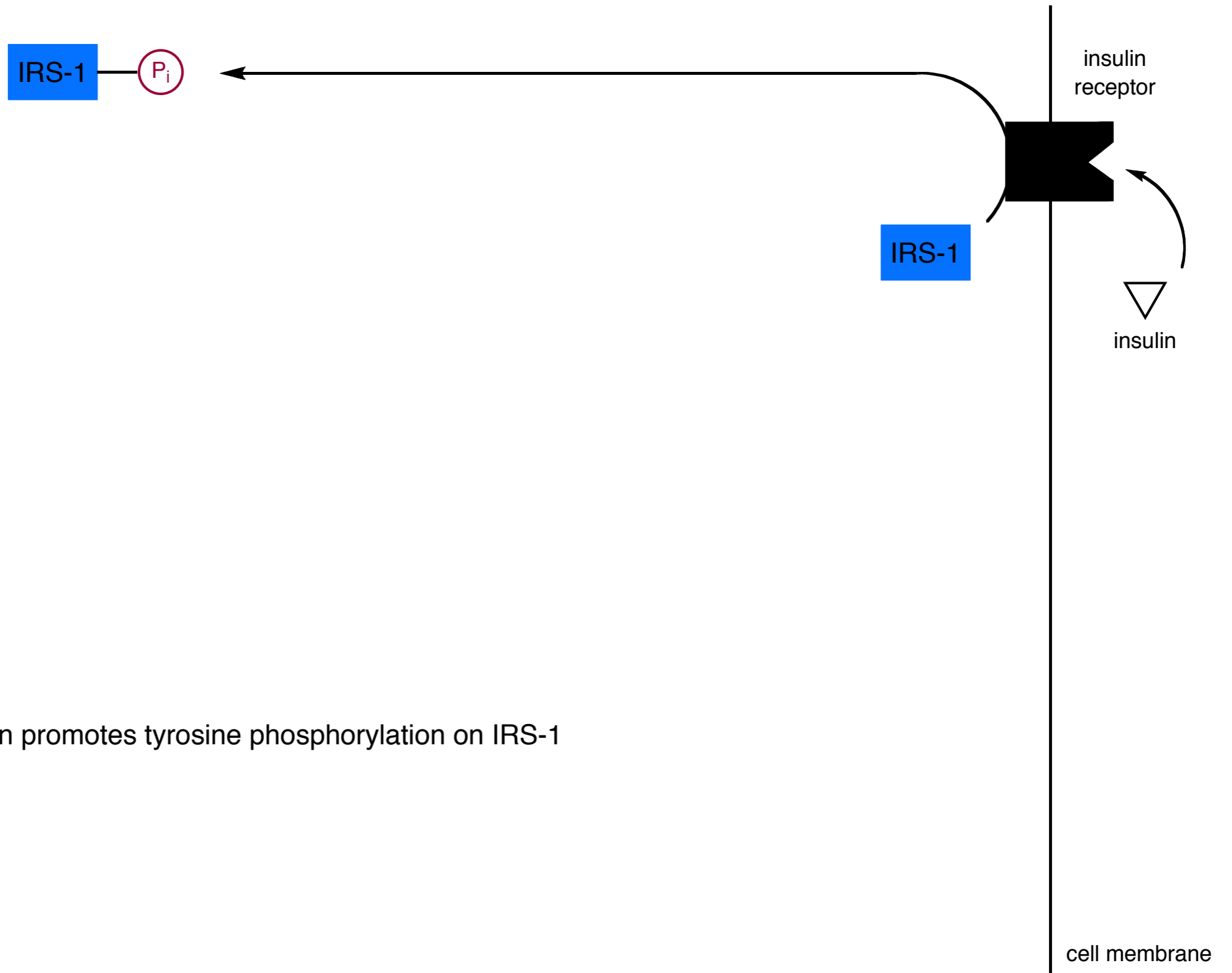


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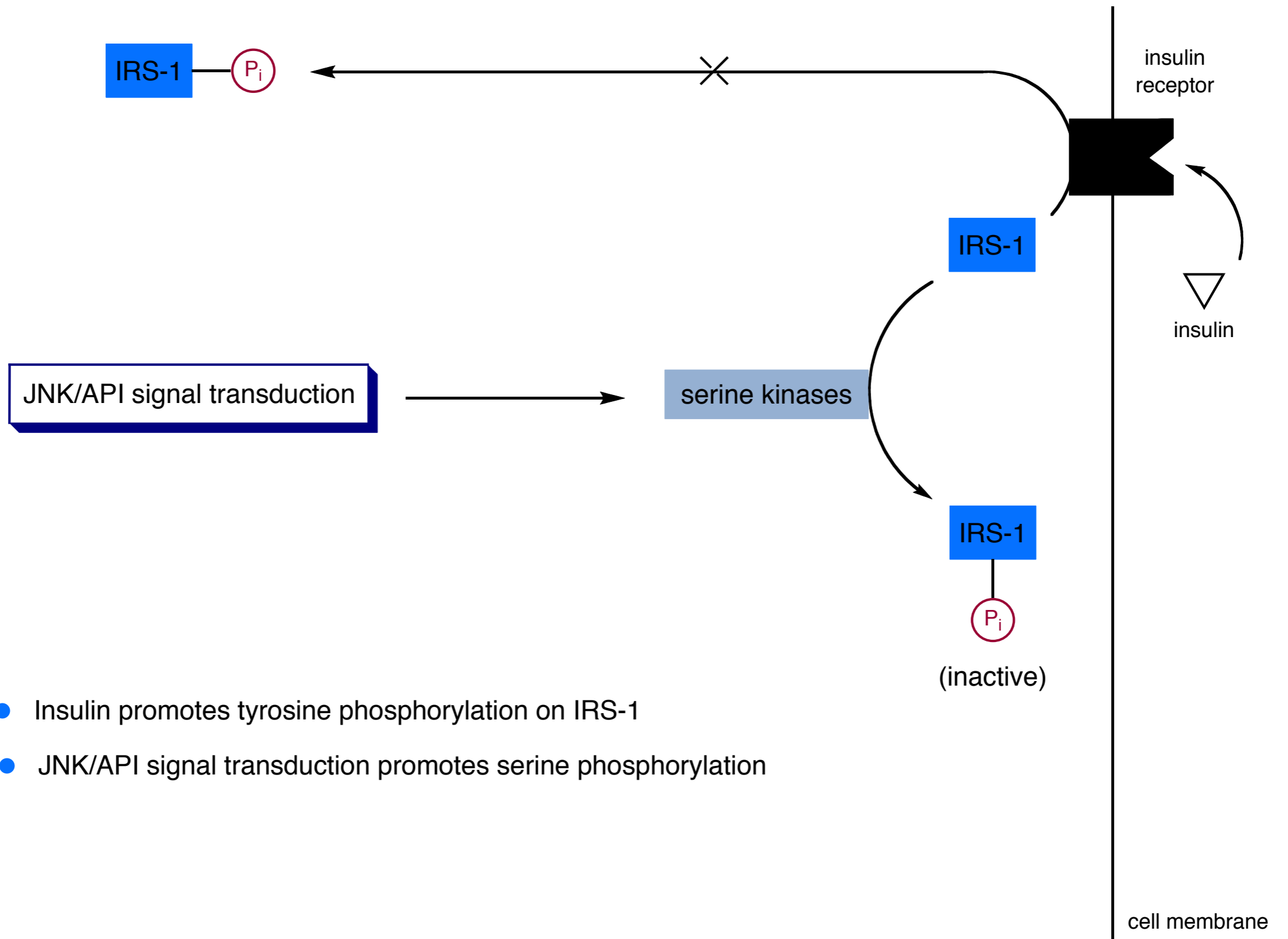


# *Insulin Resistance (Type 2 Diabetes)*



- Insulin promotes tyrosine phosphorylation on IRS-1

# Insulin Resistance (Type 2 Diabetes)



- Insulin promotes tyrosine phosphorylation on IRS-1
- JNK/API signal transduction promotes serine phosphorylation

*Current Therapeutics for Type 2 Diabetes*

## *Insulin Analogues*

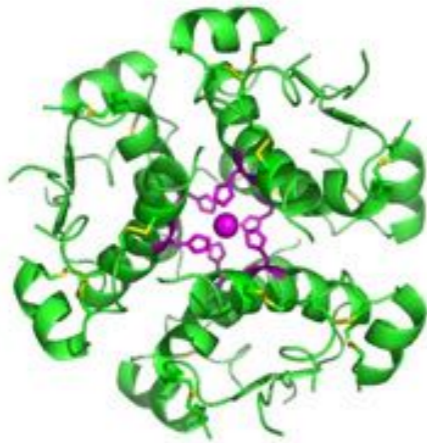
- Insulin used by injection or subcutaneous injection (into hypodermus)
- Unmodified insulin has undesired properties

epidermus  
dermus  
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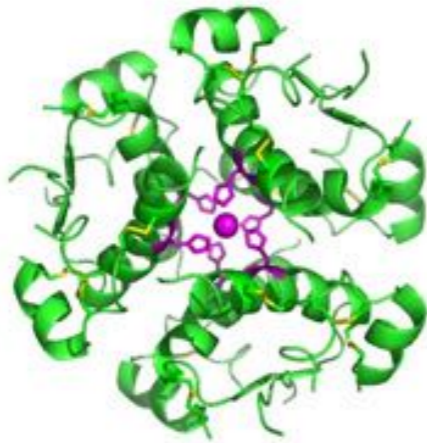


- Hexameric structure causes slow action after injection
- May need injection up to several hours before meal
- Misuse may lead to hypoglycemia

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**Hypoglycemia** - can be significantly more dangerous than hyperglycemia

- Most cells use fatty acids when glucose is scarce
- However, neurons depend almost exclusively on glucose in non-starving humans
- Neurons have very small internal stores of glycogen
- Hypoglycemia can rapidly lead to impaired CNS function, coma, or death

## *Insulin Analogues*

- Slightly modified versions of insulin provide treatments with more convenient and safer profile



*Lilly*

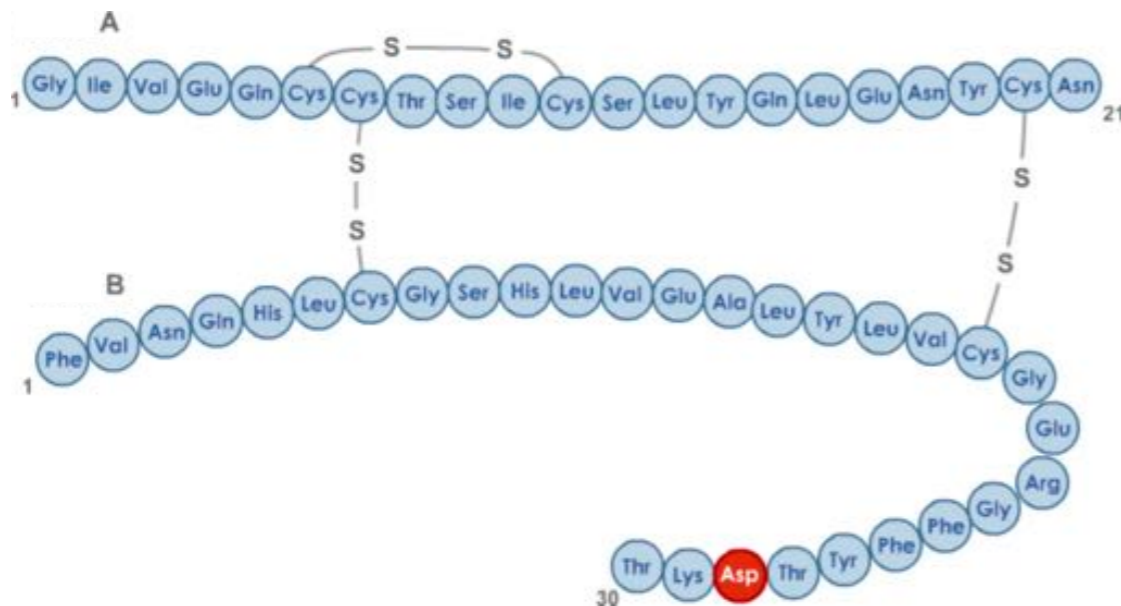


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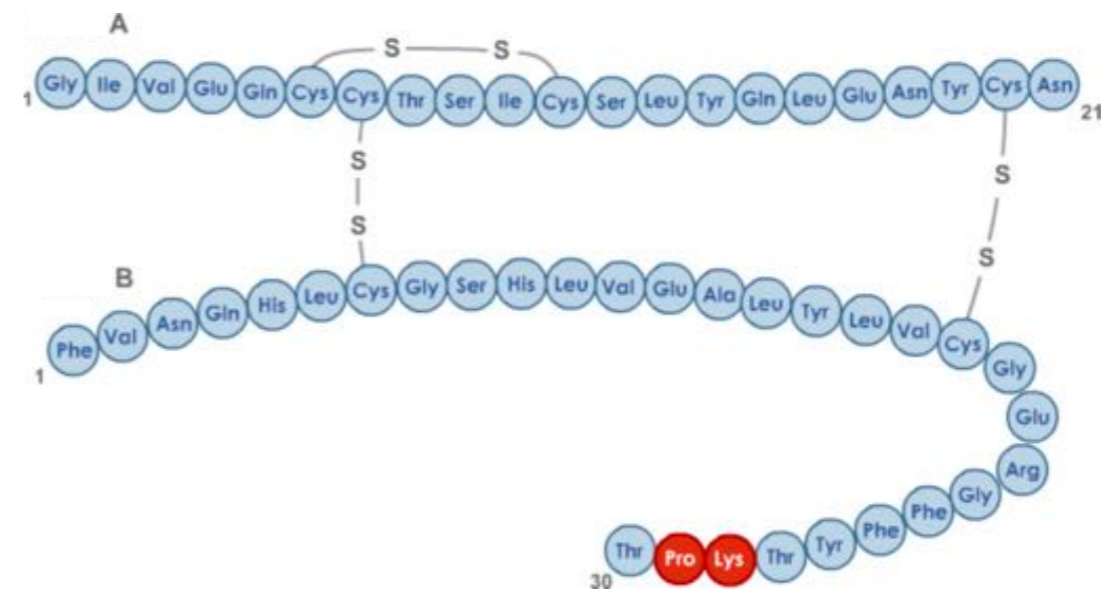
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- Rapid-acting or short-acting analogues allow injection from 5 to 30 minutes before meal



insulin aspart (novo nordisk)



insulin lispro (Eli Lilly)

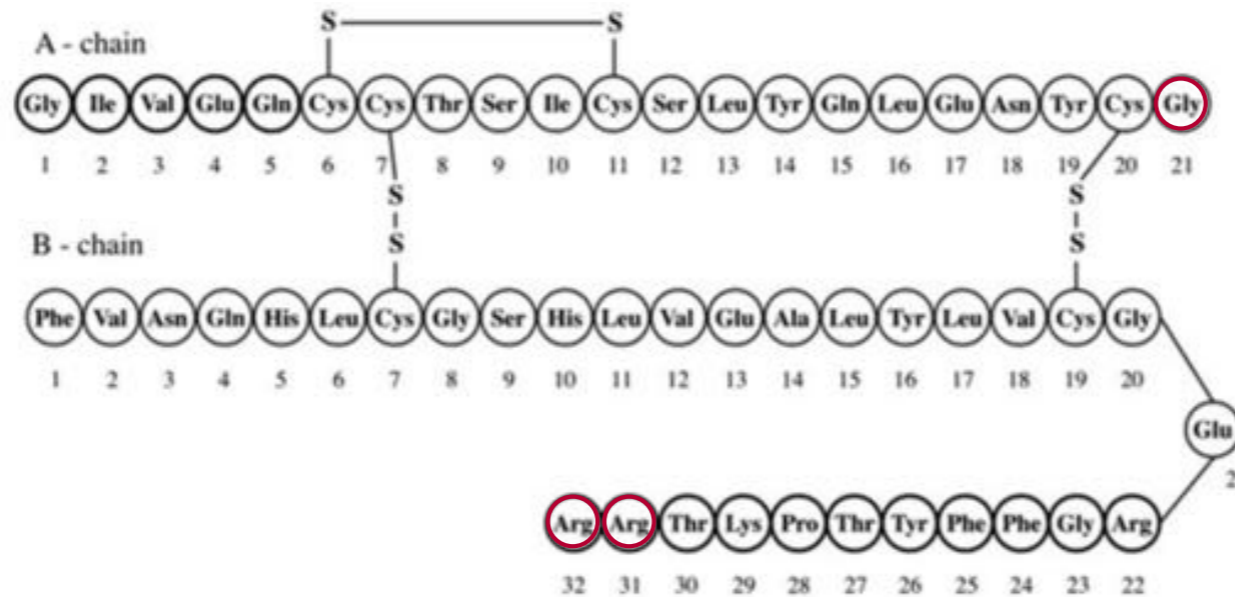


# Insulin Analogues

- Slightly modified versions of insulin provide treatments with more convenient and safer profile



- Extended release analogues have steady effect without peak or drop (18-24 hours)



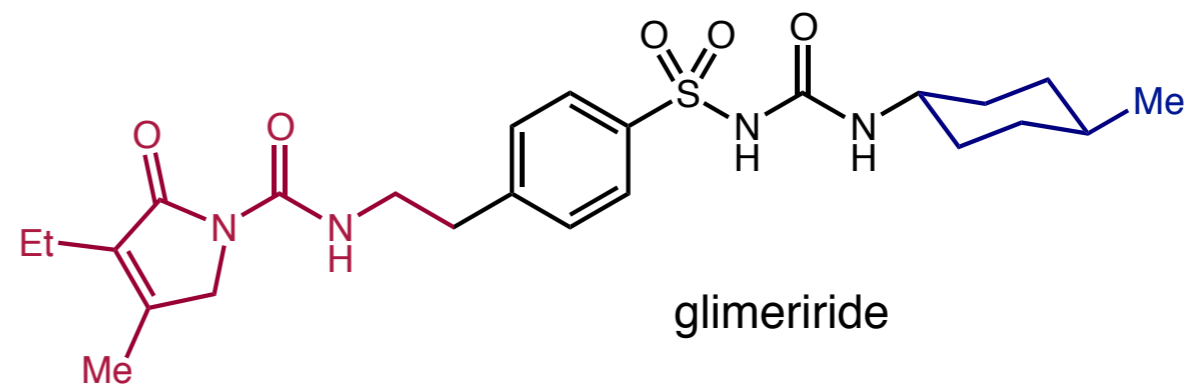
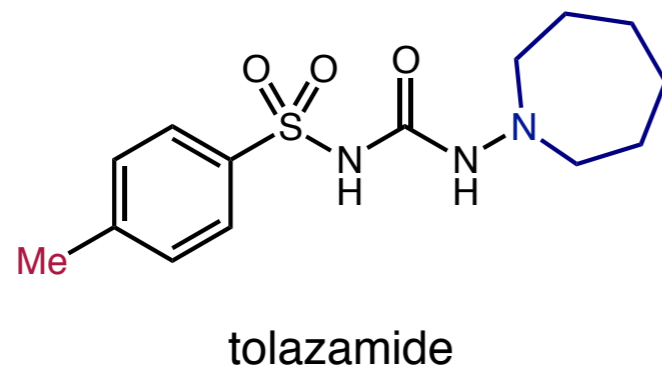
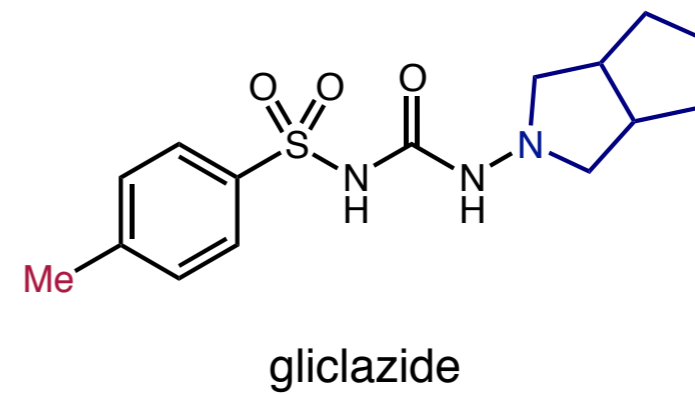
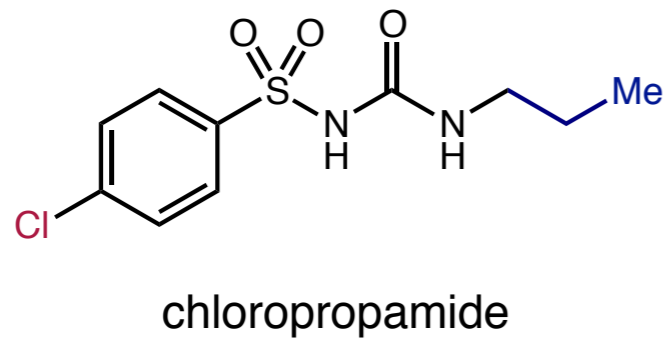
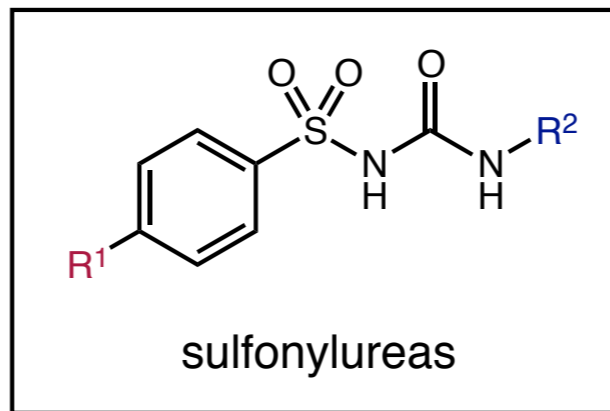
insulin glargine (sanofi aventis)

## *Traditional Small Molecule Treatments*

- Two classes of small molecules have been used to treat T2DM
- These molecules are being used less due to undesirable side effects

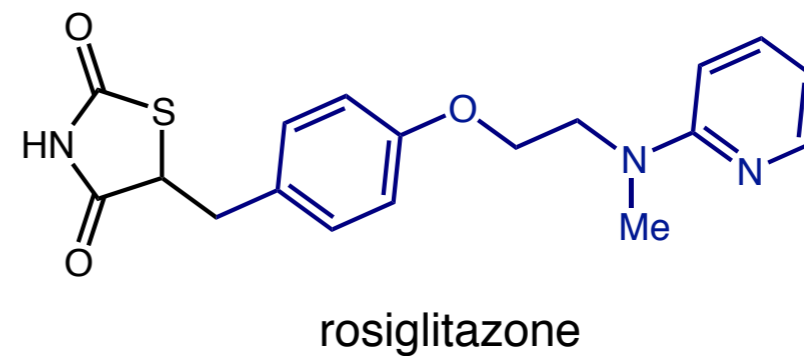
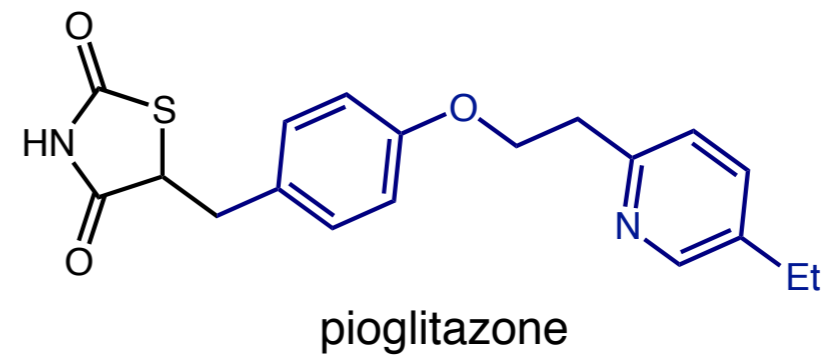
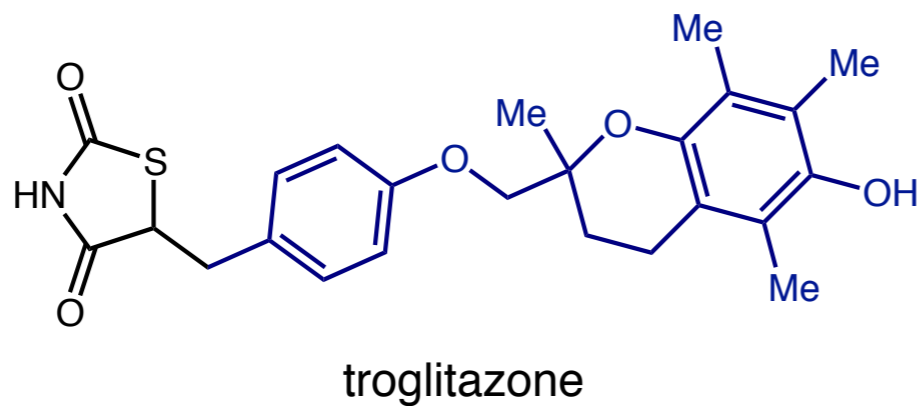
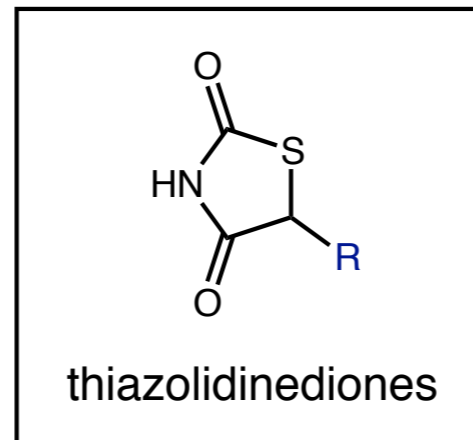
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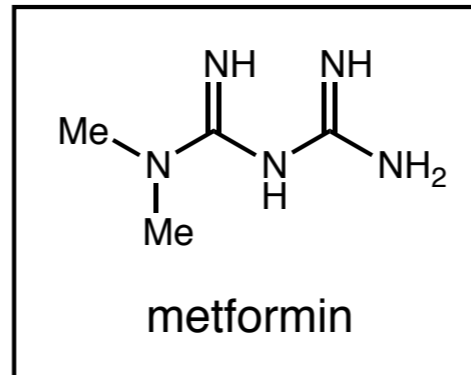
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## *Traditional Small Molecule Treatments*

- Metformin (Glucophage) is first drug choice in T2DM treatment



- Primary function is reducing hepatic gluconeogenesis by 33% on average
  - Minimal side effects (GI irritation, low risk of hypoglycemia)
- Glycemic control continues to deteriorate; metformin does not stop  $\beta$ -cell degradation

## *Current AACE and ACE Recommendations*

Lower priority on thiazolidinediones due to weight gain and heart failure

Stress much lower priority on sulfonylureas due to hypoglycemia, weight gain, and short effectiveness

Increase emphasis on incretin-based therapies (GLP-1 agonists, DPP-4 inhibitors)

[stop or reverse deterioration in  $\beta$ -cell function]

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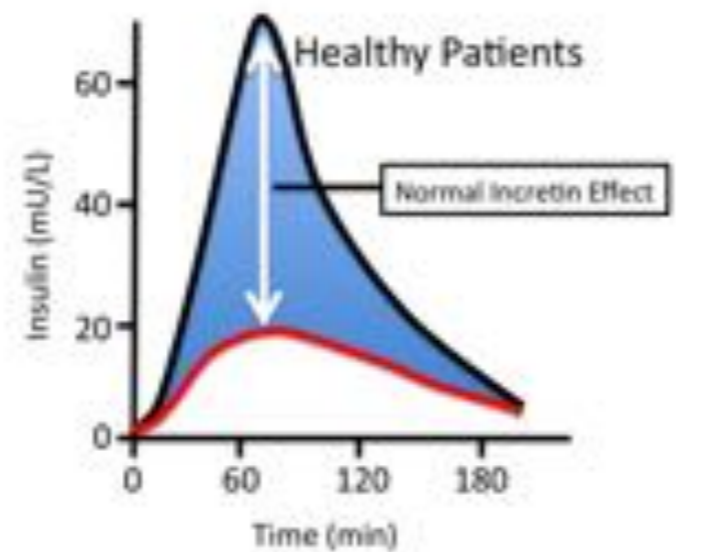
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### Incretin Effect



— Oral Glucose (50 g/400 ml)  
— Isoglycemic IV Glucose Infusion

Nauck M et al.  
Diabetologia (1986) 29:46-52

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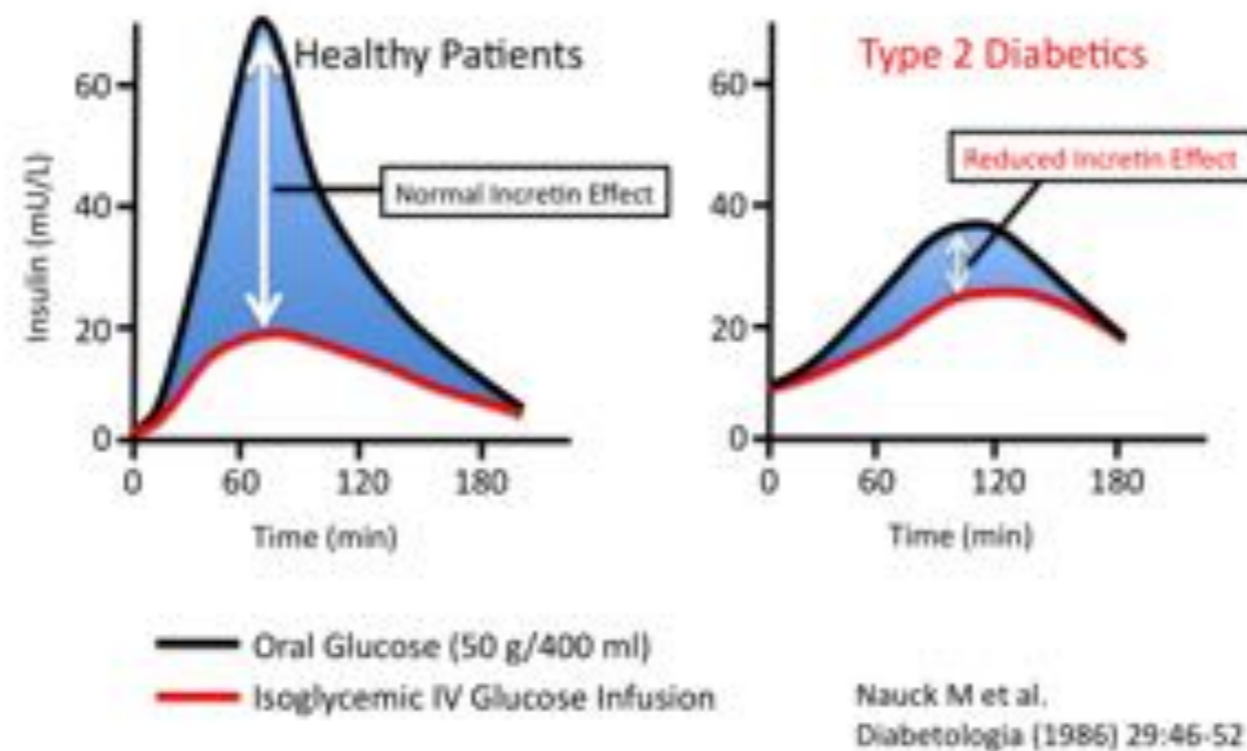
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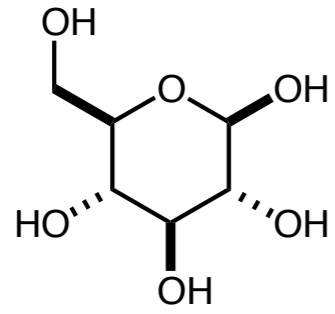
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### Incretin Effect





# *Incretin Proteins*

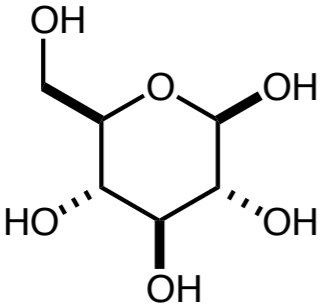


stomach



small intestine

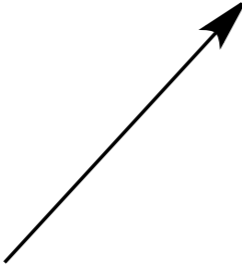
# Incretin Proteins



stomach



small intestine

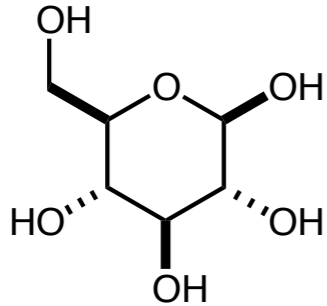


GLP-1

glucagon-like peptide-1 (GLP-1)

(incretin protein)

# Incretin Proteins



stomach

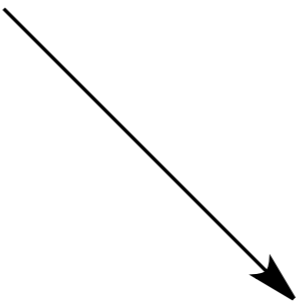
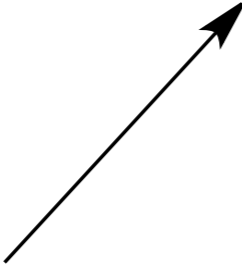


small intestine

inhibits gastric emptying



GLP-1



promotes insulin release



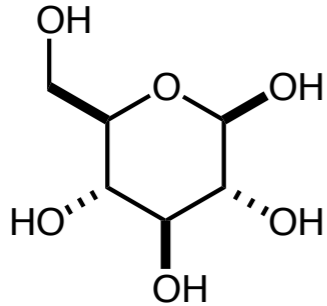
inhibits glucagon release

pancreas  $\beta$ -cells

GLP-1 and GIP contribute 60% of insulin secretion after meal

suppresses appetite

# Incretin Proteins



stomach



small intestine

inhibits gastric emptying



GLP-1

GLP-1 and GIP contribute 60% of insulin secretion after meal

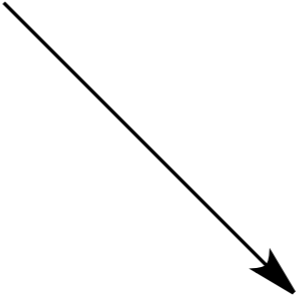
GLP-1 action dependent on amount of glucose ingested

promotes insulin release



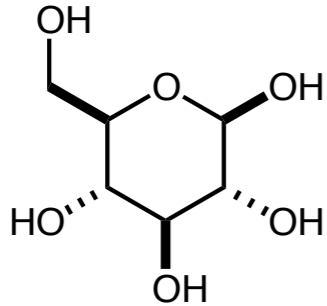
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stomach



small intestine

GLP-1

inhibits gastric emptying



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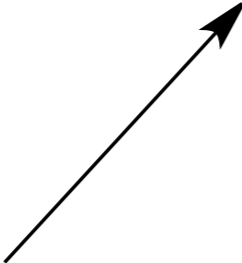
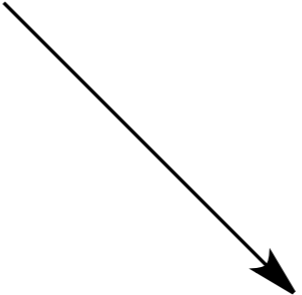


pancreas  $\beta$ -cells

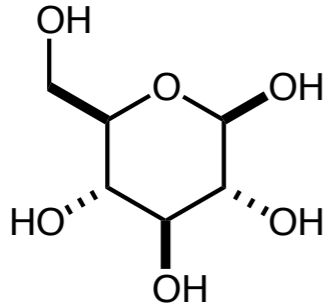
inhibits glucagon release

GLP-1 slowly increases mass of  $\beta$ -cells over time

suppresses appetite



# Incretin Proteins



stomach

small intestine

inhibits gastric emptying

GLP-1

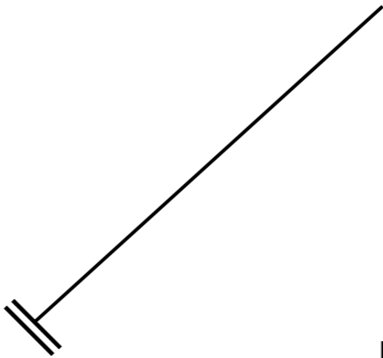
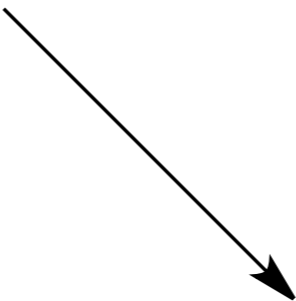
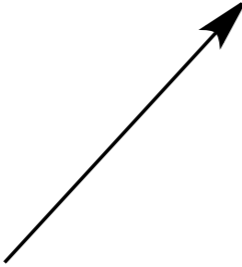
DPP-4

promotes insulin release

inhibits glucagon release

pancreas  $\beta$ -cells

suppresses appetite



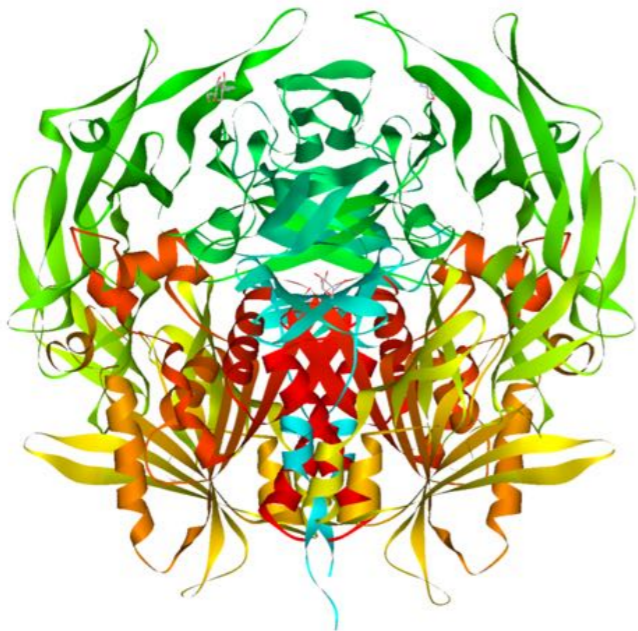
## *Incretin Proteins*



Dipeptidyl-peptidase IV (dpp-4)

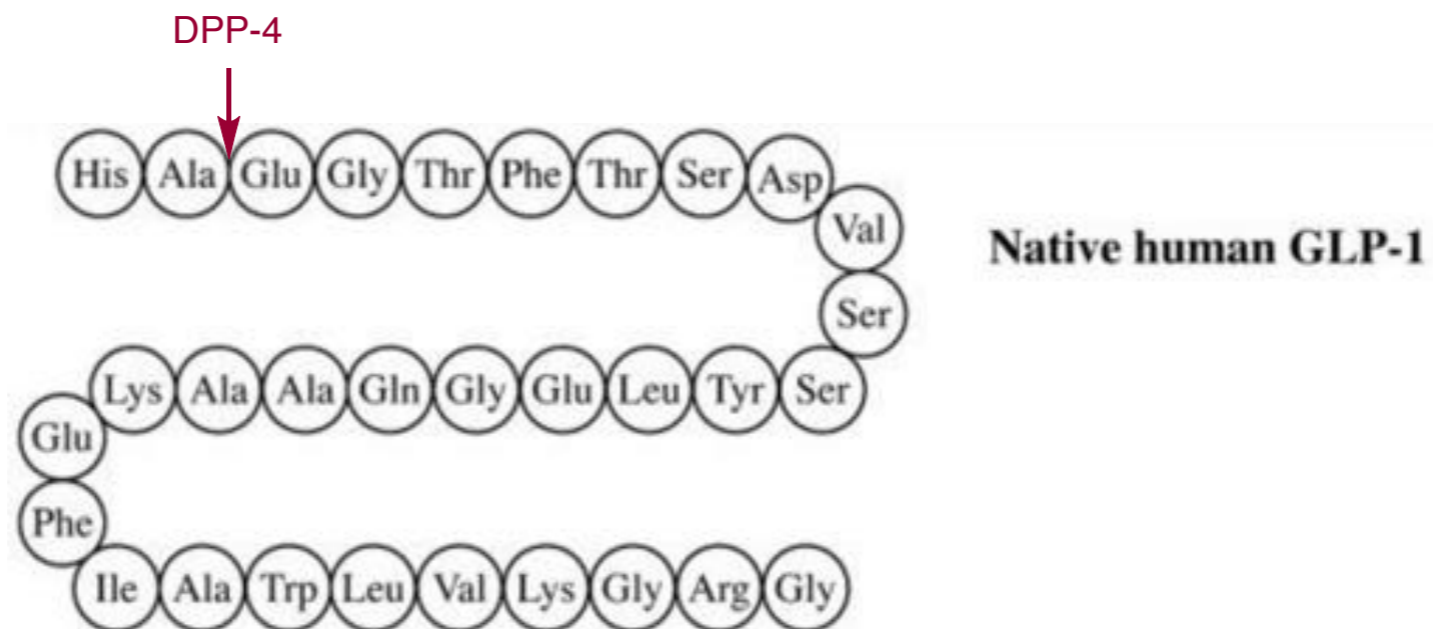
- Expressed on the surface of most cells
- Signal transduction, immune response, apoptosis
- Serine exopeptidase that cleaves X-proline or X-alanine from N-terminus of polypeptides

## Incretin Proteins



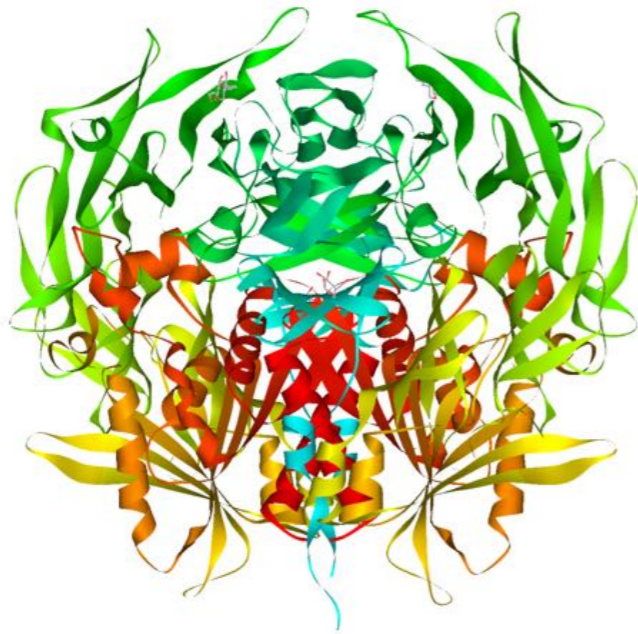
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Dipeptidyl-peptidase IV (dpp-4)





## *Incretin Proteins*

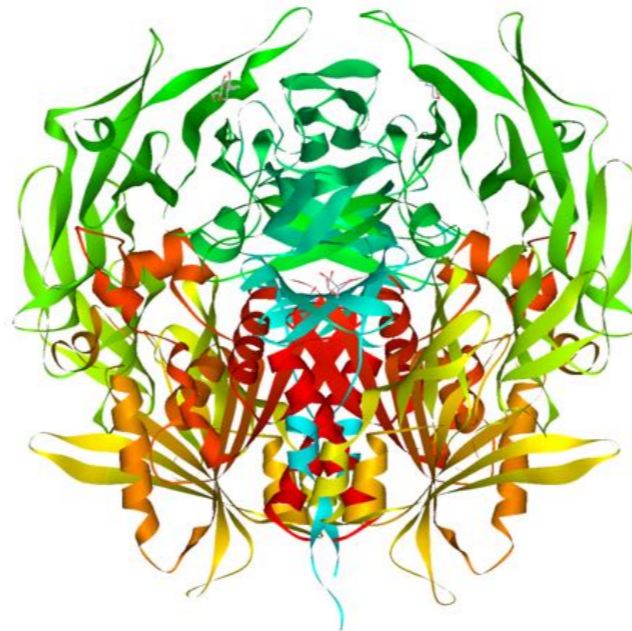


Dipeptidyl-peptidase IV (dpp-4)

- Expressed on the surface of most cells
- Signal transduction, immune response, apoptosis
- Serine exopeptidase that cleaves X-proline or X-alanine from N-terminus of polypeptides

- Enzyme responsible for GLP-1 degradation (half-life = 1-2 minutes)
- Injection of exogenous GLP-1 results in minimal effect
- Native GLP-1 is not a practical therapeutic for T2DM

## *Incretin Proteins*



Dipeptidyl-peptidase IV (dpp-4)

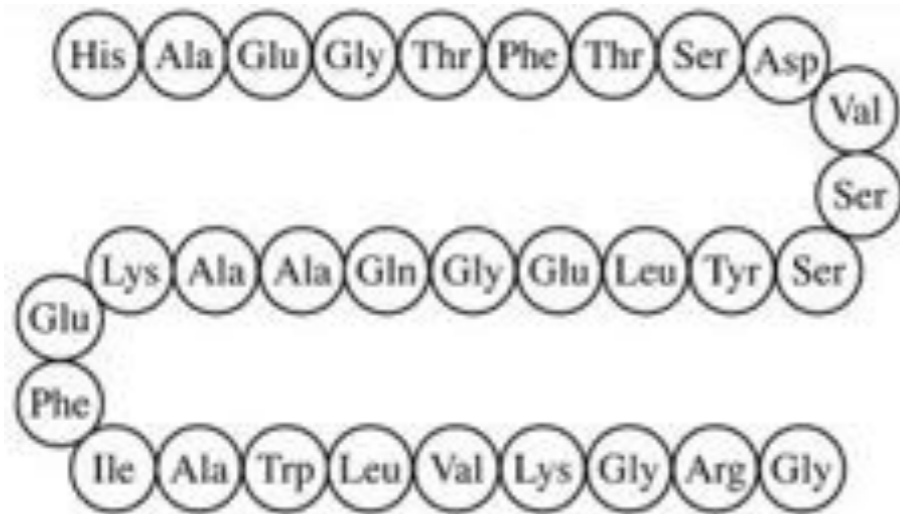
Two options for incretin therapeutic strategies:

GLP-1 receptor agonist resistant to DPP-4 cleavage (injectable polypeptide)

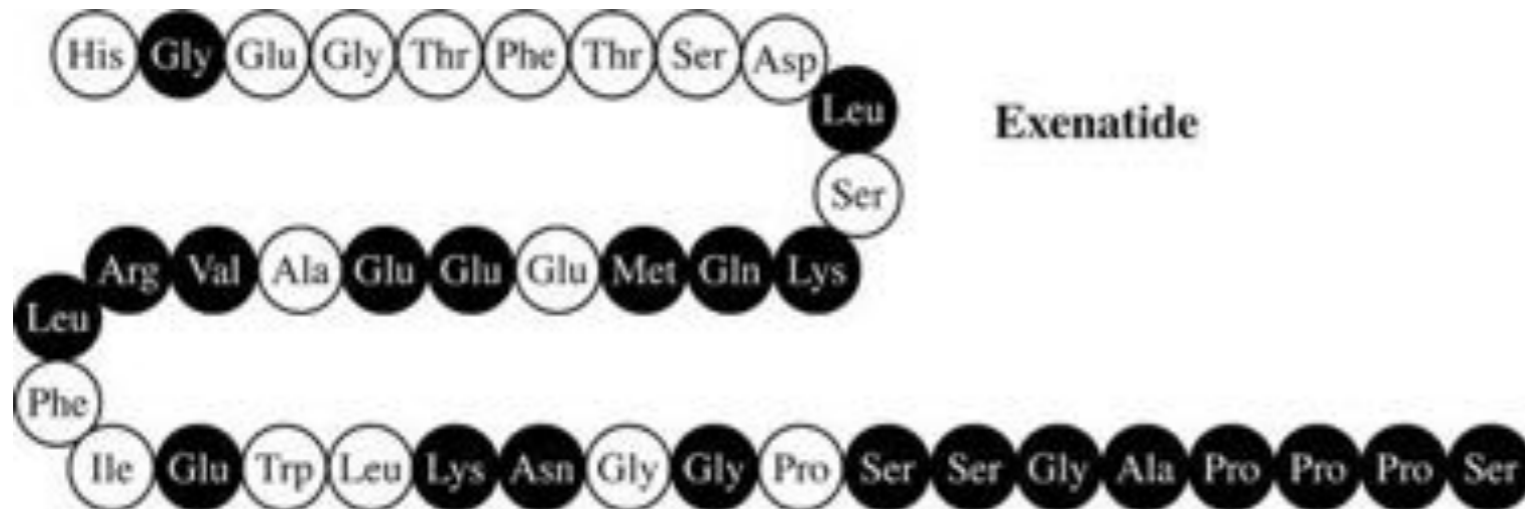
DPP-4 inhibitor (orally active small molecule)

# GLP-1 Receptor Agonists

Exenatide (Amylin and Eli Lilly)



Native human GLP-1

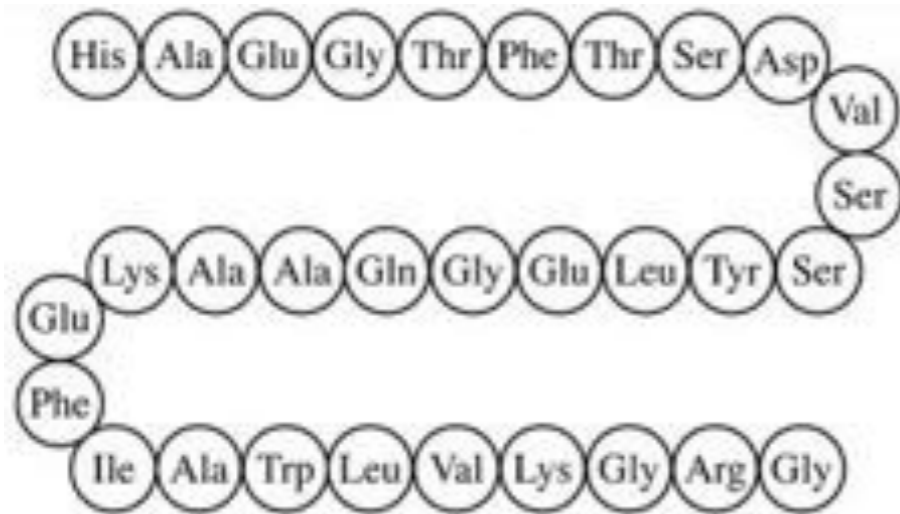


Exenatide

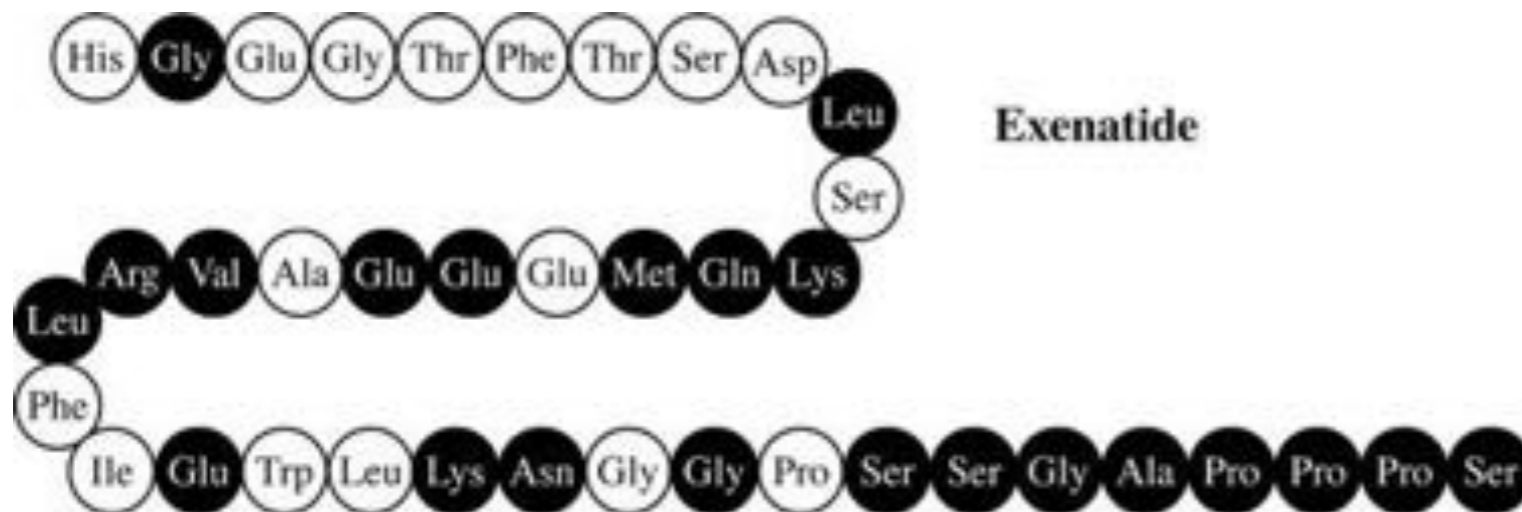
- First GLP-1 receptor agonist
- Approved in combination with metformin and/or sulfonylureas (when monotherapy fails)

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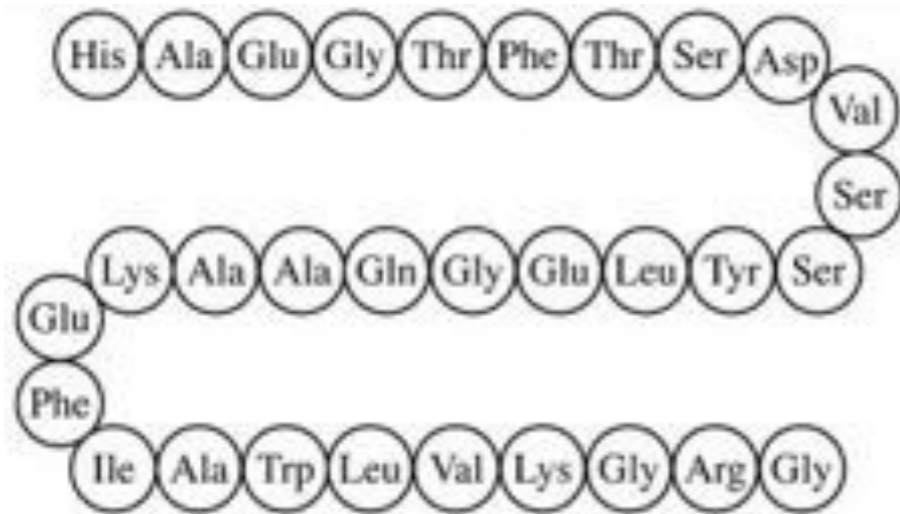
Exenatide

- First GLP-1 receptor agonist
- Approved in combination with metformin and/or sulfonylureas (when monotherapy fails)
- Synthetic form of exendin-4 (saliva of gila monster)

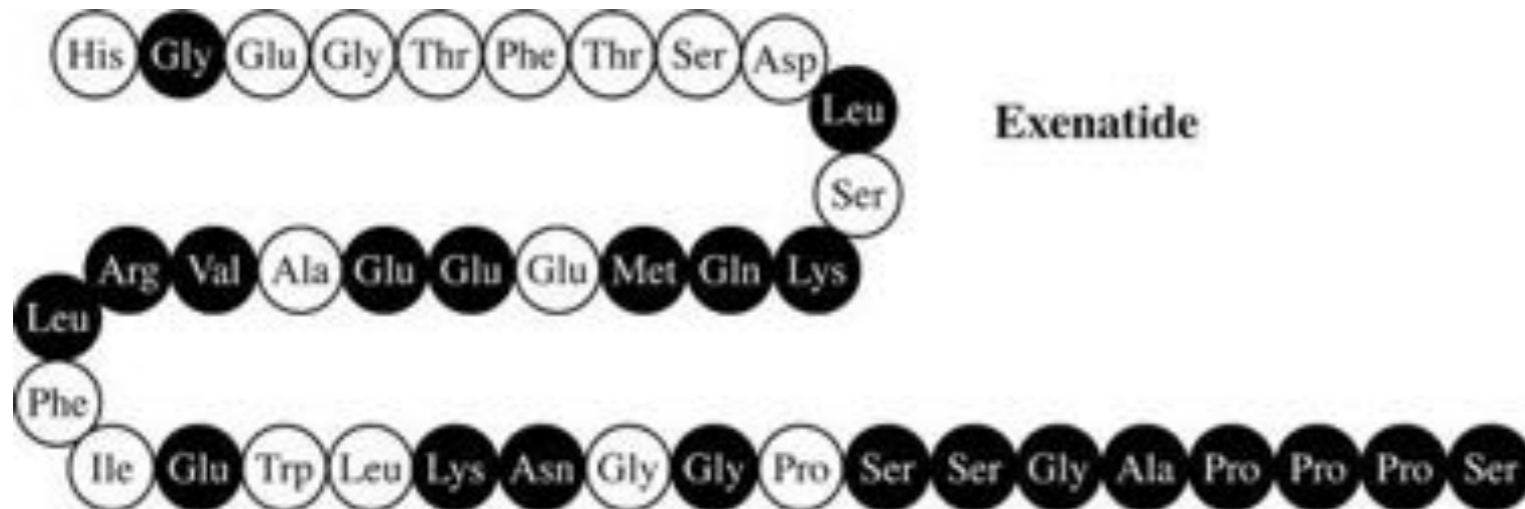


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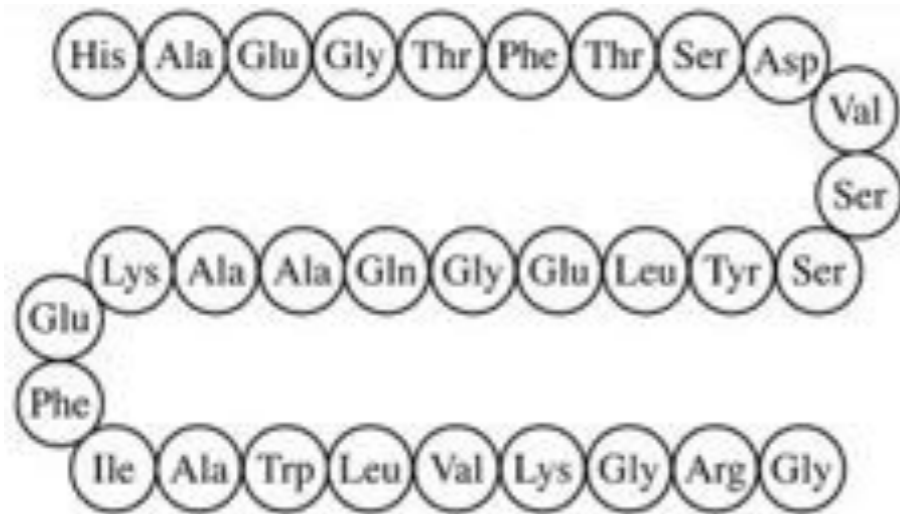
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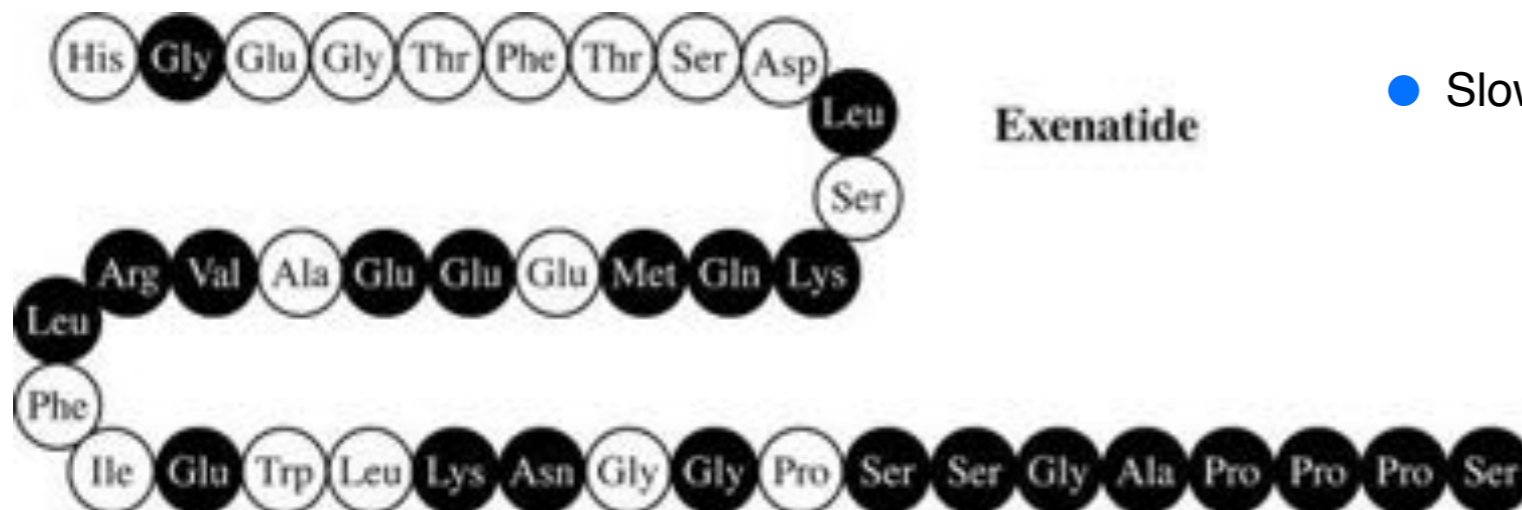


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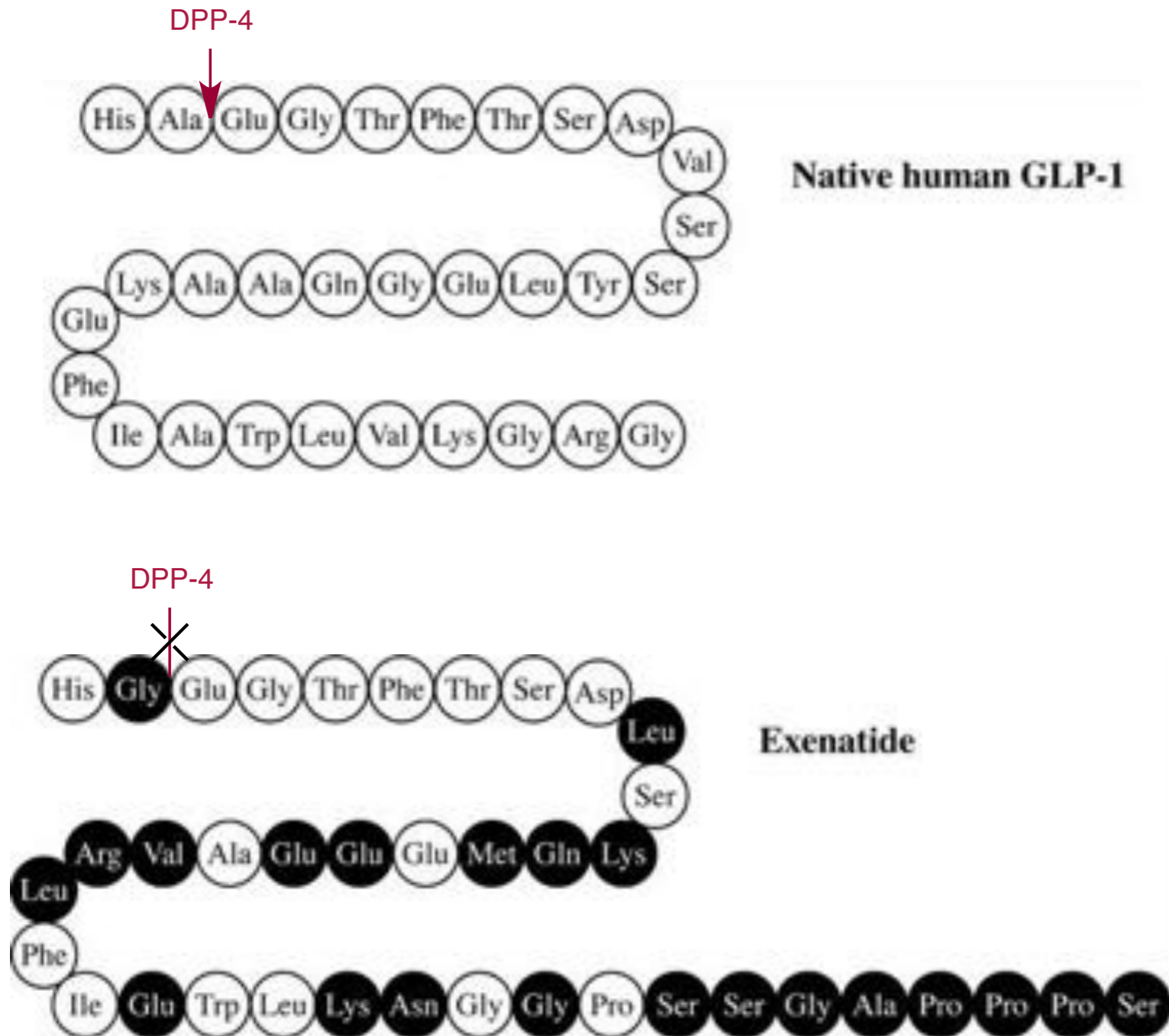


Exenatide

- First GLP-1 receptor agonist
- Approved in combination with metformin and/or sulfonylureas (when monotherapy fails)
- Synthetic form of exendin-4 (saliva of gila monster)
  - 53% amino acid sequence of human GLP-1
  - Subcutaneous injection twice daily
  - Slow release variation in progress (once weekly)

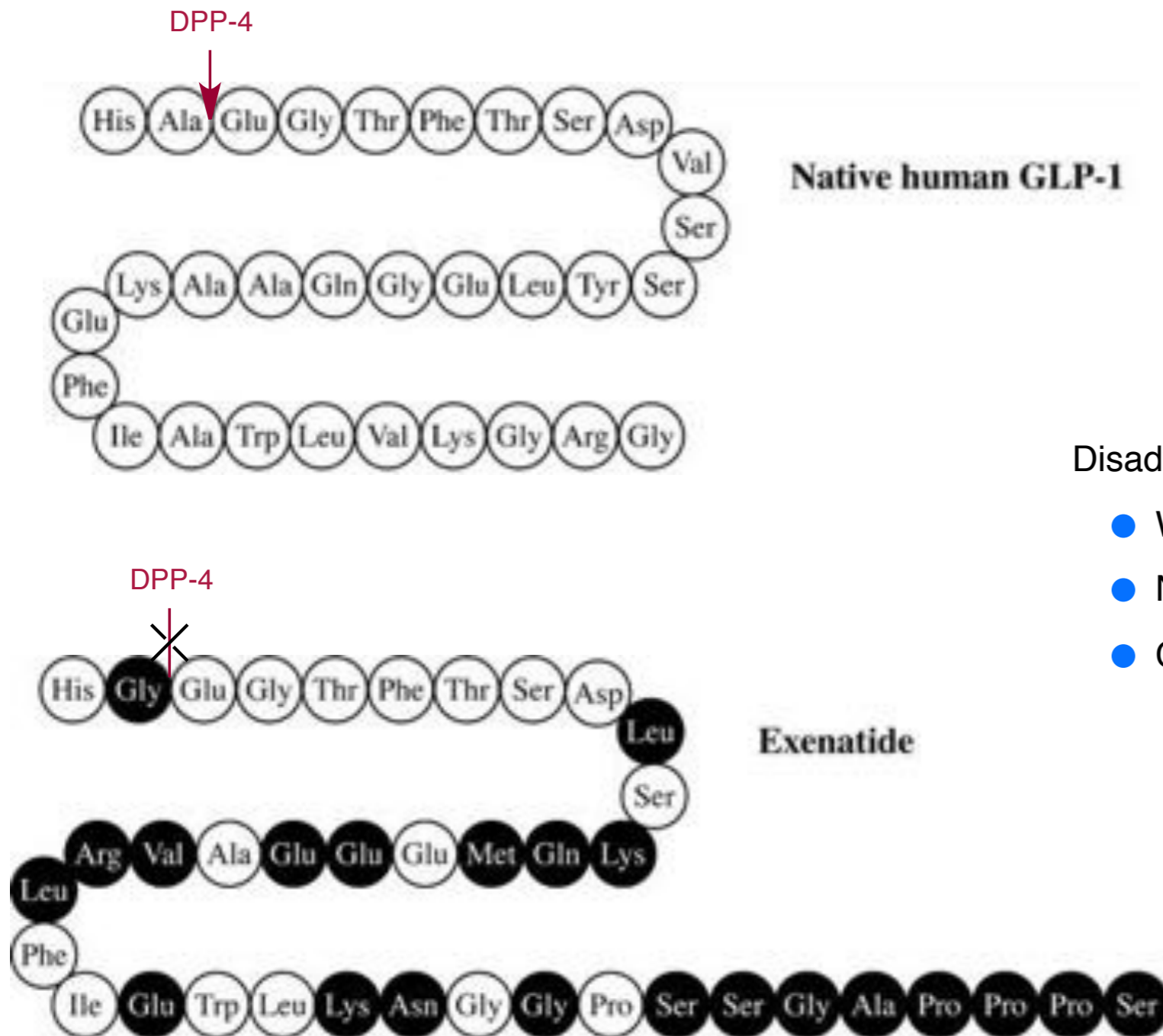
# GLP-1 Receptor Agonists

Exenatide (Amylin and Eli Lilly)



# GLP-1 Receptor Agonists

Exenatide (Amylin and Eli Lilly)



Advantages to using Exenatide:

- 5.3 kg weight loss over 3 years
- $\beta$ -cell function improves

Disadvantages to using Exenatide:

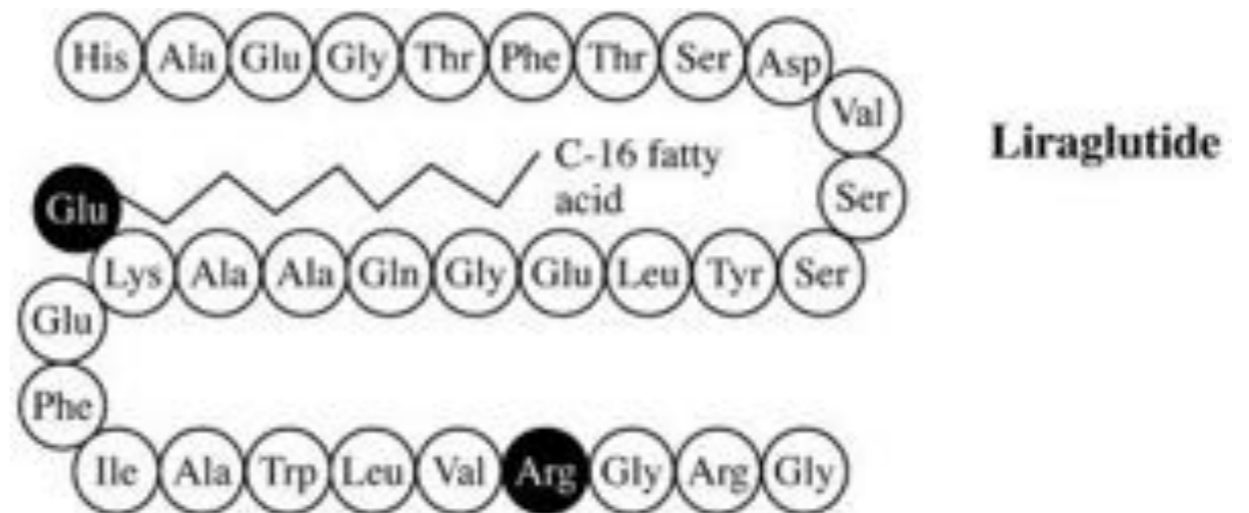
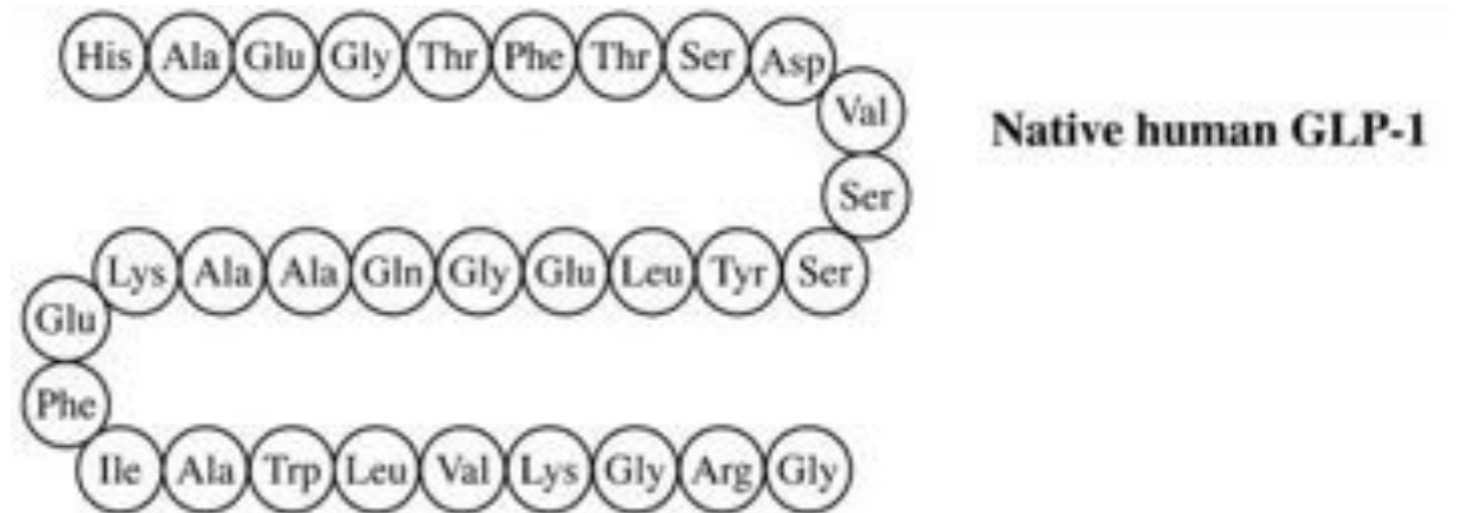
- Washout leads to decreased  $\beta$ -cell function
- Non-human peptide leads to antibodies
- Cases of acute pancreatitis



# GLP-1 Receptor Agonists

Liraglutide (Novo Nordisk)

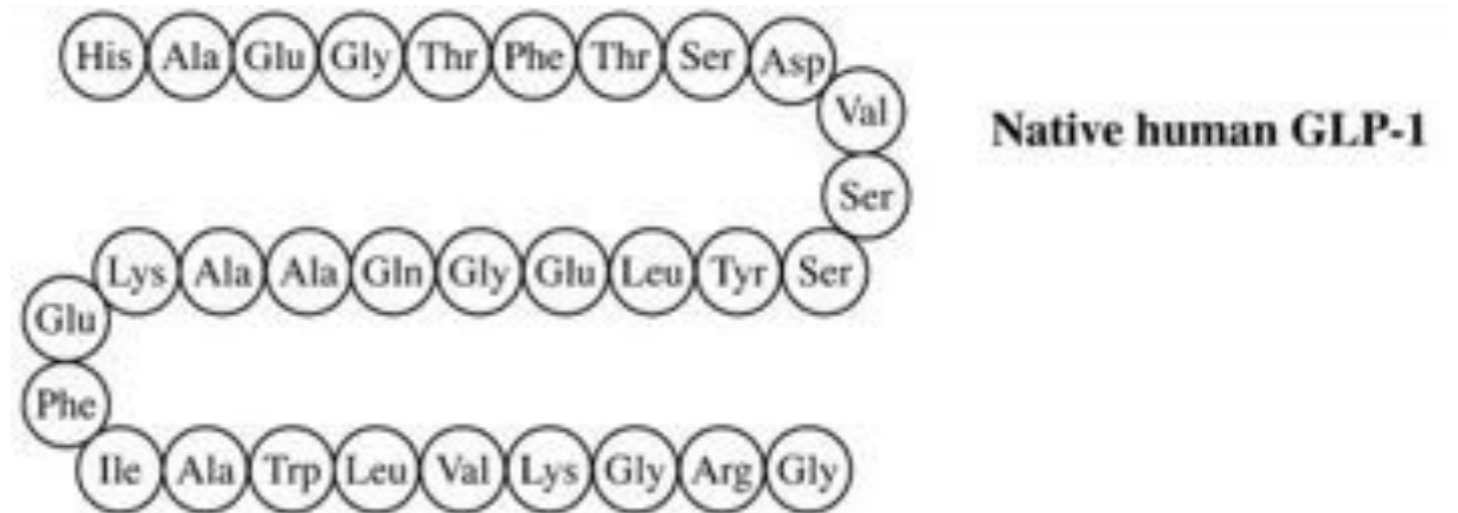
- First human GLP-1 analogue
- Only 2 amino acid modifications



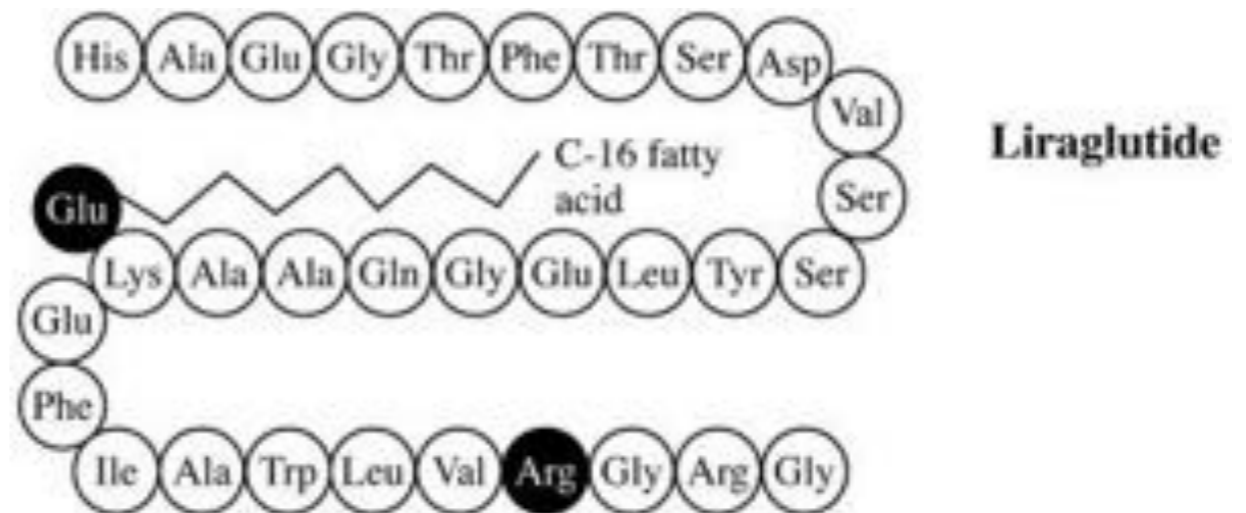
# GLP-1 Receptor Agonists

Liraglutide (Novo Nordisk)

- First human GLP-1 analogue
- Only 2 amino acid modifications
- Approved for once daily subcutaneous injection



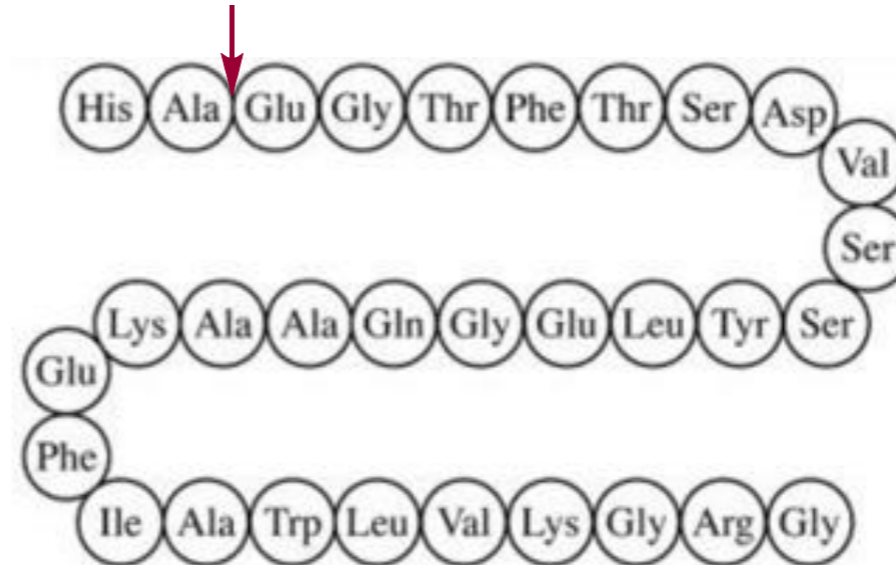
- Albumin binding to fatty acid (blocks DPP-4)



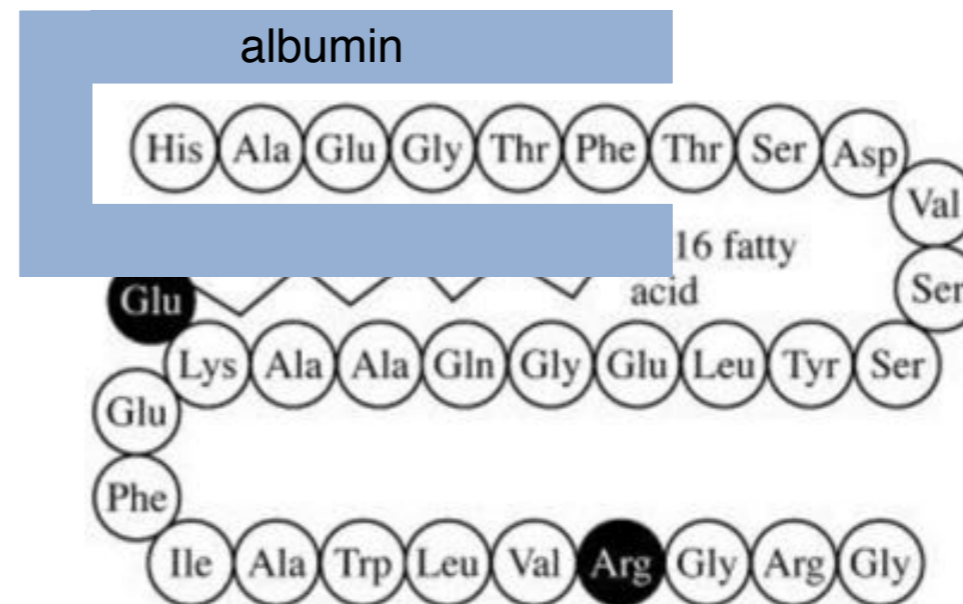
# GLP-1 Receptor Agonists

Liraglutide (Novo Nordisk)

DPP-4



DPP-4 ✗

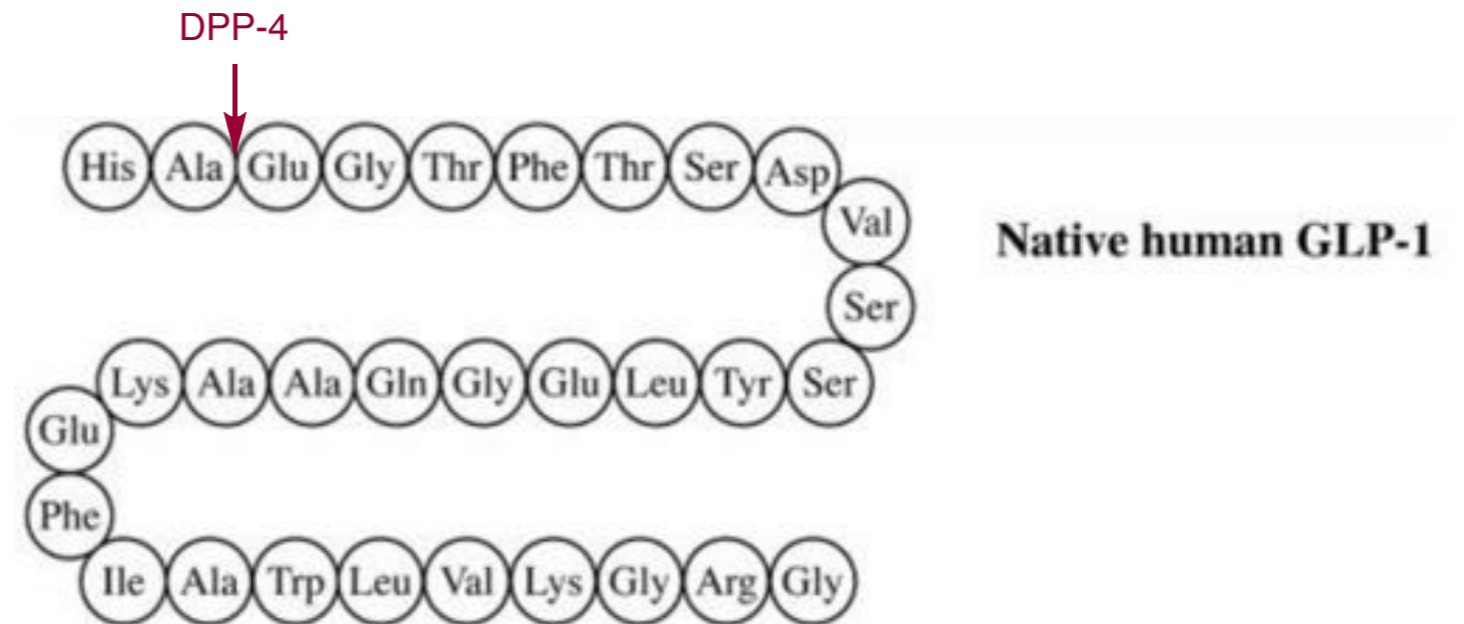


# GLP-1 Receptor Agonists

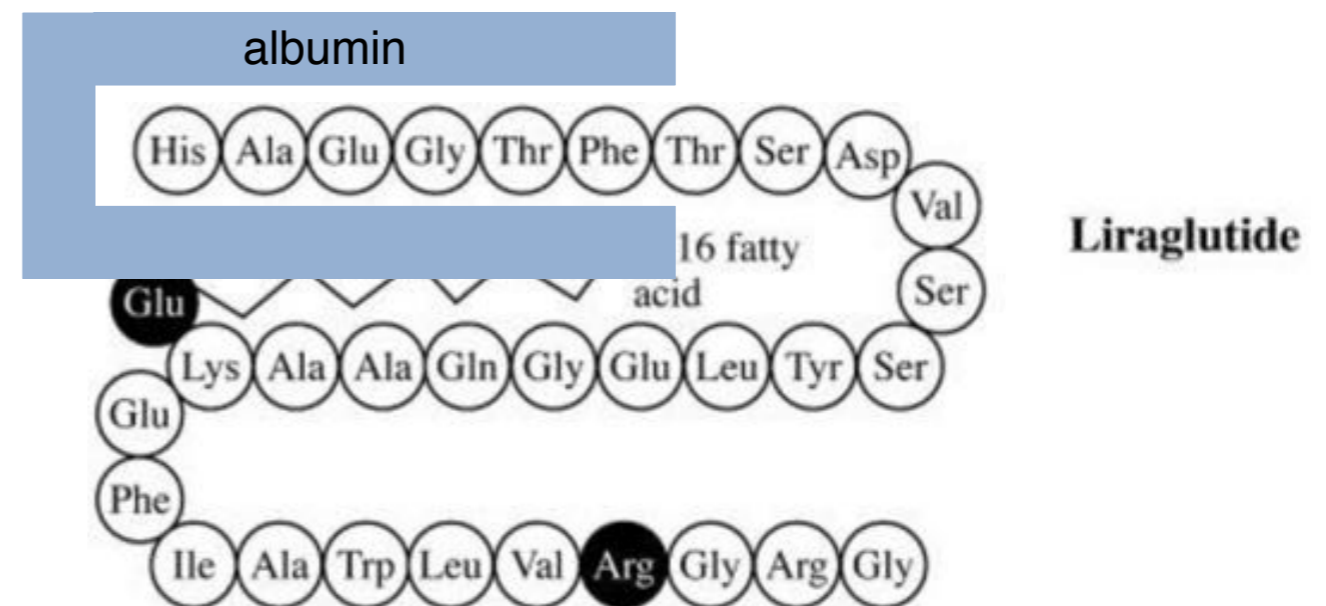
Liraglutide (Novo Nordisk)

Advantages to using Liraglutide:

- Lowers body mass and food intake
- $\beta$ -cell mass and function improve
- Systolic blood pressure lowered



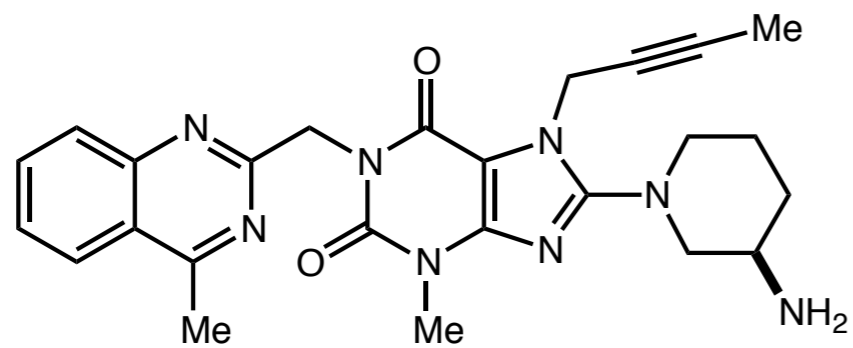
DPP-4 ✗



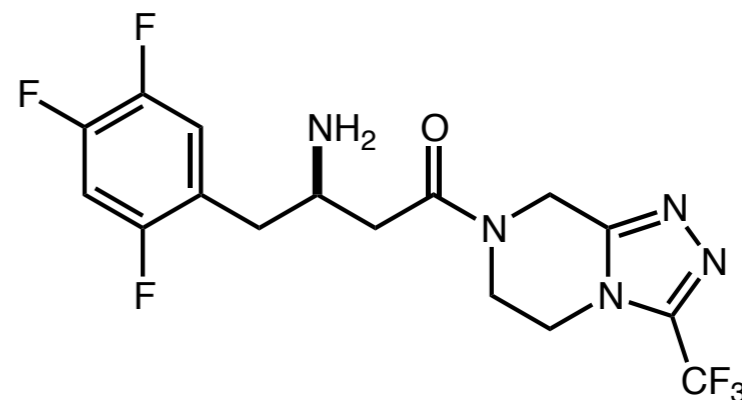
Disadvantages to using Liraglutide:

- GI irritation
- Antibodies produced (low amounts)

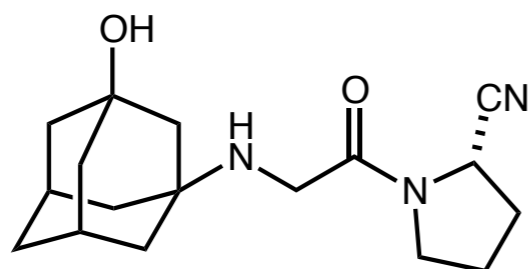
## DPP-4 Inhibitors



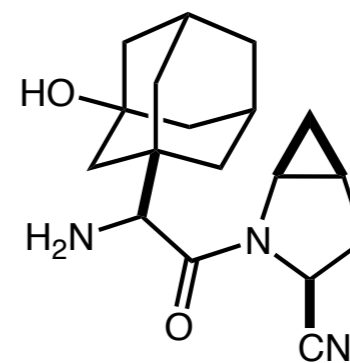
Linagliptin (Boehringer Ingelheim)



Sitagliptin (Merck)



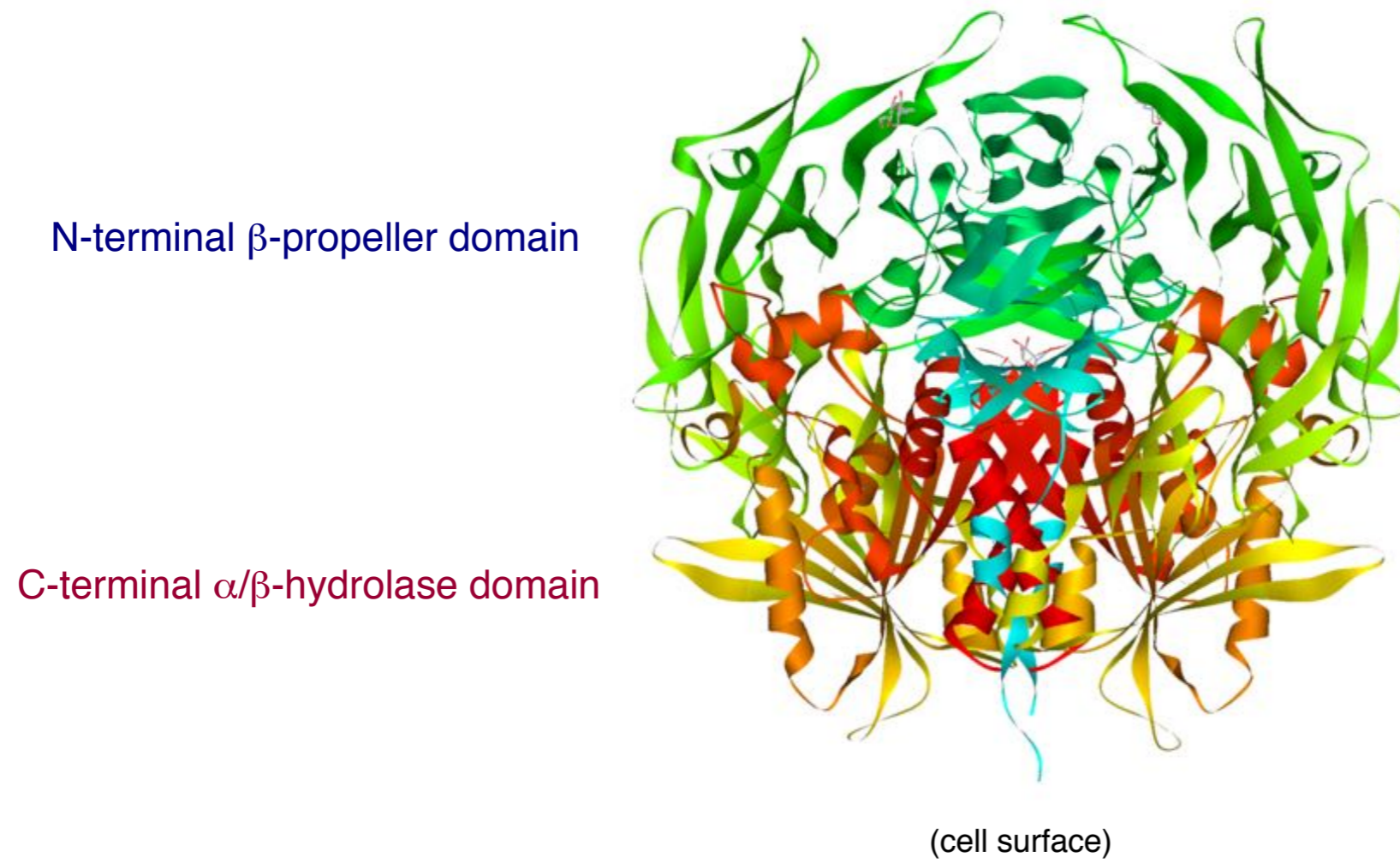
Vildagliptin (Novartis)



Saxagliptin  
(AstraZeneca and BMS)



# *DPP-4 Inhibitors*



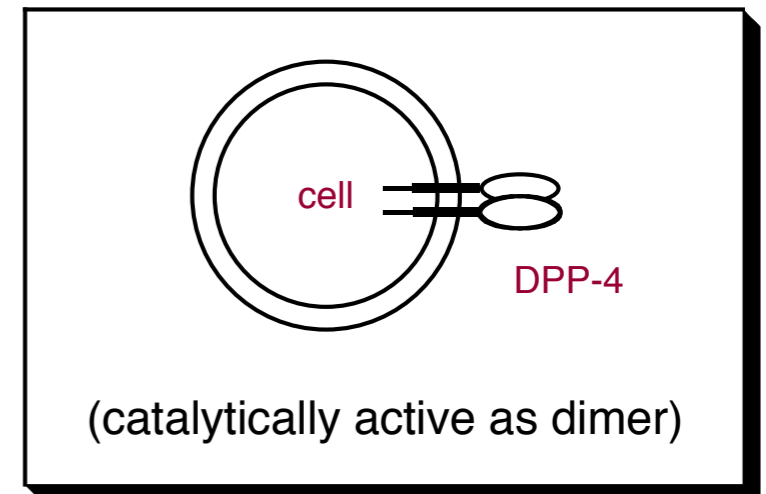
# DPP-4 Inhibitors

N-terminal  $\beta$ -propeller domain

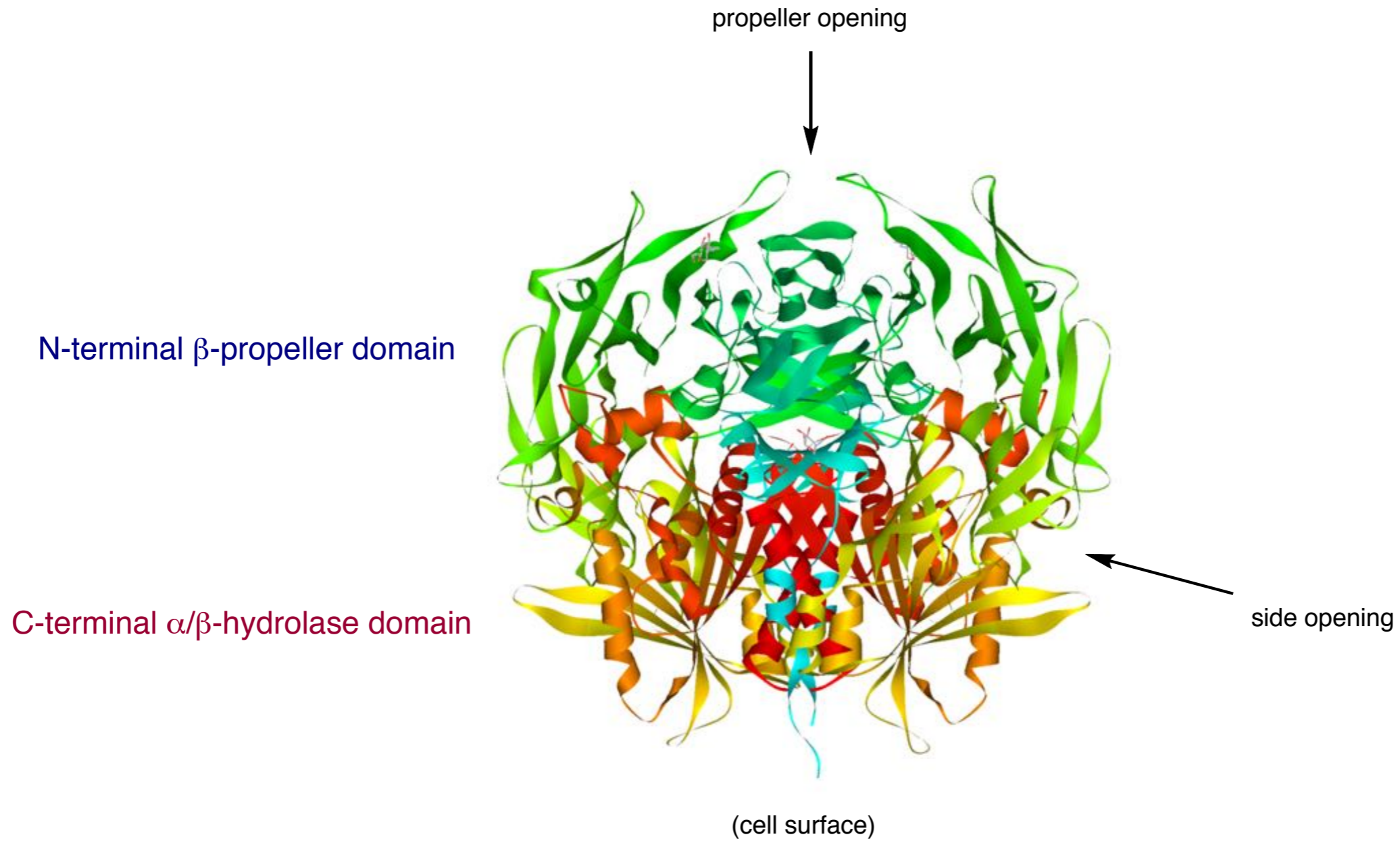
C-terminal  $\alpha/\beta$ -hydrolase domain



(cell surface)



# DPP-4 Inhibitors



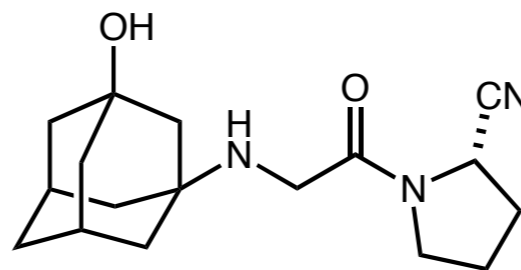
Active site at interface of domains (Ser, Asp, His catalytic triad)

Substrate access through propeller and side openings

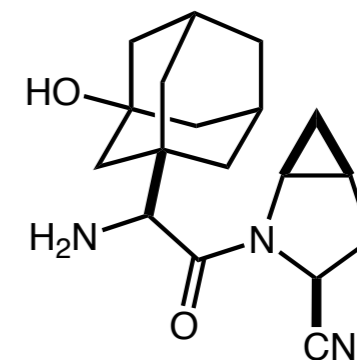


## DPP-4 Inhibitors

- Substrate-like inhibitors
  - Designed to mimic proline-containing peptide
  - More common than non-substrate-like inhibitors



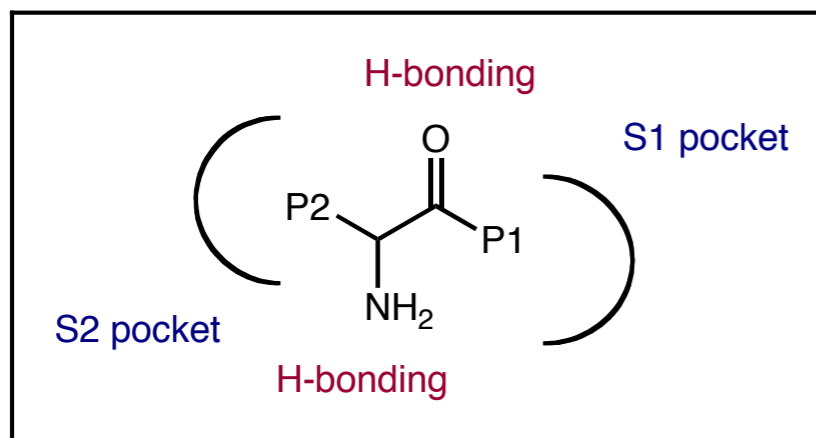
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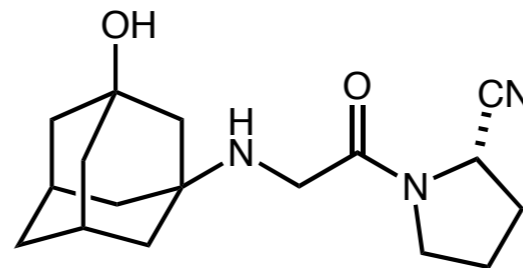
Saxagliptin  
(AstraZeneca and BMS)

# DPP-4 Inhibitors

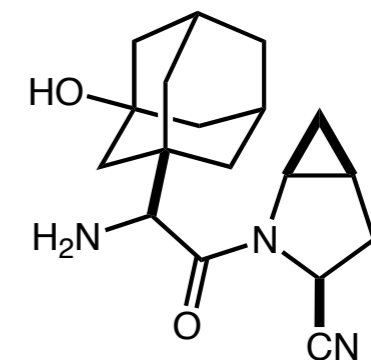
- Substrate-like inhibitors
  - Designed to mimic proline-containing peptide
  - More common than non-substrate-like inhibitors
  - Can bind either covalently or non-covalently
  - Covalent more common (nitrile, boronic acid, or phosphonate)



General binding for a substrate-like inhibitor

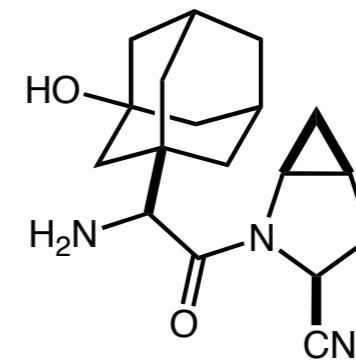
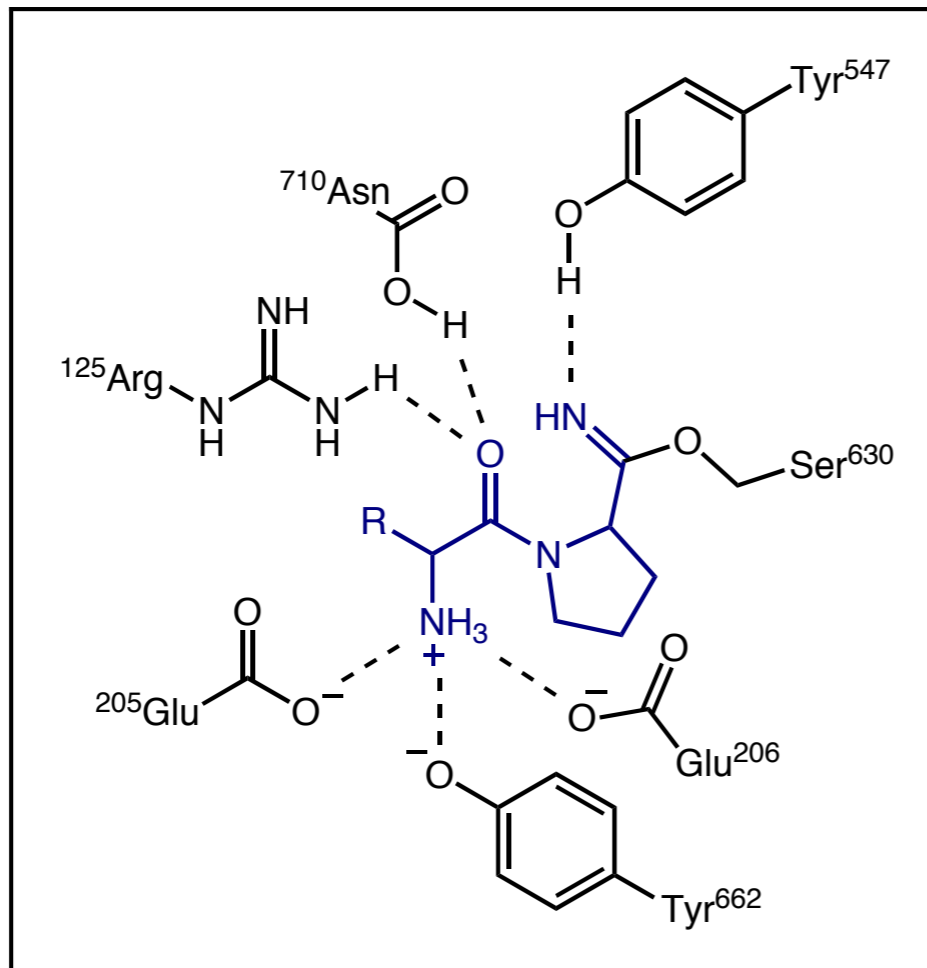


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(AstraZeneca and BMS)

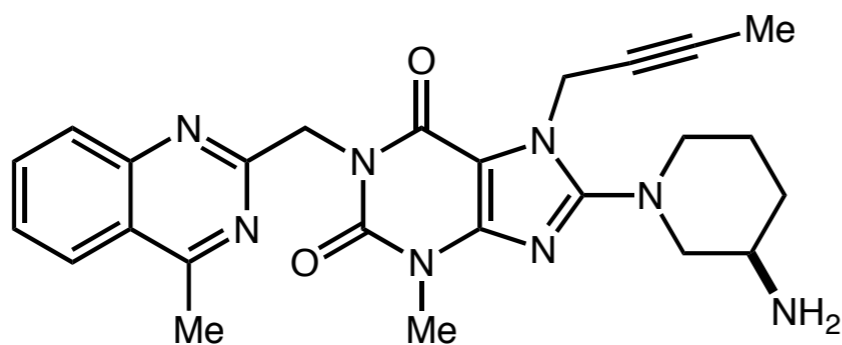
## DPP-4 Inhibitors



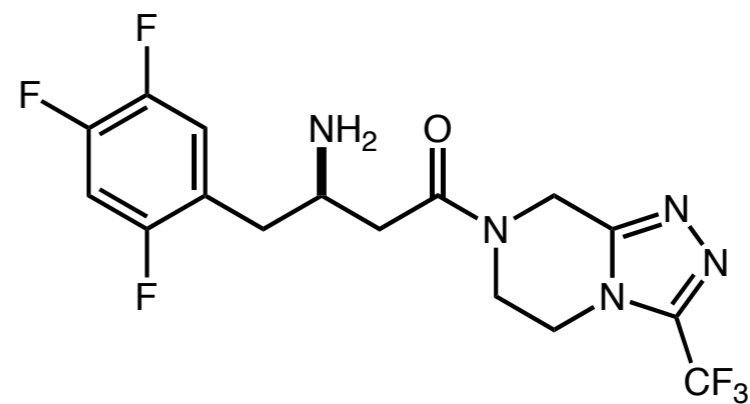
- Covalent binding with serine to form imidate
- H-bonding network to primary amine
- Slow off-rate leads to potent inhibitors
- R is generally large and lipophilic
- Substrate-like inhibitors can have poor selectivity (DPP-8 and DPP-9)

## DPP-4 Inhibitors

- Non-substrate-like inhibitors
  - Generally non-covalent binding
  - Aromatic ring usually occupies S1 pocket instead of pyrrolidine ring
  - Sitagliptin resulted from a search for >1000-fold selectivity for DPP-4



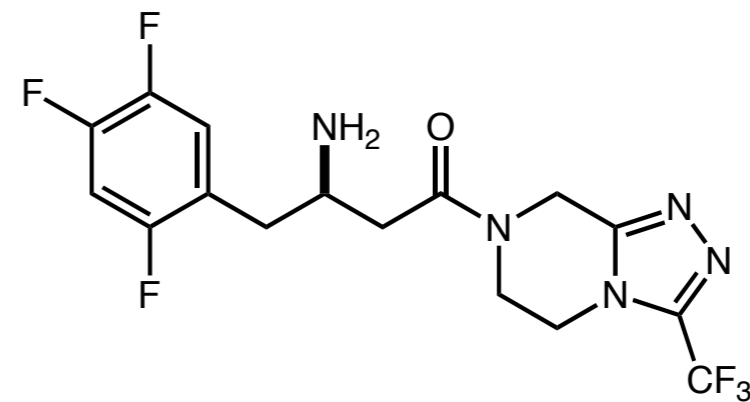
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Sitagliptin (Merck)

## DPP-4 Inhibitors

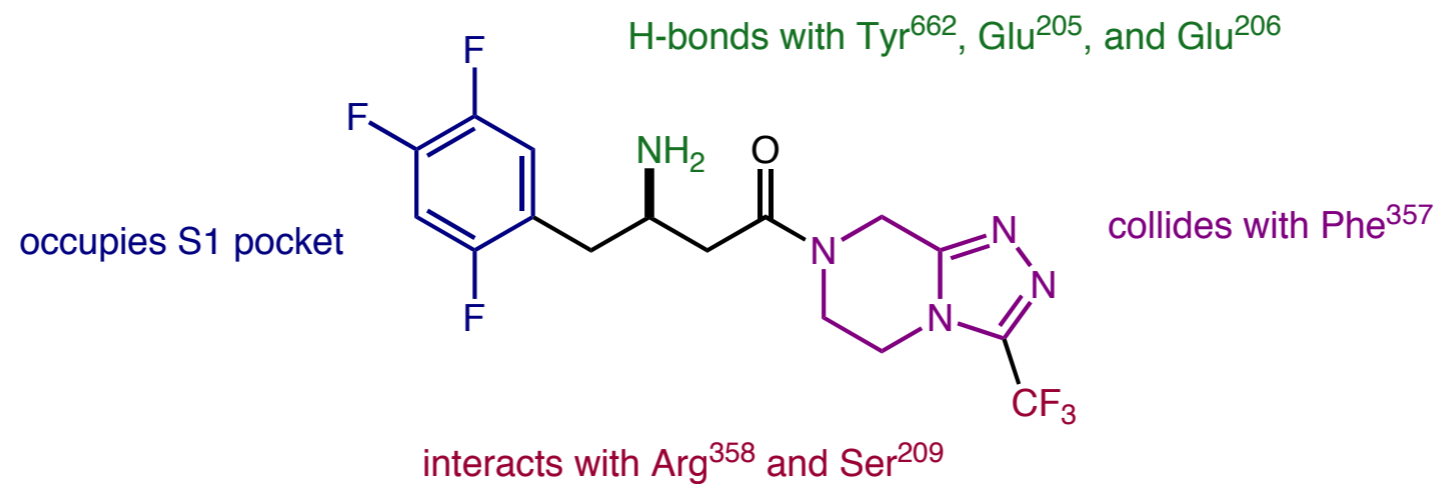
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    - Both DPP-4 and DPP-8 showed strong preference for proline dipeptides
    - Found  $\beta$ -amino acid piperazine series through SAR
    - Made piperazine into bicyclic moiety for stability



Sitagliptin (Merck)

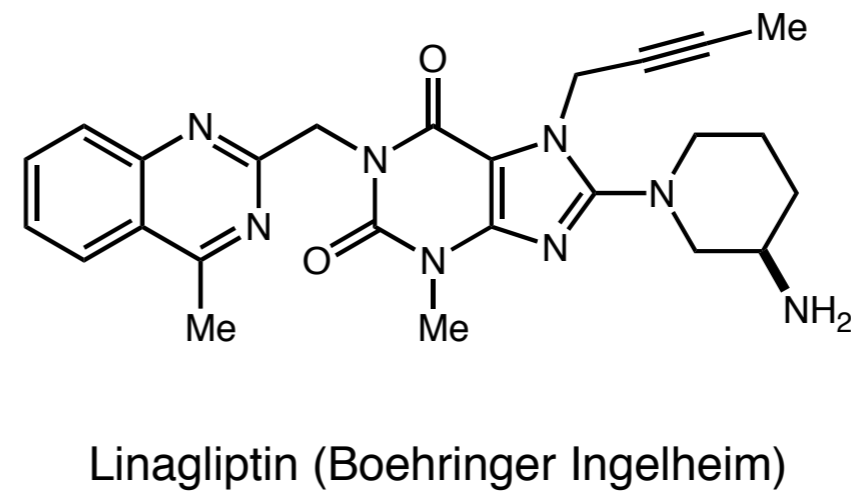
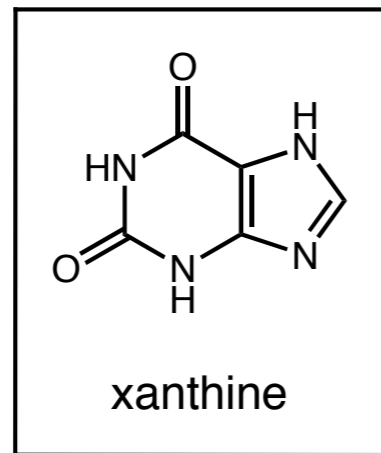
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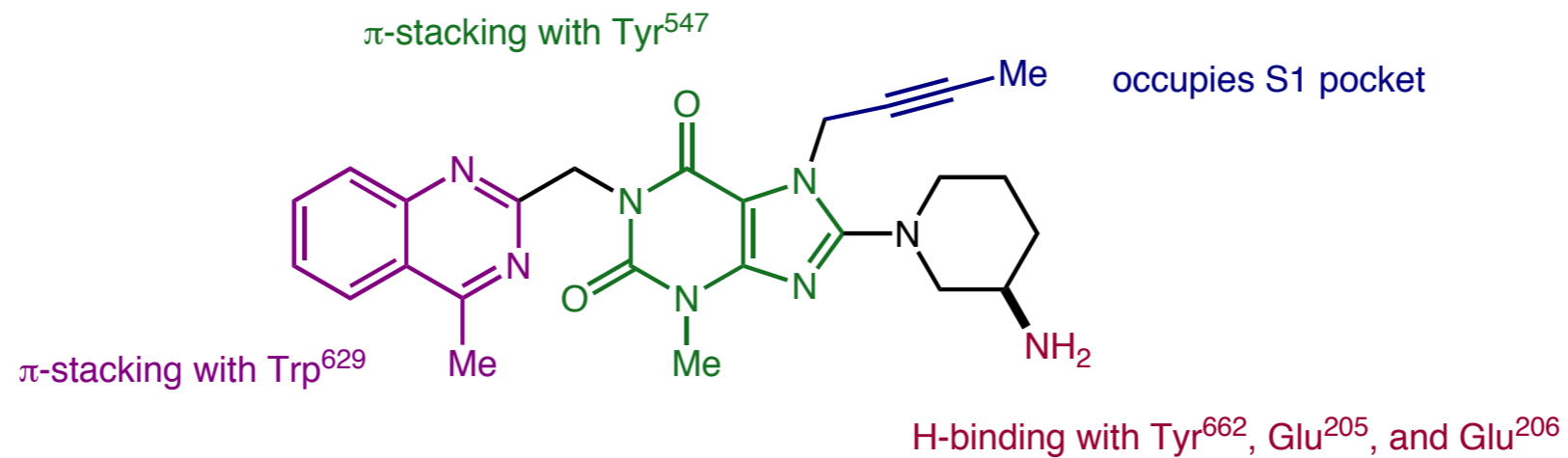
## DPP-4 Inhibitors

- Non-substrate-like inhibitors
  - Xanthine-based compounds believed to have longer-lasting improvements on glucose tolerance



# DPP-4 Inhibitors

- Non-substrate-like inhibitors
  - Xanthine-based compounds believed to have longer-lasting improvements on glucose tolerance
  - Different binding than other DPP-4 inhibitors





## *Diabetes Recap*

- T2DM results from insulin resistance with impaired  $\beta$ -cell function
- Insulin resistance from interruption of important signal transduction pathways
- Insulin analogues, GLP1R analogs, DPP-4 inhibitors
- Avoid hypoglycemia and restore  $\beta$ -cell function
- Best way to avoid, reverse effects of T2DM is to practice healthy lifestyle