

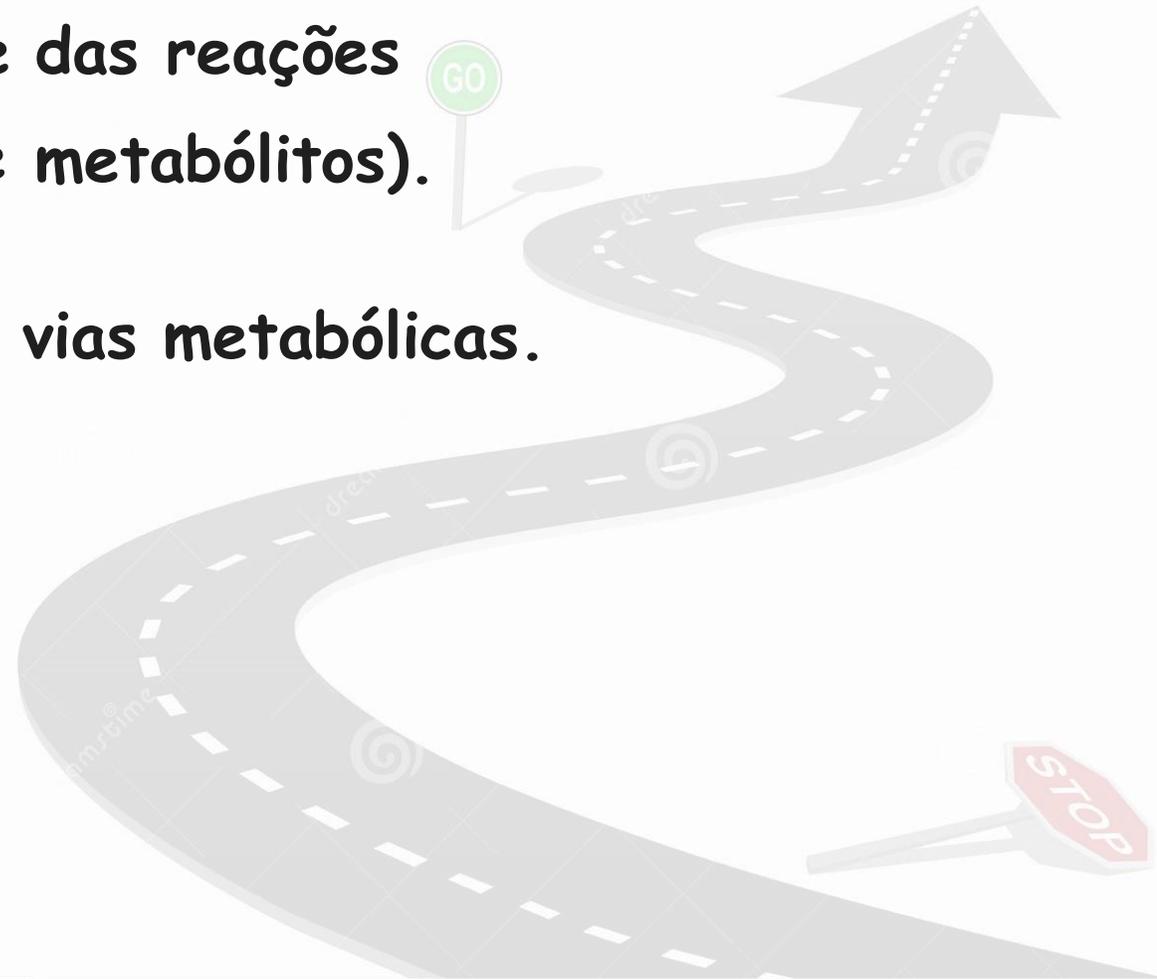
# Regulação Metabólica Geral



Interferência direta ou indireta nas reações químicas que compõe o metabolismo dos organismos vivos.

Atua aumentando ou diminuindo a velocidade das reações (aumento de enzimas, de substratos e/ou de metabólitos).

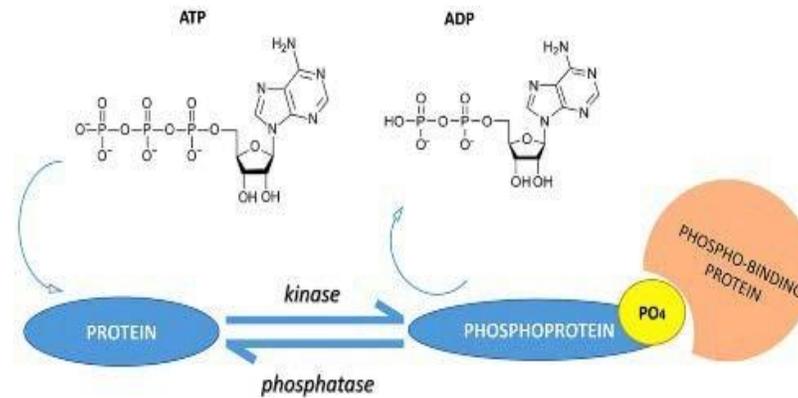
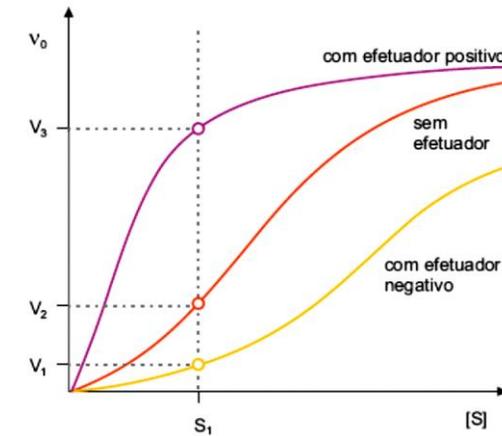
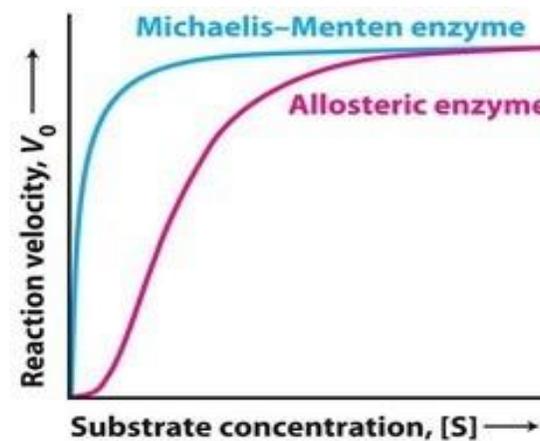
Efeitos propagados por todas as diferentes vias metabólicas.



# Estratégias de Regulação Metabólica

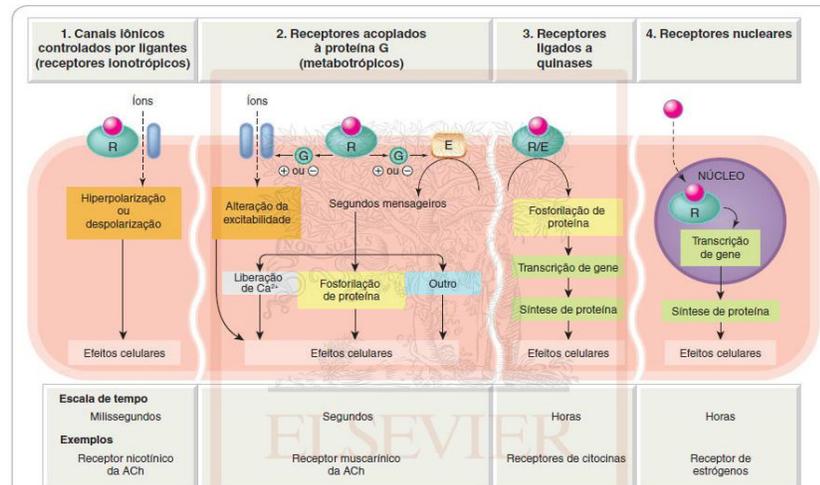
## Alterações das atividades enzimáticas []

### 1. Regulação alostérica



### 2. Modificações covalentes

### 3. Regulação hormonal



# Coenzimas são efetadores alostéricos importantes

**Tabela 19.1 Enzimas alostéricas e seus efetadores.**

Enzima	Efetadores alostéricos	
	Negativos	Positivos
Fosfofrutoquinase 1	ATP, Citrato	AMP, Frutose 2,6-bisfosfato
Frutose 1,6-bisfosfatase	Frutose 2,6-bisfosfato	
6-Fosfofruto-2-quinase	Fosfoenolpiruvato	
Frutose 2,6-bisfosfatase	Frutose 6-fosfato	Fosfoenolpiruvato
Piruvato quinase	Alanina	Frutose 1,6-bisfosfato
Piruvato carboxilase		Acetil-CoA
Piruvato desidrogenase	Acetil-CoA, NADH	Piruvato
Isocitrato desidrogenase	NADH	ADP
$\alpha$ -Cetoglutarato desidrogenase	Succinil-CoA, NADH, ATP	
Camitina acil transferase I	Malonil-CoA	
Citrato liase	Acil-CoA	
Acetil-CoA carboxilase	Acil-CoA	Citrato

# A modificação covalente regula a atividade das enzimas

**Tabela 19.2 Modificação da atividade enzimática por fosforilação.**

<b>Via metabólica</b>	<b>Enzima fosforilada</b>	<b>Forma</b>
Glicogenólise	Glicogênio fosforilase quinase	Ativa
Glicogênese	Glicogênio fosforilase	Ativa
	Glicogênio sintase	Inativa
Glicólise e gliconeogênese	6-Fosfofruto-2-quinase	Inativa
	Frutose 2,6-bisfosfatase	Ativa
	Piruvato quinase	Inativa
Piruvato → Acetil-CoA	Piruvato desidrogenase	Inativa
Lipólise	Lipase	Ativa
Lipogênese	Citrato liase	Inativa
	Acetil-CoA carboxilase	Inativa
	3-Hidroxi-3-metilglutaril-CoA redutase	Inativa

## A ação hormonal regula a atividade das enzimas

**Tabela 19.3** Efeitos metabólicos de adrenalina, insulina e glucagon.

	<b>Adrenalina</b>	<b>Glucagon</b>	<b>Insulina</b>
Glicemia	↑	↑	↓
Glicólise	–	↓	↑
Gliconeogênese	↑	↑	↓
Glicogenólise	↑	↑	↓
Glicogenogênese	–	↓	↑
Lipólise	↑	↑	↓
Lipogênese	–	↓	↑
Cetogênese	–	↑	↓

↑ = glicemia ou velocidade da via aumentada; ↓ = glicemia ou velocidade da via diminuída.



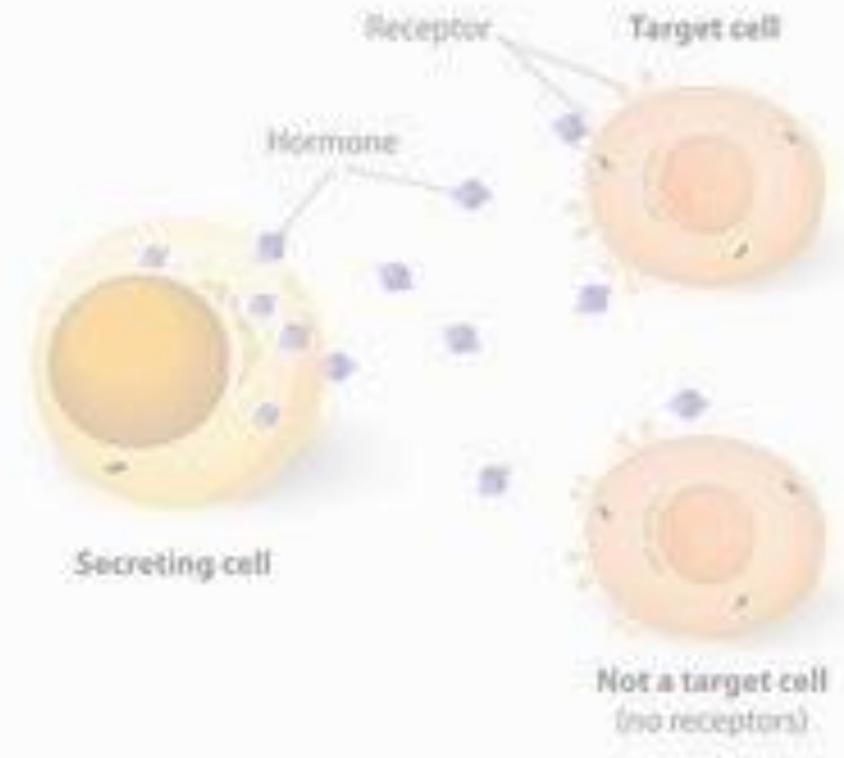
# O que são hormônios?

<https://youtu.be/-SPRPkLoKp8>

<https://www.youtube.com/watch?v=NSIxpnkdaU8>

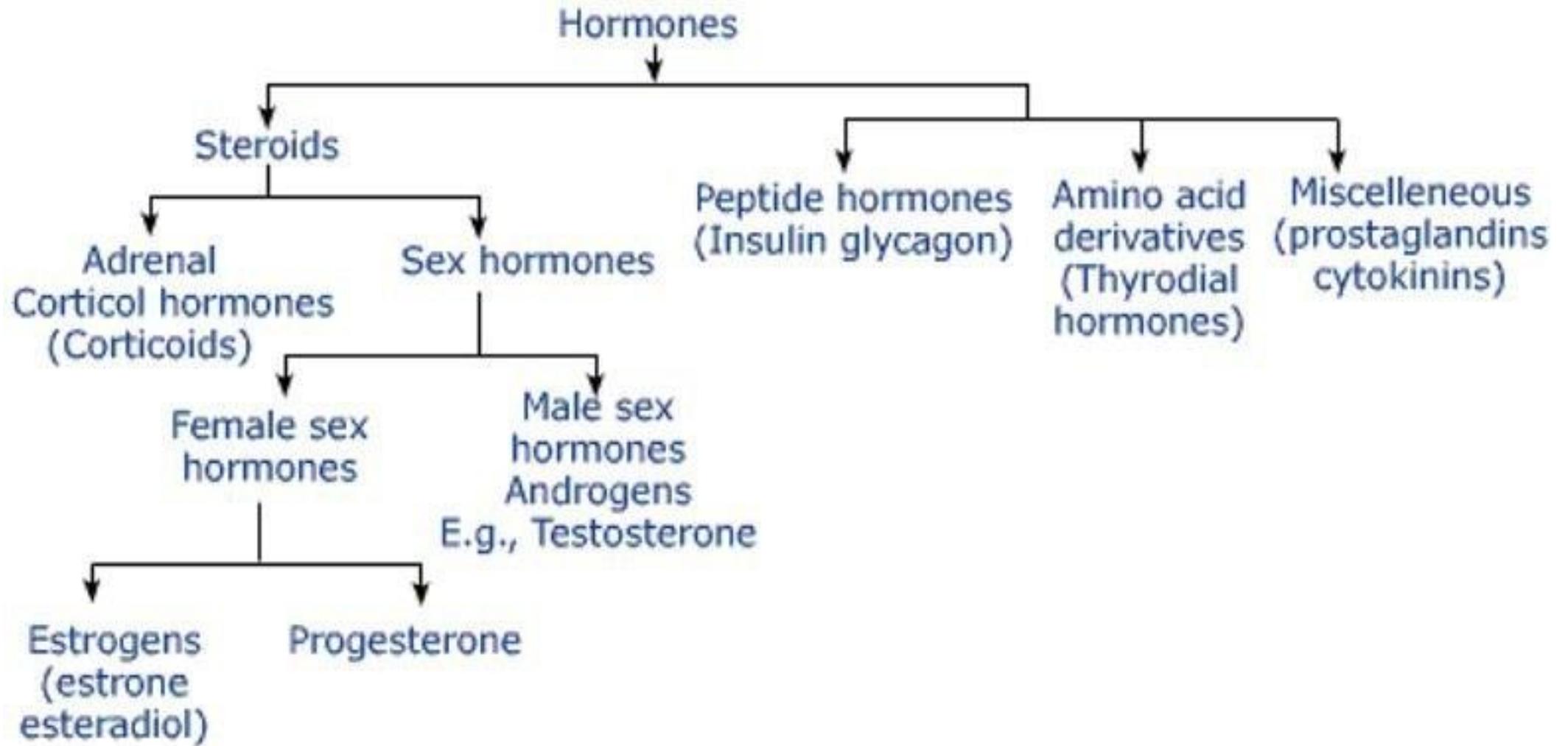
# Hormônios

- Biomoléculas produzidas em uma determinada parte do corpo que regulam funções a distância
- Agem em baixas quantidades/concentrações
- Essenciais para a homeostase de organismos multicelulares
- Agem por meio de receptores específicos nas células-alvo

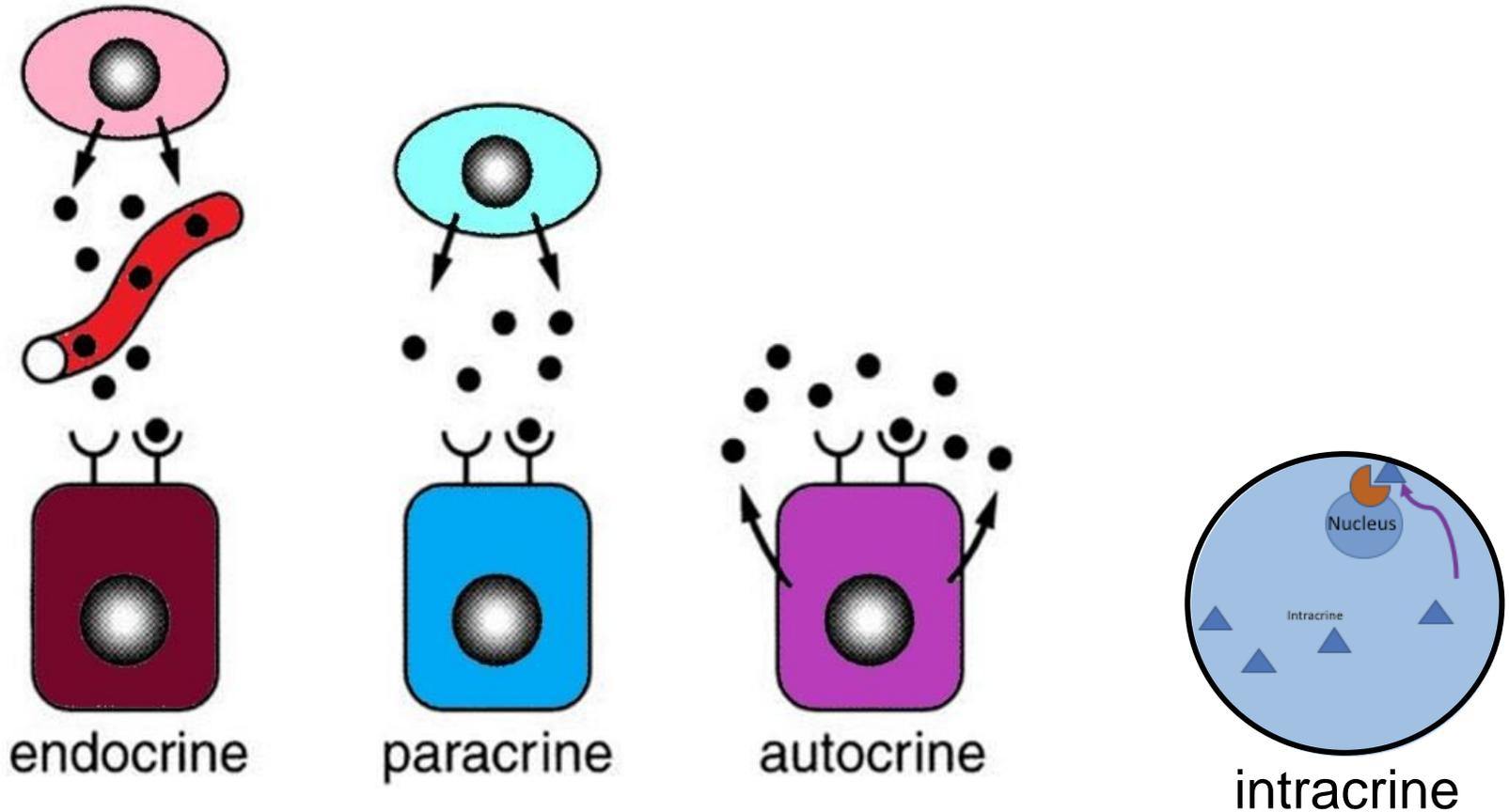


## Regulação

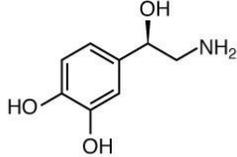
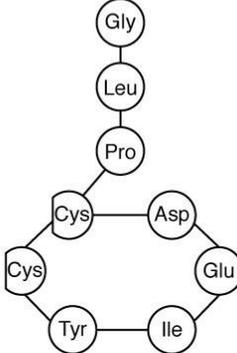
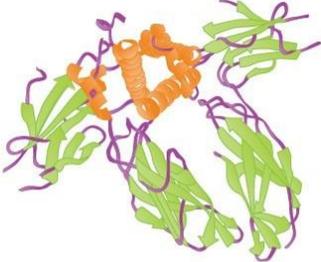
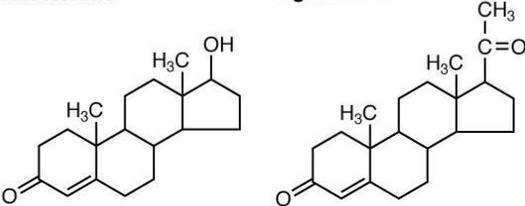
Biossíntese → Estocagem → Secreção → Transporte →  
Reconhecimento → Resposta Celular → Degradação



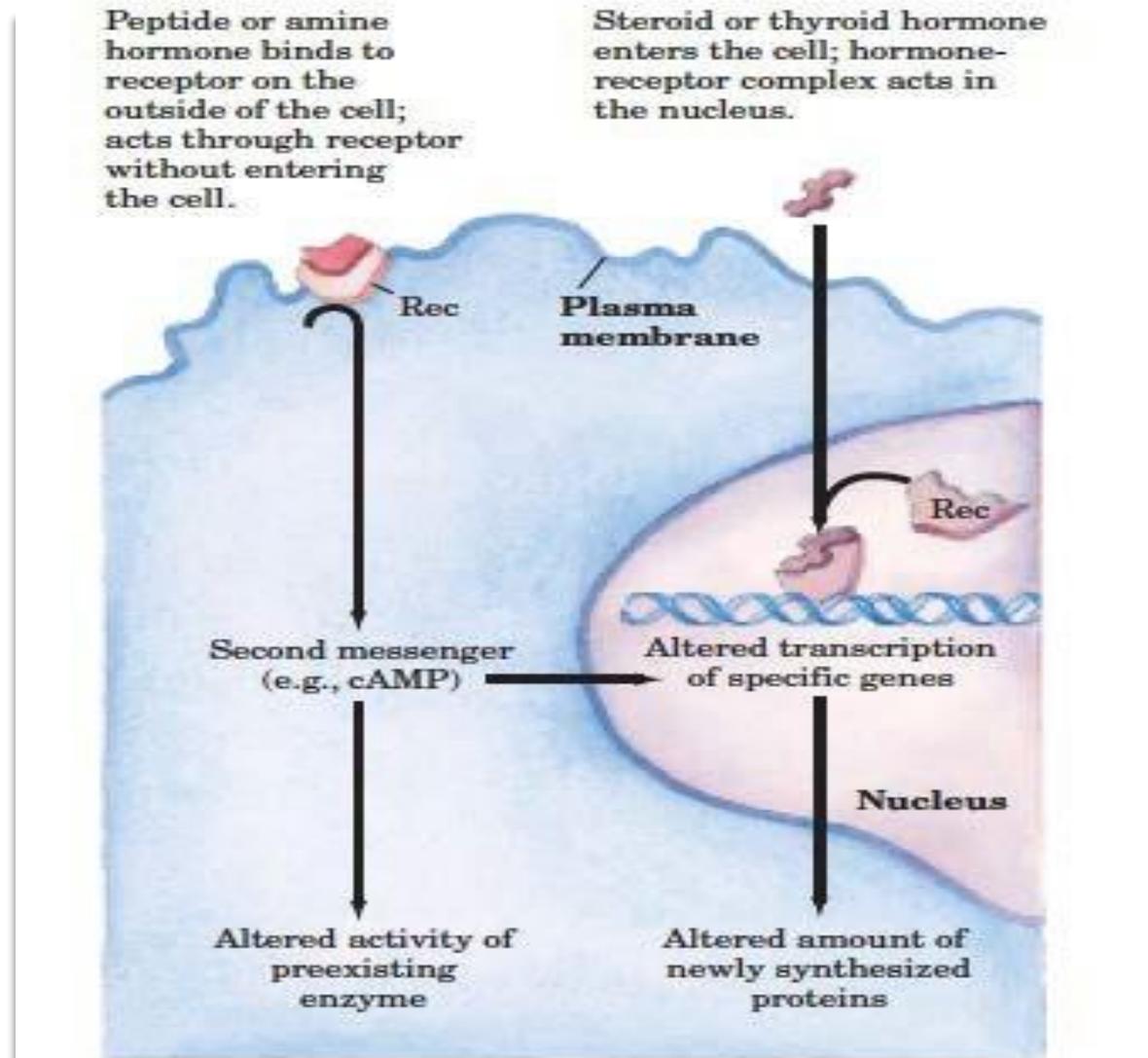
Hormônios podem ser classificados pela maneira na qual são transportados de uma célula para outra e pela atuação sobre seus alvos



# Hormônios podem ser classificados de acordo com sua estrutura química

Hormone Class	Components	Example(s)
<b>Amine Hormone</b>	Amino acids with modified groups (e.g. norepinephrine's carboxyl group is replaced with a benzene ring)	<p><b>Norepinephrine</b></p> 
<b>Peptide Hormone</b>	Short chains of linked amino acids	<p><b>Oxytocin</b></p> 
<b>Protein Hormone</b>	Long chains of linked amino acids	<p><b>Human Growth Hormone</b></p> 
<b>Steroid Hormones</b>	Derived from the lipid cholesterol	<p><b>Testosterone</b>      <b>Progesterone</b></p> 

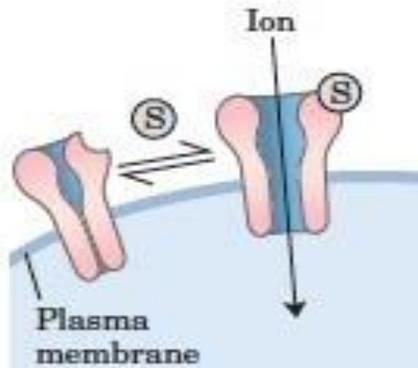
# Todos os hormônios agem através de receptores de alta afinidade



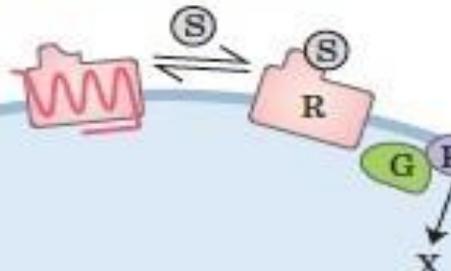
**FIGURE 23-4** Two general mechanisms of hormone action. The peptide and amine hormones are faster acting than steroid and thyroid hormones.

# Tipos de transdutores de sinais hormonais

**Gated ion channel**  
Opens or closes in response to concentration of signal ligand (S) or membrane potential.



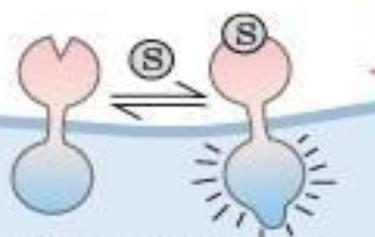
**Serpentine receptor**  
External ligand binding to receptor (R) activates an intracellular GTP-binding protein (G), which regulates an enzyme (Enz) that generates an intracellular second messenger, X.



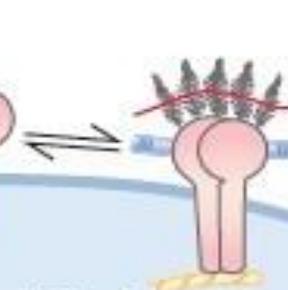
**Receptor with no intrinsic enzyme activity**  
Interacts with cytosolic protein kinase, which activates a gene-regulating protein (directly or through a cascade of protein kinases), changing gene expression.



**Receptor enzyme**  
Ligand binding to extracellular domain stimulates enzyme activity in intracellular domain.



**Adhesion receptor**  
Binds molecules in extracellular matrix, changes conformation, thus altering its interaction with cytoskeleton.



**Steroid receptor**  
Steroid binding to a nuclear receptor protein allows the receptor to regulate the expression of specific genes.

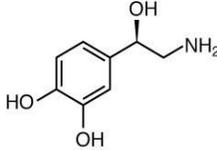
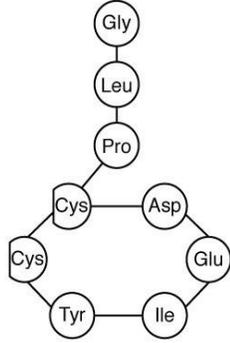
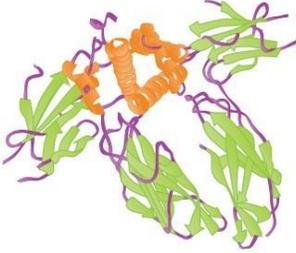
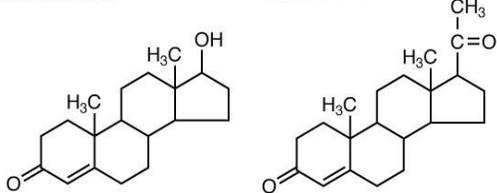


**Kinase cascade**  
A series of protein kinases that activate each other in a sequence, leading to the activation of a gene-regulating protein.

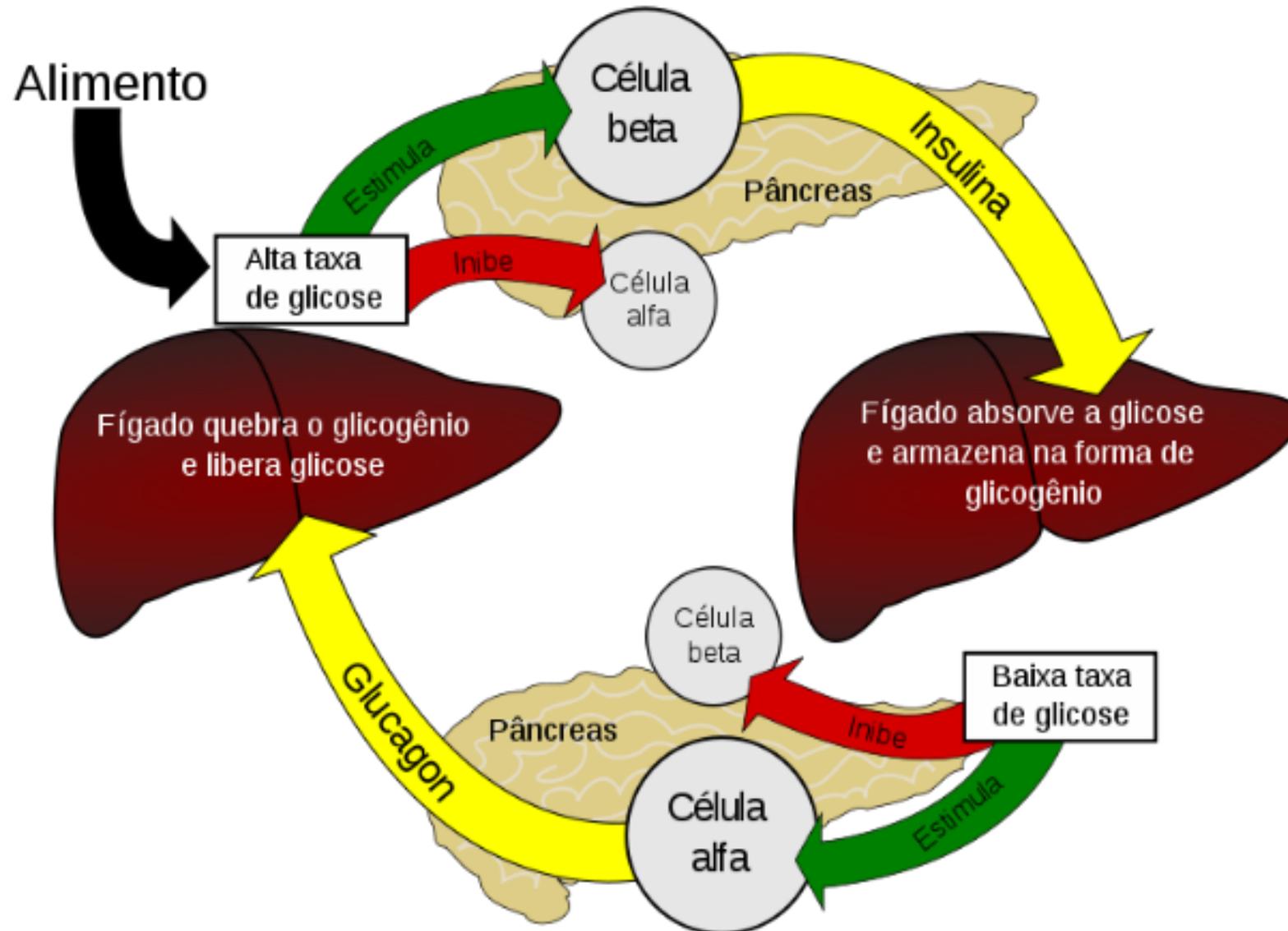


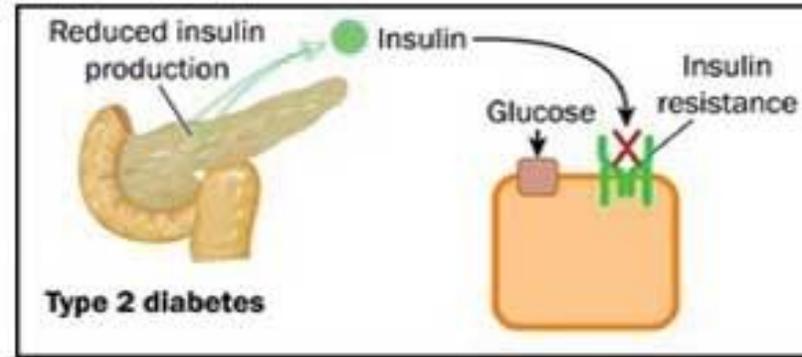
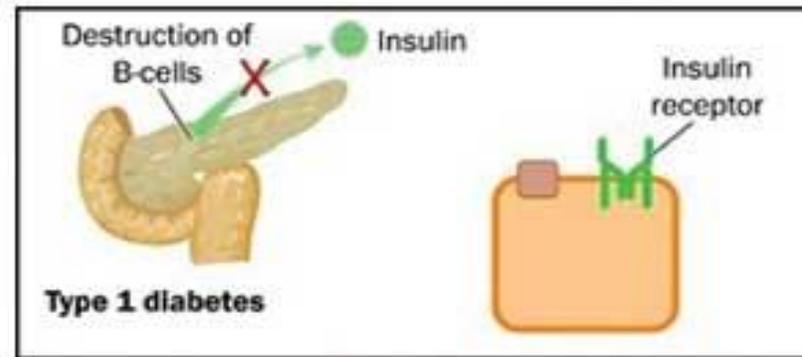
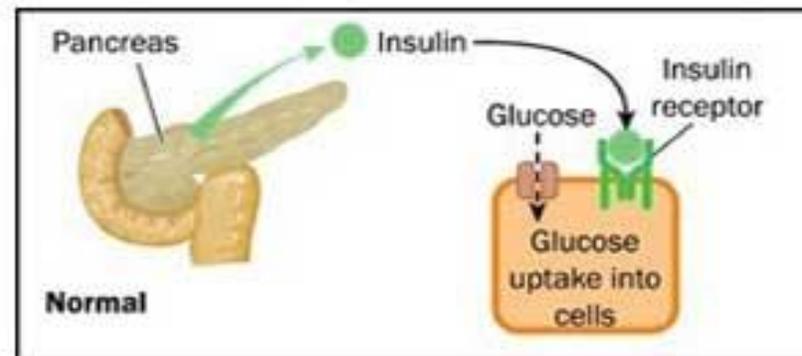
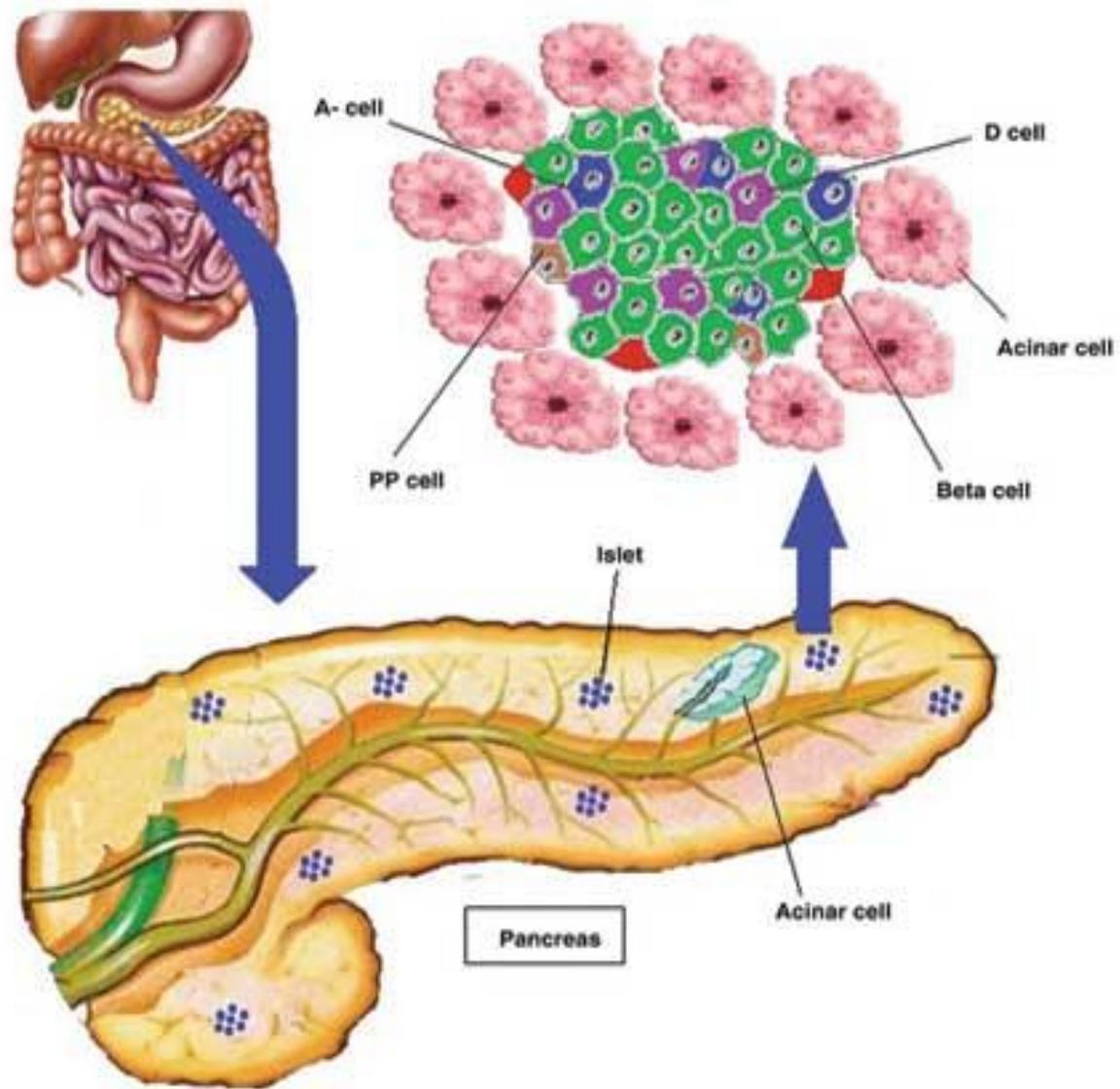
FIGURE 12-2 Six general types of signal transducers.

# Hormônios Peptídicos

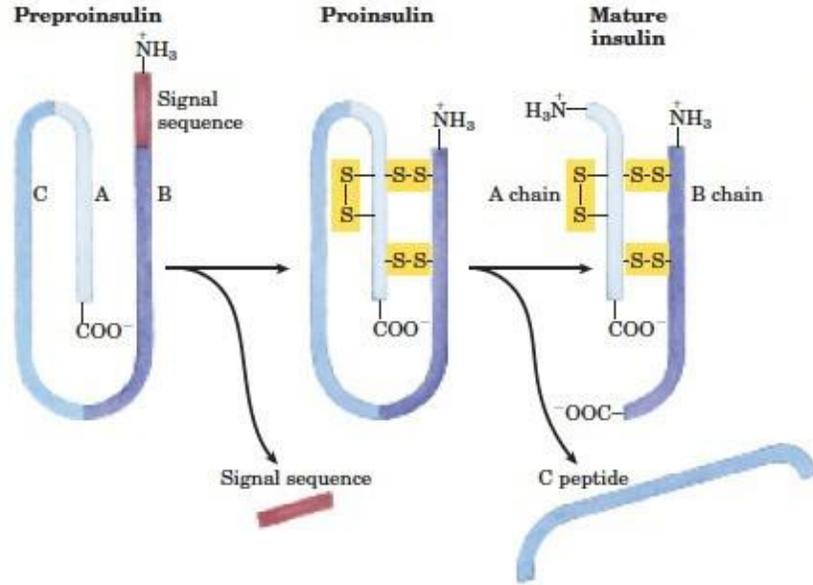
Hormone Class	Components	Example(s)
<b>Amine Hormone</b>	Amino acids with modified groups (e.g. norepinephrine's carboxyl group is replaced with a benzene ring)	<p><b>Norepinephrine</b></p> 
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<b>Steroid Hormones</b>	Derived from the lipid cholesterol	<p><b>Testosterone</b>      <b>Progesterone</b></p> 

# Insulina e Glucagon

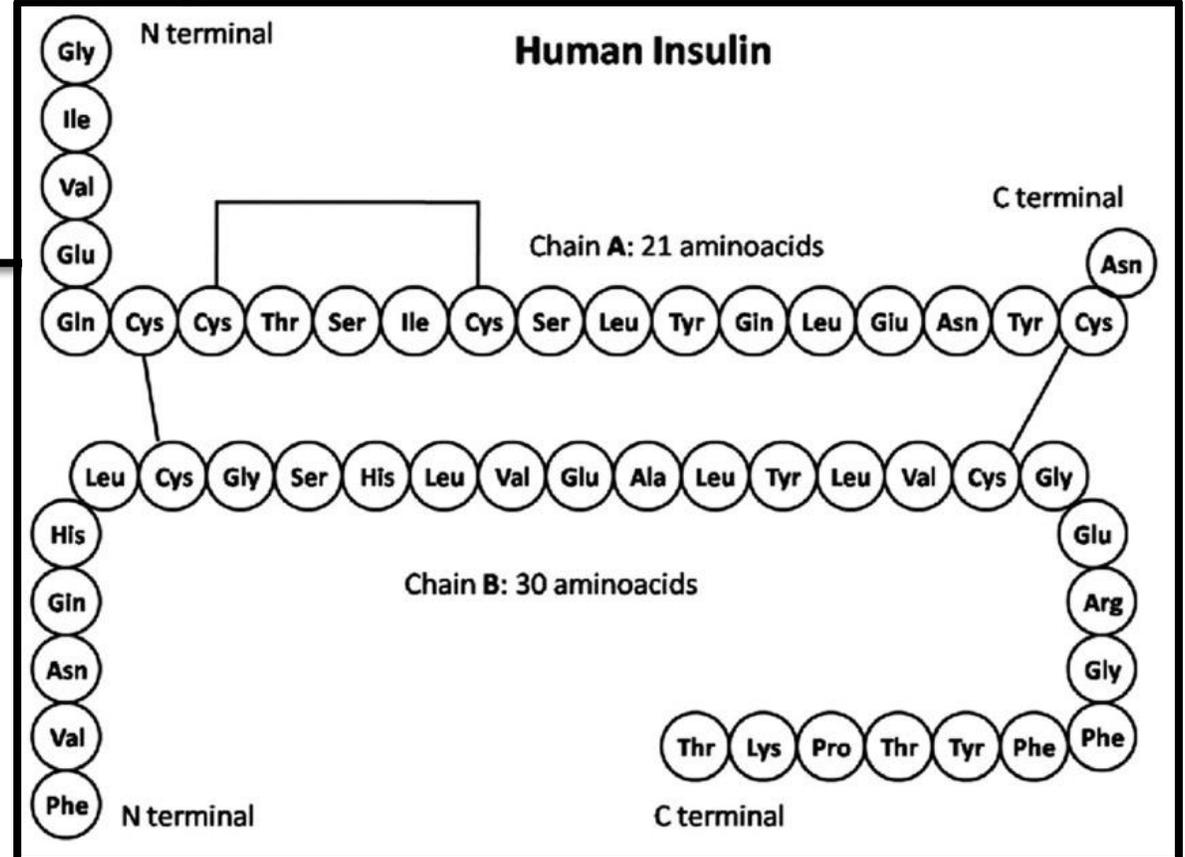




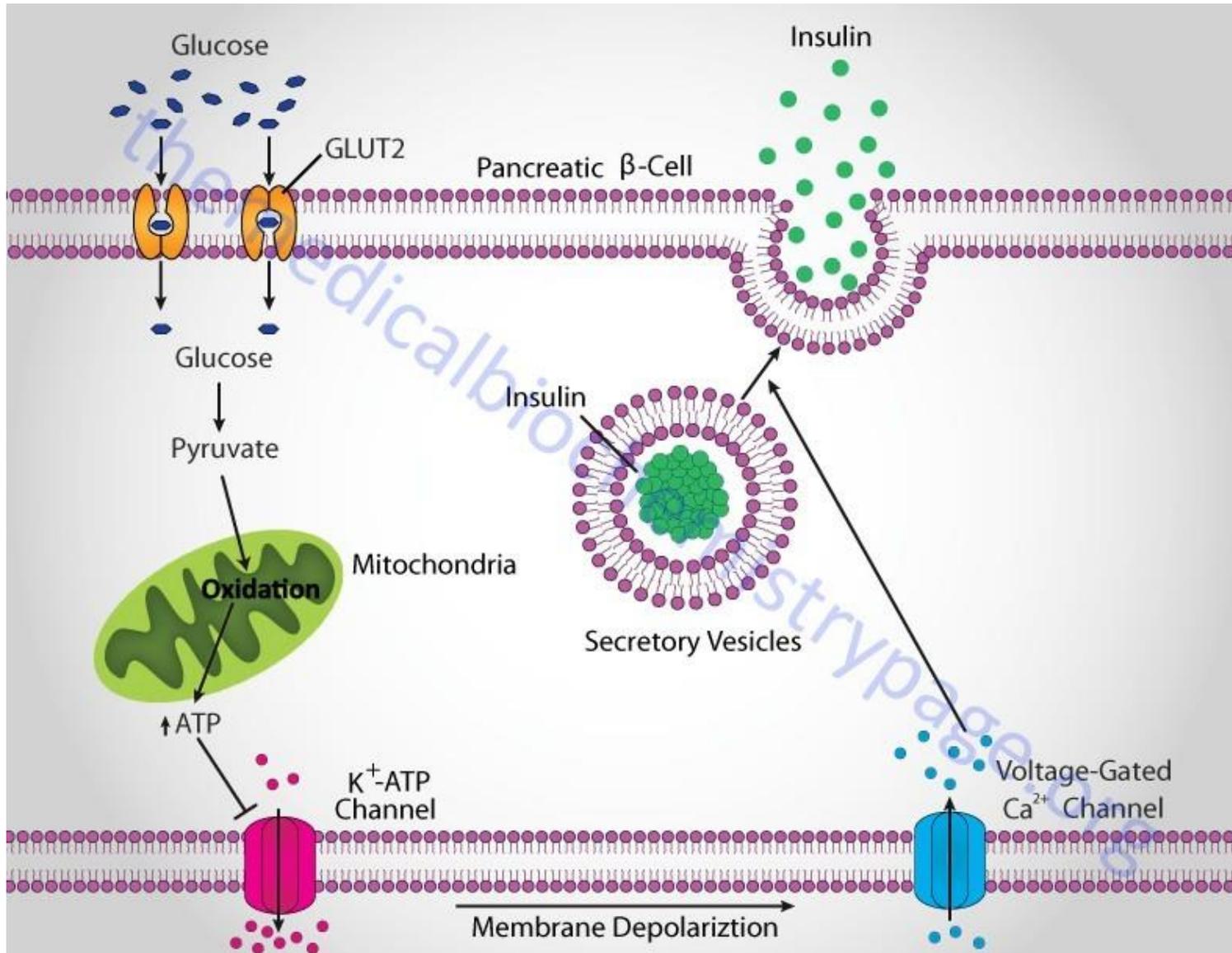
# Hormônios peptídicos/protéicos sofrem processamento pós-traducional



**FIGURE 23-5 Insulin.** Mature insulin is formed from its larger precursor preproinsulin by proteolytic processing. Removal of a 23 amino acid segment (the signal sequence) at the amino terminus of preproinsulin and formation of three disulfide bonds produces proinsulin. Further proteolytic cuts remove the C peptide from proinsulin to produce mature insulin, composed of A and B chains. The amino acid sequence of bovine insulin is shown in Figure 3-24.

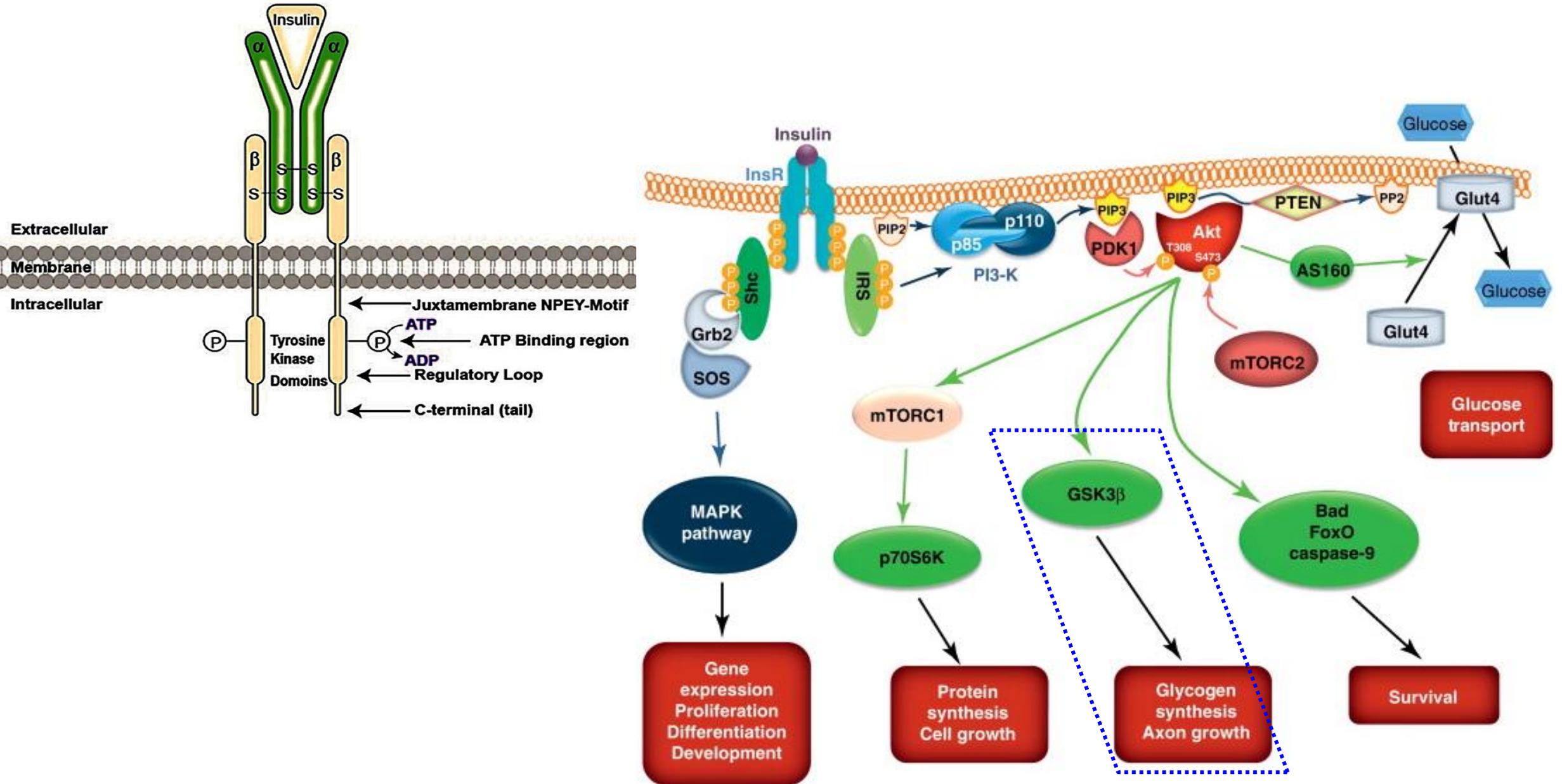


# Regulação da Secreção da Insulina



- Células  $\beta$  possuem GLUT2
- Células  $\beta$  possuem glicoquinase
- $\uparrow$  glicemia =  $\uparrow$  ATP
- ATP inibe canais para  $K^+$
- Despolarização
- Ativação da entrada de  $Ca^{2+}$
- Secreção de insulina
- Síntese de insulina

# Ações moleculares hormonais da insulina no metabolismo



# Insulina nas vias de síntese e degradação de glicogênio

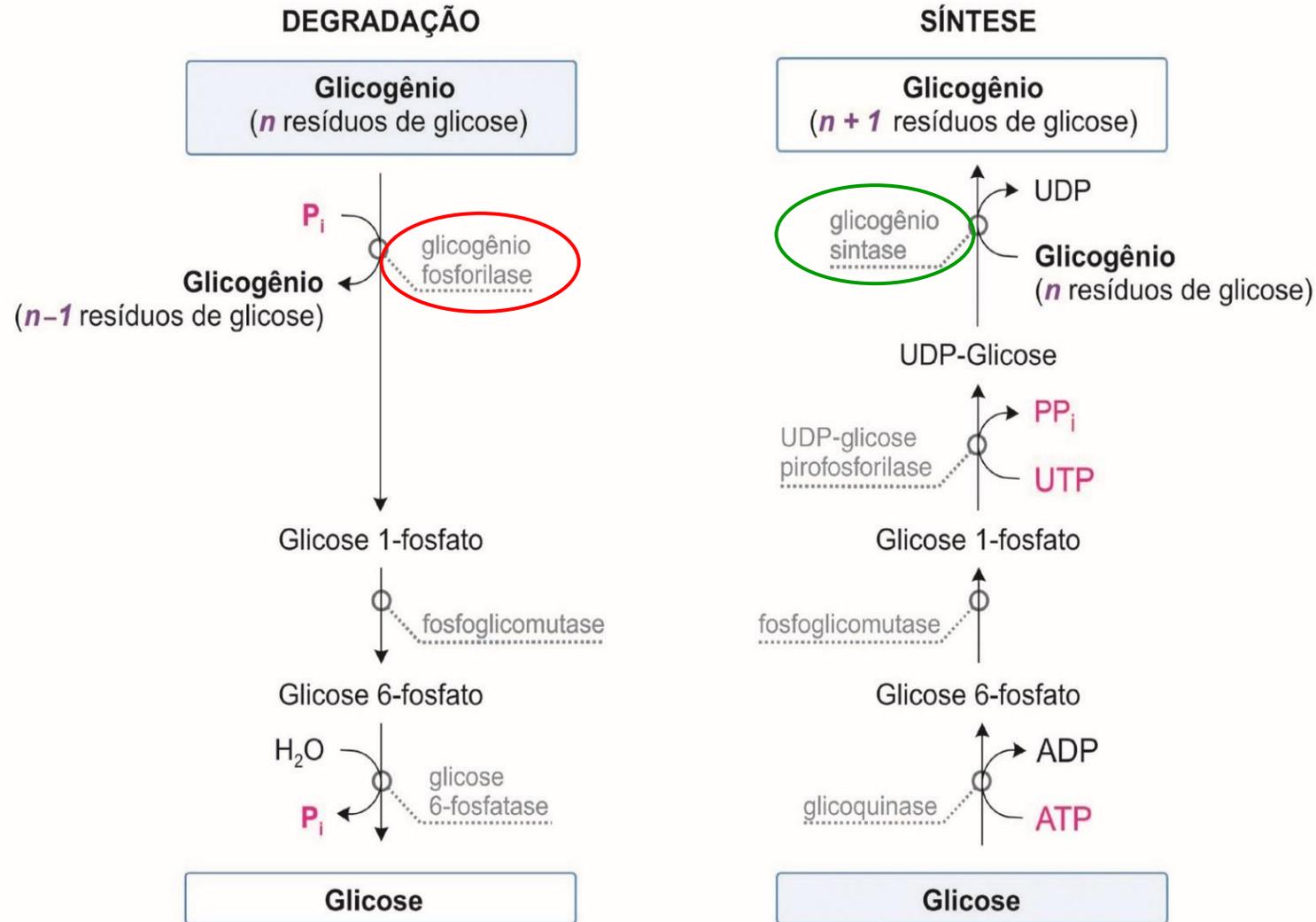
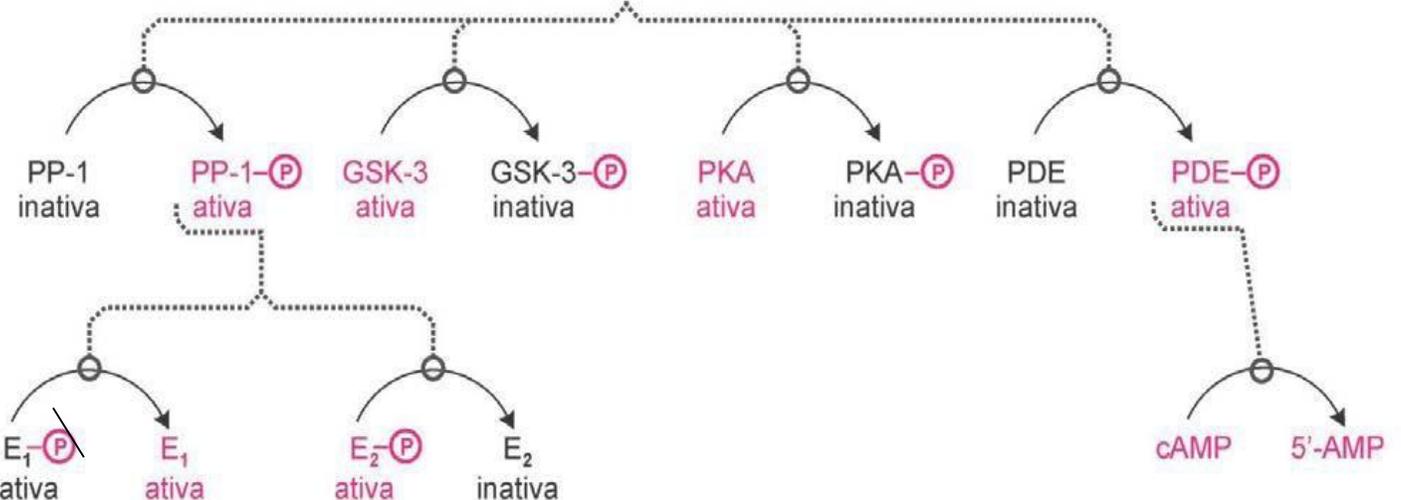
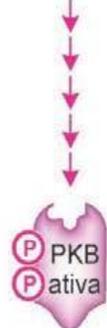


Fig. 13.5 Esquema geral da degradação e síntese de glicogênio no fígado.

# Regulação do metabolismo do glicogênio pela Insulina

Insulina

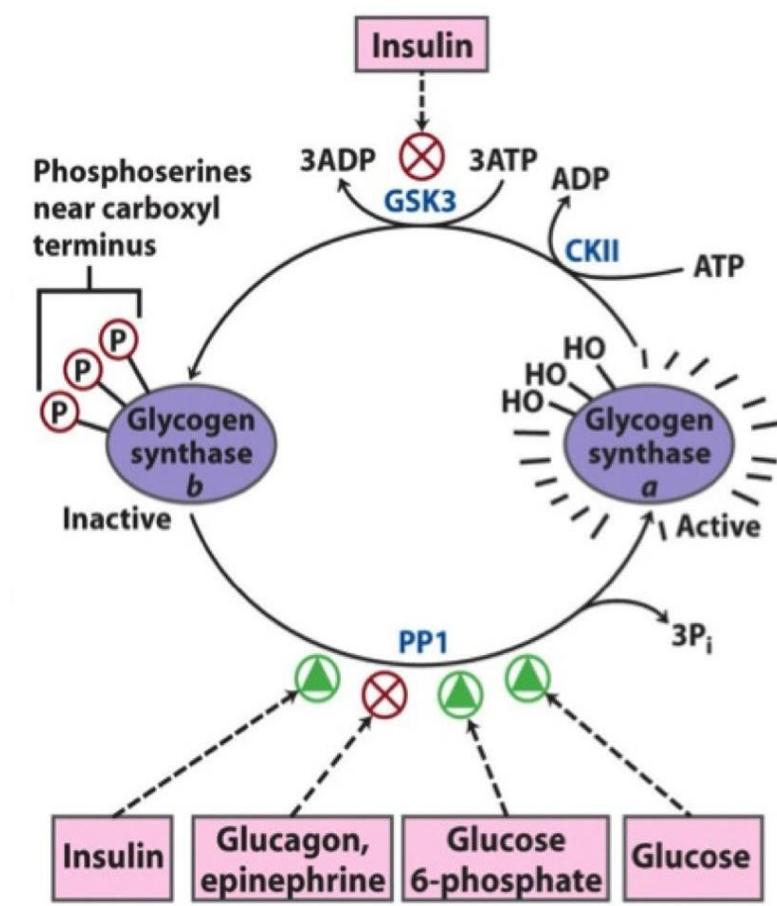


Fosfatase PP1

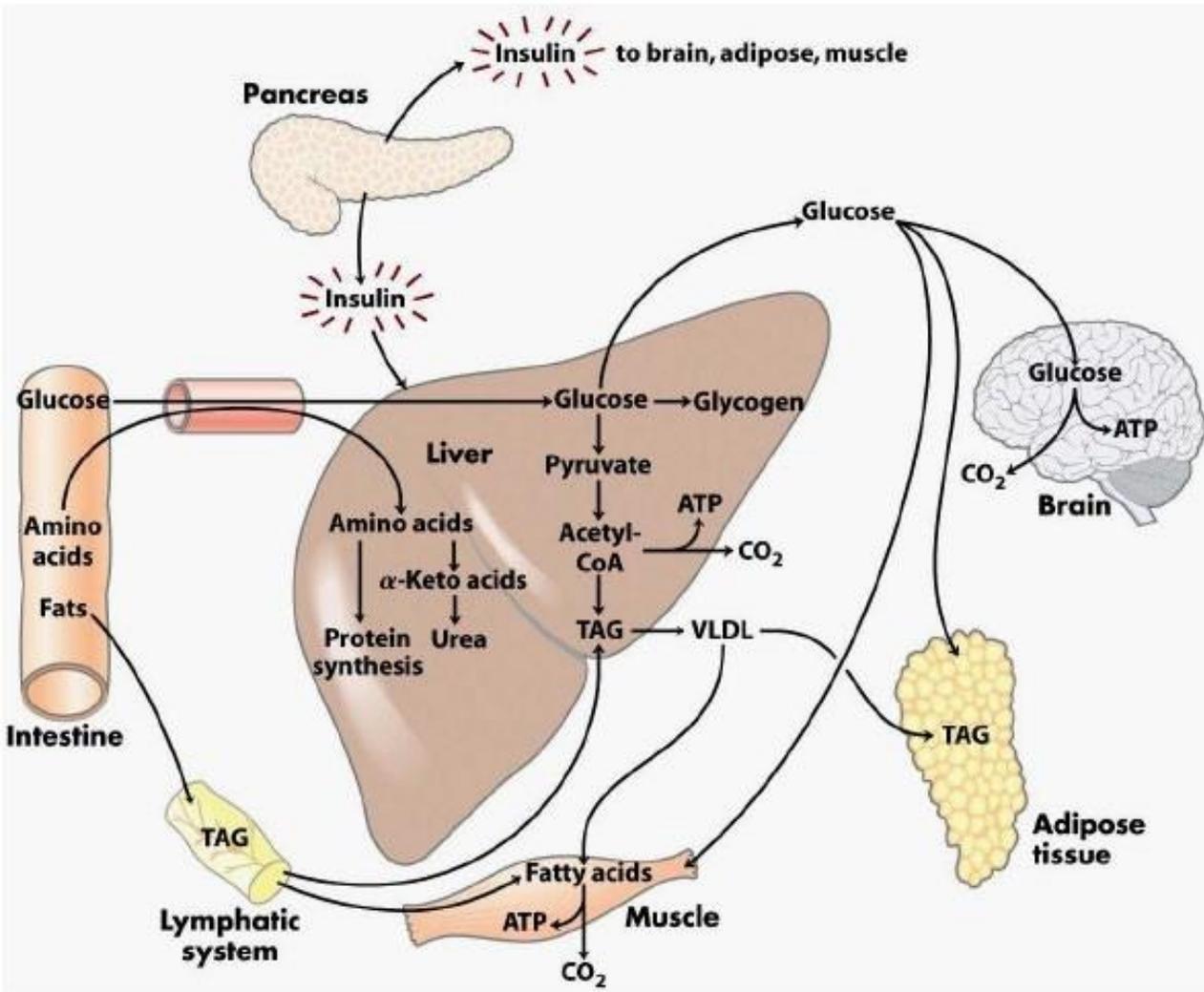
Glicogênio sintase      Glicogênio fosforilase

Estímulo da glicogênese

Inibição da glicogenólise



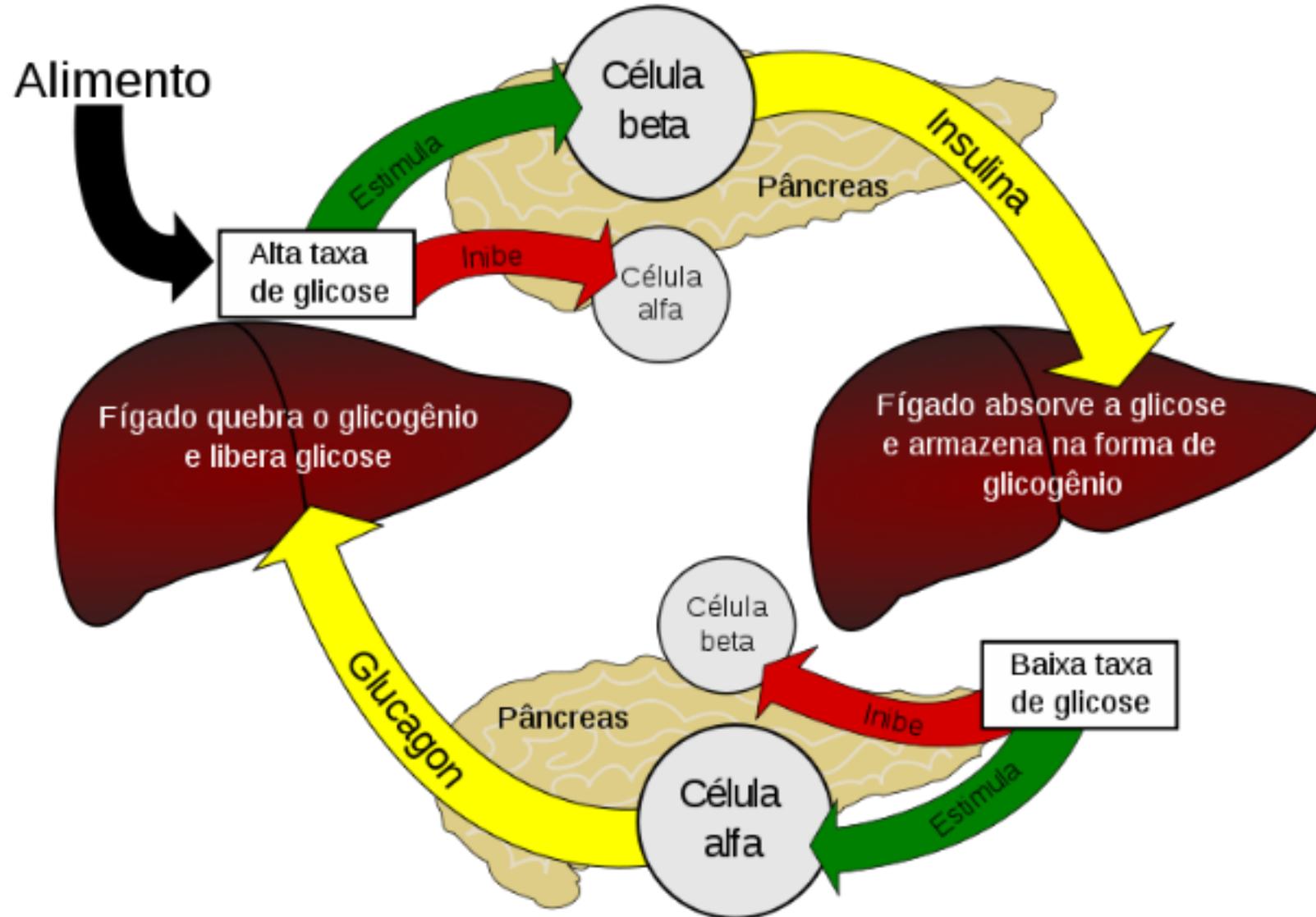
# Regulação do metabolismo pela Insulina



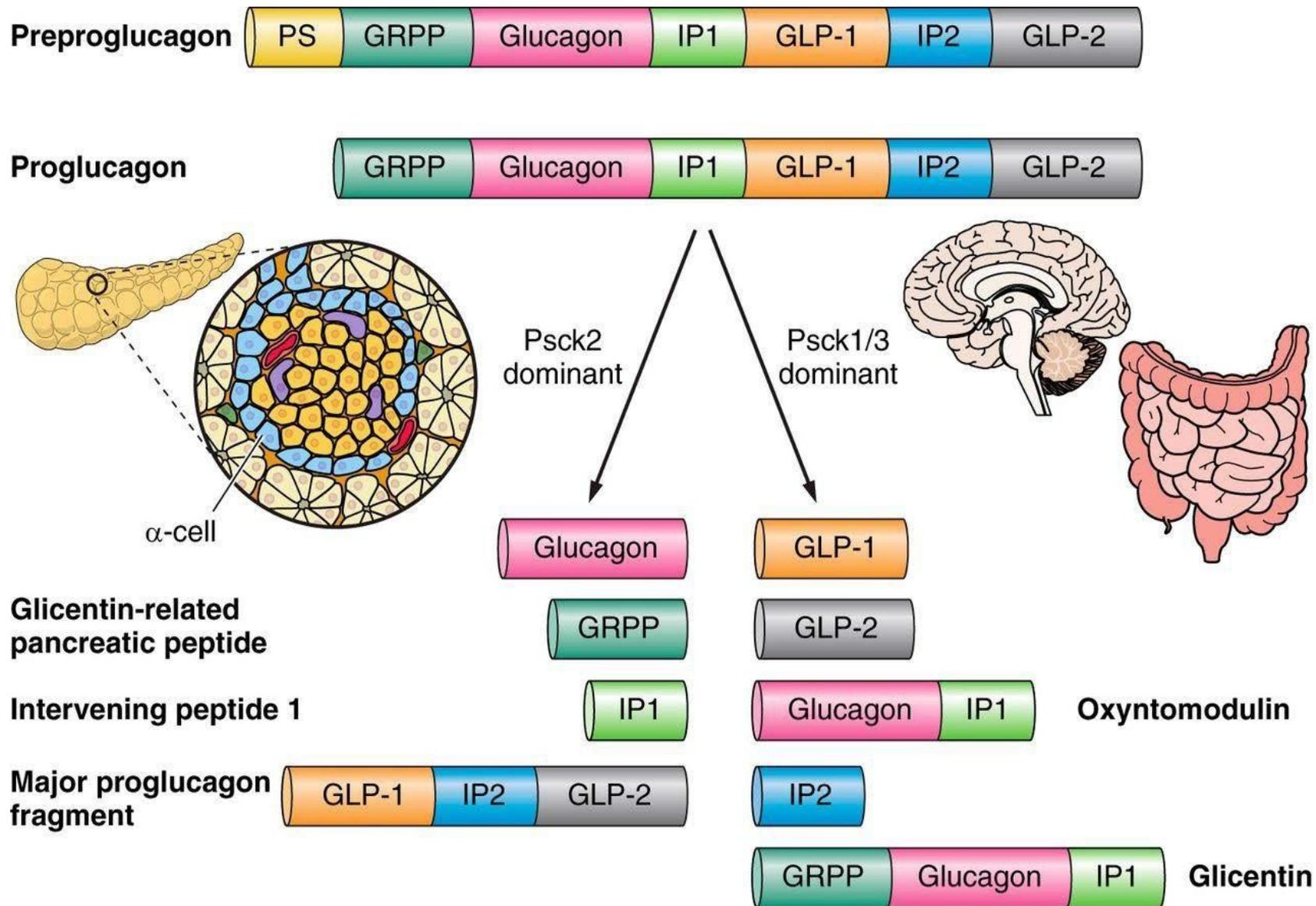
**TABLE 23-3** Effects of Insulin on Blood Glucose: Uptake of Glucose by Cells and Storage as Triacylglycerols and Glycogen

Metabolic effect	Target enzyme
↑ Glucose uptake (muscle, adipose)	↑ Glucose transporter (GLUT4)
↑ Glucose uptake (liver)	↑ Glucokinase (increased expression)
↑ Glycogen synthesis (liver, muscle)	↑ Glycogen synthase
↓ Glycogen breakdown (liver, muscle)	↓ Glycogen phosphorylase
↑ Glycolysis, acetyl-CoA production (liver, muscle)	↑ PFK-1 (by ↑ PFK-2)
	↑ Pyruvate dehydrogenase complex
↑ Fatty acid synthesis (liver)	↑ Acetyl-CoA carboxylase
↑ Triacylglycerol synthesis (adipose tissue)	↑ Lipoprotein lipase

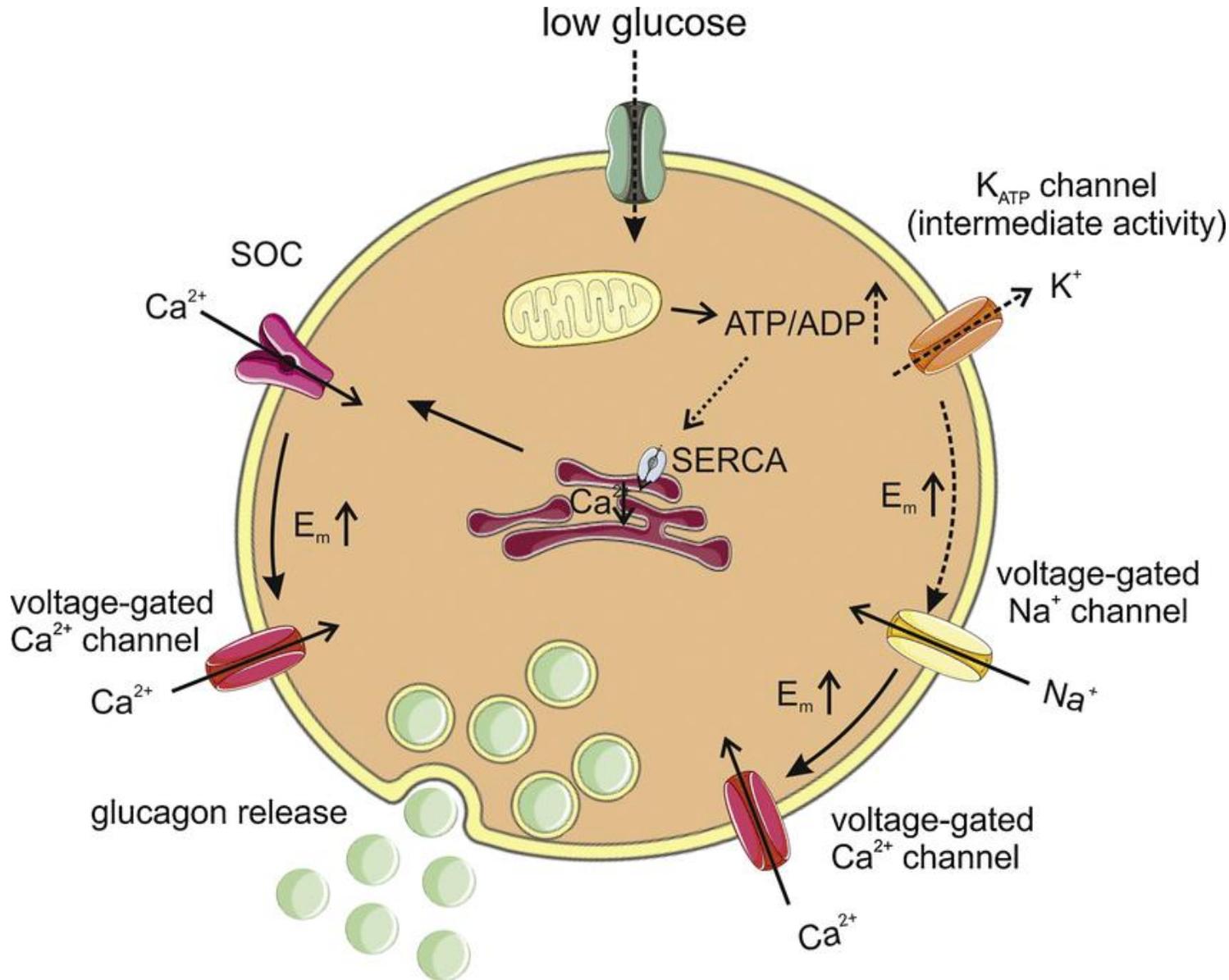
# Insulina e Glucagon







# Regulação da Secreção do Glucagon



- Células  $\alpha$  possuem GLUT1
- Células  $\alpha$  possuem glicoquinase
- $\downarrow$  glicemia =  $\downarrow$  ATP
- $\downarrow$  ATP ativa canais para saída de  $K^+$
- Despolarização
- Ativação da entrada de  $Na^{1+}$  e  $Ca^{2+}$
- Ativação da liberação de  $Ca^{2+}$  do RE
- Síntese de glucagon
- Secreção de glucagon em vesículas

# Mecanismo de Sinalização pelo Glucagon: Glicogenólise

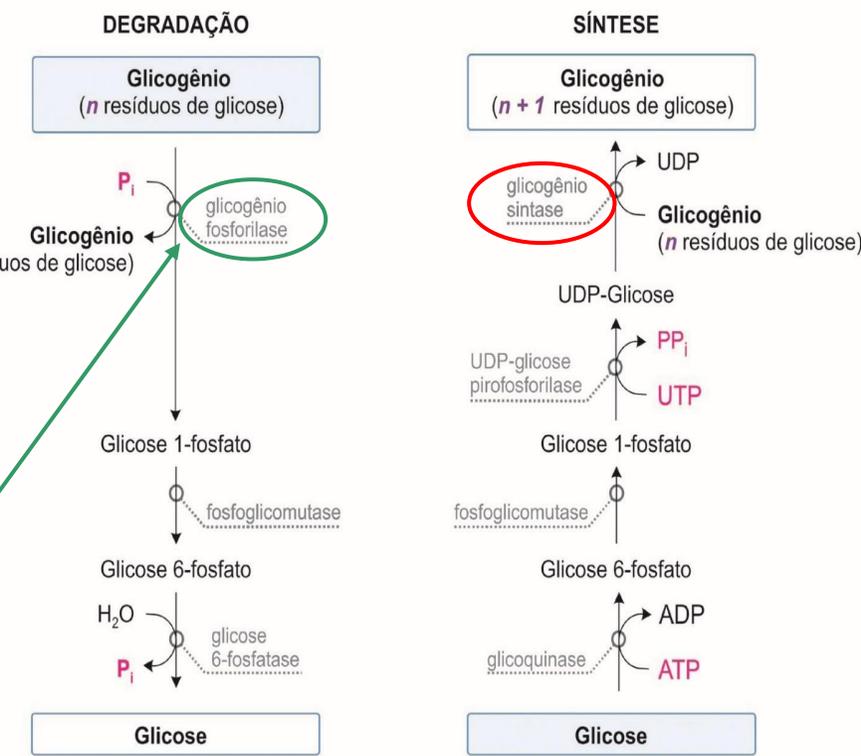
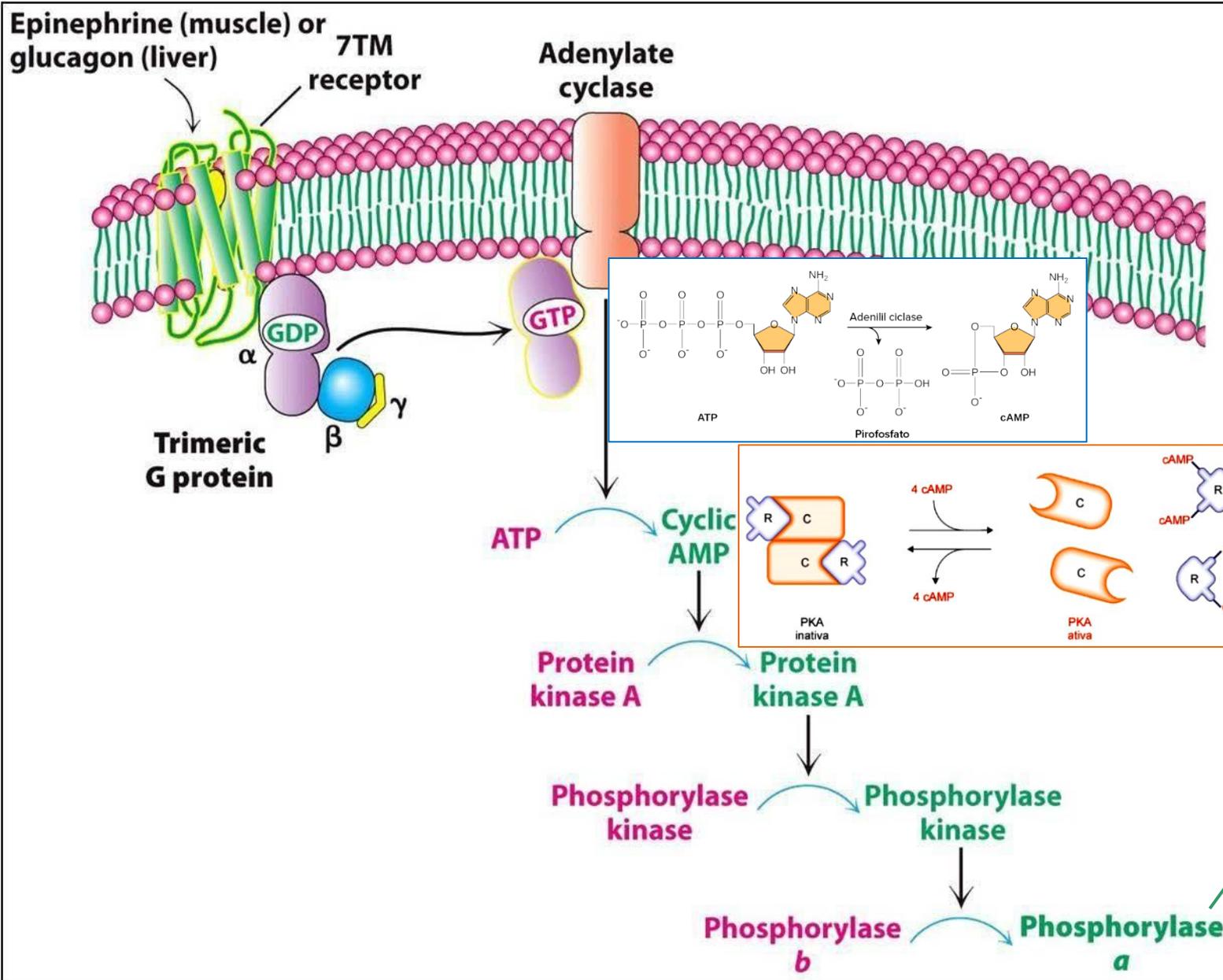
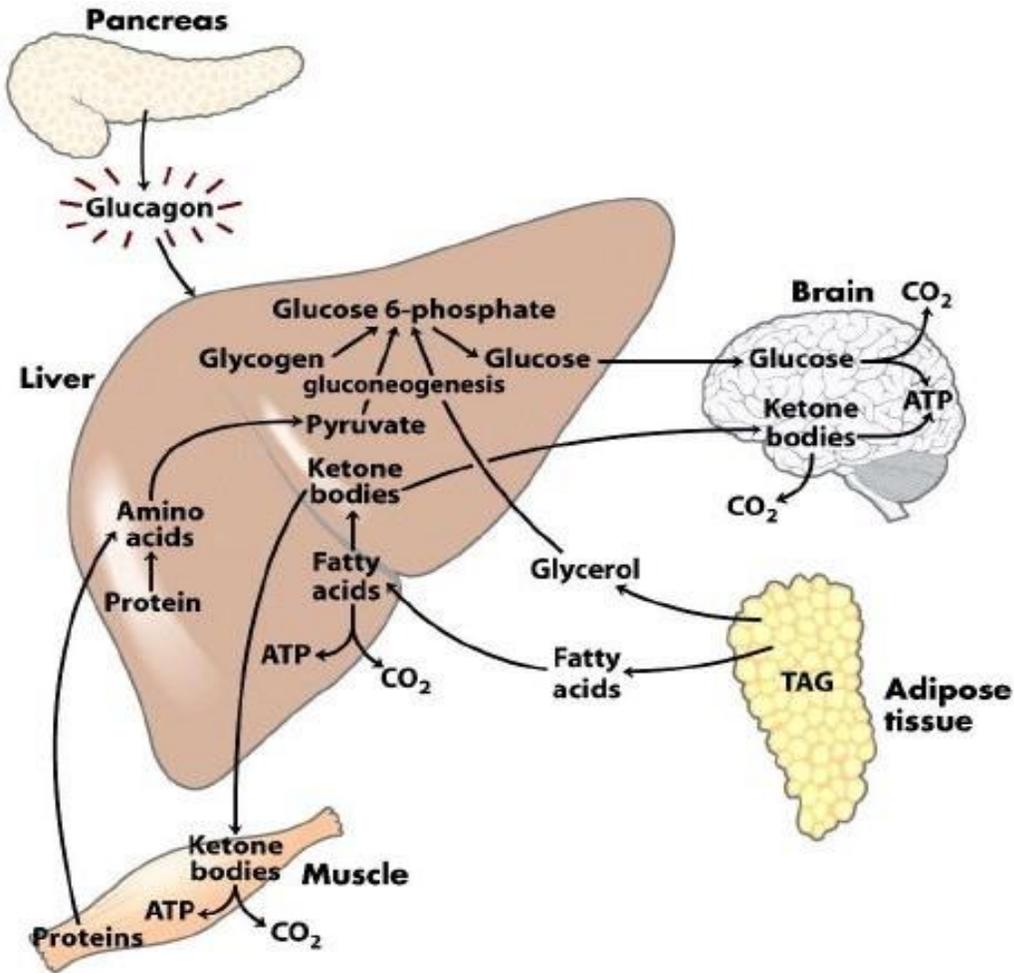


Fig. 13.5 Esquema geral da degradação e síntese de glicogênio no fígado.

# Regulação do metabolismo pelo Glucagon



**TABLE 23-4** Effects of Glucagon on Blood Glucose: Production and Release of Glucose by the Liver

Metabolic effect	Effect on glucose metabolism	Target enzyme
↑ Glycogen breakdown (liver)	Glycogen → glucose	↑ Glycogen phosphorylase
↓ Glycogen synthesis (liver)	Less glucose stored as glycogen	↓ Glycogen synthase
↓ Glycolysis (liver)	Less glucose used as fuel in liver	↓ PFK-1
↑ Gluconeogenesis (liver)	Amino acids } Glycerol } → glucose Oxaloacetate }	↑ FBPase-2 ↓ Pyruvate kinase
↑ Fatty acid mobilization (adipose tissue)	Less glucose used as fuel by liver, muscle	↑ Triacylglycerol lipase Perilipin phosphorylation
↑ Ketogenesis	Provides alternative to glucose as energy source for brain	↑ Acetyl-CoA carboxylase

# Transporte de Glicose através da MP: GLUT = Glucose Transporter

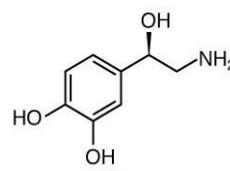
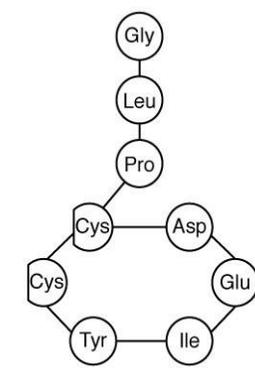
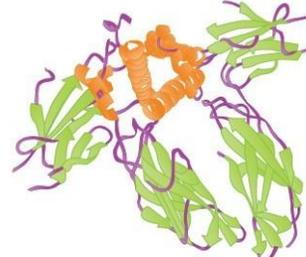
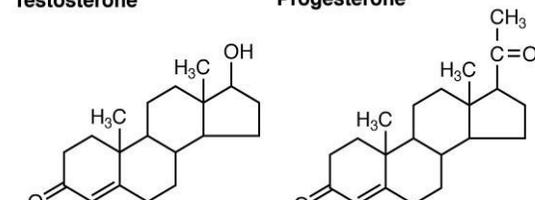
- Processo passivo
- GLUTs de 1-14; mais expressas e caracterizadas: GLUTs 1-4
- GLUT2: menor afinidade por glicose
- GLUT4: dependente de insulina

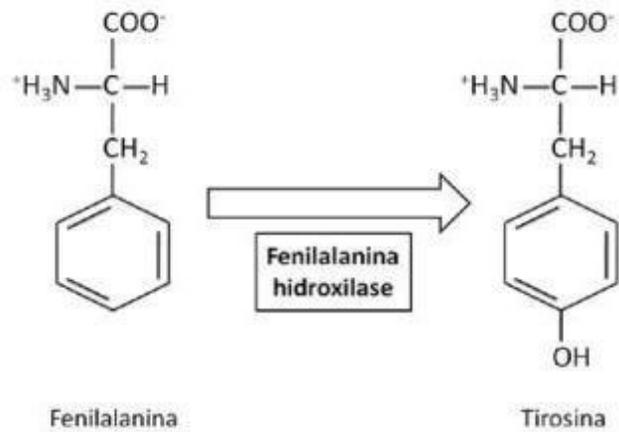
Tabela 19.4 Transportadores de glicose em mamíferos.

Transportador	Localização	$K_M$ para glicose (mM)	Dependência de insulina
GLUT 1	Todos os tecidos, abundante em cérebro e hemácias	1-5	Não
GLUT 2	Fígado, células $\beta$ do pâncreas, rins, intestino delgado	15-25	Não
GLUT 3	Cérebro	1-5	Não
GLUT 4	Tecido adiposo, músculos esqueléticos e cardíaco	1-5	Sim

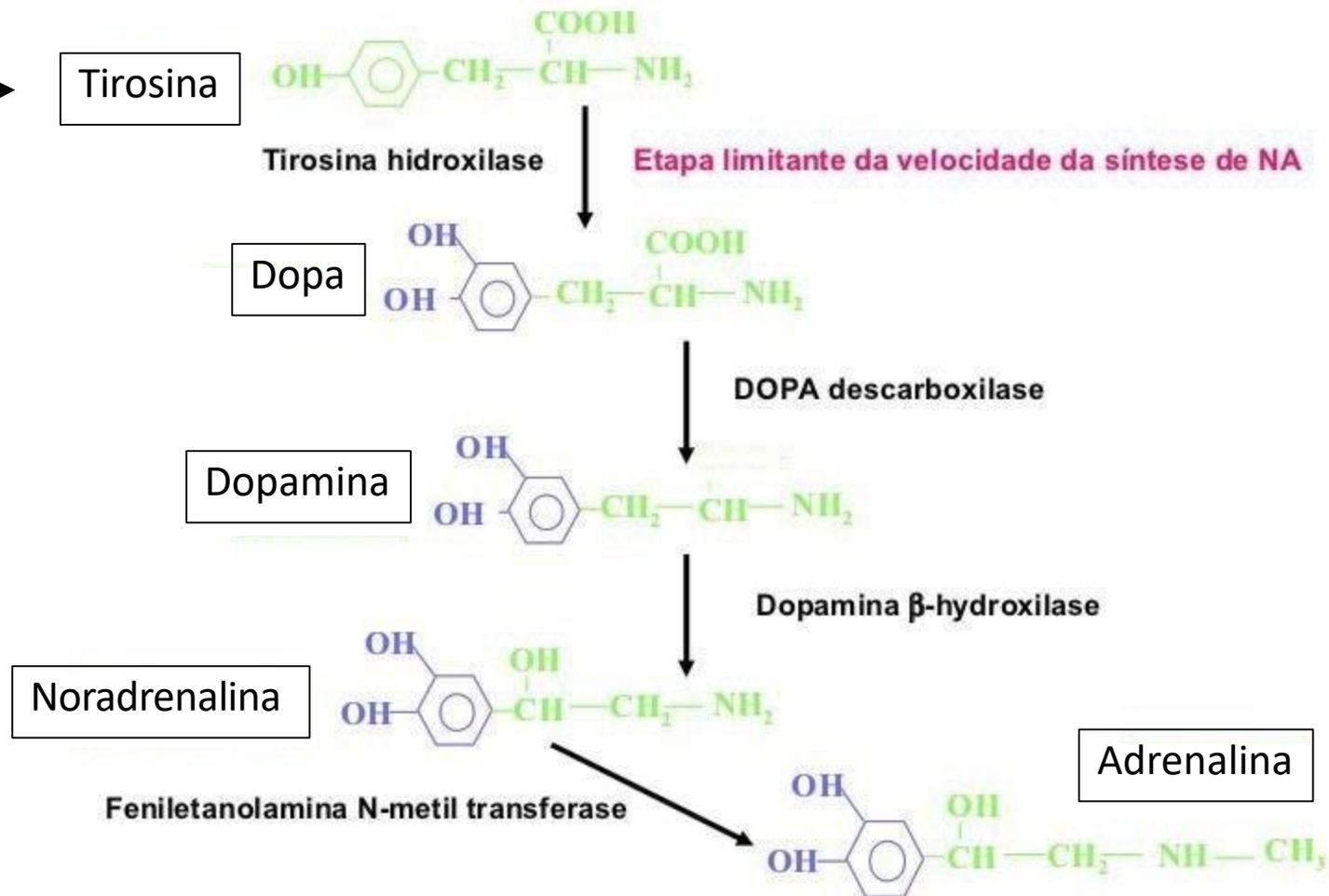
Concentração normal de glicose sanguínea = 5 a 8 mM.

# Hormônios derivados de Aminoácidos

Hormone Class	Components	Example(s)
<b>Amine Hormone</b>	Amino acids with modified groups (e.g. norepinephrine's carboxyl group is replaced with a benzene ring)	<p><b>Norepinephrine</b></p> 
<b>Peptide Hormone</b>	Short chains of linked amino acids	<p><b>Oxytocin</b></p> 
<b>Protein Hormone</b>	Long chains of linked amino acids	<p><b>Human Growth Hormone</b></p> 
<b>Steroid Hormones</b>	Derived from the lipid cholesterol	<p><b>Testosterone</b>      <b>Progesterone</b></p> 

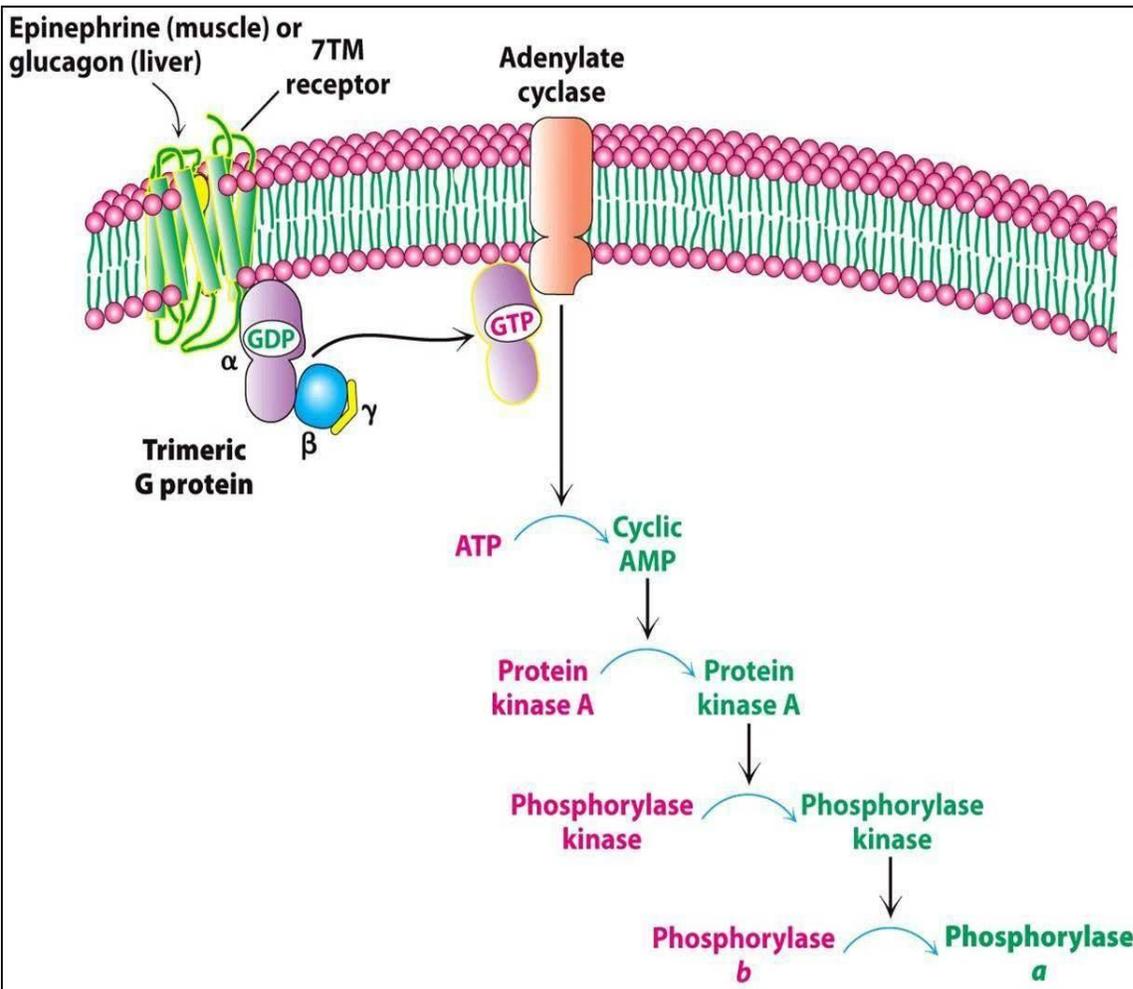


## BIOSSÍNTESE DAS CATECOLAMINAS



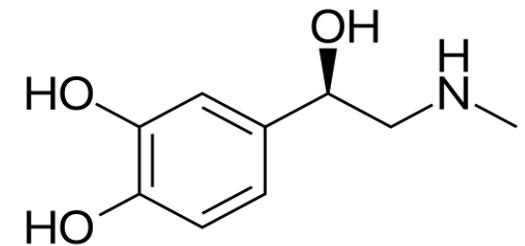
**Adrenalina e Noradrenalina (epinefrina e norepinefrina)** sintetizados pela supra-renal funcionam como neurotransmissores (sinapses do cérebro e músculo) e como hormônios reguladores do metabolismo no fígado e no músculo

# Sinalização da adrenalina: resposta a um estresse ambiental/metabólico



**TABLE 23-6** Physiological and Metabolic Effects of Epinephrine: Preparation for Action

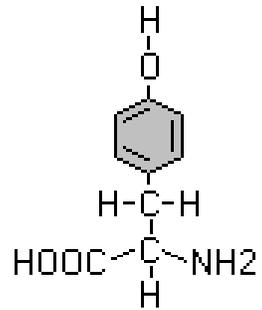
Immediate effect	Overall effect
<b>Physiological</b> ↑ Heart rate ↑ Blood pressure ↑ Dilation of respiratory passages	Increase delivery of O <sub>2</sub> to tissues (muscle)
<b>Metabolic</b> ↑ Glycogen breakdown (muscle, liver) ↓ Glycogen synthesis (muscle, liver) ↑ Gluconeogenesis (liver)	
↑ Glycolysis (muscle) ↑ Fatty acid mobilization (adipose tissue) ↑ Glucagon secretion ↓ Insulin secretion	
	Increase production of glucose for fuel
	Increases ATP production in muscle Increases availability of fatty acids as fuel
	Reinforce metabolic effects of epinephrine



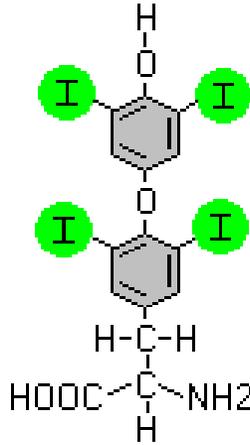
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<https://commons.wikimedia.org/w/index.php?curid=5902493>

Uso clinicamente em parada cardíaca, choque, anafilaxia

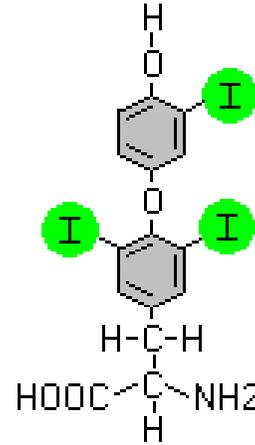
# Hormônios Tireoidianos



Tyrosine



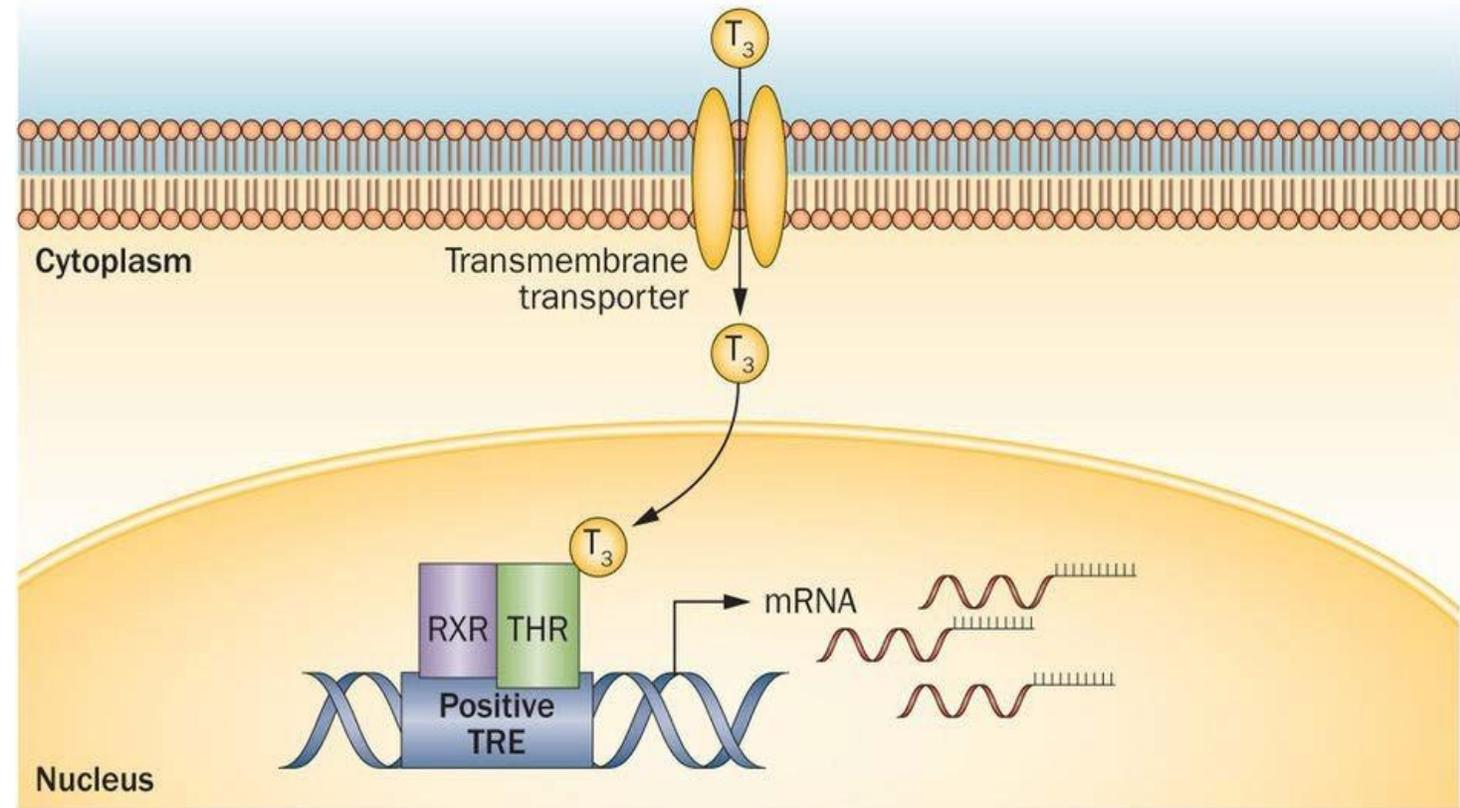
Thyroxine (T4)



Triiodothyronine (T3)

• **thyroxine** (also known as T4 or L-3,5,3',5'-tetraiodothyronine)

• **triiodothyronine** (T3 or L-3,5,3'-triiodothyronine)

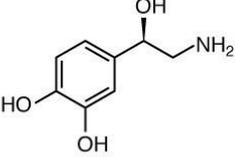
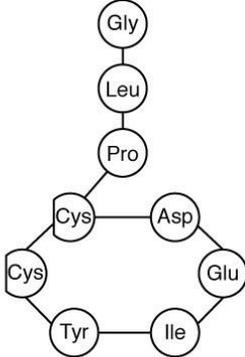
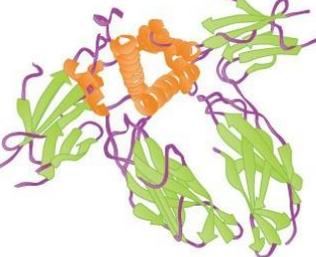


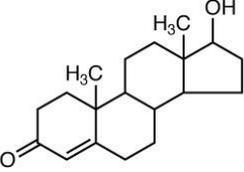
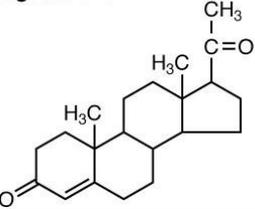
# Hormônios Tireoidianos

Parameter	↓ T <sub>3</sub> , T <sub>4</sub>	↑ T <sub>3</sub> , T <sub>4</sub>
Basal metabolic rate	↓	↑
Carbohydrate metabolism	↓ Gluconeogenesis ↓ Glycogenolysis Normal serum [glucose]	↑ Gluconeogenesis ↑ Glycogenolysis Normal serum [glucose]
Protein metabolism	↓ Synthesis ↓ Proteolysis	↑ Synthesis ↑ Proteolysis Muscle wasting
Lipid metabolism	↓ Lipogenesis ↓ Lipolysis ↑ Serum [cholesterol]	↑ Lipogenesis ↑ Lipolysis ↓ Serum [cholesterol]
Thermogenesis	↓	↑

Table 48-1, Boron & Boulpaep

# Hormônios Esteróides

Hormone Class	Components	Example(s)
<b>Amine Hormone</b>	Amino acids with modified groups (e.g. norepinephrine's carboxyl group is replaced with a benzene ring)	<p><b>Norepinephrine</b></p> 
<b>Peptide Hormone</b>	Short chains of linked amino acids	<p><b>Oxytocin</b></p> 
<b>Protein Hormone</b>	Long chains of linked amino acids	<p><b>Human Growth Hormone</b></p> 

<b>Steroid Hormones</b>	Derived from the lipid cholesterol	<p><b>Testosterone</b></p>  <p><b>Progesterone</b></p> 
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# Glicocorticóides

Doença de Addison's autoimunidade contra o cortex adrenal

Doença de Cushing's hipersecreção de glicocorticóide

