

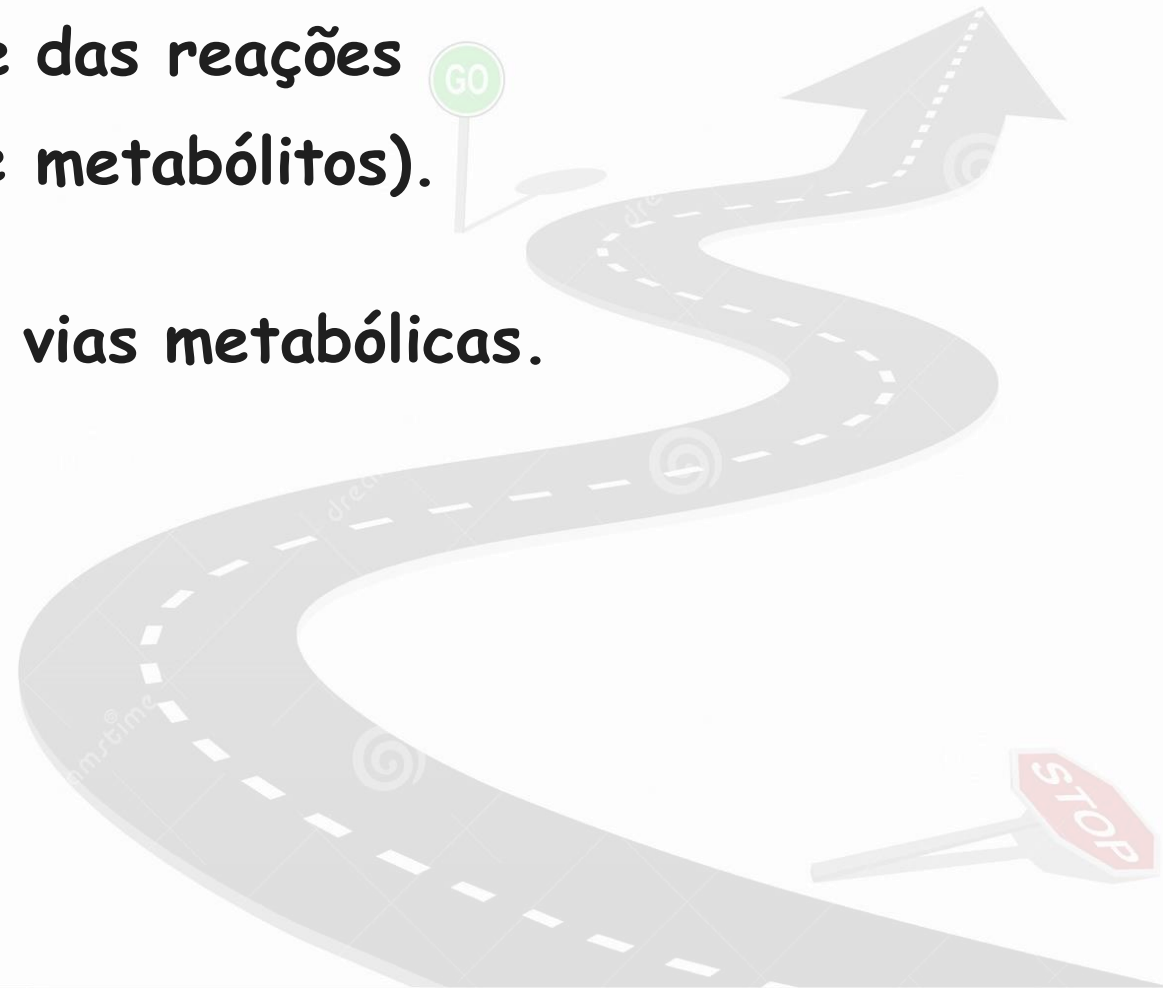
Regulação Metabólica Geral



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

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

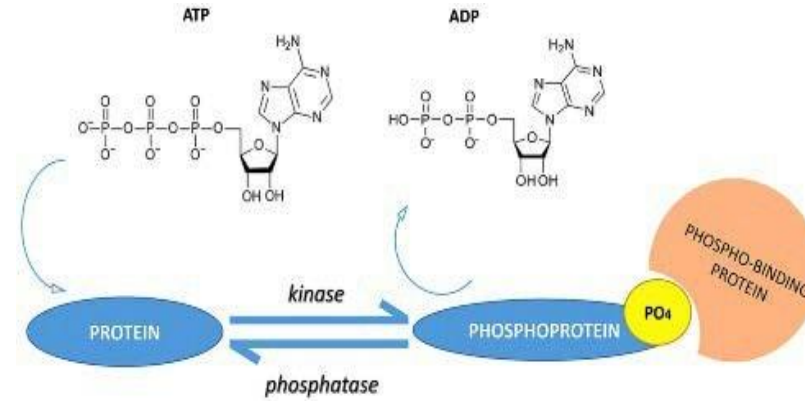
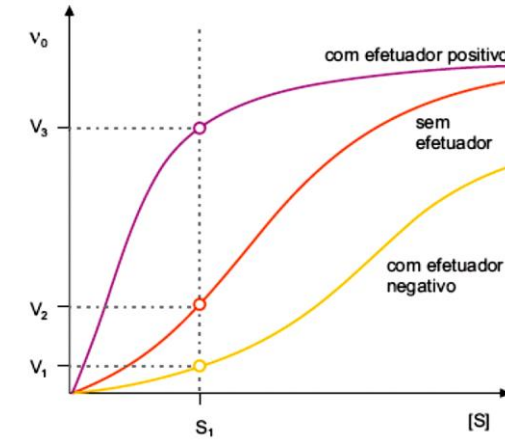
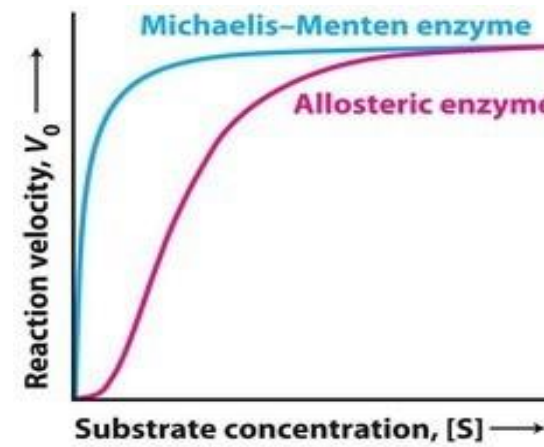
Efeitos propagados por todas as diferentes vias metabólicas.



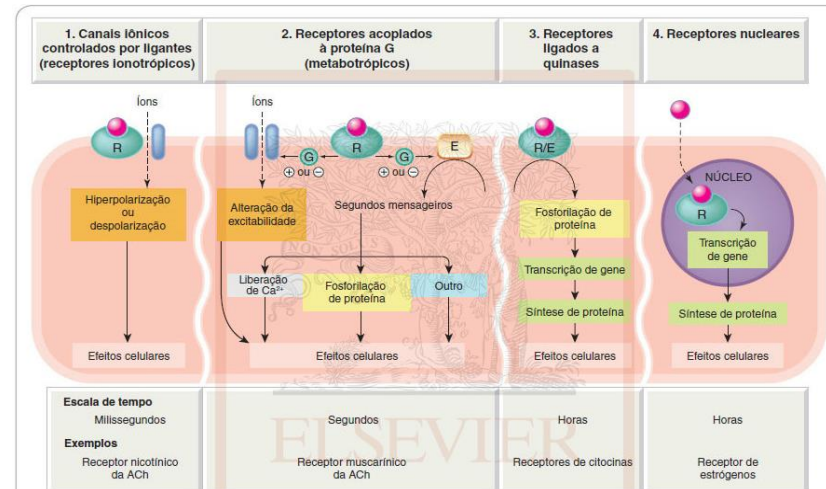
Estratégias de Regulação Metabólica

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
α -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.

Via metabólica	Enzima fosforilada	Forma
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

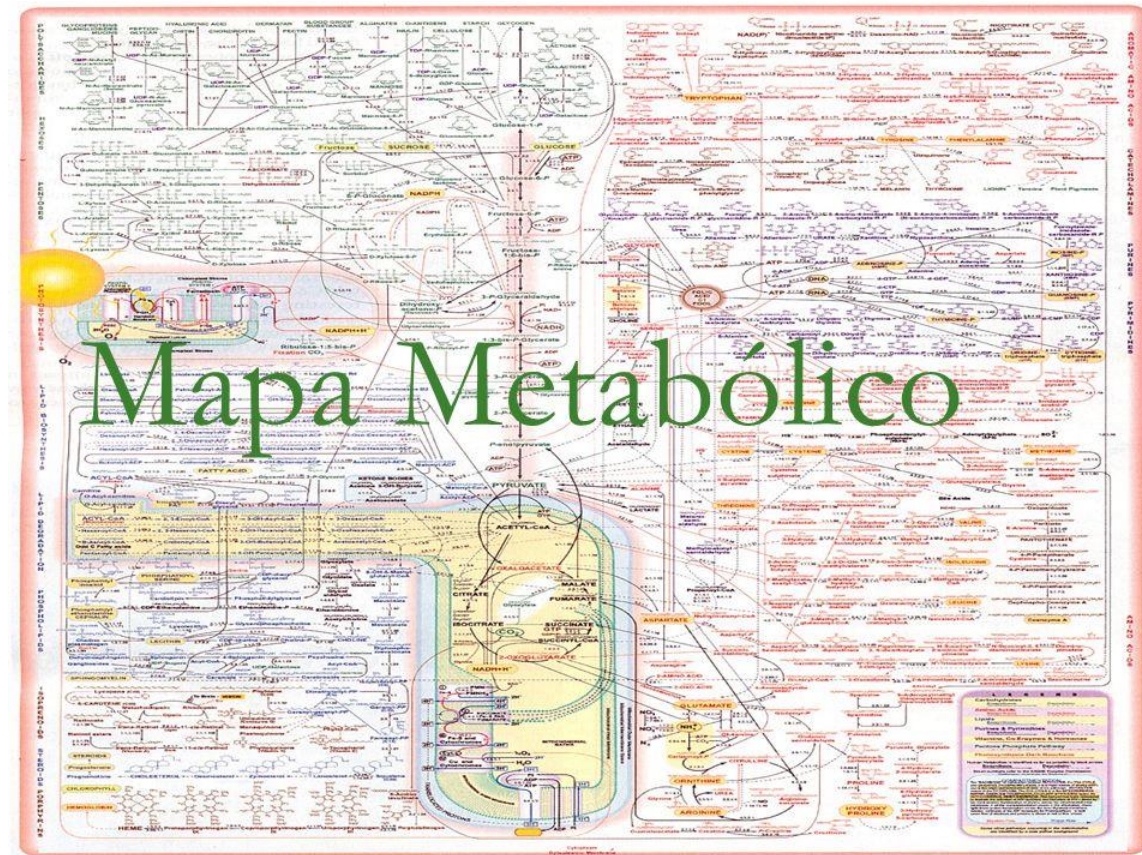
Tabela 19.3 Efeitos metabólicos de adrenalina, insulina e glucagon.

	Adrenalina	Glucagon	Insulina
Glicemia	↑	↑	↓
Glicólise	–	↓	↑
Gliconeogênese	↑	↑	↓
Glicogenólise	↑	↑	↓
Glicogenogênese	–	↓	↑
Lipólise	↑	↑	↓
Lipogênese	–	↓	↑
Cetogênese	–	↑	↓

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

Integração Metabólica

- Respostas do organismo diante da abundância e escassez de nutrientes.
- Adaptações às oscilações diárias das concentrações de nutrientes.
- Adaptações às necessidades fisiológicas.



Integração a nível celular e do organismo com um todo é feita por hormônios !



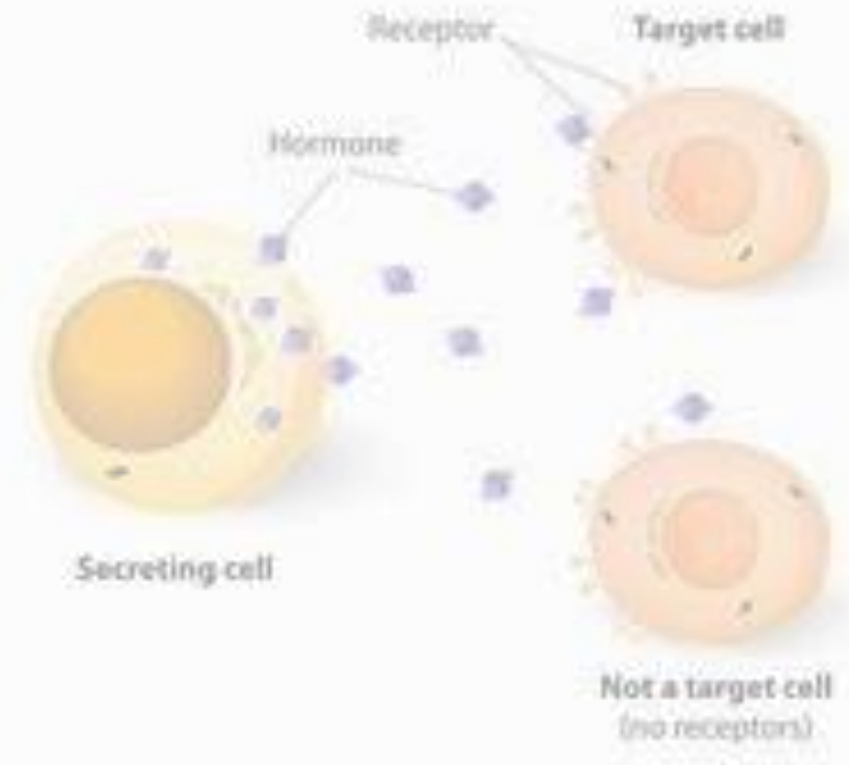
O que são hormônios?

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

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

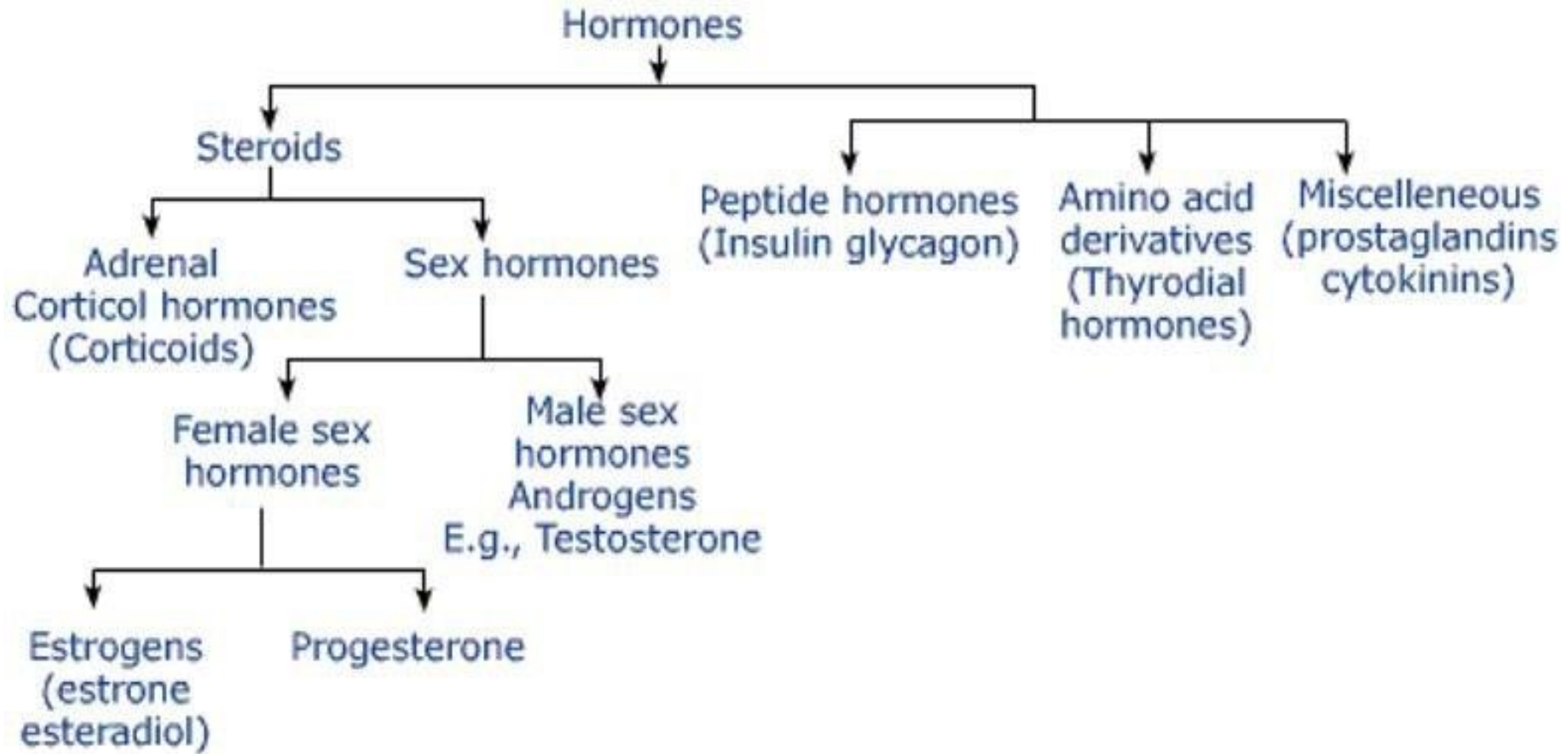
Hormônios

- 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

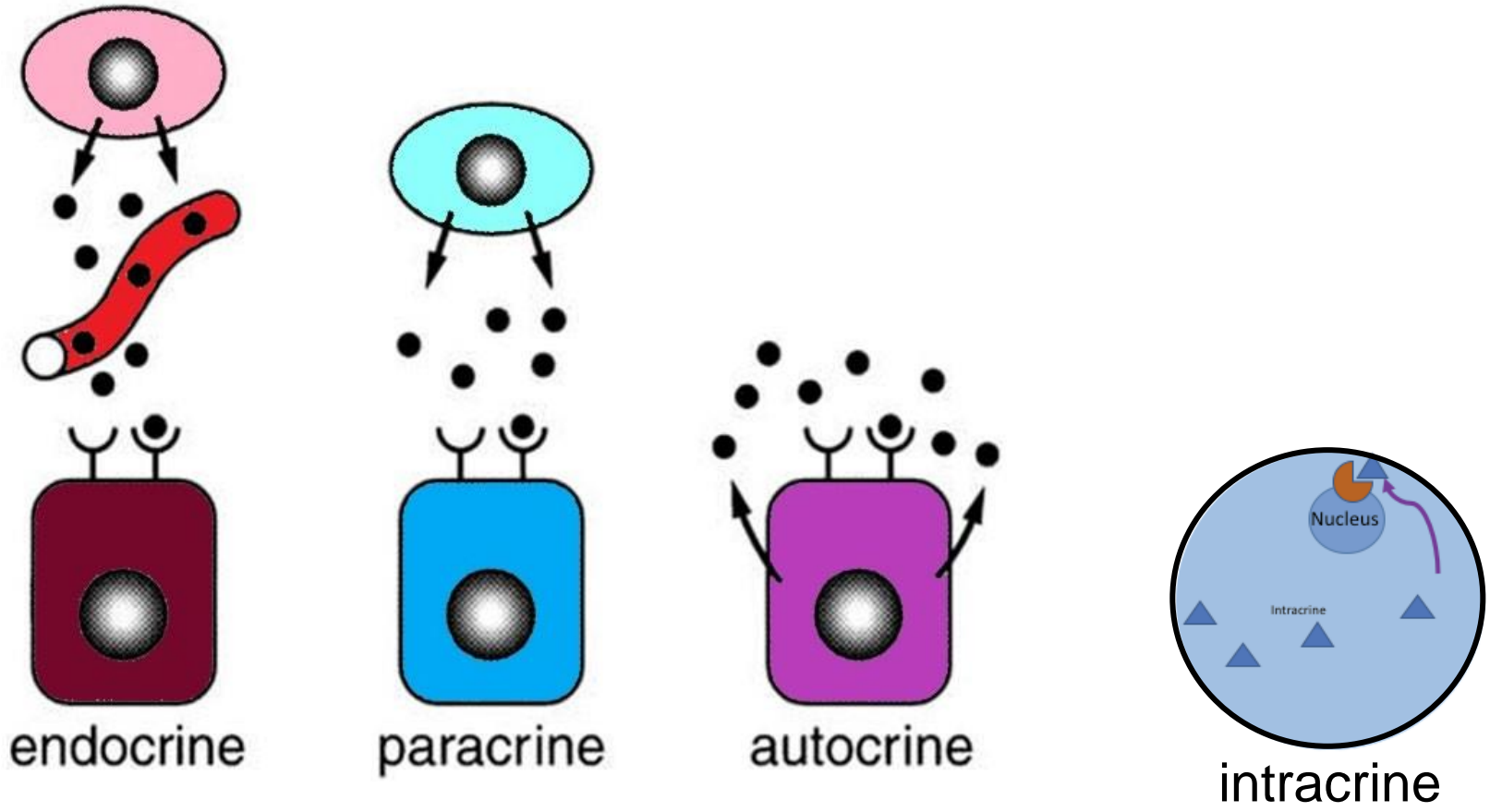


Regulação

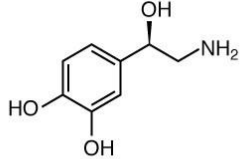
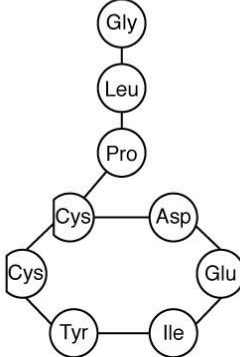
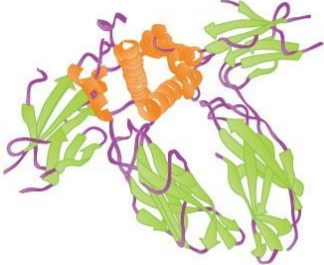
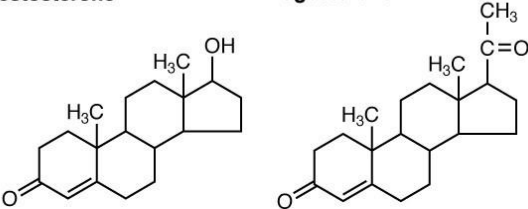
Biossíntese → Estocagem → Secreção → Transporte →
Reconhecimento → Resposta Celular → Degradação



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

Todos os hormônios agem através de receptores de alta afinidade

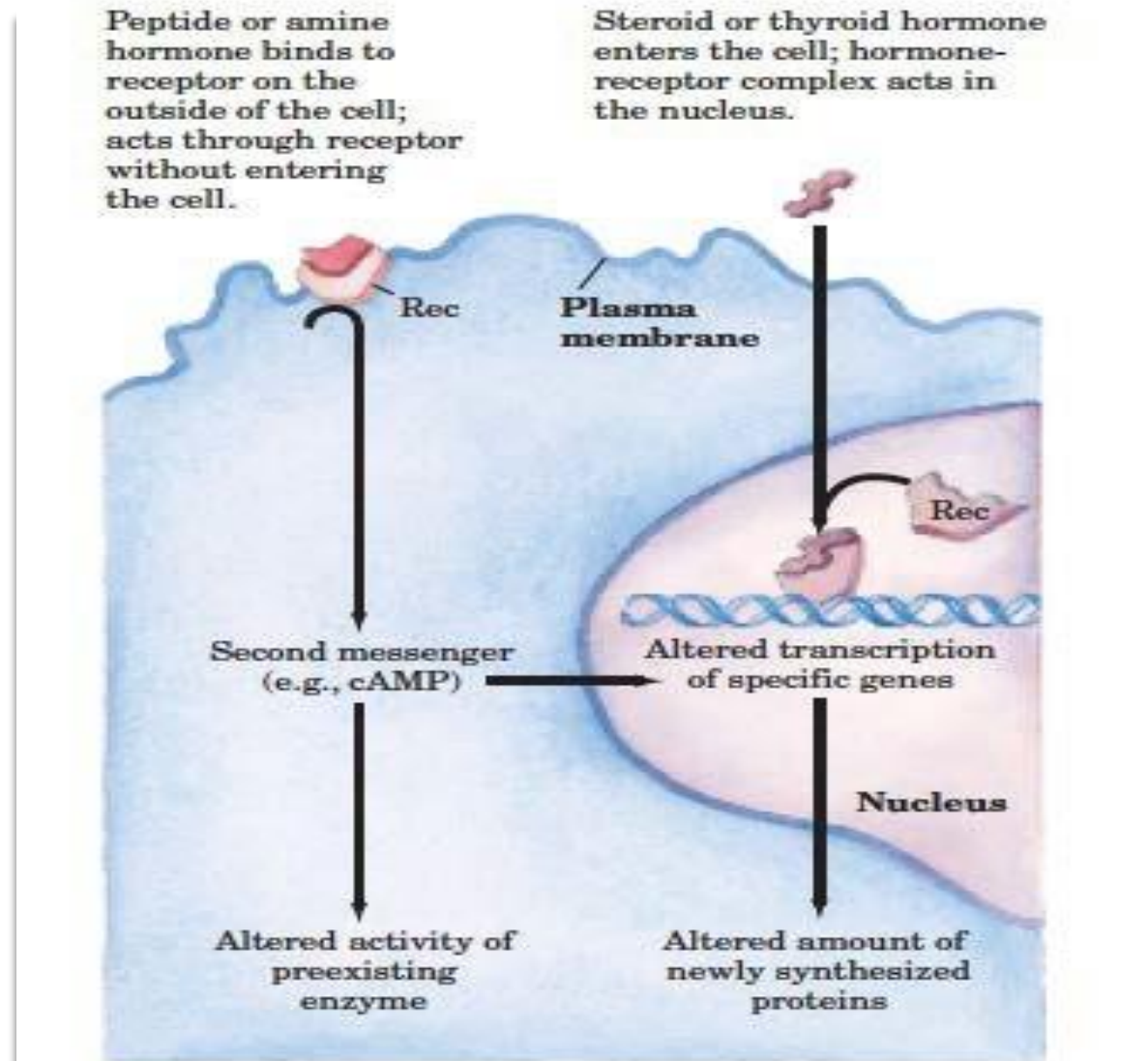
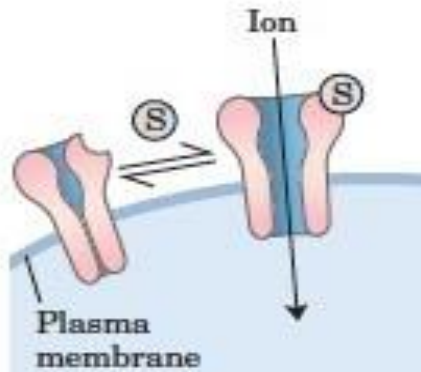


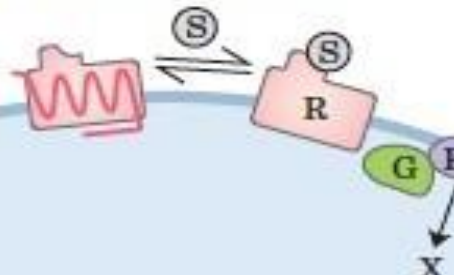
FIGURE 23-4 Two general mechanisms of hormone action. The peptide and amine hormones are faster acting than steroid and thyroid hormones.

Tipos de transdutores de sinais hormonais

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



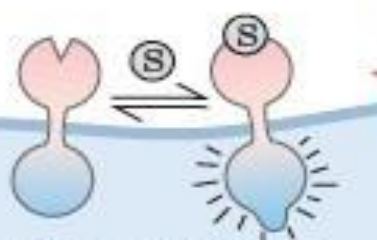
Serpentine receptor
External ligand binding to receptor (R) activates an intracellular GTP-binding protein (G), which regulates an enzyme (Enz) that generates an intracellular second messenger, X.



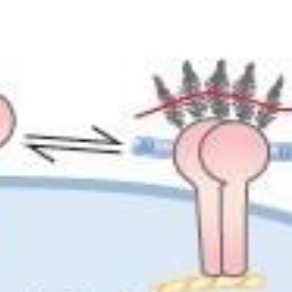
Receptor with no intrinsic enzyme activity
Interacts with cytosolic protein kinase, which activates a gene-regulating protein (directly or through a cascade of protein kinases), changing gene expression.



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.

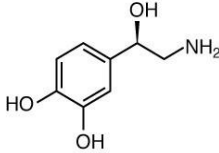
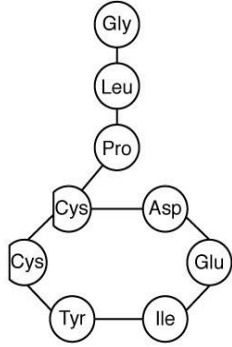
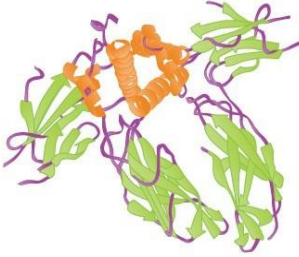
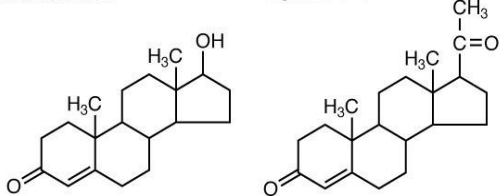


Kinase cascade
A series of protein kinases that activate each other in a sequence, leading to the activation of a gene-regulating protein.

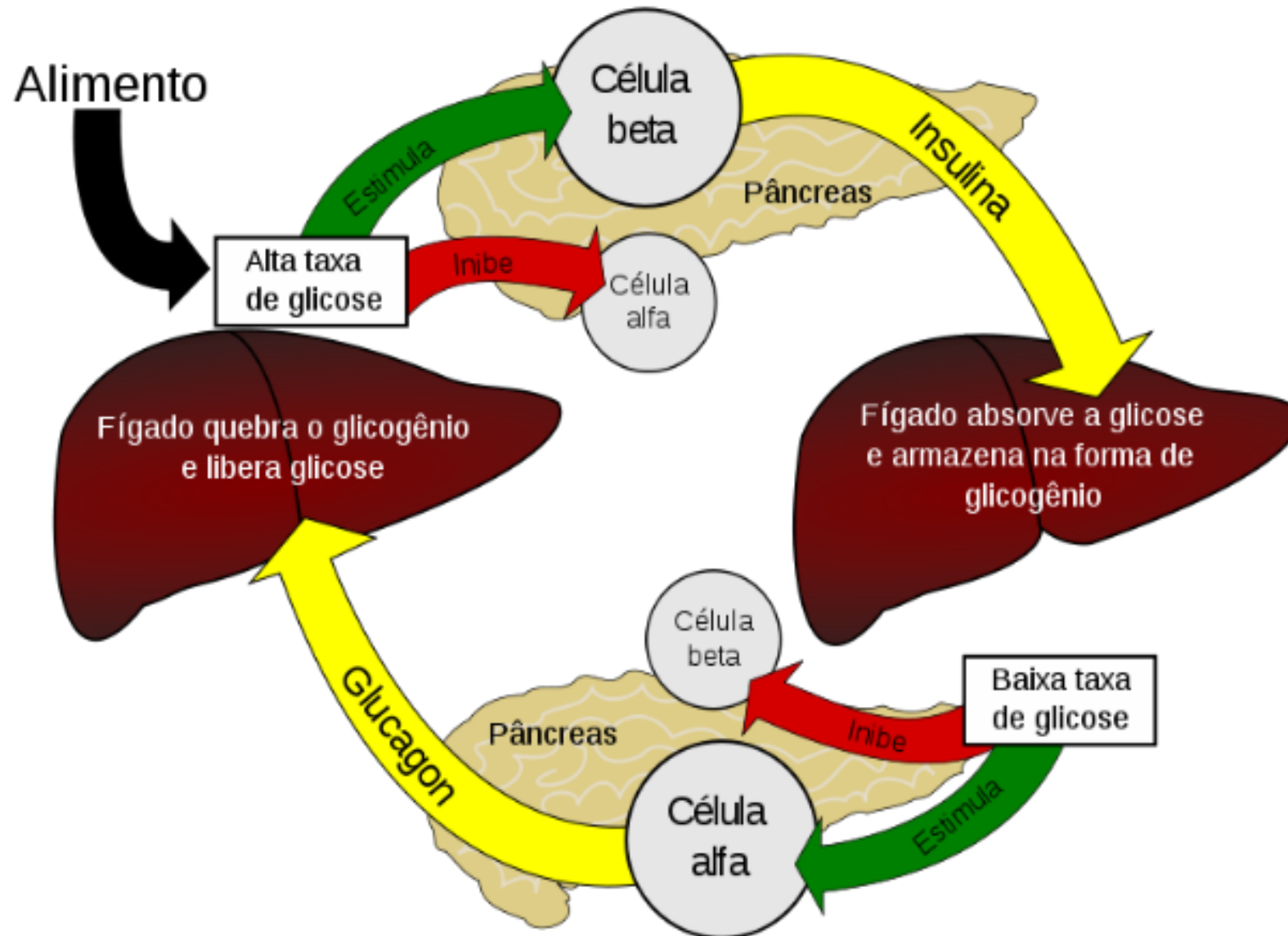


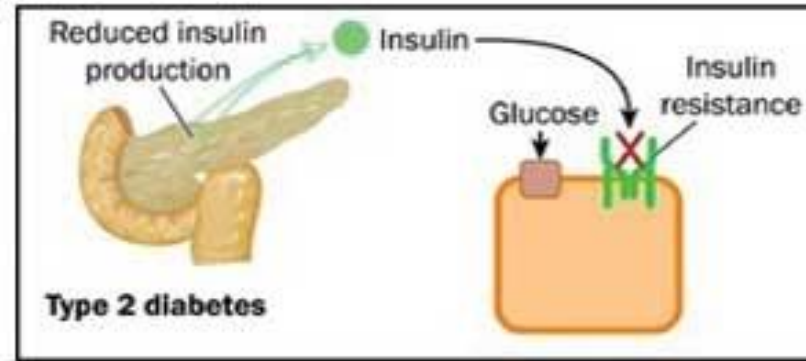
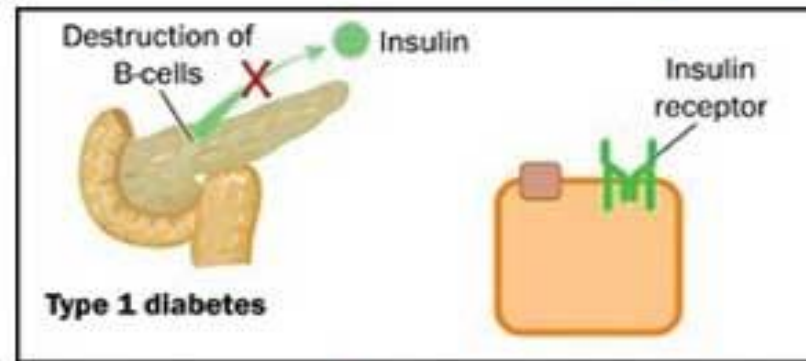
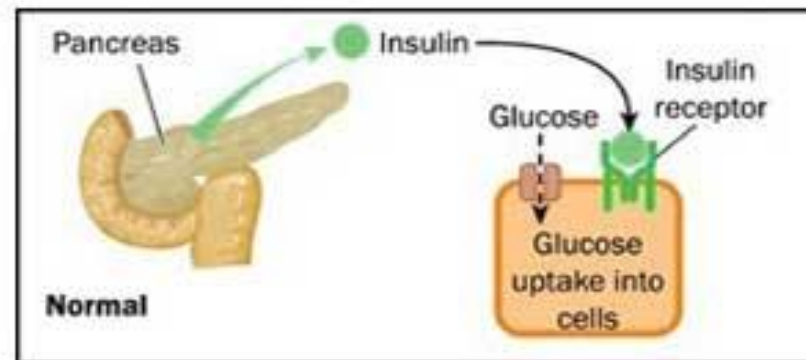
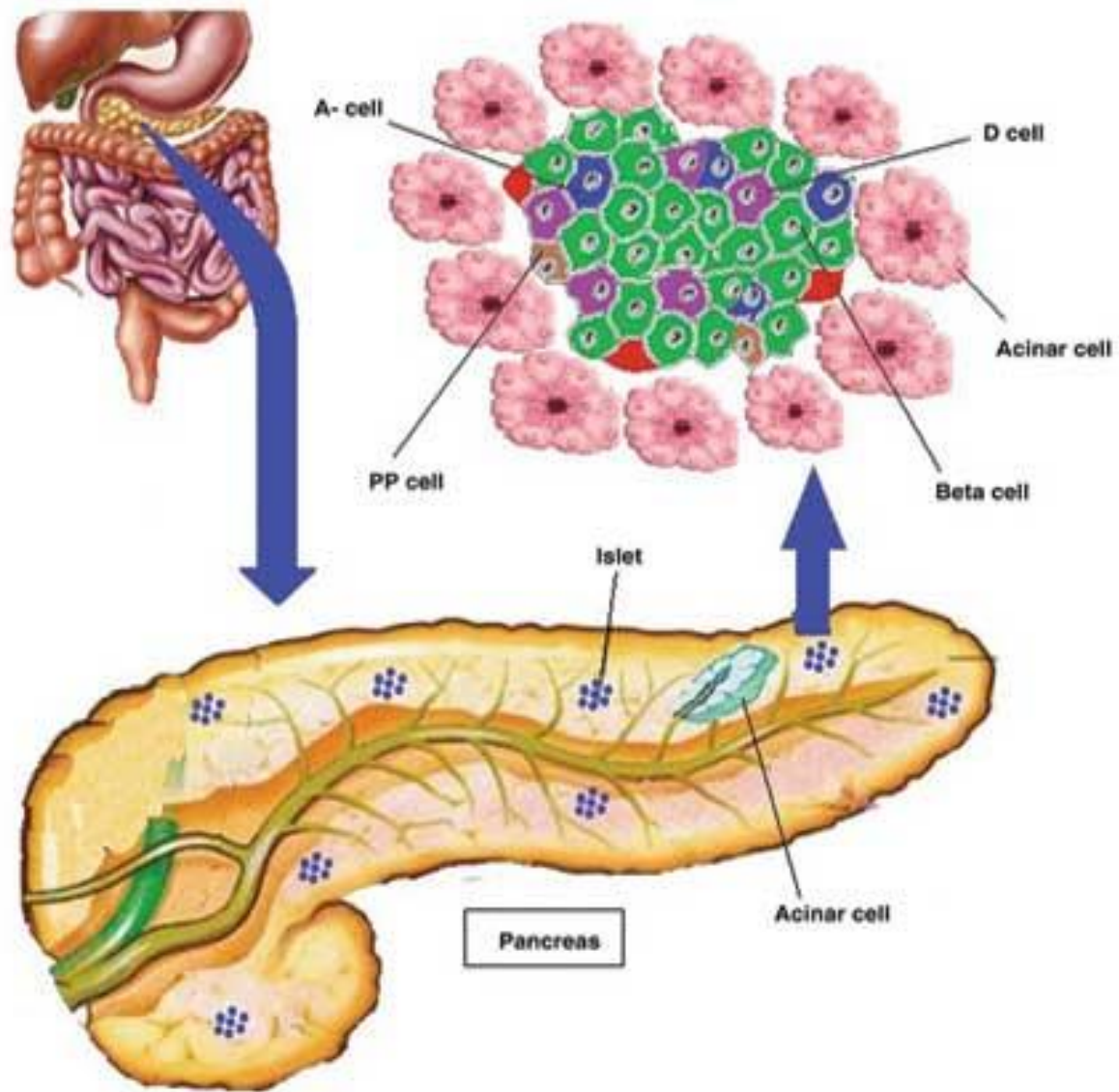
FIGURE 12-2 Six general types of signal transducers.

Hormônios Peptídicos

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

Insulina e Glucagon





Hormônios peptídicos/protéicos sofrem processamento pós-traducional

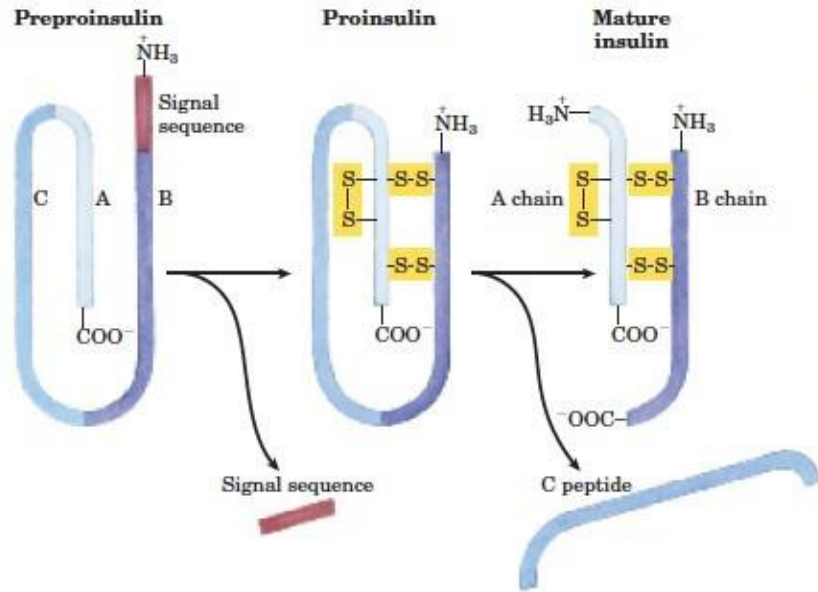
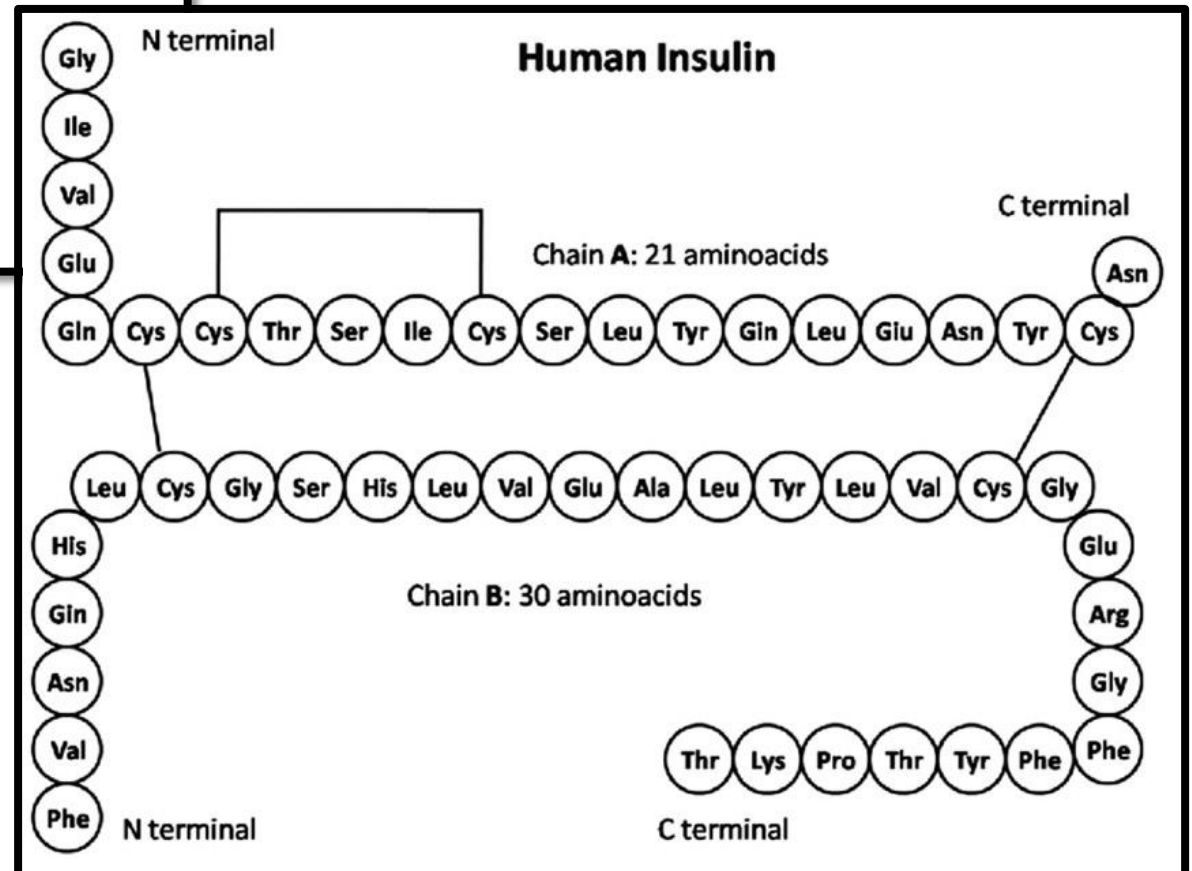
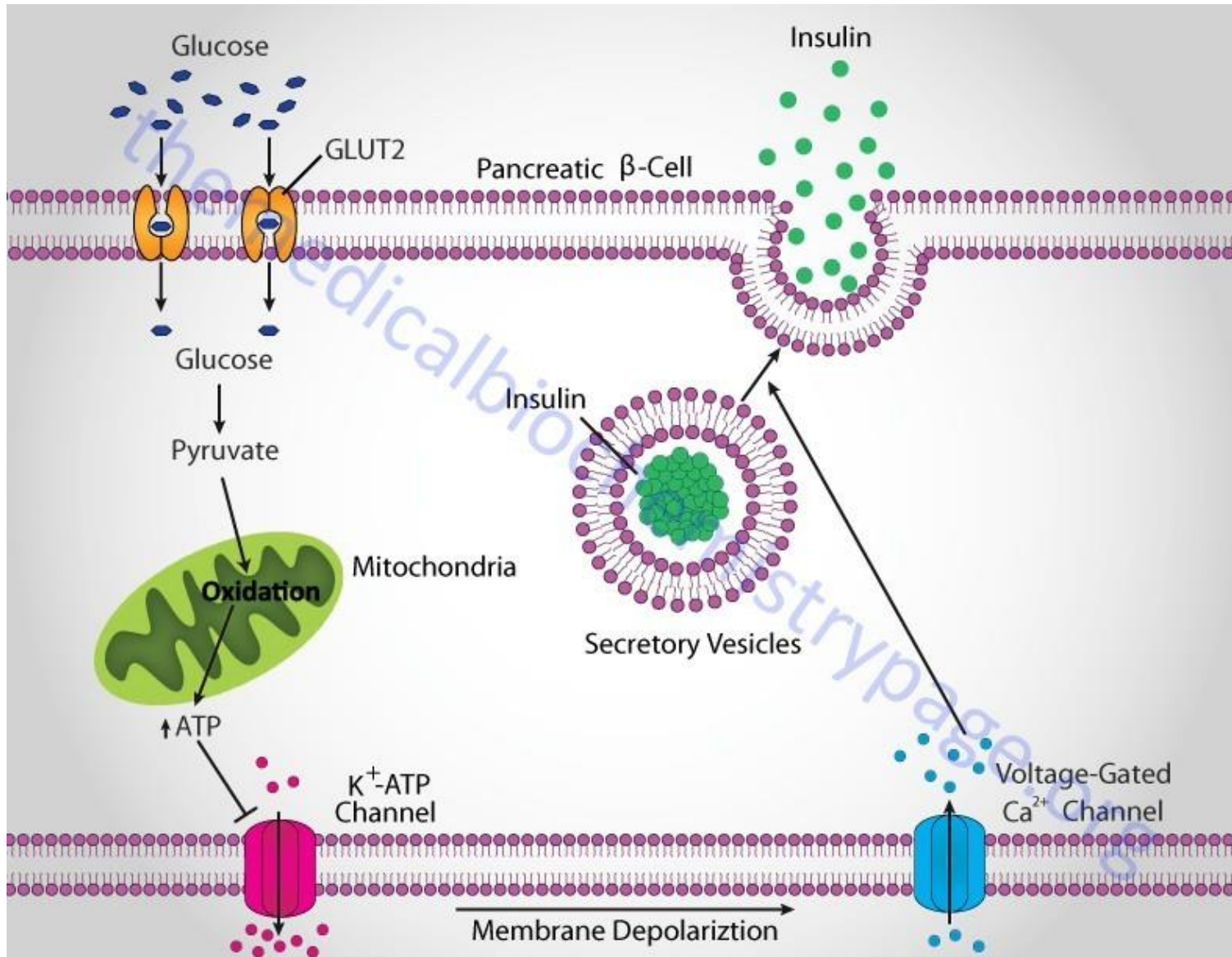


FIGURE 23-5 Insulin. Mature insulin is formed from its larger precursor preproinsulin by proteolytic processing. Removal of a 23 amino acid segment (the signal sequence) at the amino terminus of preproinsulin and formation of three disulfide bonds produces proinsulin. Further proteolytic cuts remove 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.

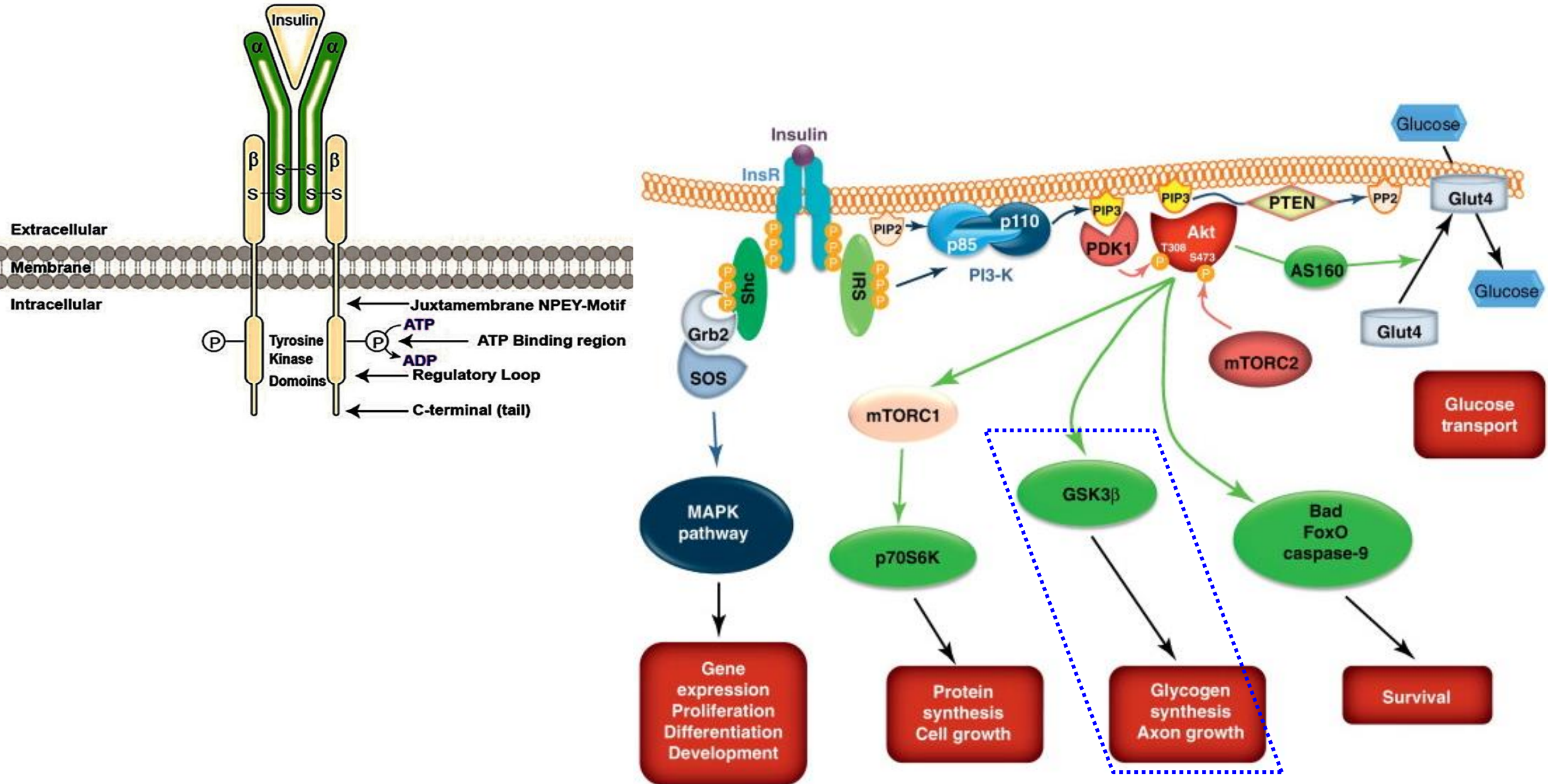


Regulação da Secreção da Insulina



- Células β possuem GLUT2
- Células β 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

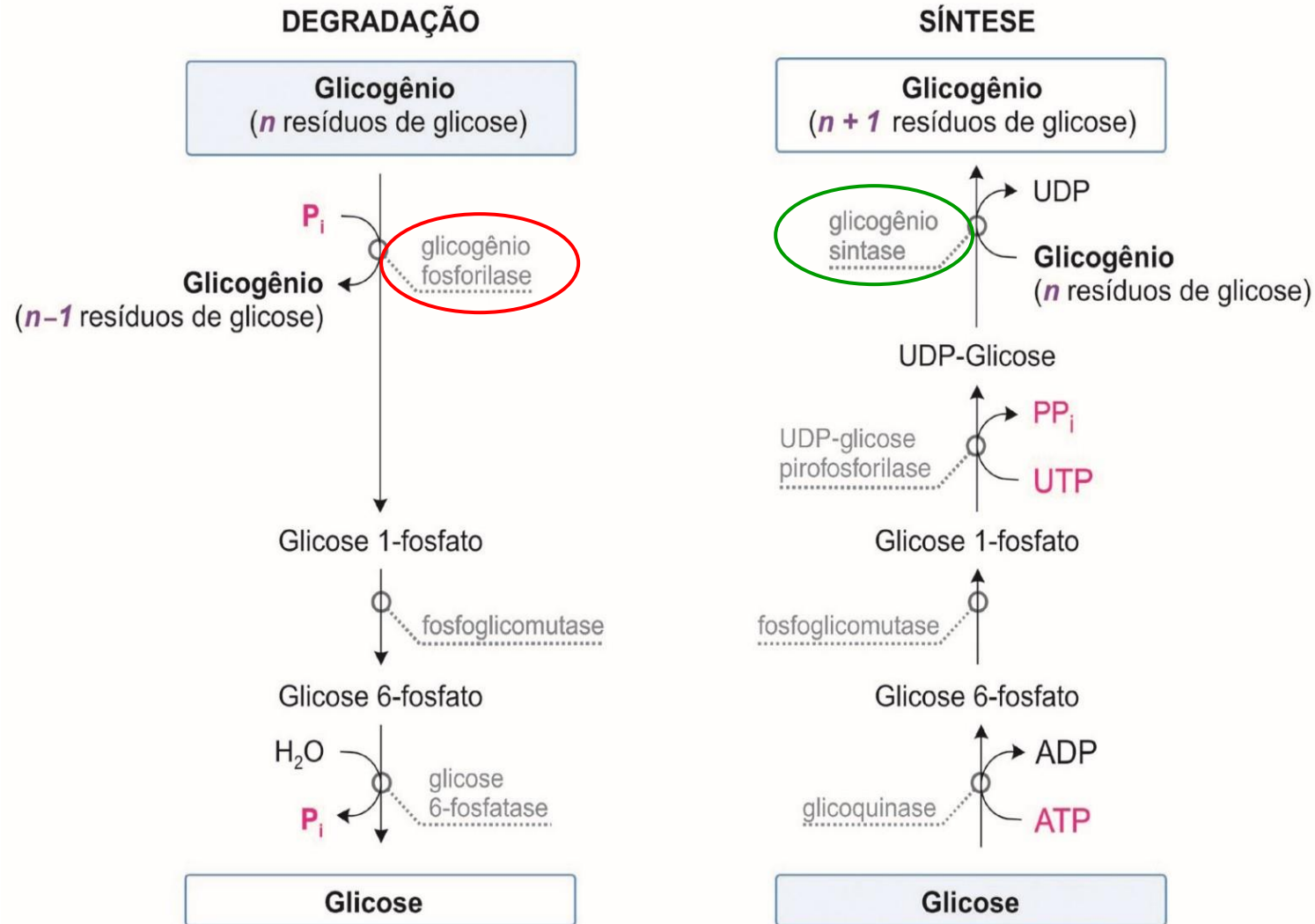
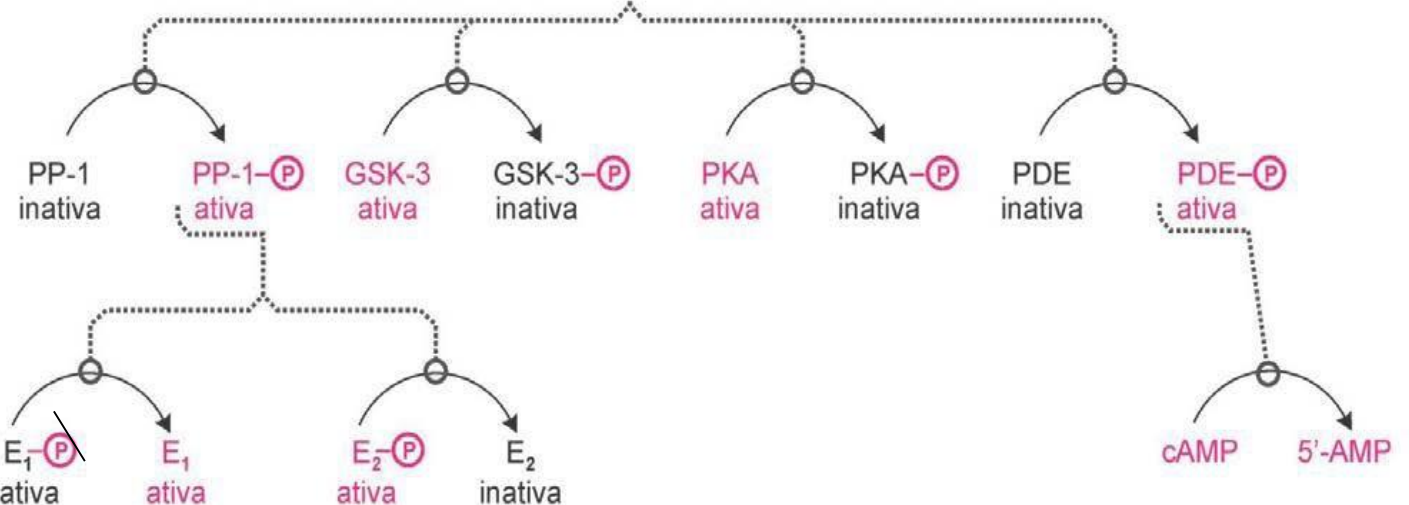
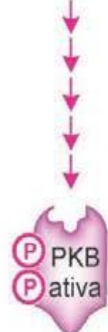


Fig. 13.5 Esquema geral da degradação e síntese de glicogênio no fígado.

Regulação do metabolismo do glicogênio pela Insulina

Insulina

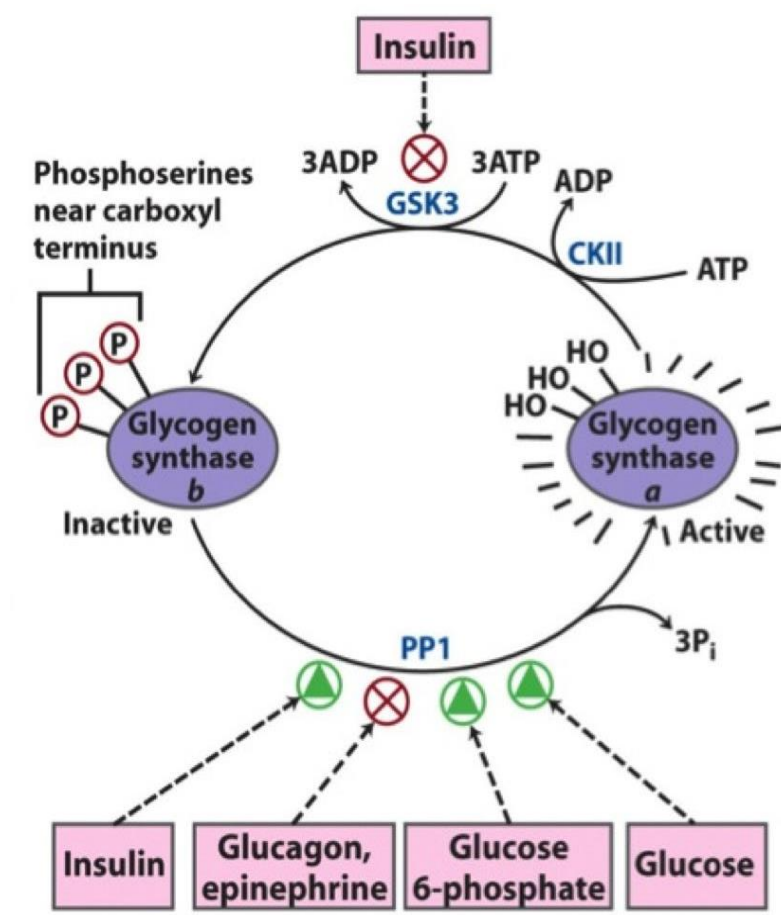


Fosfatase PP1

Glicogênio sintase Glicogênio fosforilase

Estímulo da glicogênese

Inibição da glicogenólise



Regulação do metabolismo pela Insulina

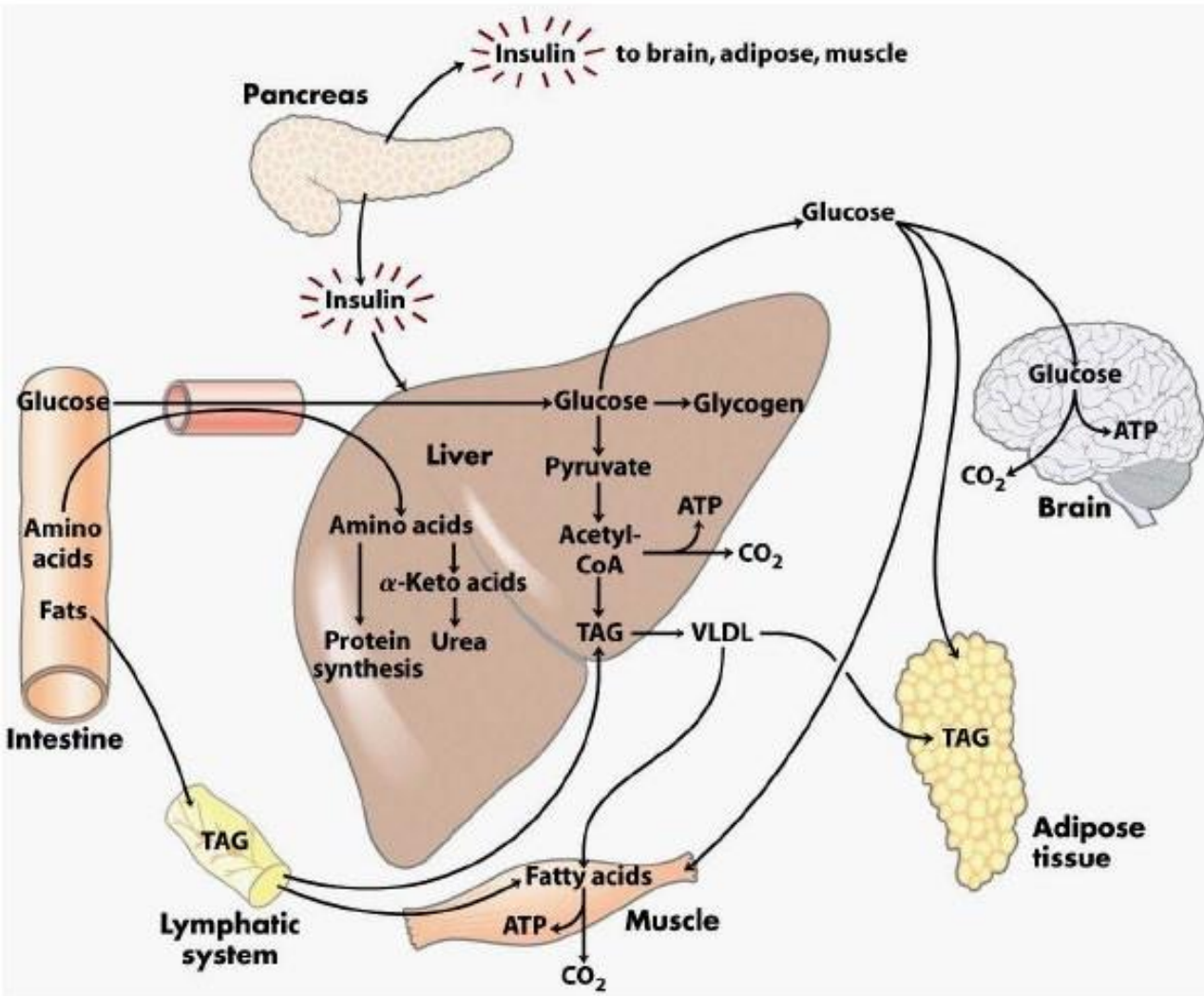
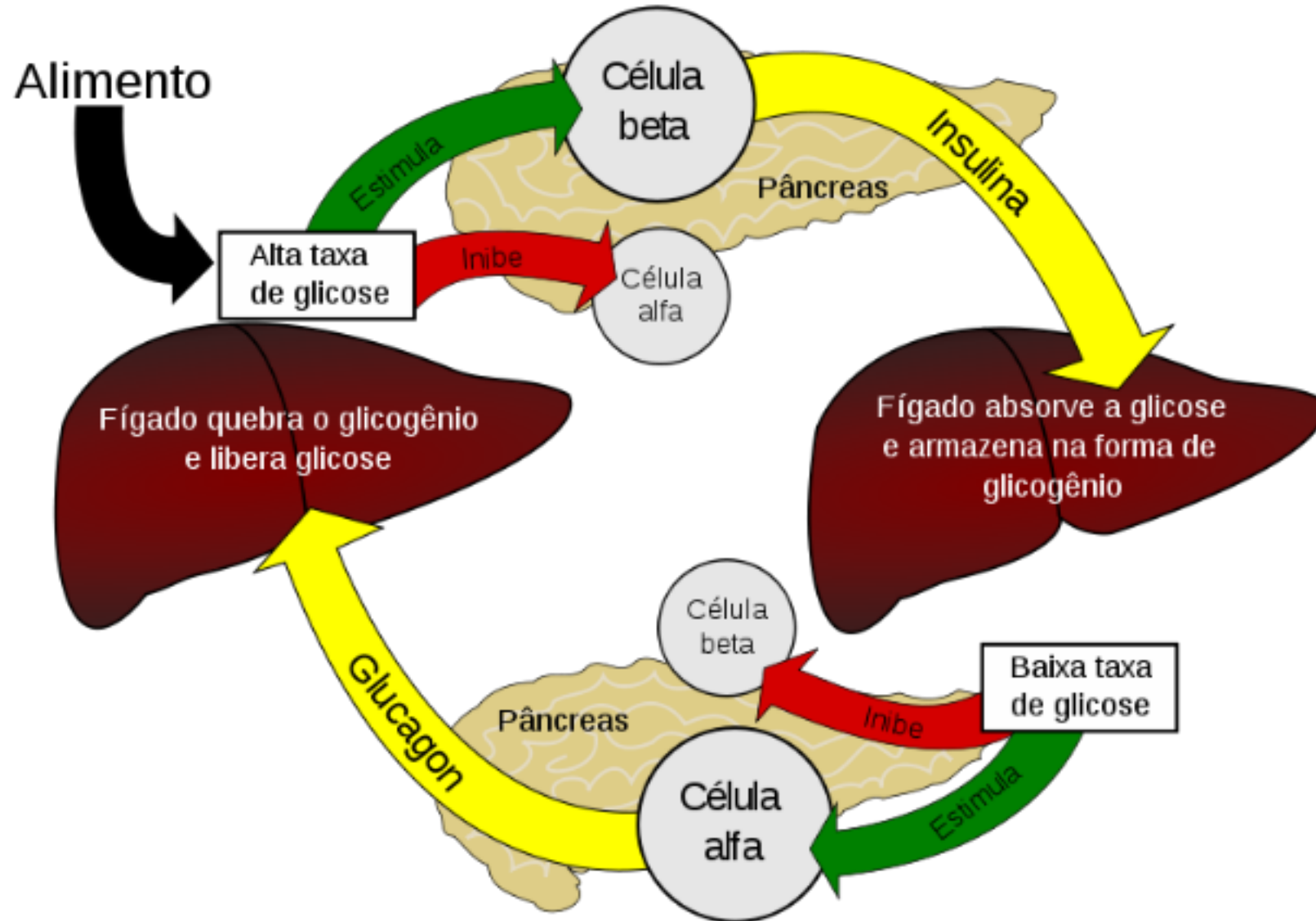
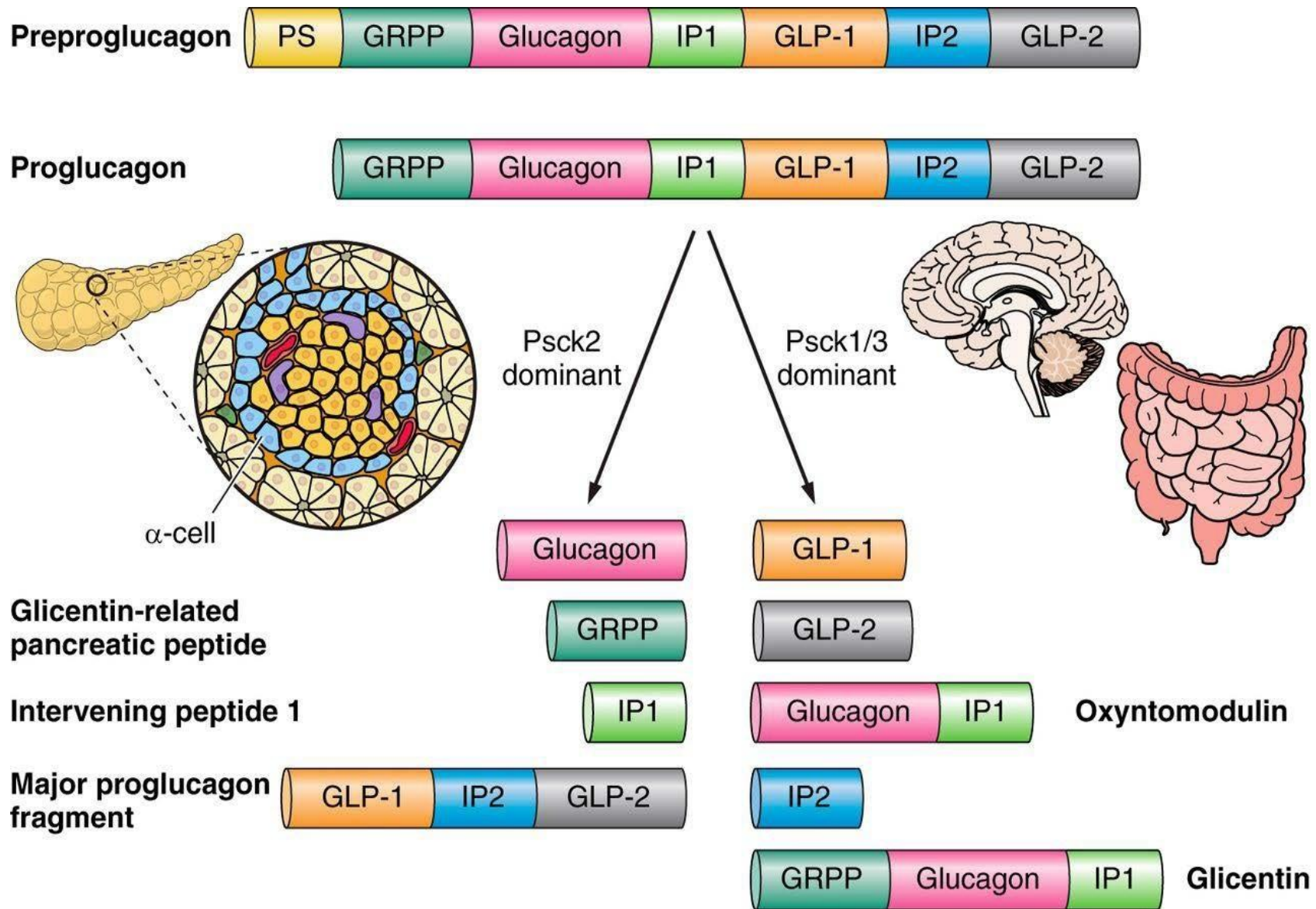


TABLE 23-3 Effects of Insulin on Blood Glucose: Uptake of Glucose by Cells and Storage as Triacylglycerols and Glycogen

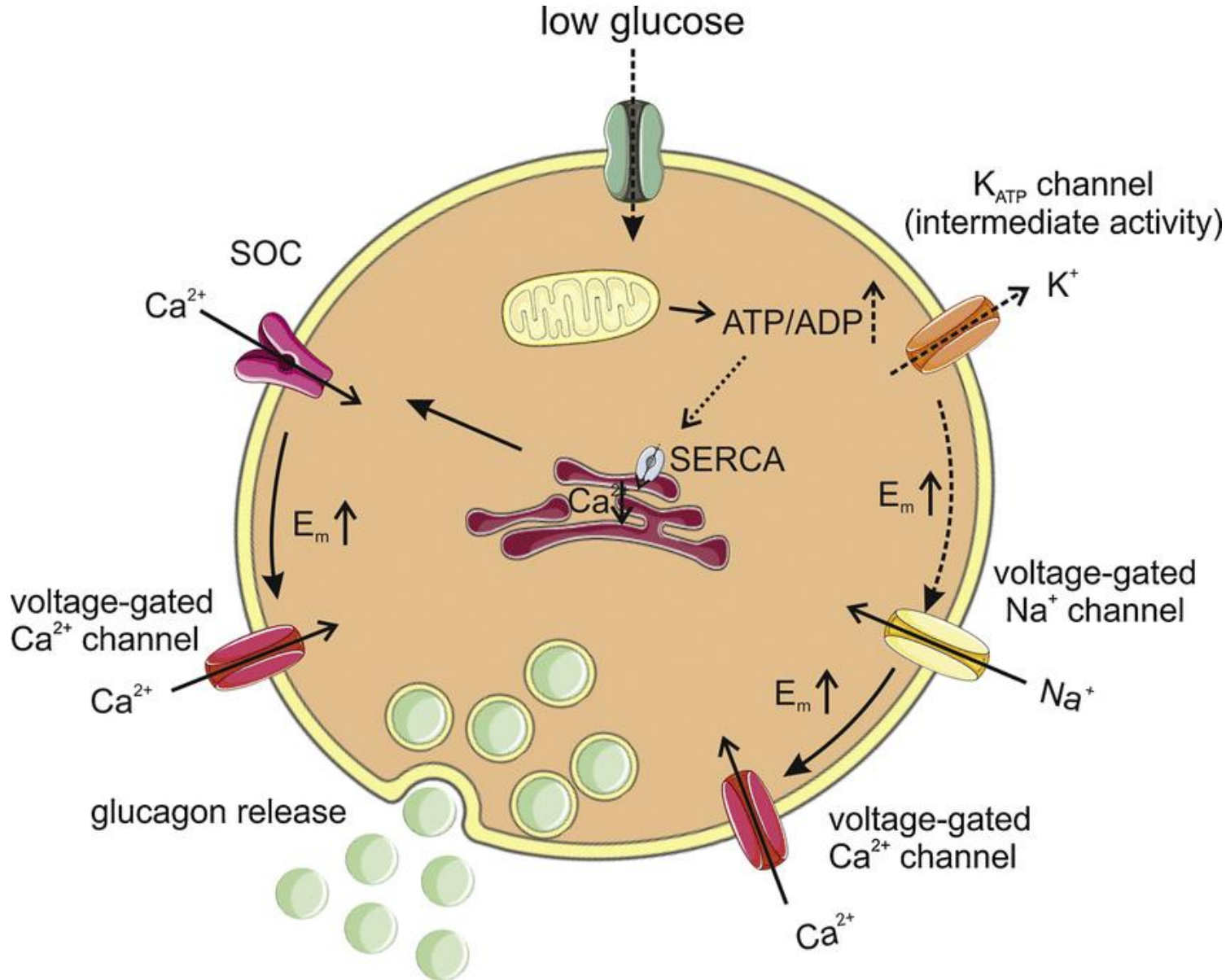
Metabolic effect	Target enzyme
↑ Glucose uptake (muscle, adipose)	↑ Glucose transporter (GLUT4)
↑ Glucose uptake (liver)	↑ Glucokinase (increased expression)
↑ Glycogen synthesis (liver, muscle)	↑ Glycogen synthase
↓ Glycogen breakdown (liver, muscle)	↓ Glycogen phosphorylase
↑ Glycolysis, acetyl-CoA 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 α possuem GLUT1
- Células α possuem glicoquinase
- ↓ glicemia = ↓ ATP
- ↓ ATP ativa canais para saída de K⁺
- Despolarização
- Ativação da entrada de Na¹⁺ e Ca²⁺
- Ativação da liberação de Ca²⁺ do RE
- Síntese de glucagon
- Secreção de glucagon em vesículas

Mecanismo de Sinalização pelo Glucagon: Glicogenólise

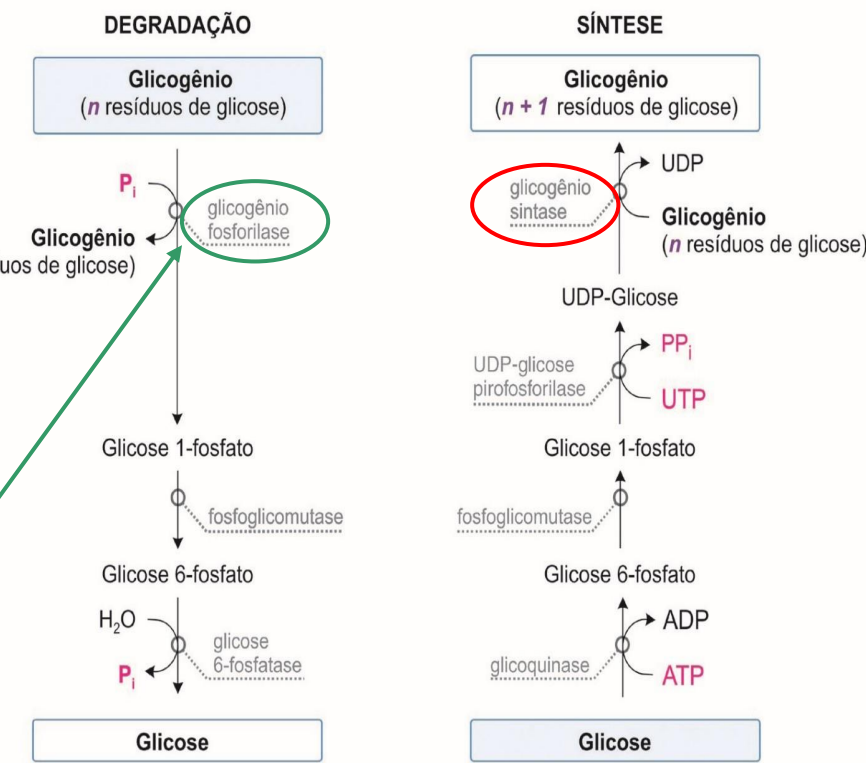
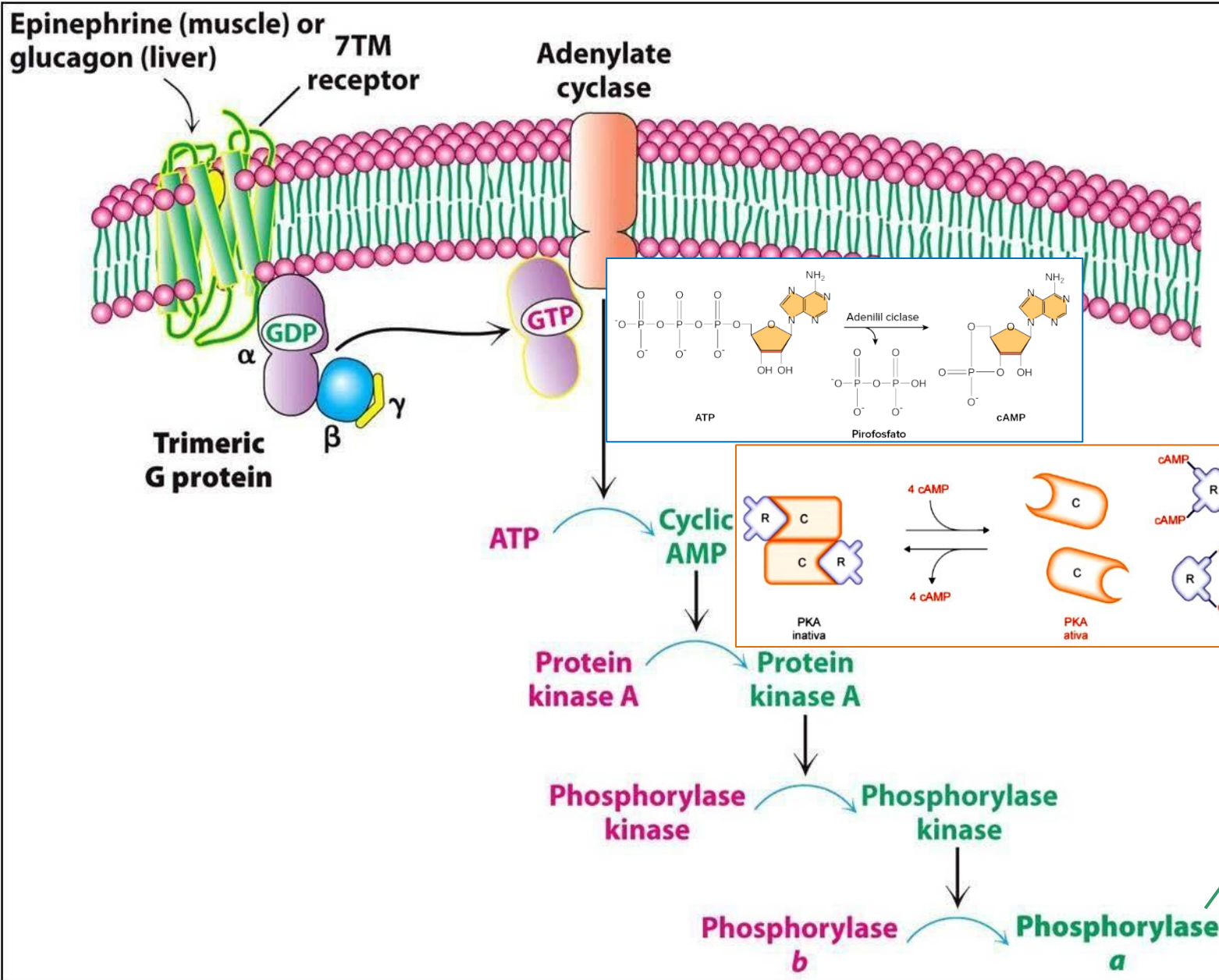


Fig. 13.5 Esquema geral da degradação e síntese de glicogênio no fígado.

Regulação do metabolismo pelo Glucagon

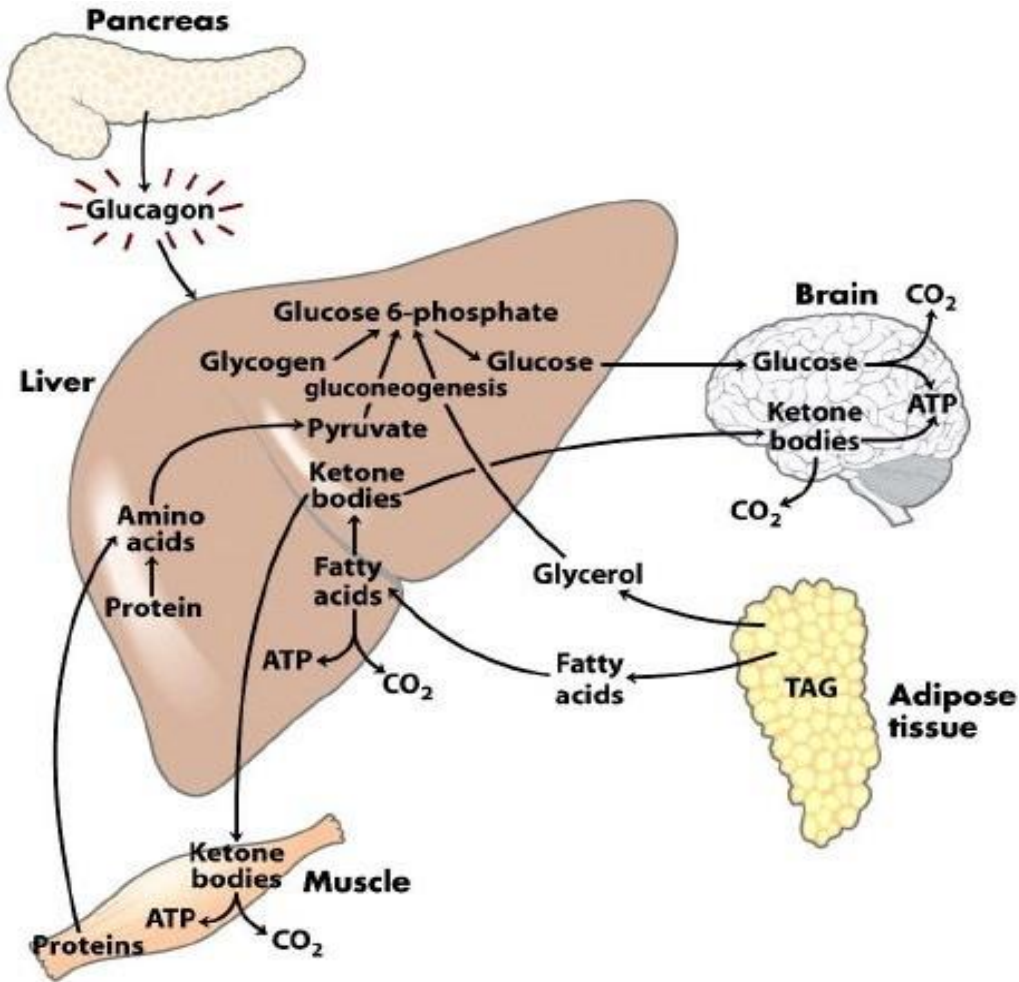


TABLE 23-4 Effects of Glucagon on Blood Glucose: Production and Release of Glucose by the Liver

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	↑ PEP carboxykinase ↑ 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

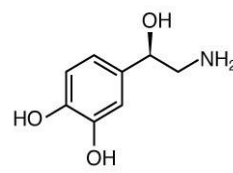
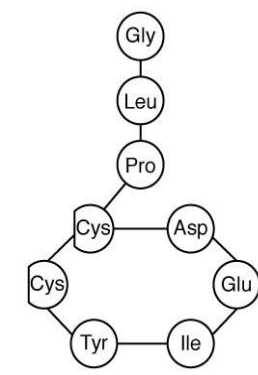
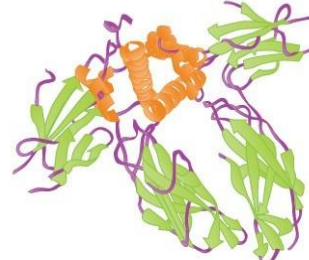
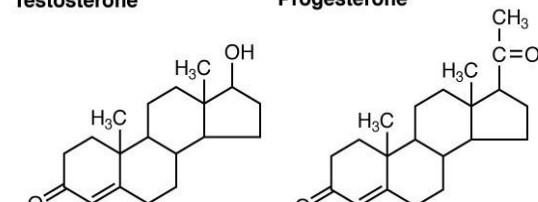
- Processo passivo
- GLUTs de 1-14; mais expressas e caracterizadas: GLUTs 1-4
- GLUT2: menor afinidade por glicose
- GLUT4: dependente de insulina

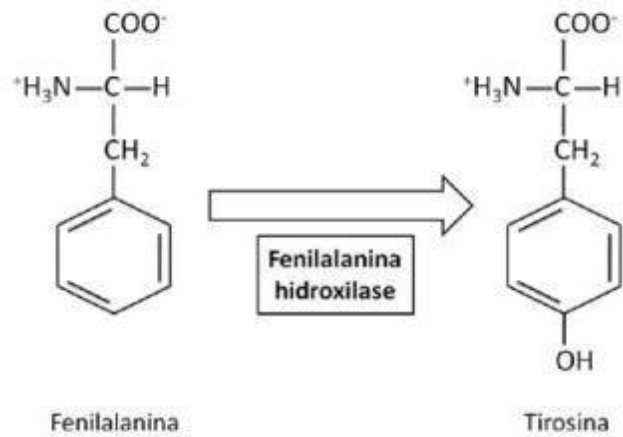
Tabela 19.4 Transportadores de glicose em mamíferos.

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 β 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

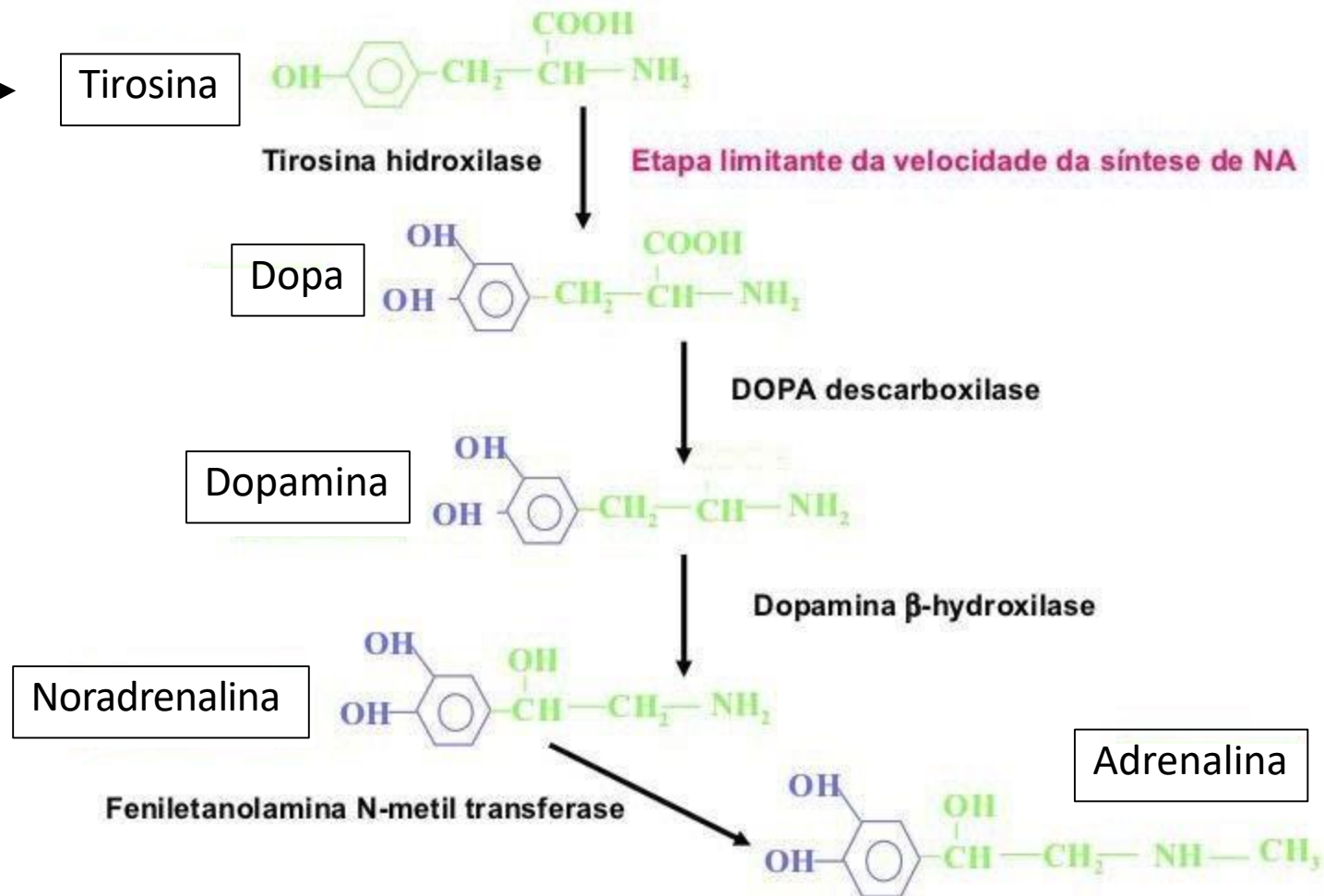
Concentração normal de glicose sanguínea = 5 a 8 mM.

Hormônios derivados de Aminoácidos

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

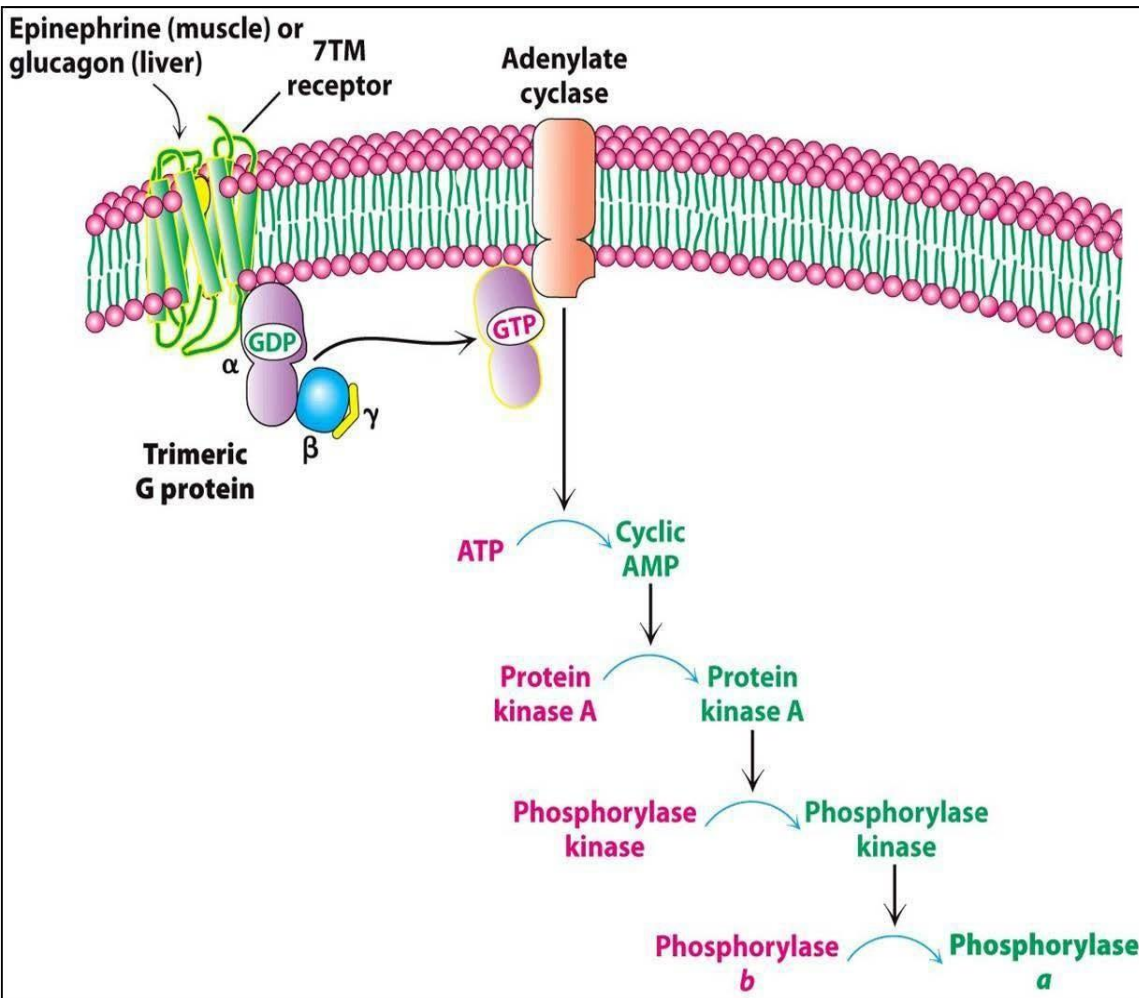
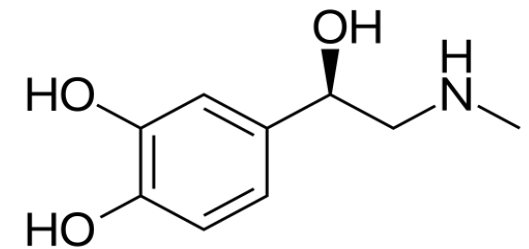


TABLE 23-6 Physiological and Metabolic Effects of Epinephrine: Preparation for Action

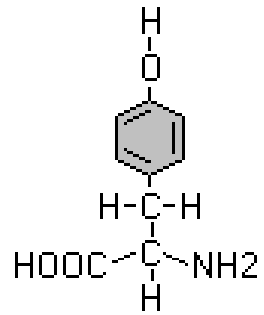
Immediate effect	Overall effect
Physiological ↑ Heart rate ↑ Blood pressure ↑ Dilation of respiratory passages	Increase delivery of O ₂ to tissues (muscle)
Metabolic ↑ Glycogen breakdown (muscle, liver) ↓ Glycogen synthesis (muscle, liver) ↑ Gluconeogenesis (liver)	
↑ Glycolysis (muscle) ↑ Fatty acid 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



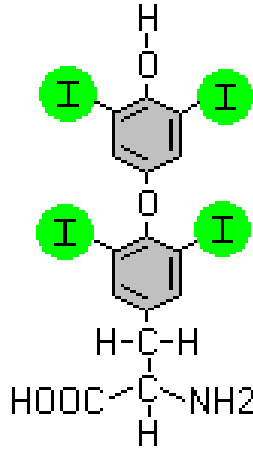
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<https://commons.wikimedia.org/w/index.php?curid=5902493>

Uso clinicamente em parada cardíaca, choque, anafilaxia

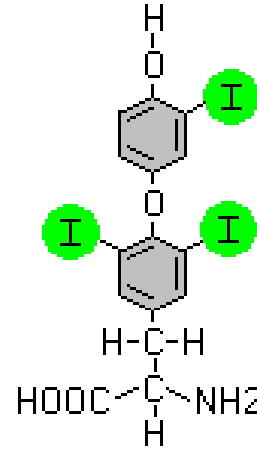
Hormônios Tireoidianos



Tyrosine



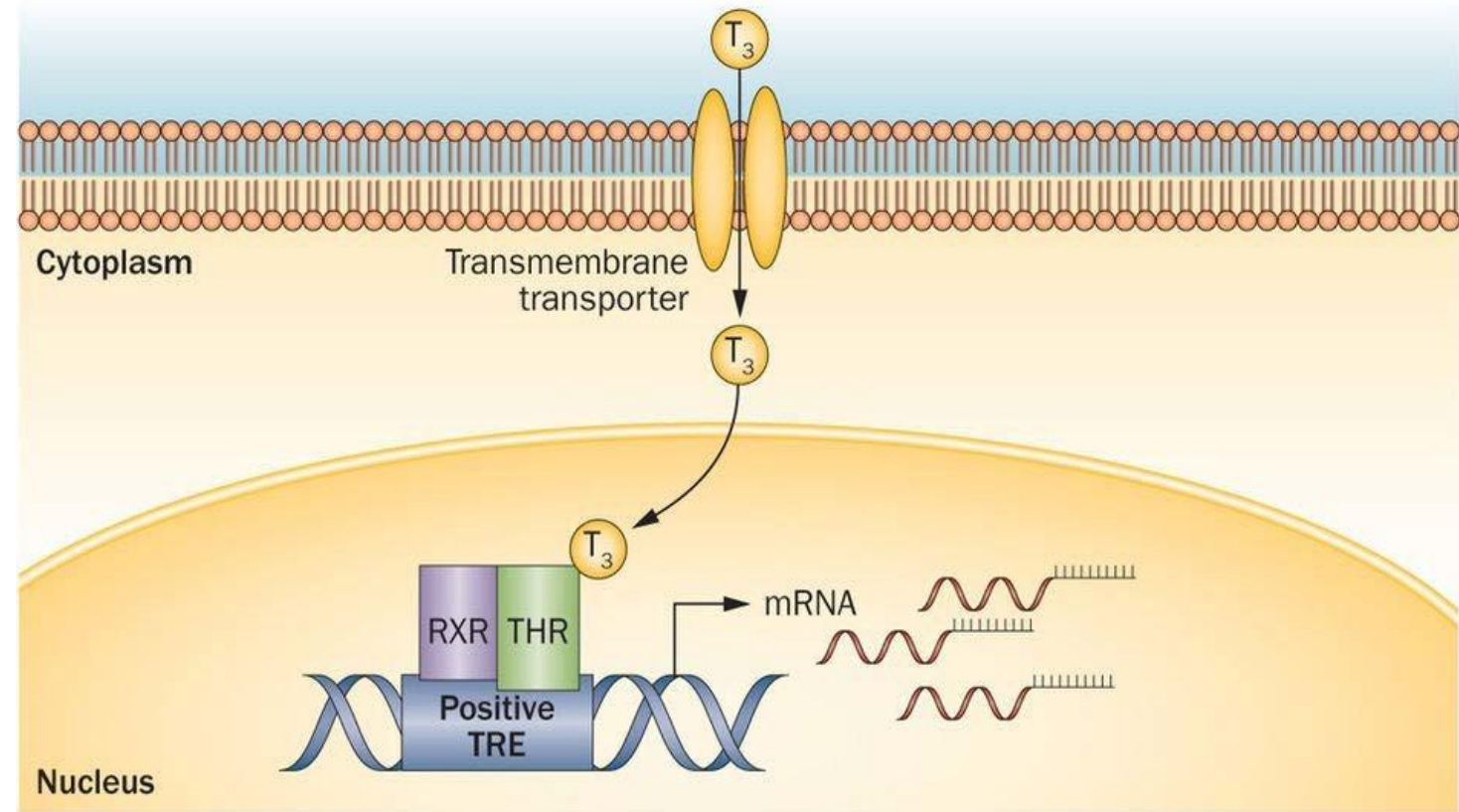
Thyroxine (T4)



Triiodothyronine (T3)

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

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

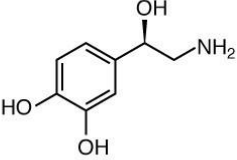
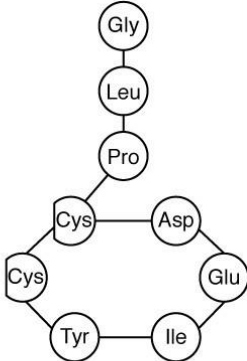
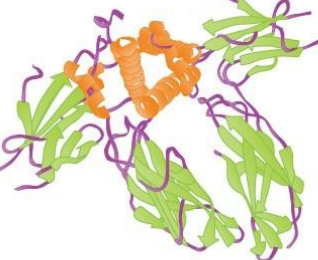


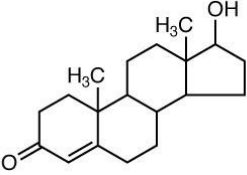
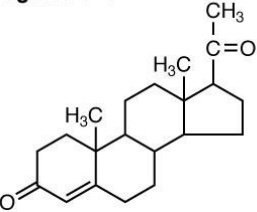
Hormônios Tireoidianos

Parameter	↓ T ₃ , T ₄	↑ T ₃ , T ₄
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)
Amine Hormone	Amino acids with modified groups (e.g. norepinephrine's carboxyl group is replaced with a benzene ring)	<p>Norepinephrine</p> 
Peptide Hormone	Short chains of linked amino acids	<p>Oxytocin</p> 
Protein Hormone	Long chains of linked amino acids	<p>Human Growth Hormone</p> 

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

Doença de Addison's autoimunidade contra o cortex adrenal

Doença de Cushing's hipersecreção de glicocorticóide

