



UNIVERSIDADE DE SÃO PAULO
FACULDADE DE MEDICINA DE RIBEIRÃO PRETO



CURSO DE MEDICINA - 2019

HORMÔNIOS CONTRARREGULADORES E RESISTÊNCIA À INSULINA

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Departamento de Fisiologia
FMRP-USP

Produção hepática de glicose **(neoglicogênese e glicogenólise)**



**Glicose
plasmática**



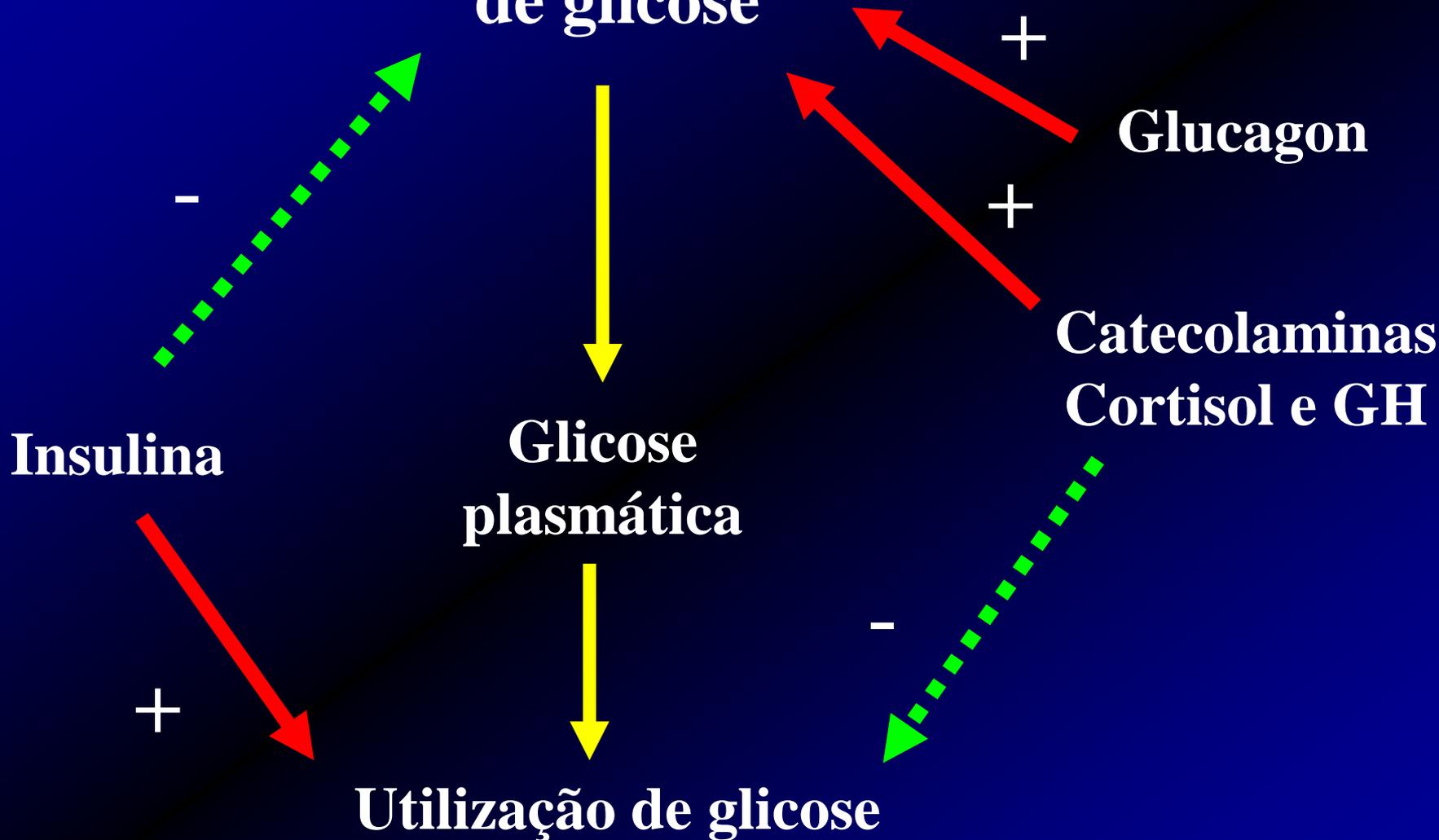
Utilização de glicose

**(glicólise, oxidação de glicose, síntese de glicogênio e de
ácidos graxos, etc...)**

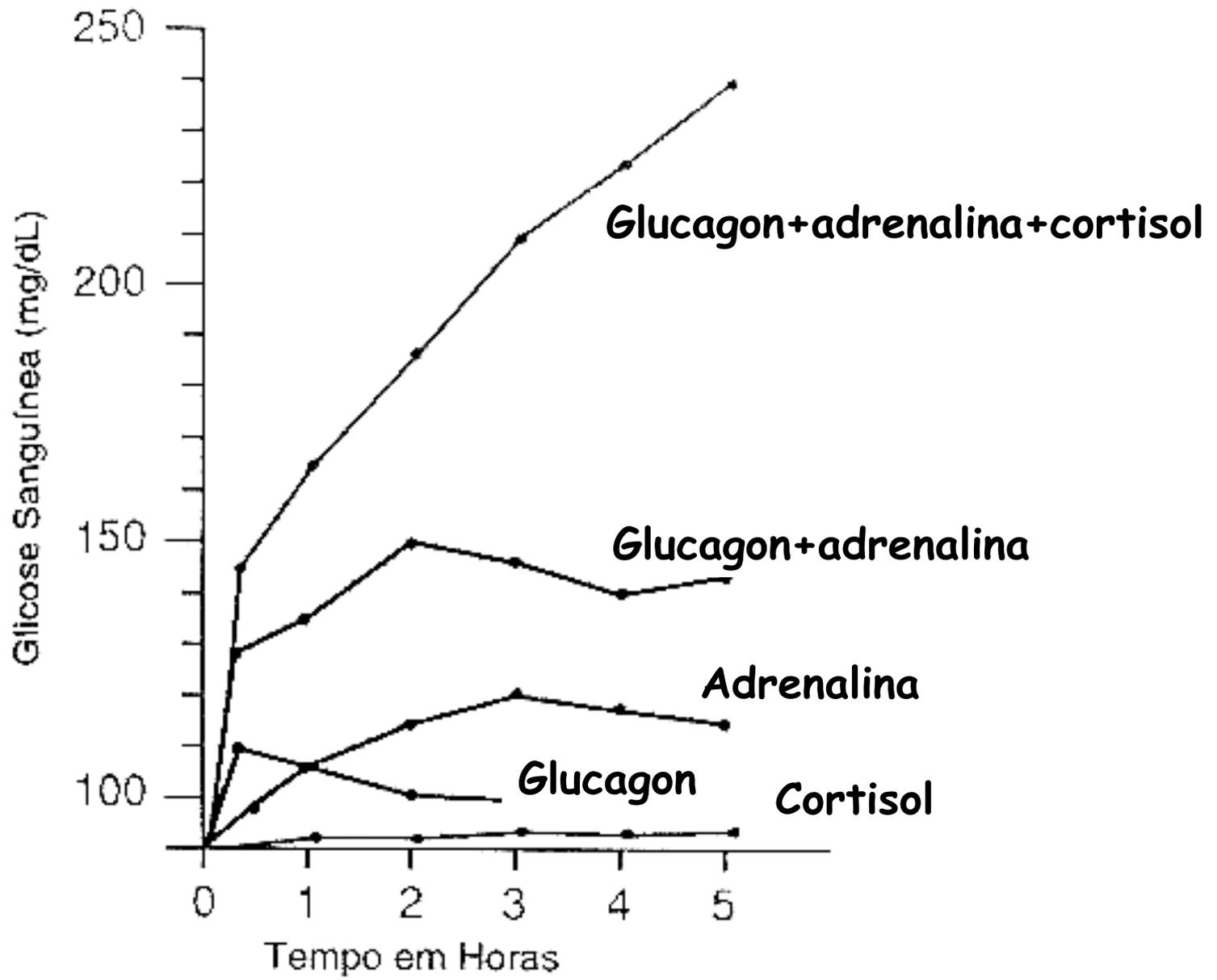
Produção hepática de glicose (neoglicogênese e glicogenólise)



Produção hepática de glicose



(glicólise, oxidação de glicose, síntese de glicogênio e de ácidos graxos, etc...)



Situações Fisiológicas de Demanda Energética

Jejum

Frio

Exercício

Hipóxia

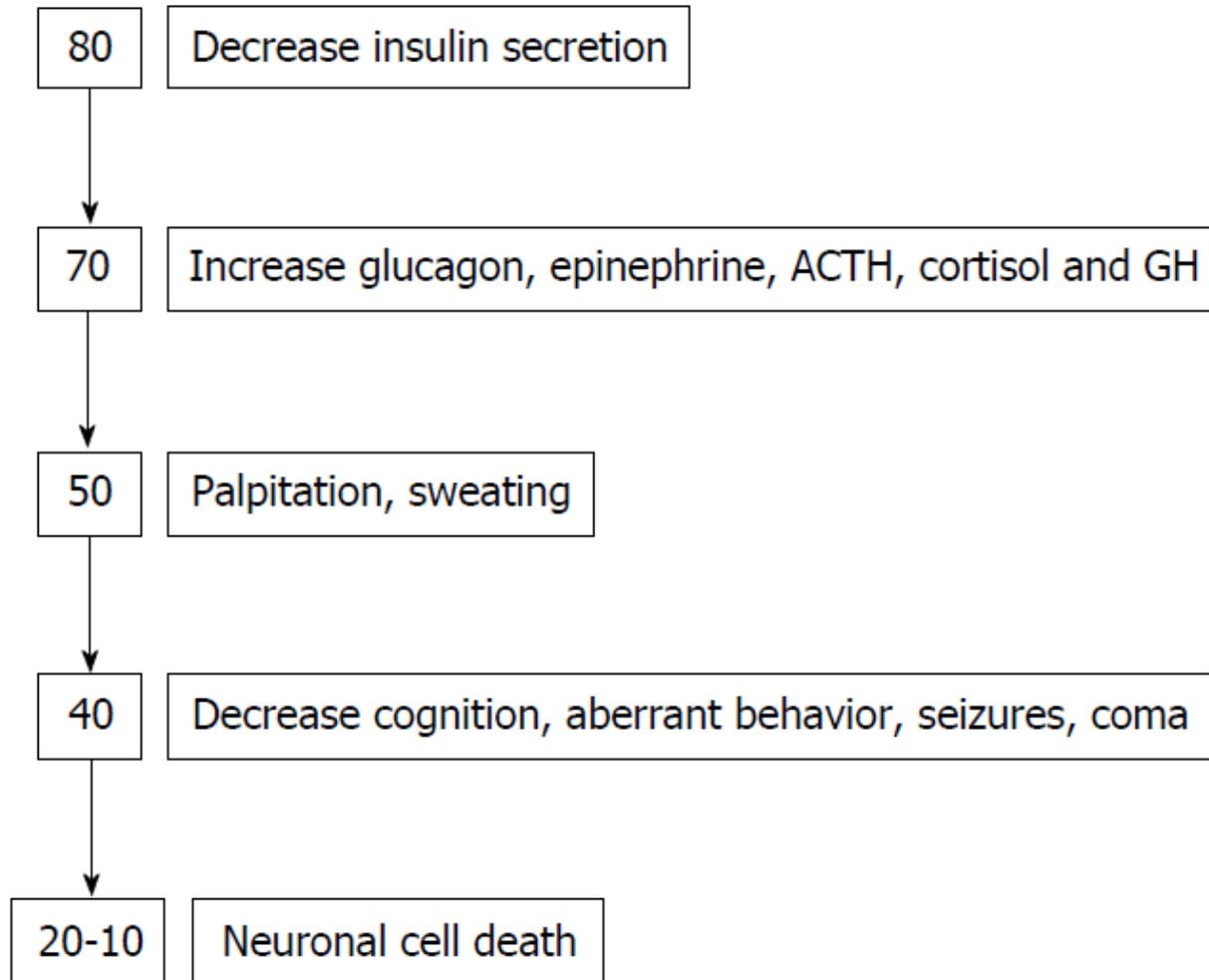
**Estresse Cirúrgico e
Psicológico**

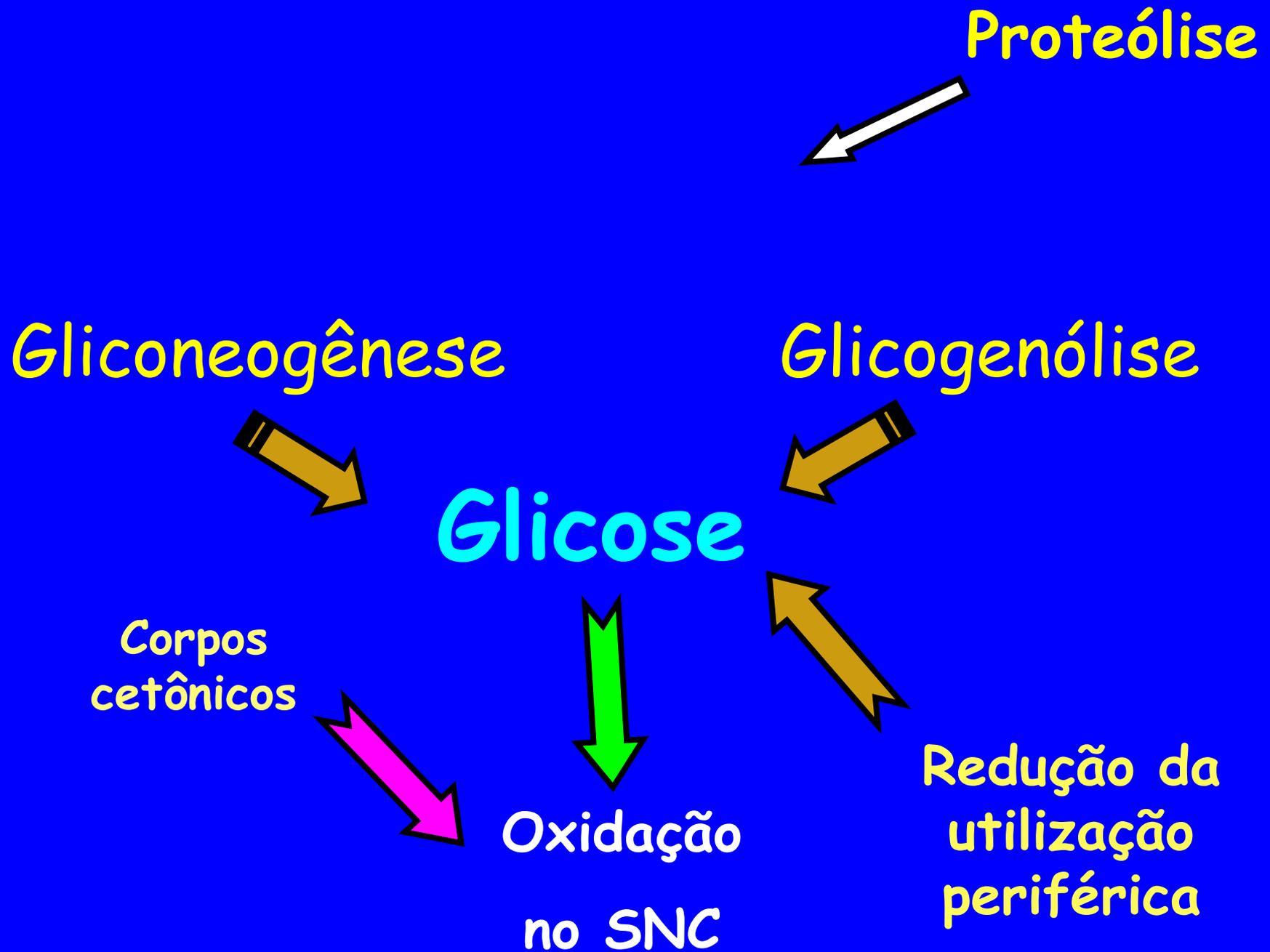
Valor de referência da glicemia de jejum

100 mg/dL

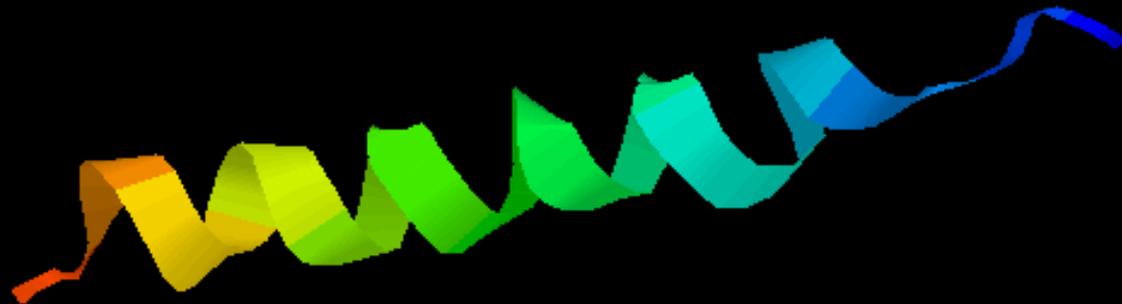
Sinais e sintomas associados à hipoglicemia

Blood glucose (mg/dL)





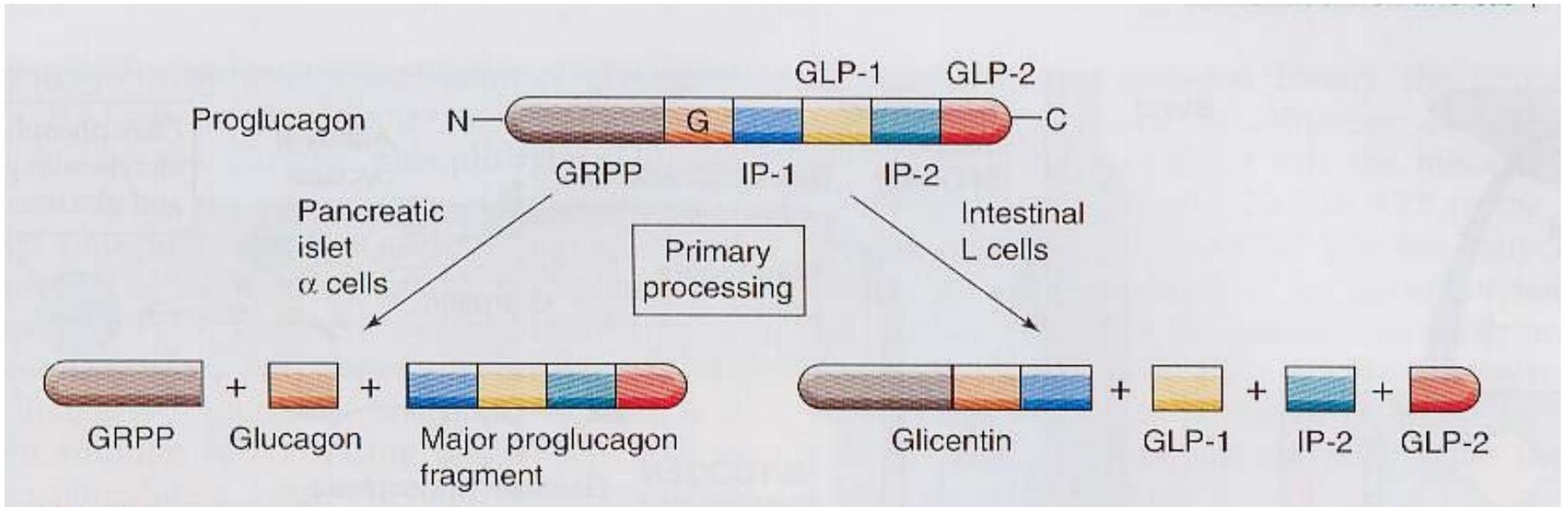
GLUCAGON



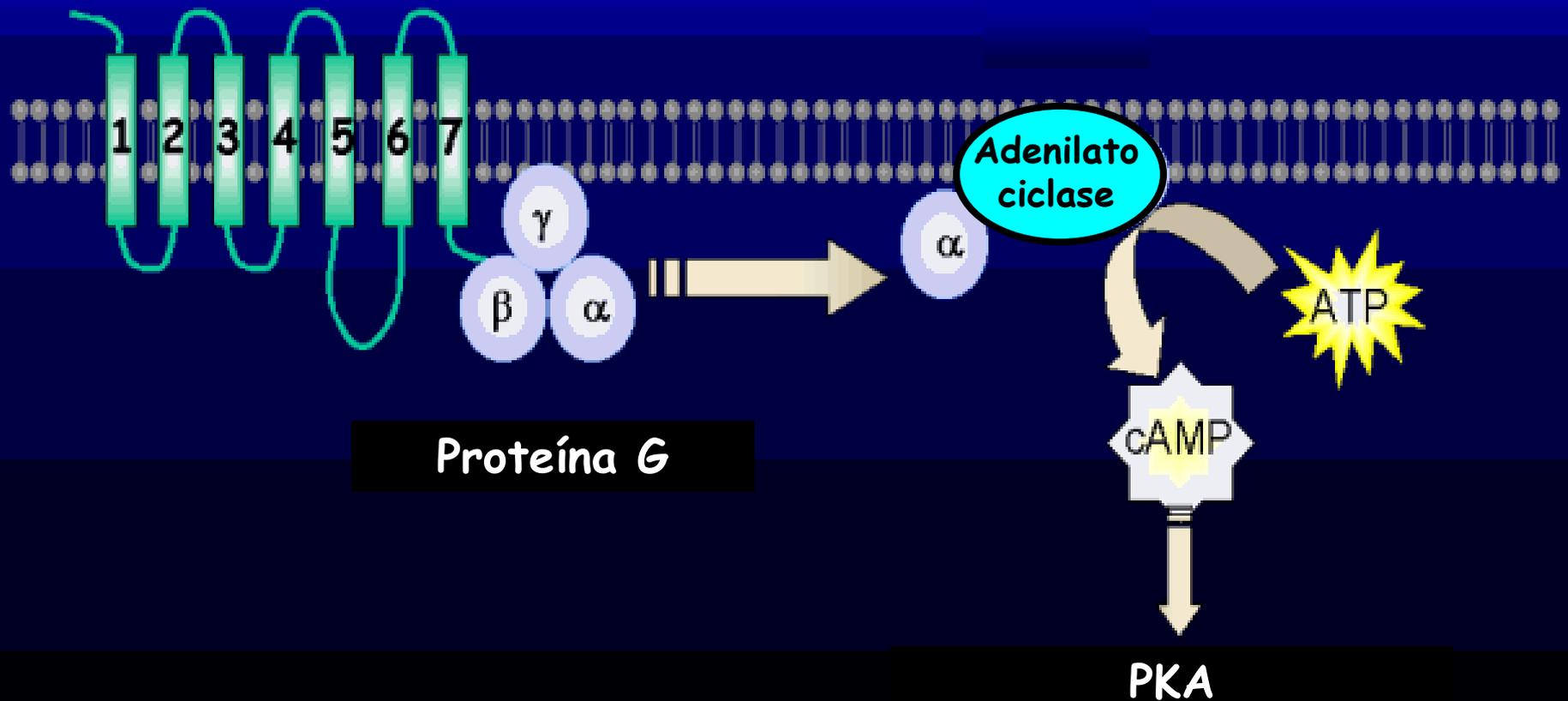
H_3N^+ —His—Ser—Glu—Gly—Thr—Phe—Thr—Ser—Asp—Tyr—10

Ser—Lys—Tyr—Leu—Asp—Ser—Arg—Arg—Ala—Gln—20

Asp—Phe—Val—Gln—Trp—Leu—Met—Asn—Thr— COO^- 29



Receptor do glucagon



Glicogênio

Fosforilase

Inativa

Ativa-PO₄



Glicogênio



Glicose



Ativa

Inativa-PO₄

Glicogênio

Sintetase

GLUCAGON

(Efeitos Metabólicos)

Glicogenólise ↑

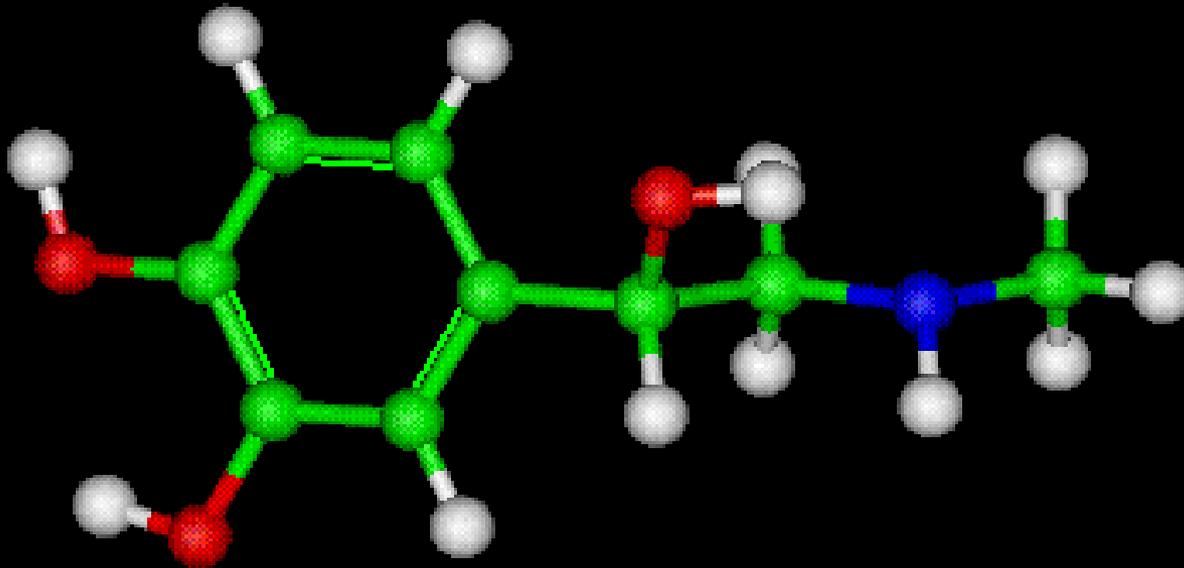
Neoglicogênese ↑

Glicólise ↓

Lipólise ↑

Cetogênese ↑

CATECOLAMINAS



ADRENALINA

(Efeitos Metabólicos)

Glicogenólise ↑

Neoglicogênese ↑

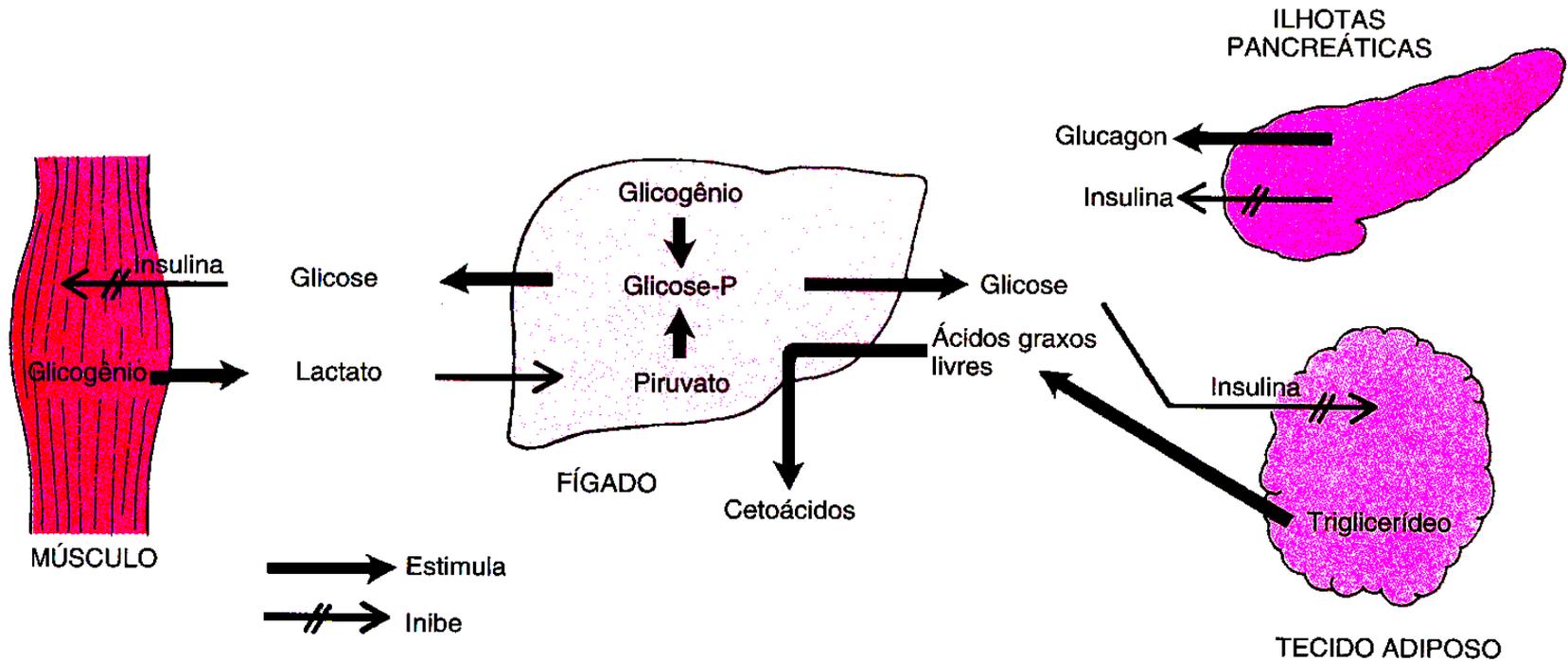
Glicólise ↑

Lipólise ↑

Cetogênese ↑

Captação de Glicose no Músculo e TA ↓

AÇÕES DAS CATECOLAMINAS NO METABOLISMO INTERMEDIÁRIO



Inibem a proteólise muscular

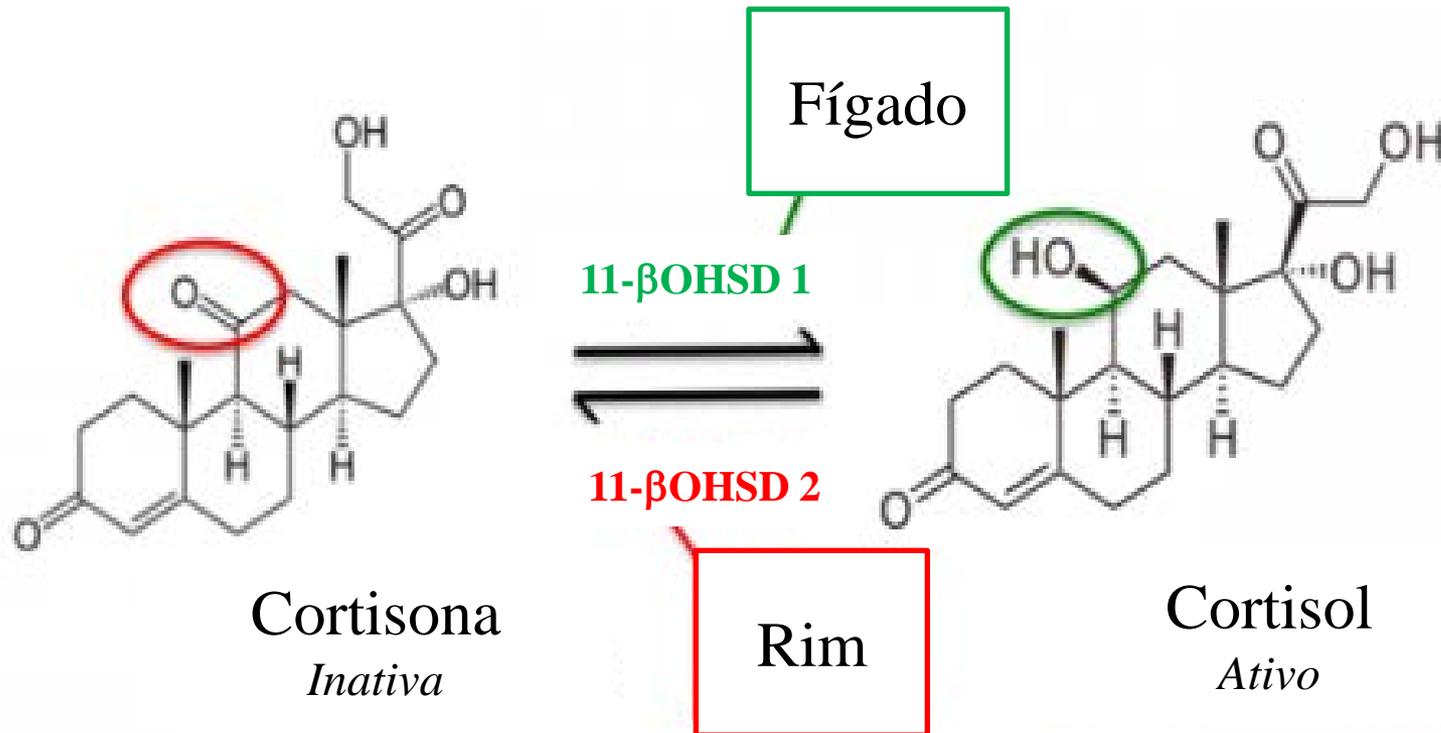
Estimulam síntese protéica

Effects of oral administration of β_2 -agonists

Animal	Body Weight (%)	Muscle Weight (%)
Cattle	+ 10	+ 10
Chicken	+ 2	+ 2
Pig	+ 4	+ 4
Lamb	+ 15	+ 25

Adapted from Mersmann (1998)

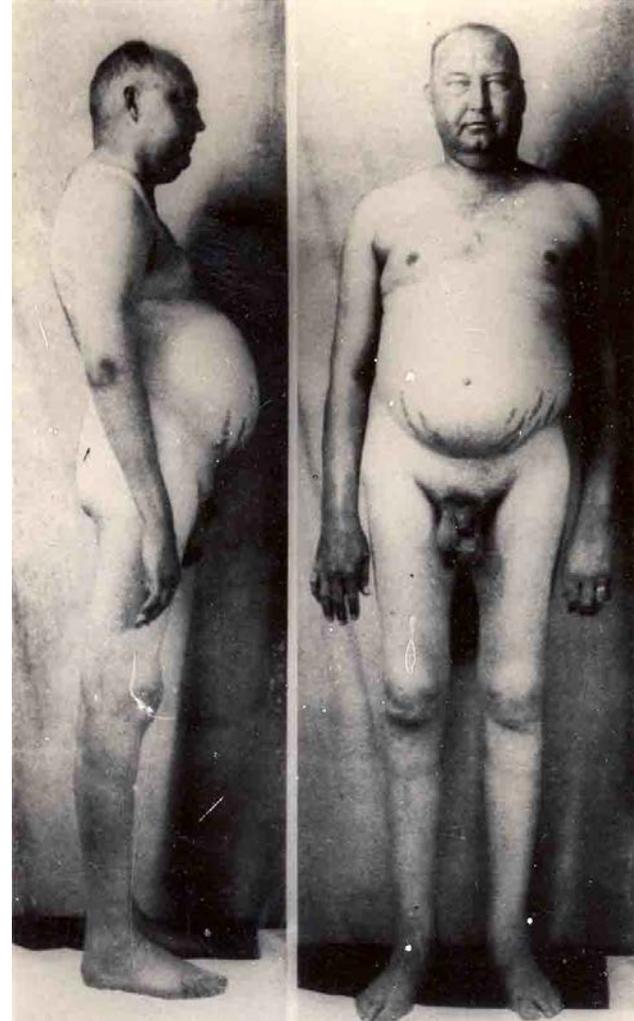
A Biodisponibilidade dos Glicocorticoides



Síndrome de Cushing



Harvey Cushing
(1869-1939)



Bull. Johns Hopkins Hosp. 50: 137-195, 1932

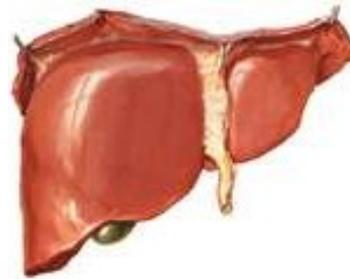
Os substratos para a NEOGLICOGÊNESE são mobilizados pelos glicocorticóides



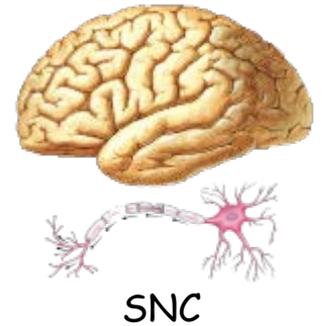
PRÓTEÓLISE ↑
SÍNTESE PROTEICA ↓

Aminoácidos

NEOGLICOGÊNESE ↑

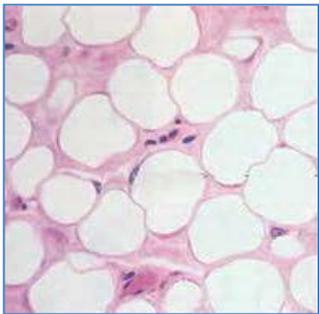


Glicose



SNC

Glicerol



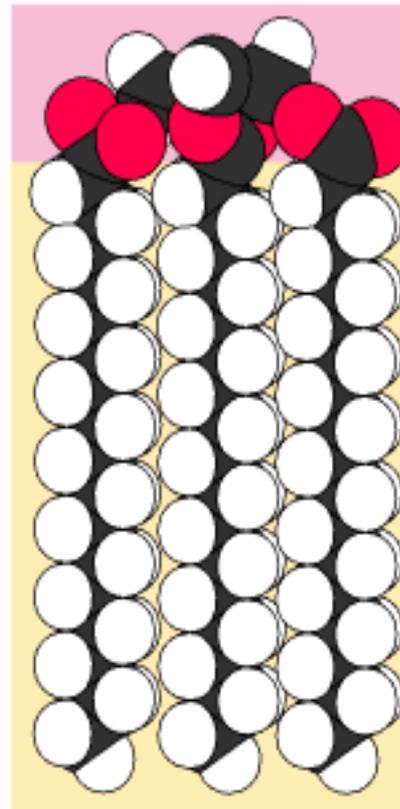
LIPÓLISE ↑

Efeitos do cortisol no metabolismo lipídico

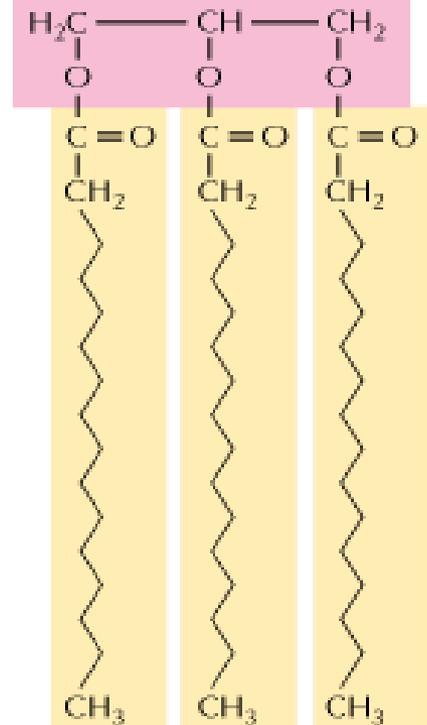
TRIACILGLICEROL



Paciente com S. de Cushing

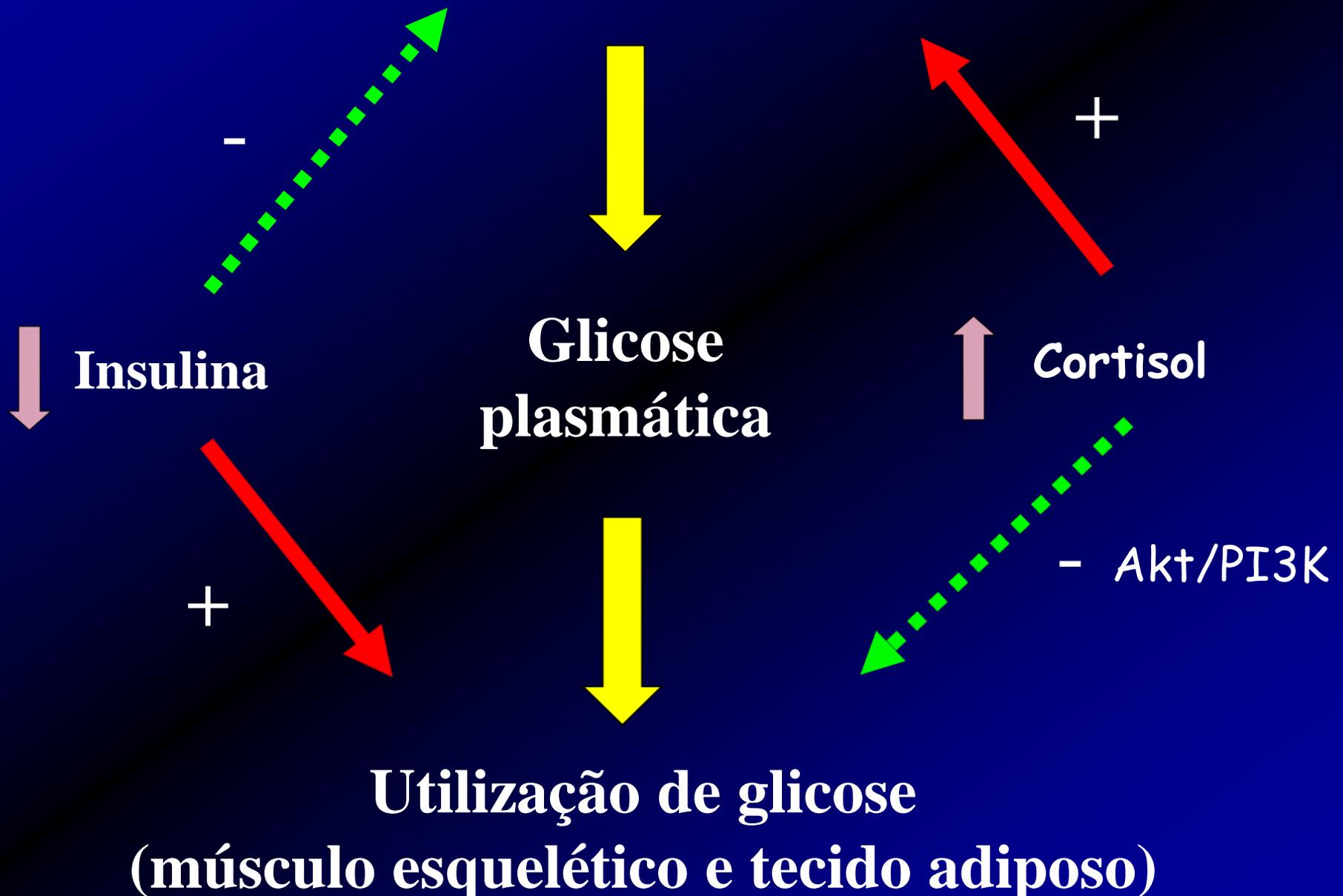


Glicerol



Ácidos
Graxos

Produção hepática de glicose (neoglicogênese)



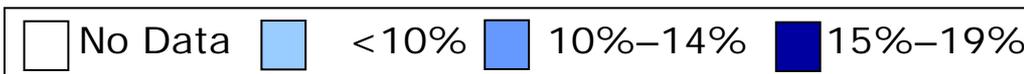
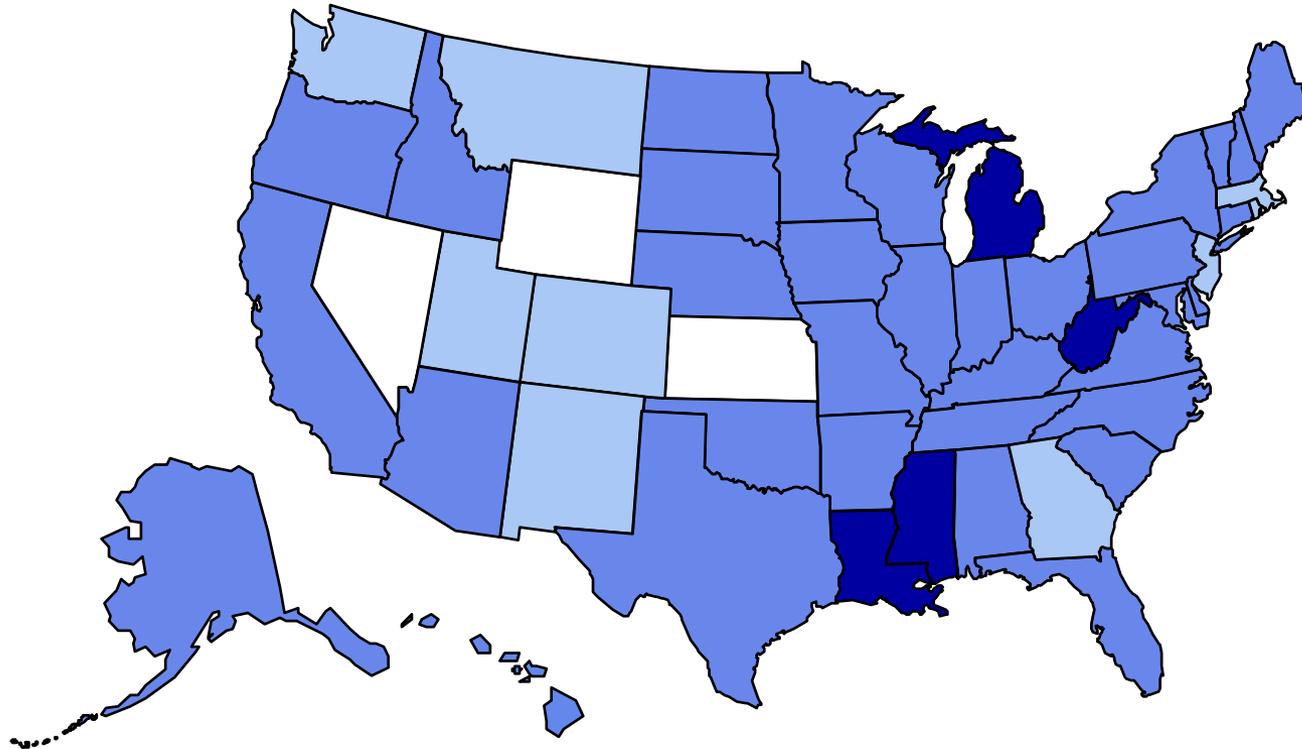
Definição de Resistência à Insulina

É o fator etiológico chave do diabetes tipo 2 que se caracteriza por alterações em diversos pontos da via de transmissão do sinal da insulina.

Obesity Trends* Among U.S. Adults

BRFSS, 1991

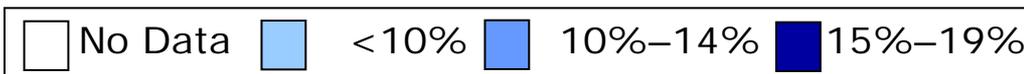
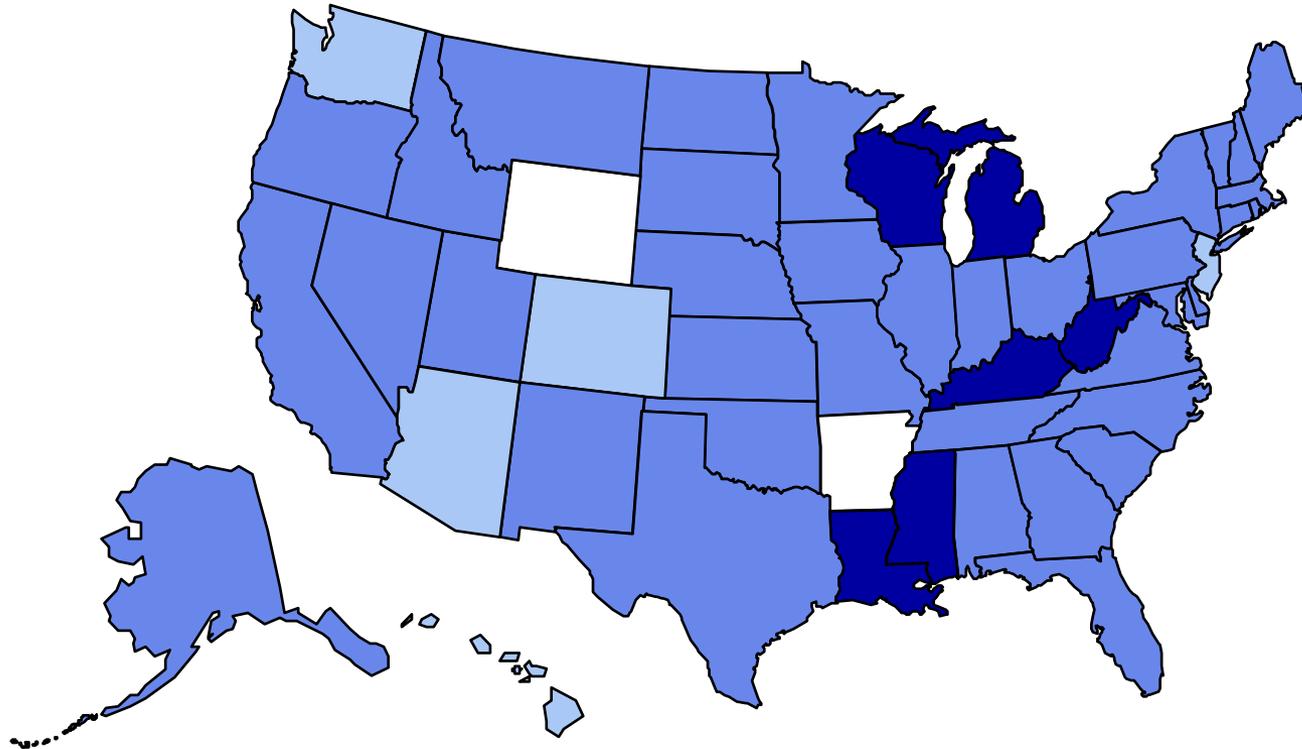
(*BMI ≥ 30 , or ~ 30 lbs overweight for 5' 4" woman)



Obesity Trends* Among U.S. Adults

BRFSS, 1992

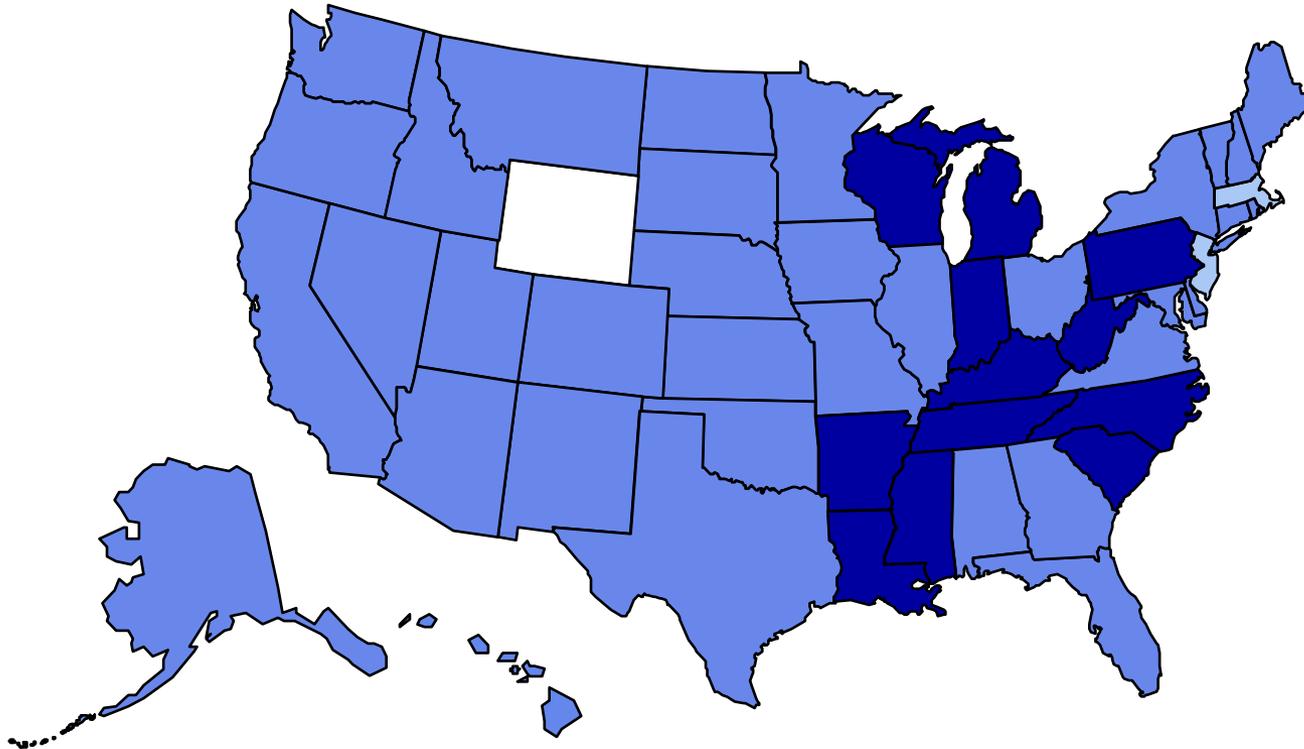
(*BMI ≥ 30 , or ~ 30 lbs overweight for 5' 4" woman)



Obesity Trends* Among U.S. Adults

BRFSS, 1993

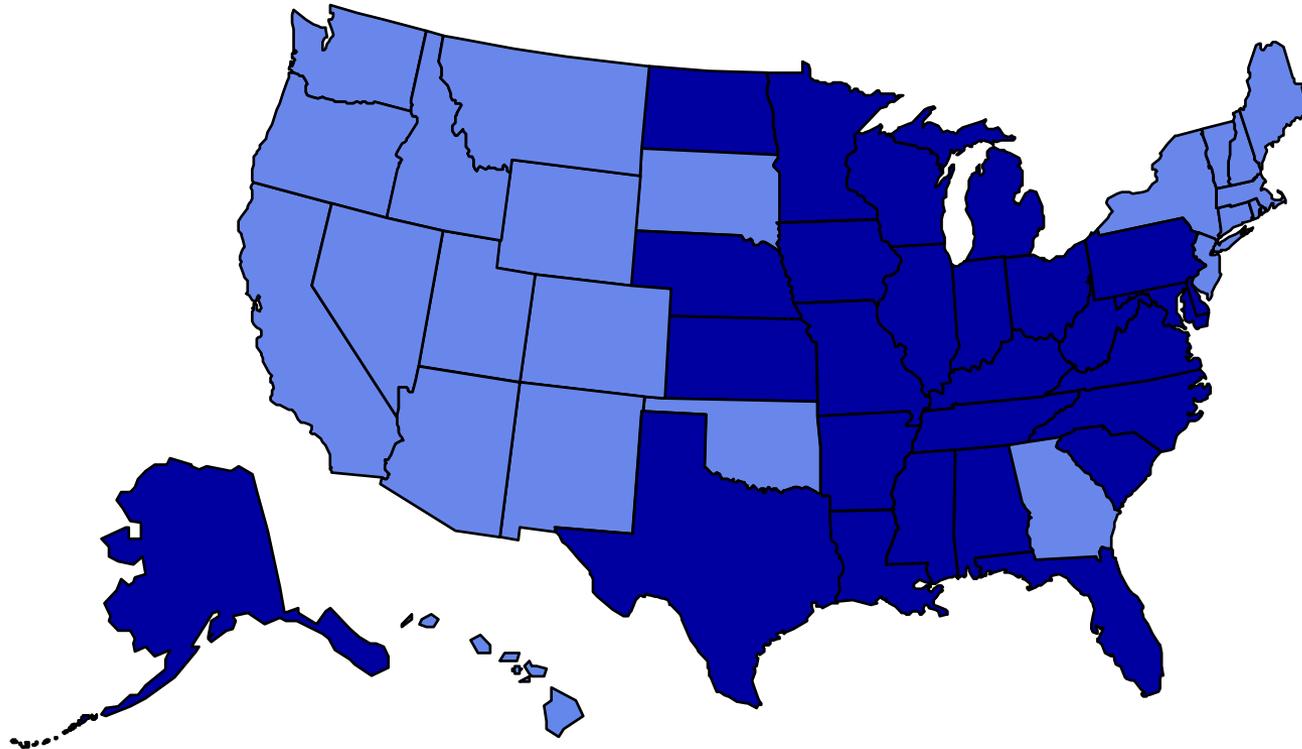
(*BMI ≥ 30 , or ~ 30 lbs overweight for 5' 4" woman)



Obesity Trends* Among U.S. Adults

BRFSS, 1995

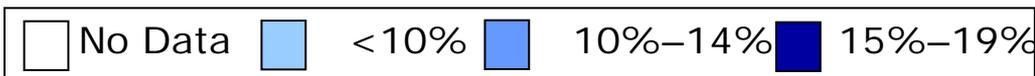
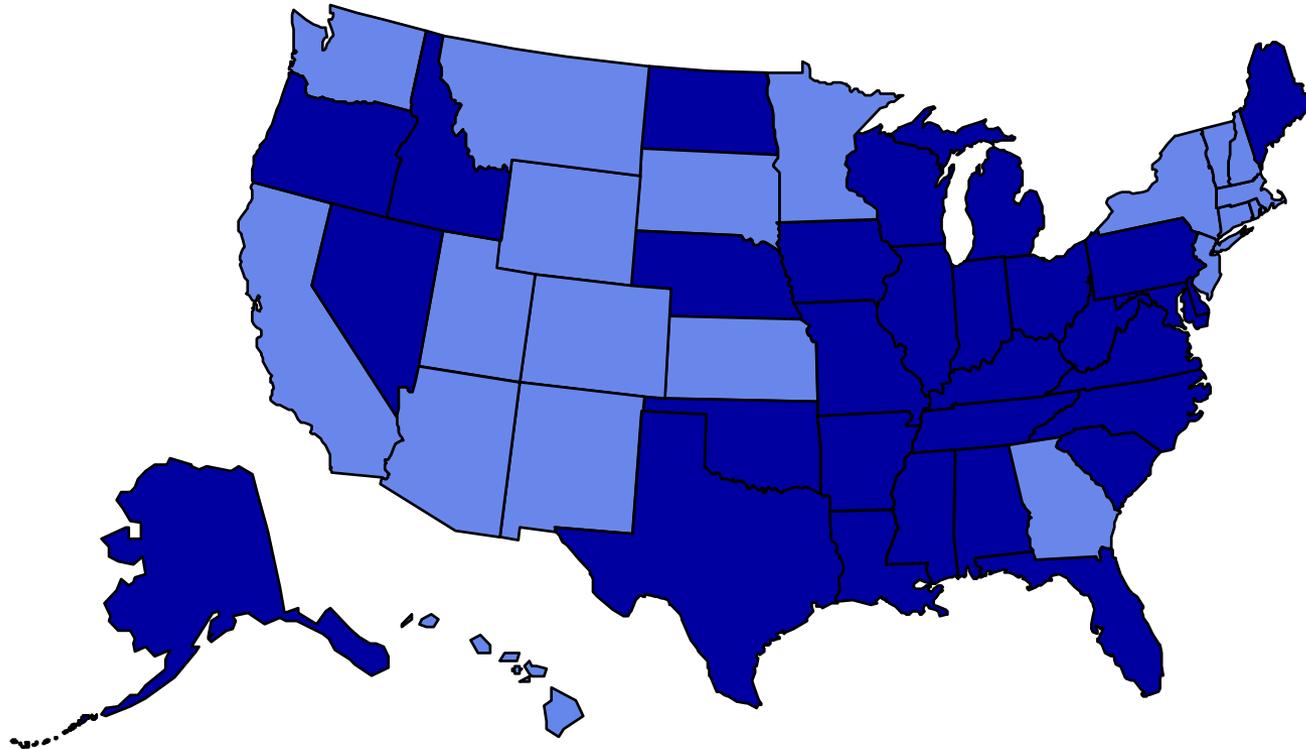
(*BMI ≥ 30 , or ~ 30 lbs overweight for 5' 4" woman)



Obesity Trends* Among U.S. Adults

BRFSS, 1996

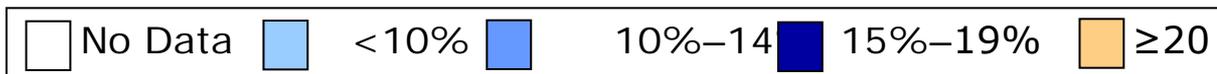
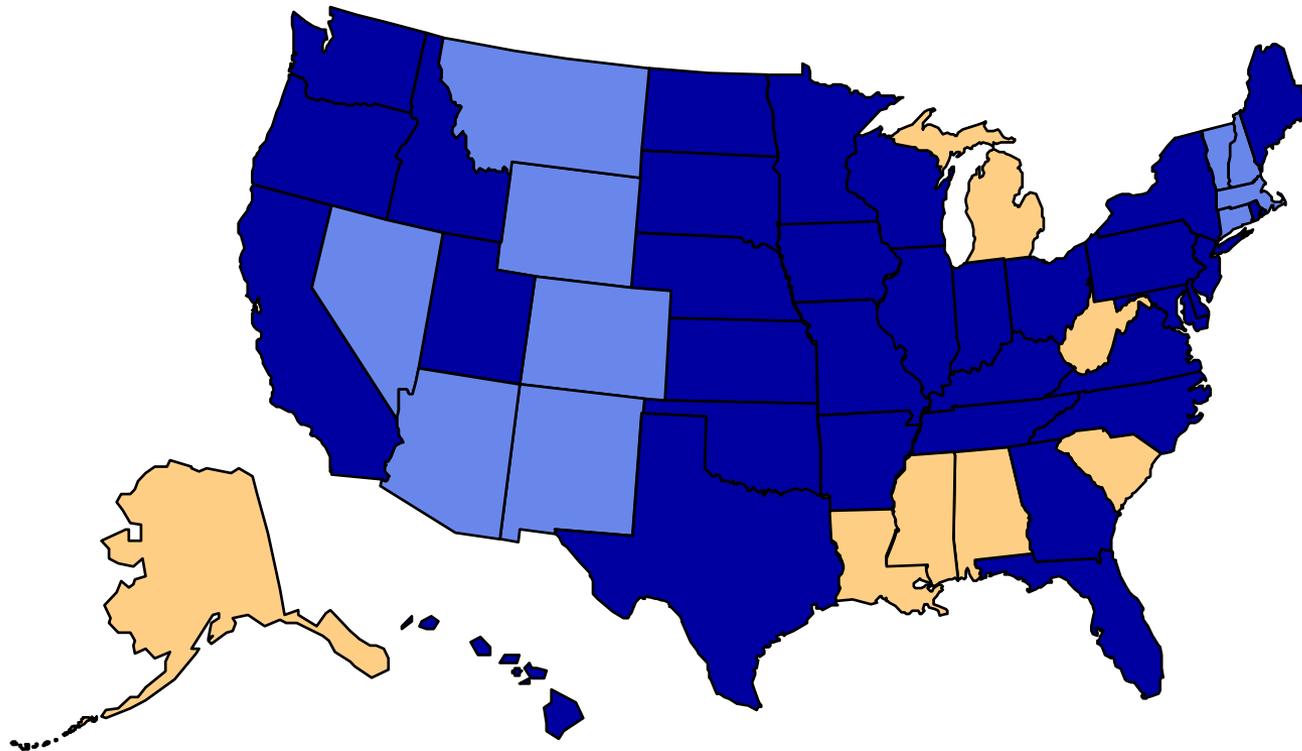
(*BMI ≥ 30 , or ~ 30 lbs overweight for 5' 4" woman)



Obesity Trends* Among U.S. Adults

BRFSS, 1998

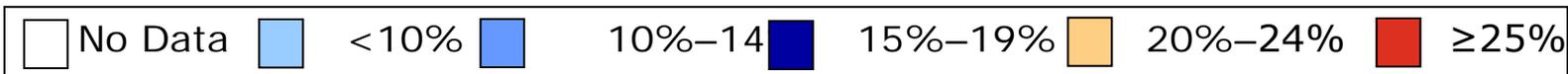
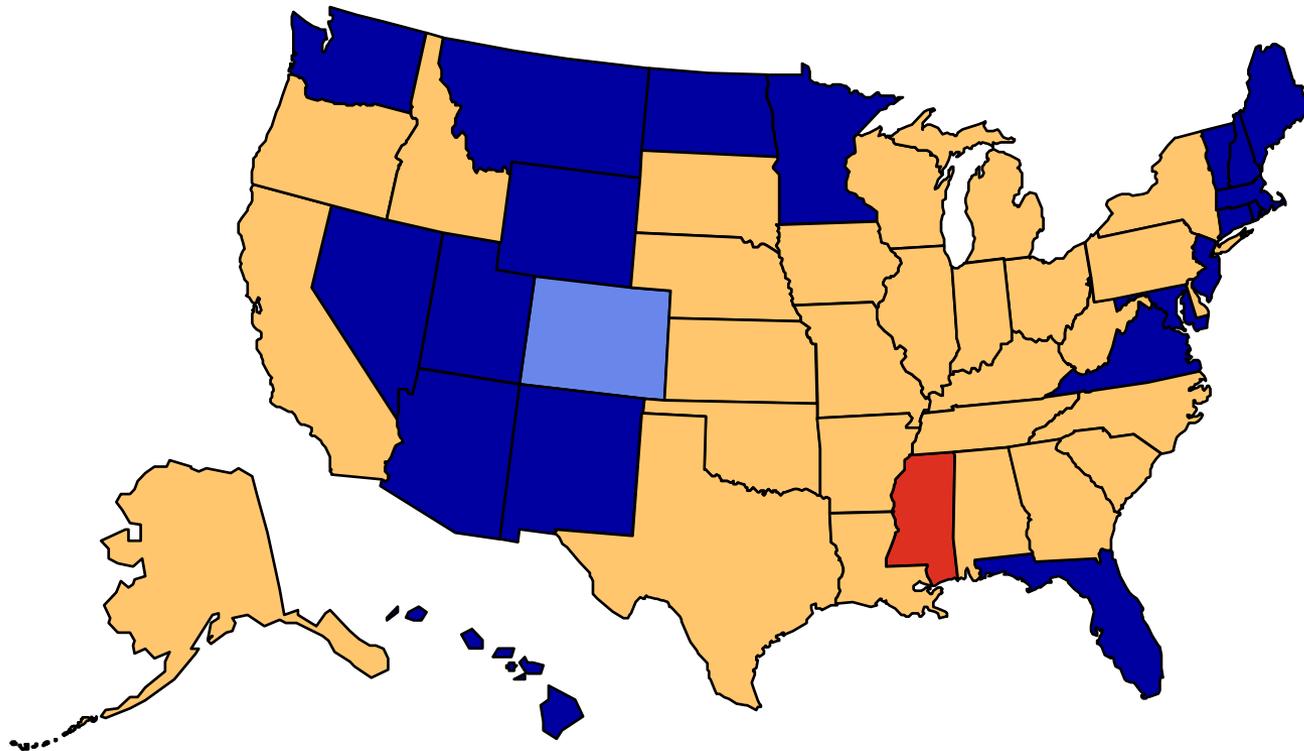
(*BMI ≥ 30 , or ~ 30 lbs overweight for 5' 4" woman)



Obesity Trends* Among U.S. Adults

BRFSS, 2001

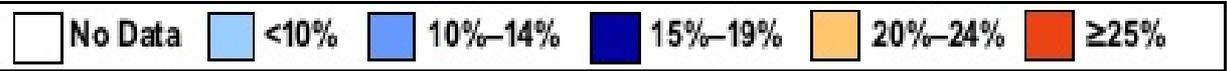
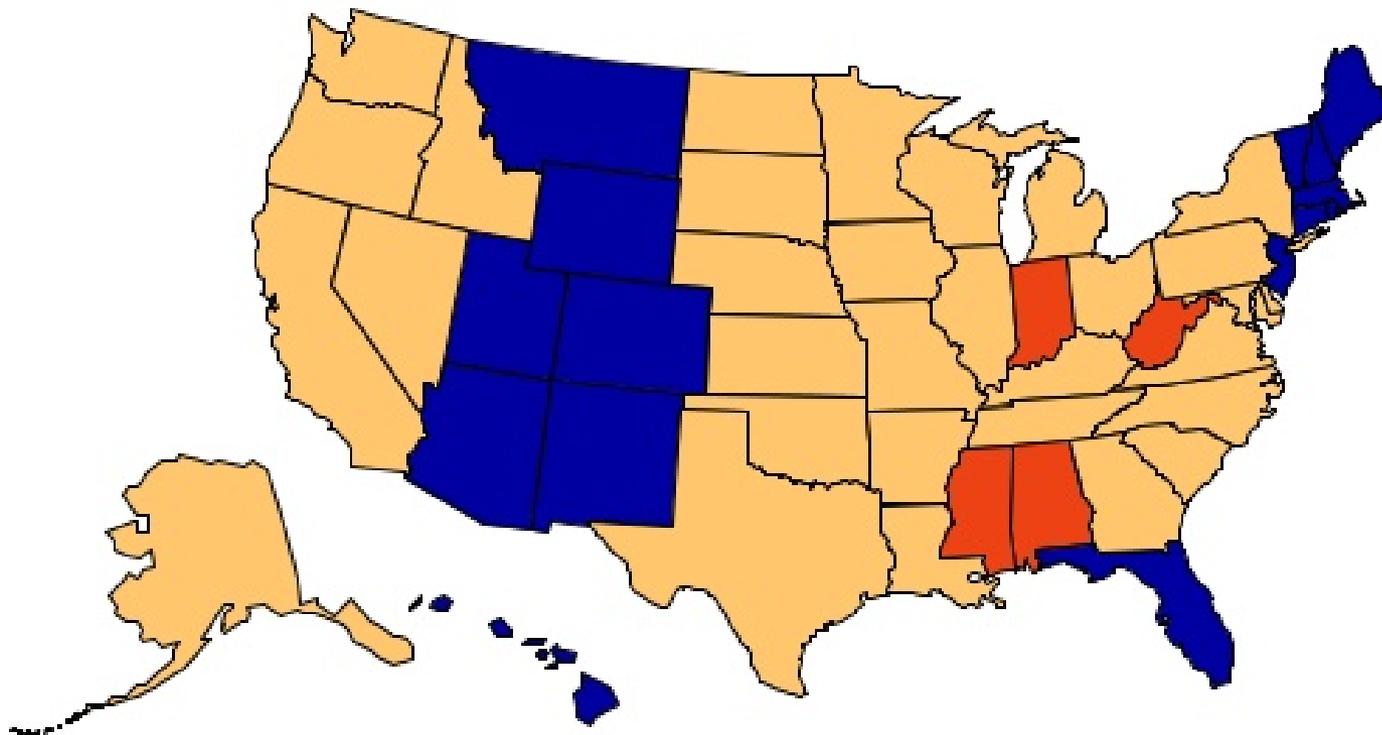
(*BMI ≥ 30 , or ~ 30 lbs overweight for 5' 4" woman)



Obesity Trends* Among U.S. Adults

BRFSS, 2003

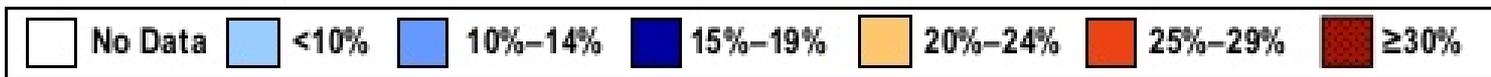
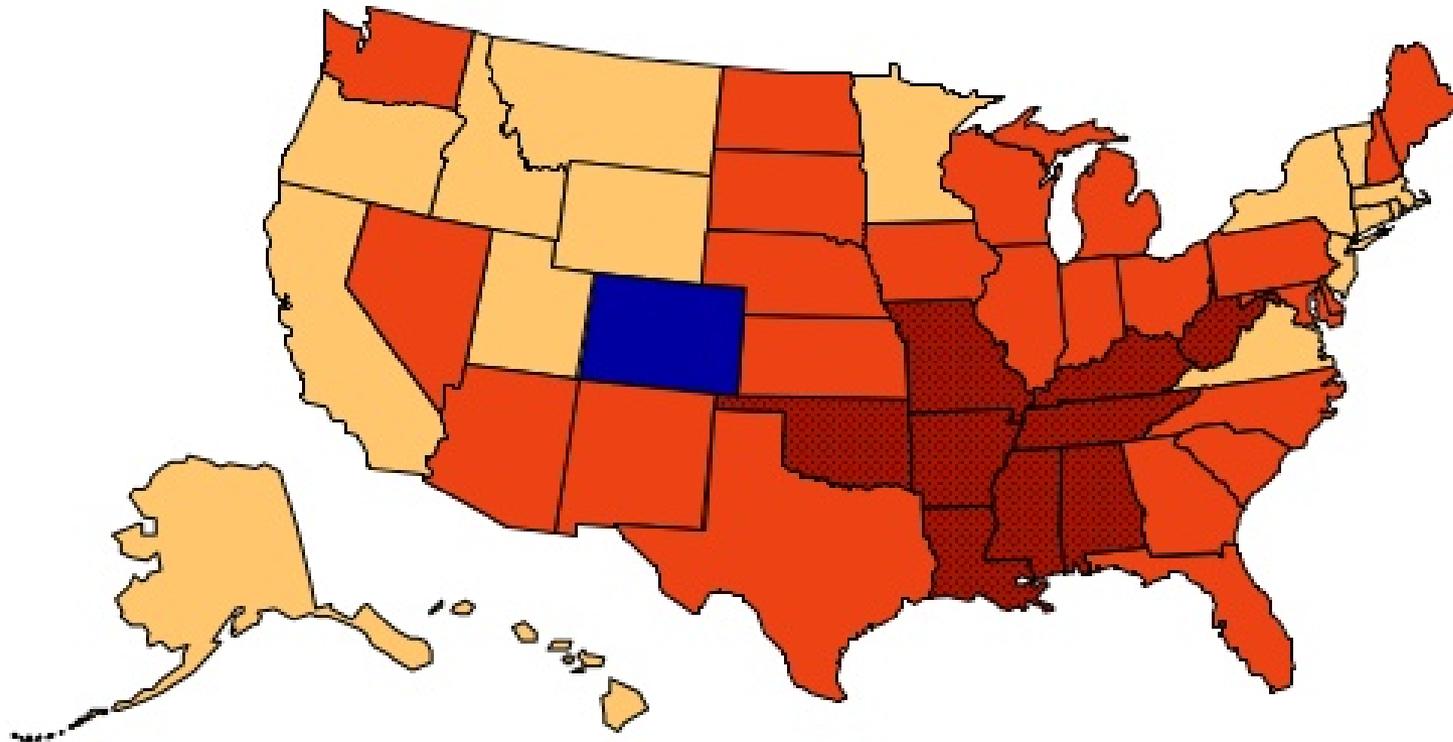
(*BMI ≥ 30 , or ~ 30 lbs. overweight for 5' 4" person)



Source: Behavioral Risk Factor Surveillance System, CDC.

Obesity Trends* Among U.S. Adults, BRFSS 2009

(*BMI ≥ 30 , or ~ 30 lbs. overweight for 5' 4" person)



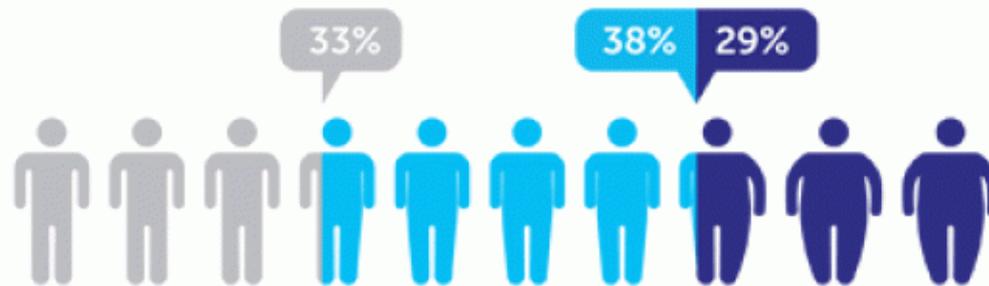
Source: Behavioral Risk Factor Surveillance System, CDC.



IF TRENDS CONTINUE, ALMOST 4 IN 10 ADULTS ARE PREDICTED TO BE OBESE BY 2035

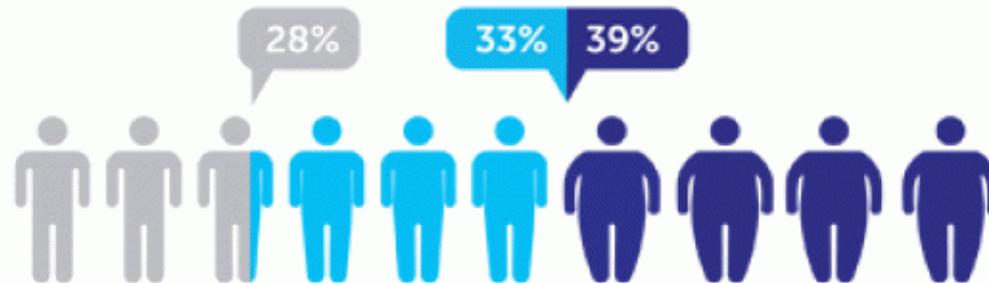
 Healthy Weight  Overweight  Obese

IN
2015

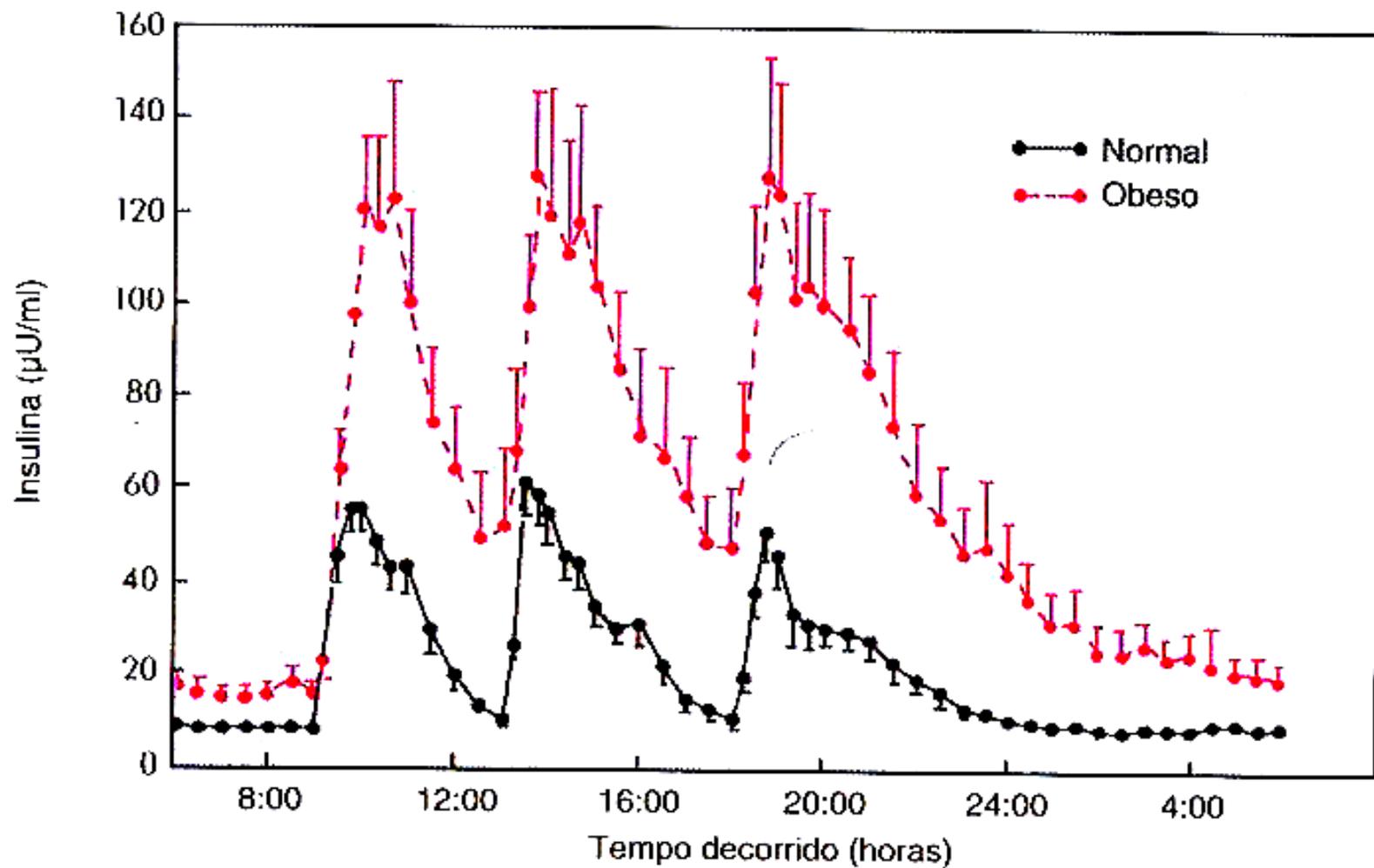


Around **3 in 10** adults are obese.

IN
2035



Around **4 in 10** adults will be obese.

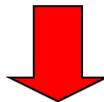


OBESIDADE



RESISTÊNCIA PERIFÉRICA

HIPERINSULINISMO



IDADE



FALÊNCIA CÉLULA β

GENÉTICA

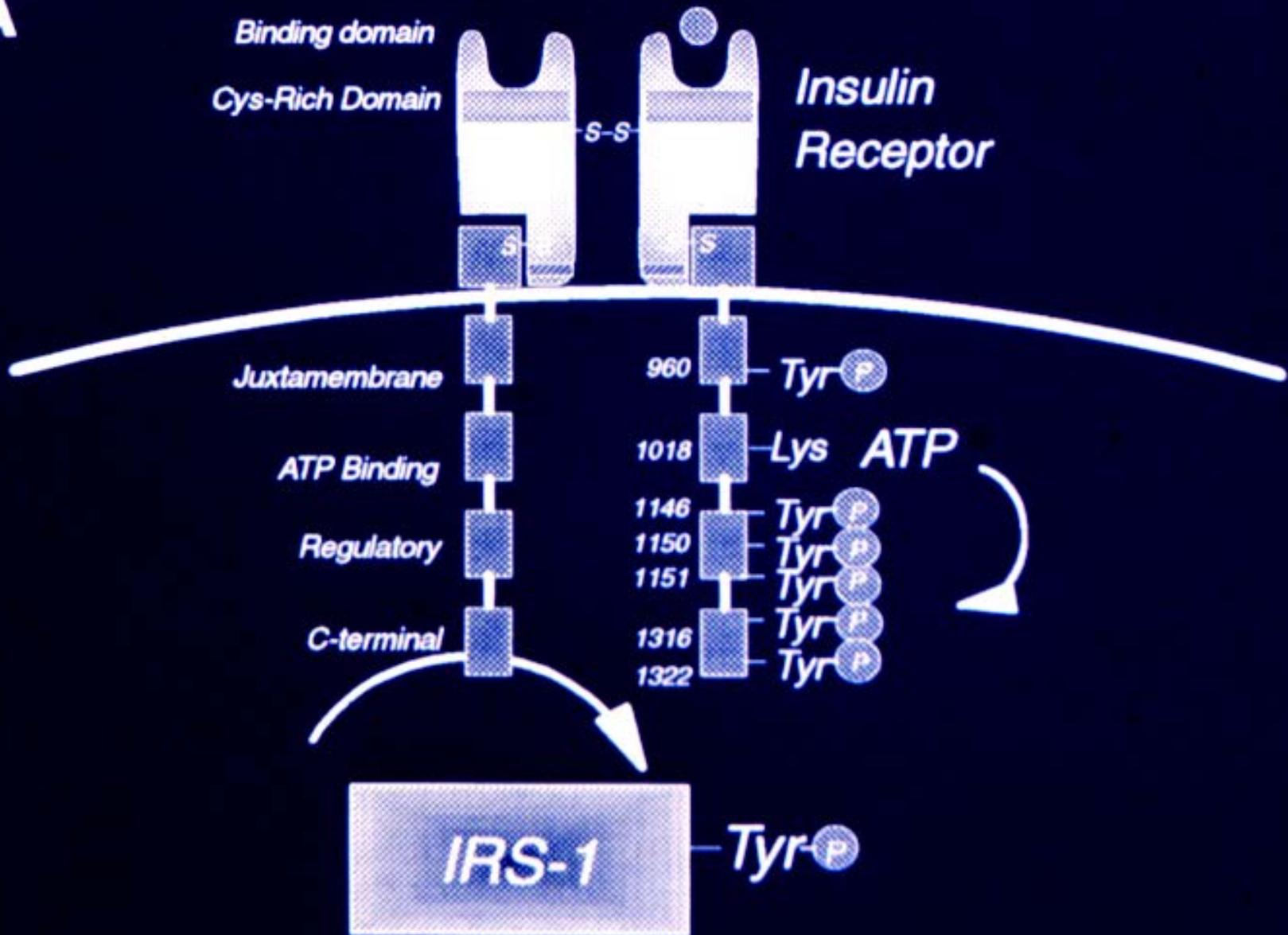


**Por que a obesidade
causa resistência ?**

A

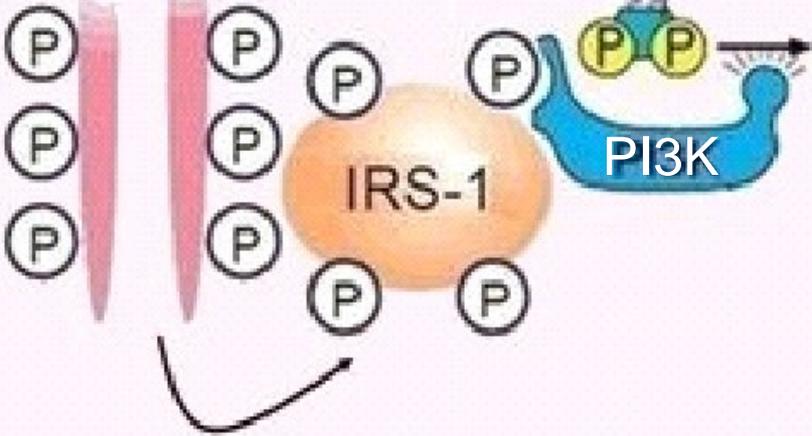
Binding domain
Cys-Rich Domain

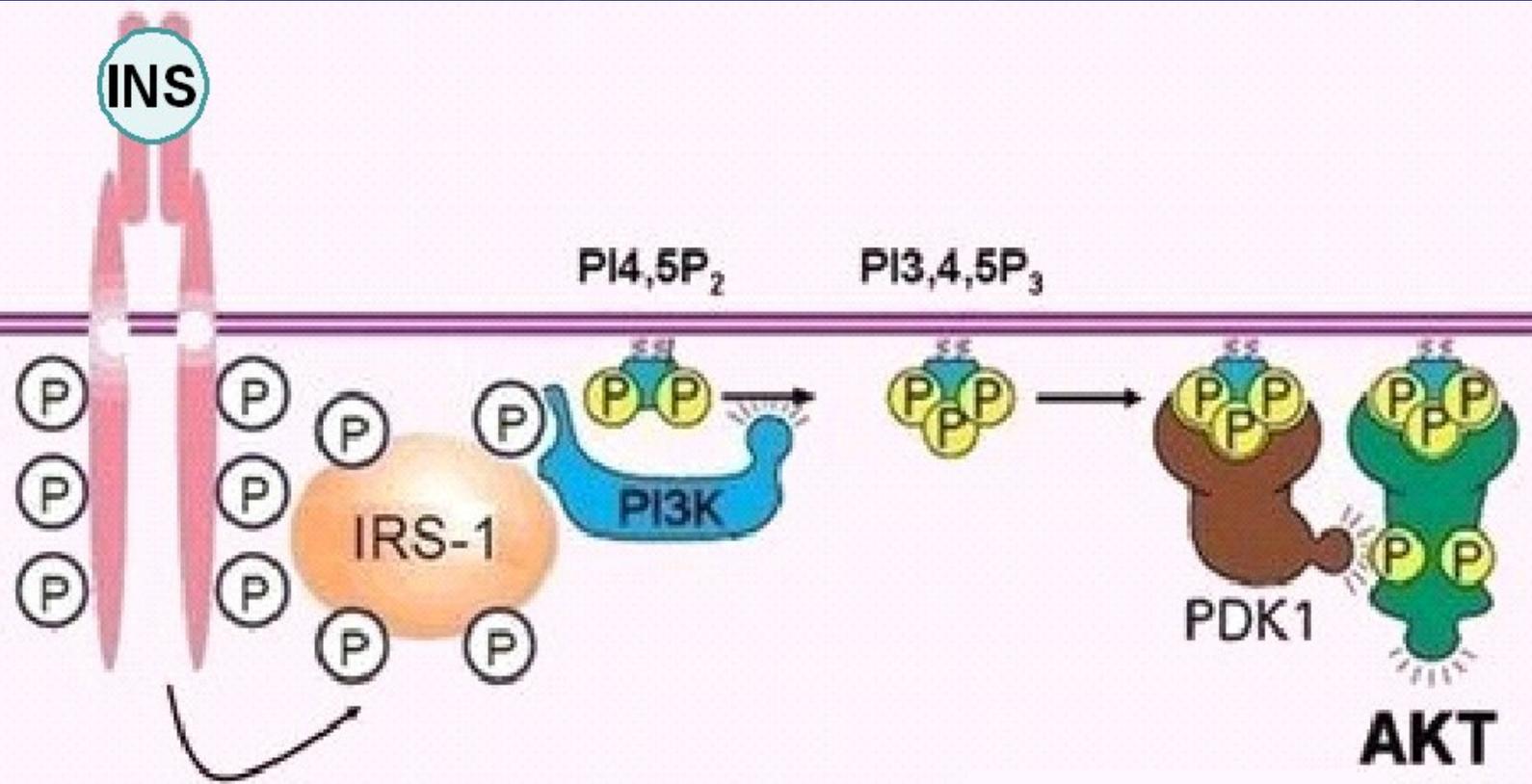
Insulin Receptor

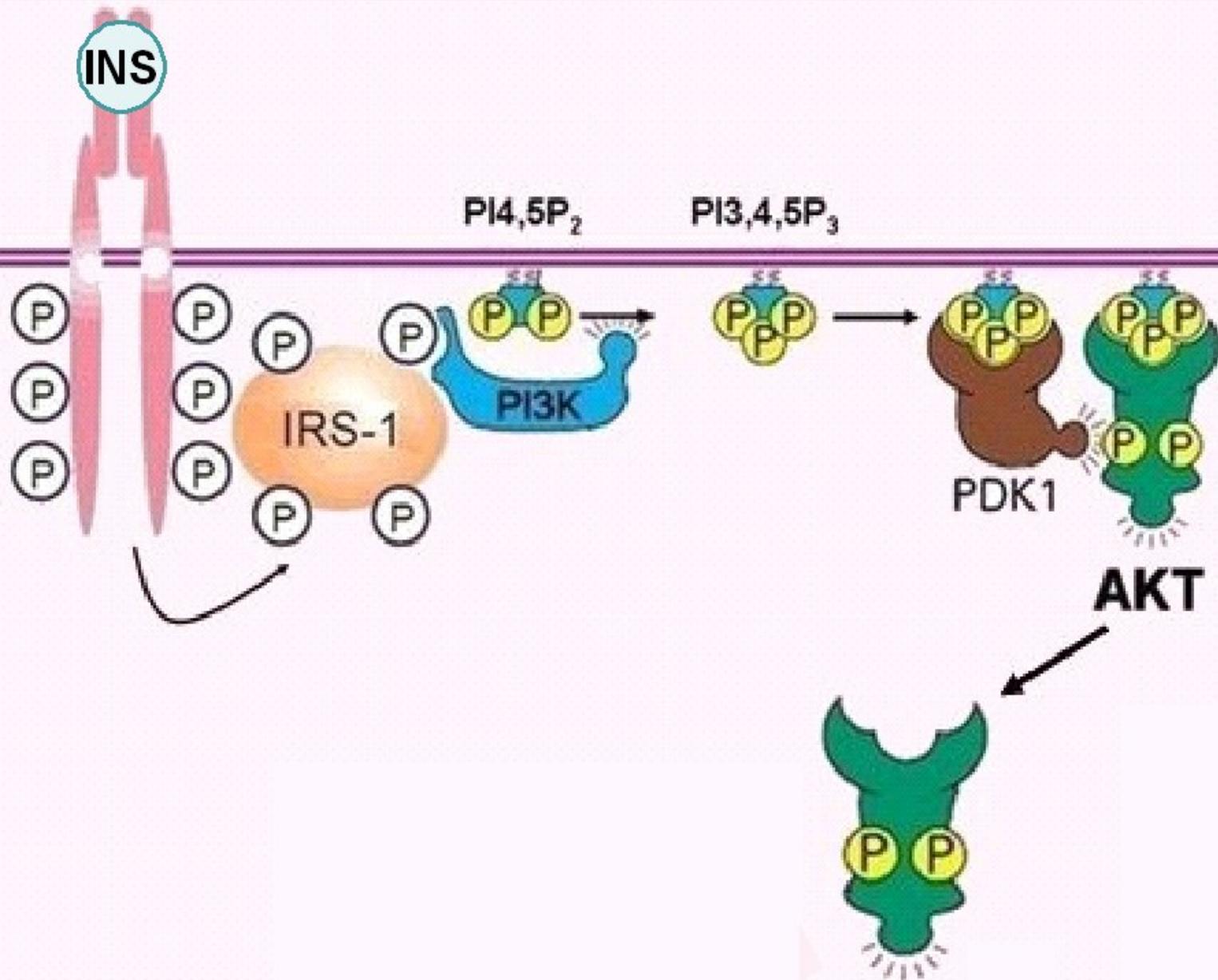


INS

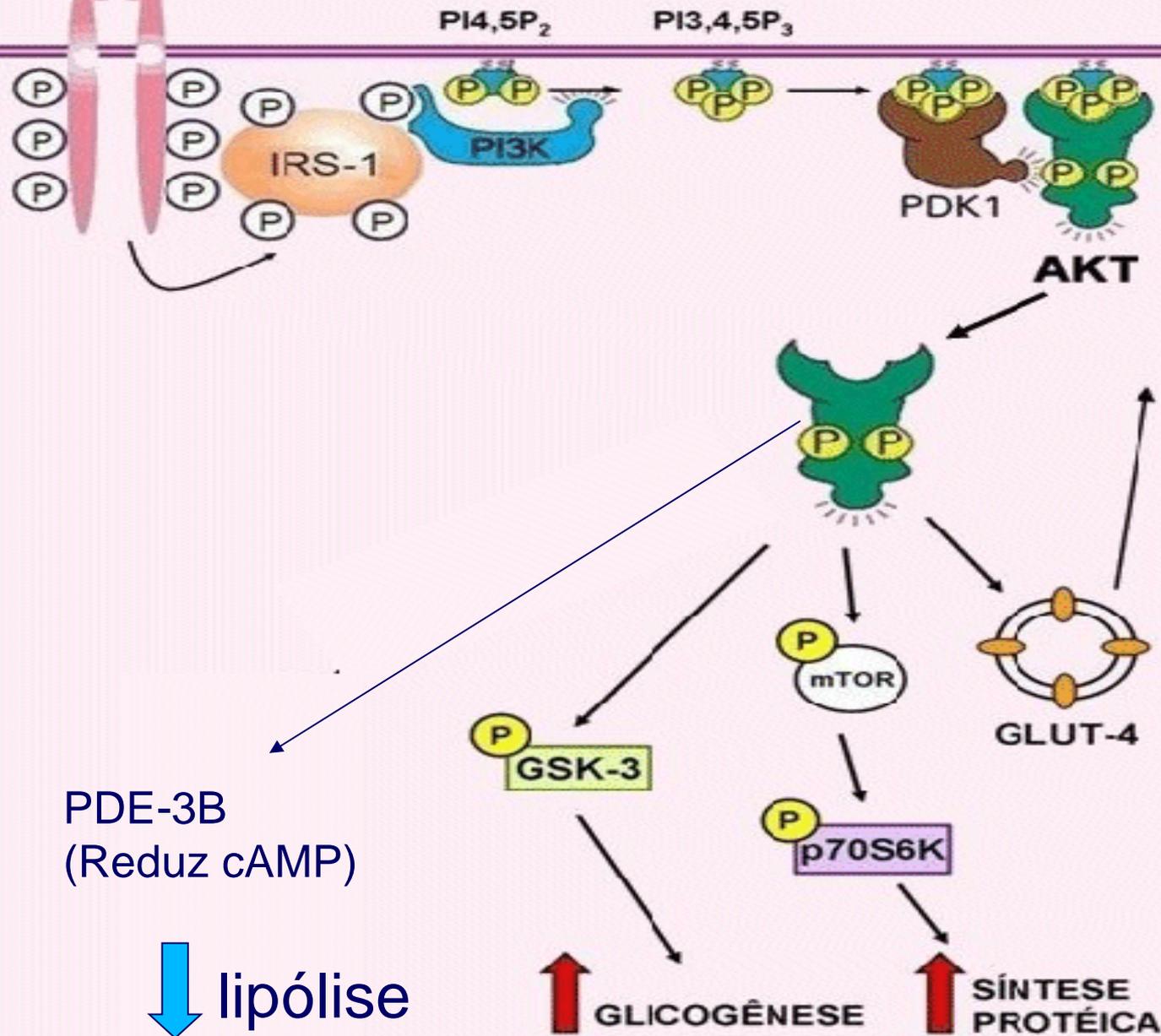
PI4,5P₂







insulina



Fator Metabólico



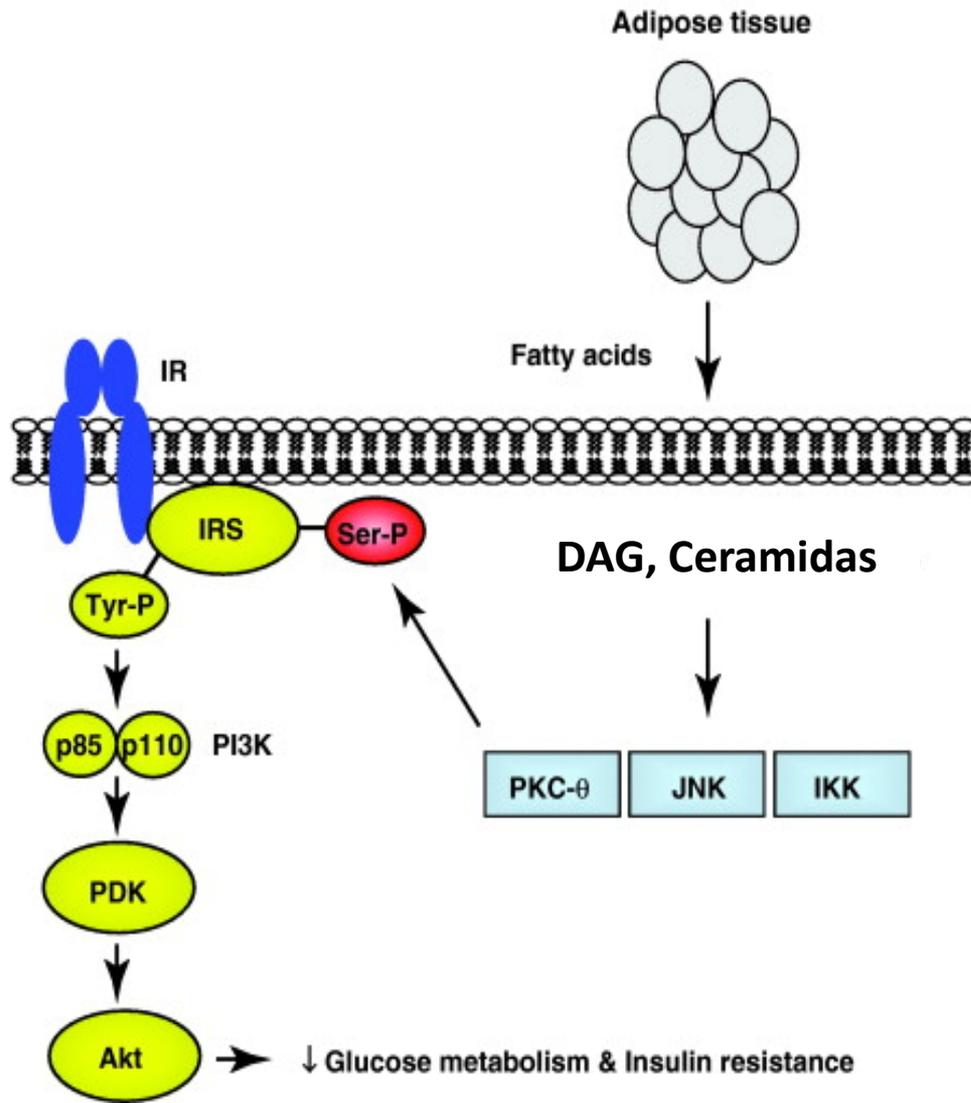
AGL



Fígado

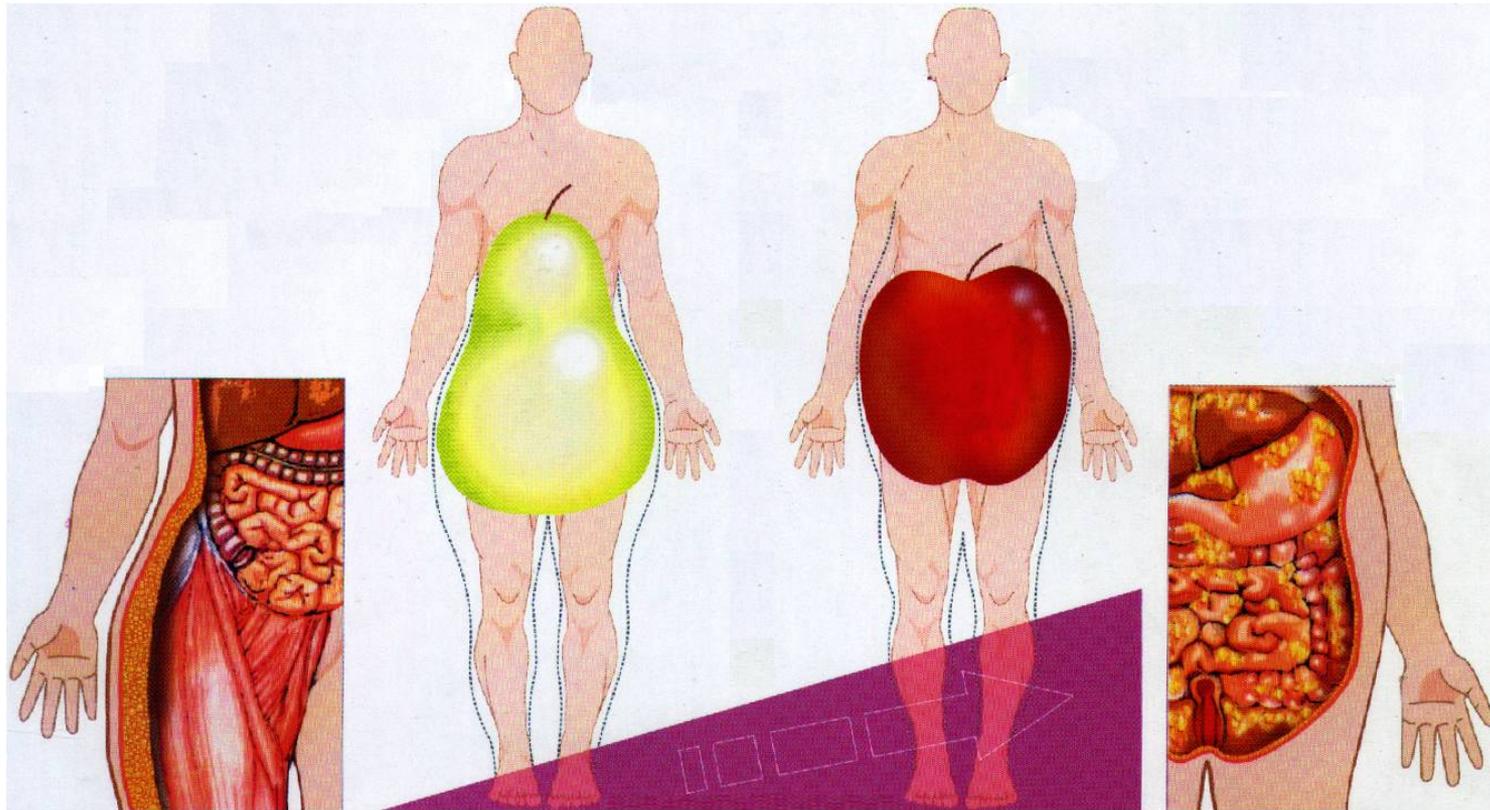
**Músculo
Esquelético**

A gordura ectópica interfere com a via de sinalização da insulina



Tipos de Tecido Adiposo Branco

(Subcutâneo X Visceral)



Fator Endócrino

Adipocinas no Obeso

(proteínas secretadas pelos adipócitos)

Leptina ↑

Resistina ↑

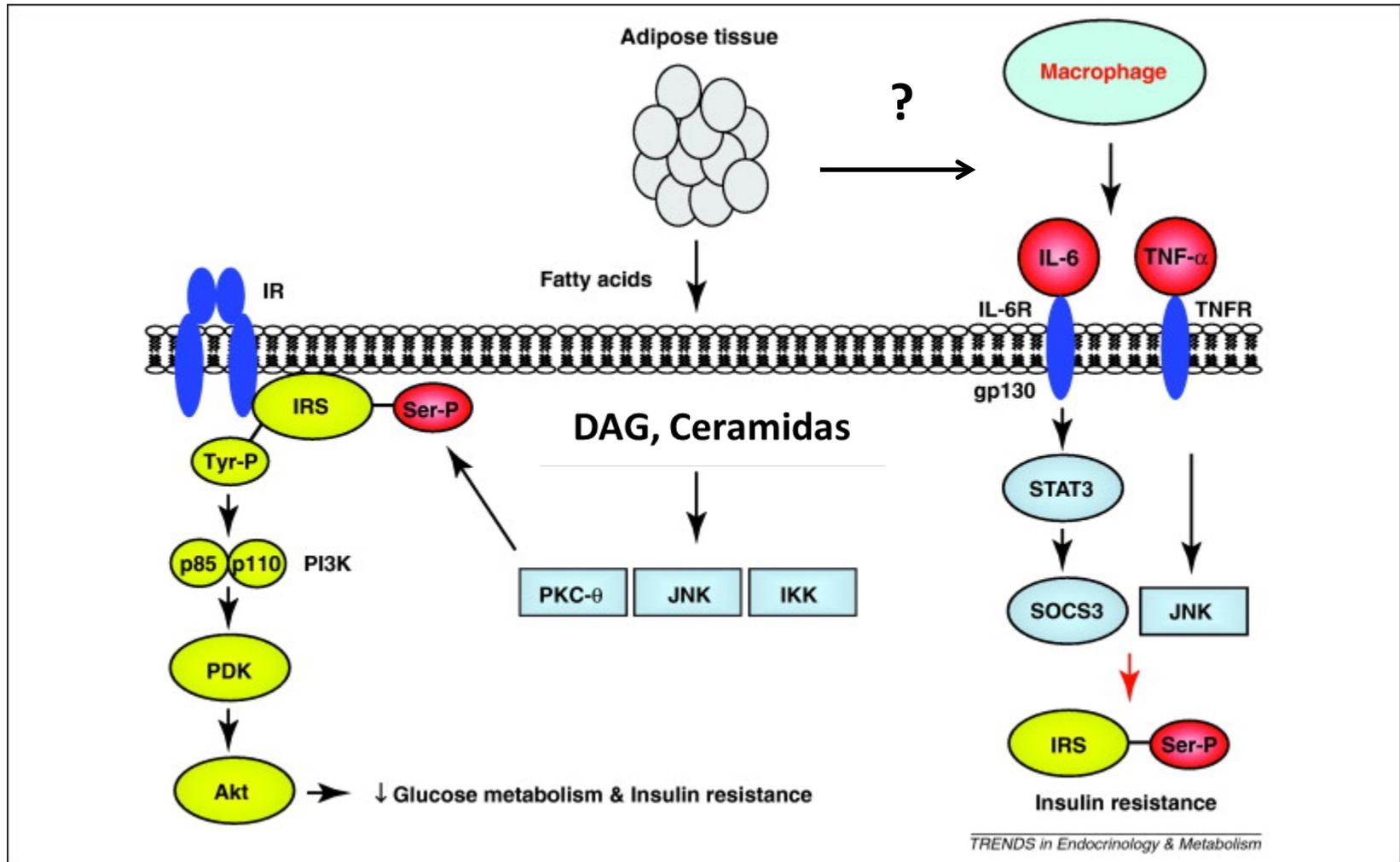
Adiponectina ↓

IL-6 ↑

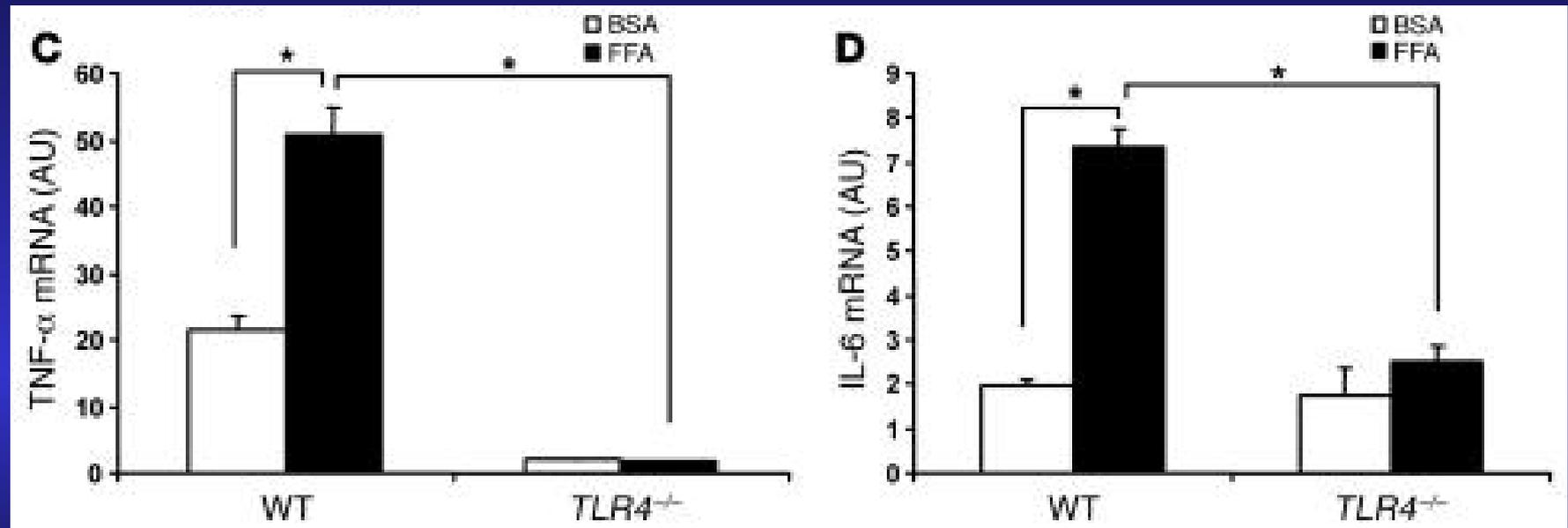
TNF-alfa ↑

Fator Inflamatório

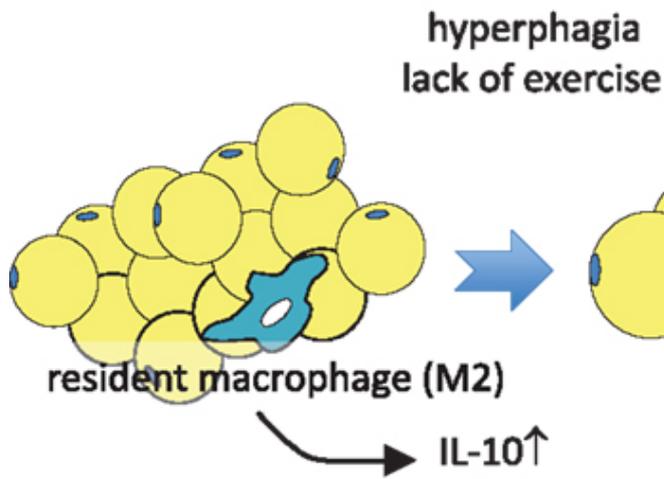
A obesidade é caracterizada por um estado de inflamação crônica



O TLR-4 é o elo de ligação entre os AGLs e a inflamação em adipócitos

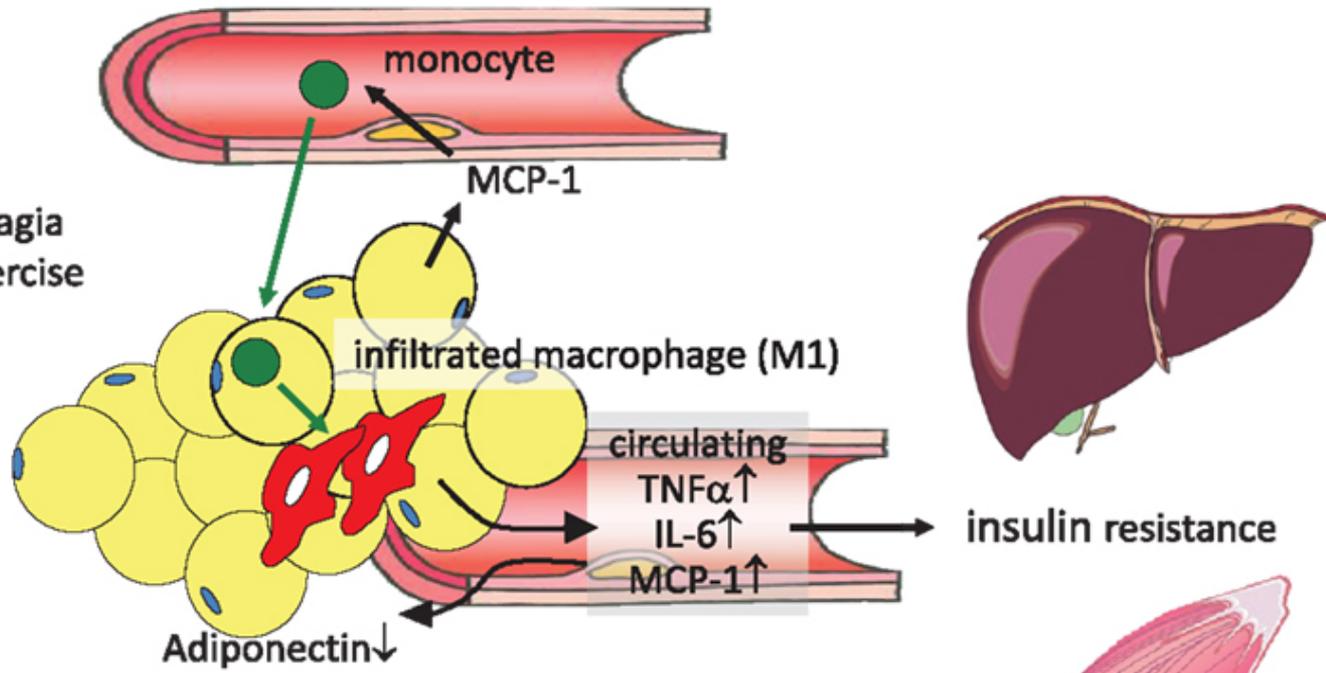


A *Lean state*



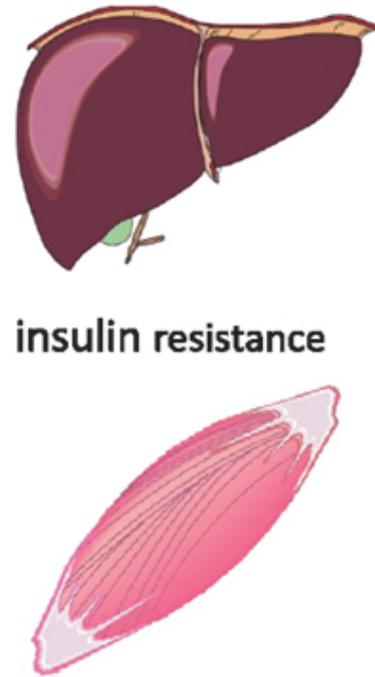
normal adipocytes

B *Obese state*



hypertrophied adipocytes

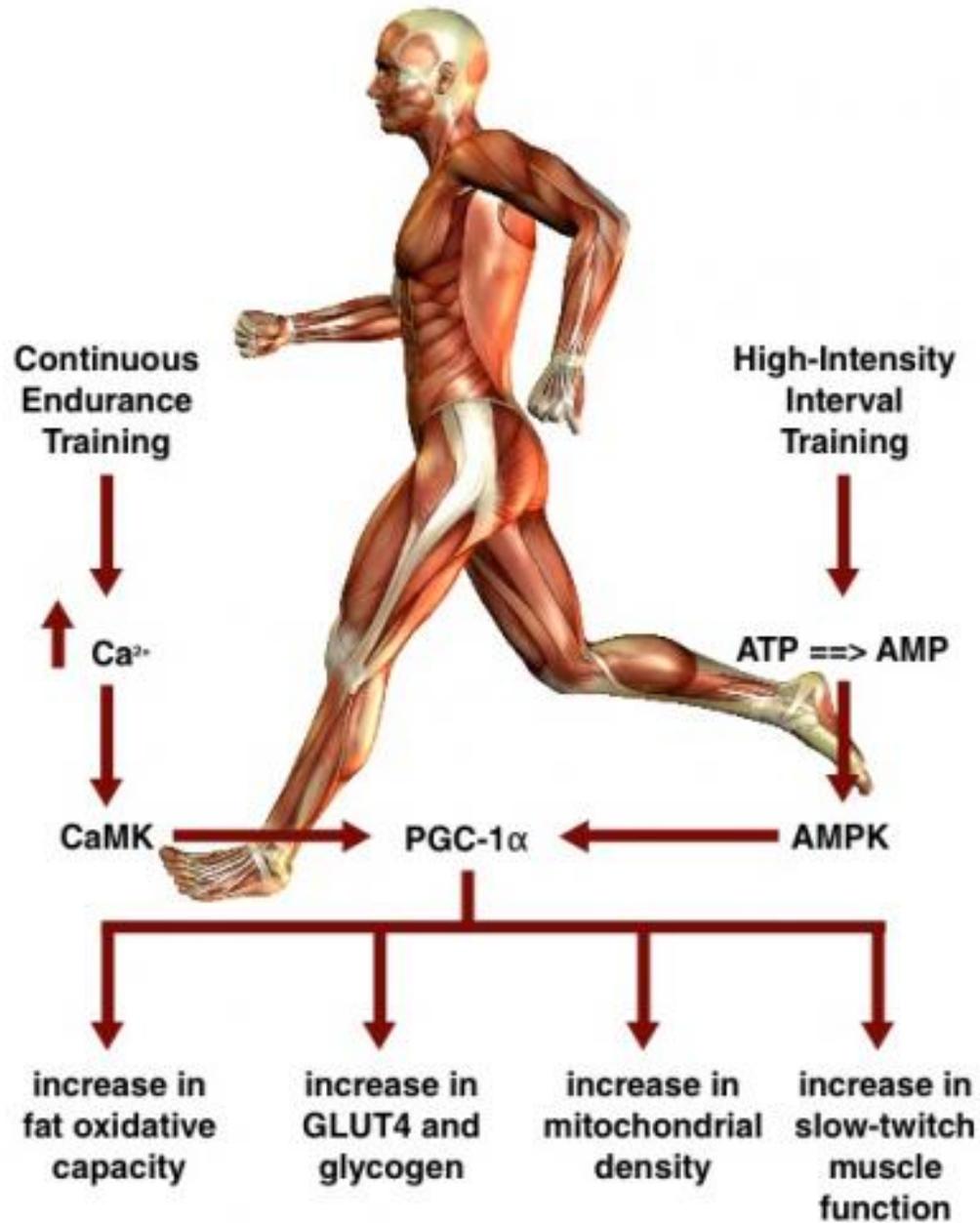
insulin-sensitive tissues



Papel dos lipídios na patogênese da RI em obesos

- 1-Induzem disfunção mitocondrial por meio da produção de EROS
- 2-Levam à formação intracelular de derivados do metabolismo dos AGLs (DAG e Ceramida)
- 3-Aumentam a secreção de adipocinas circulantes associadas à RI
- 4-Estimulam a produção de citocinas por macrófagos M2

**Como combater o
problema ?**



Efeito do exercício agudo na captação de glicose induzida pela insulina: Papel da AMPK

