RNM 4201

Integração Metabólica

Controle do metabolismo do tecido adiposo

Profa.Dra. Isis do Carmo Kettelhut

Tecido Adiposo Branco

Tecido Adiposo Branco

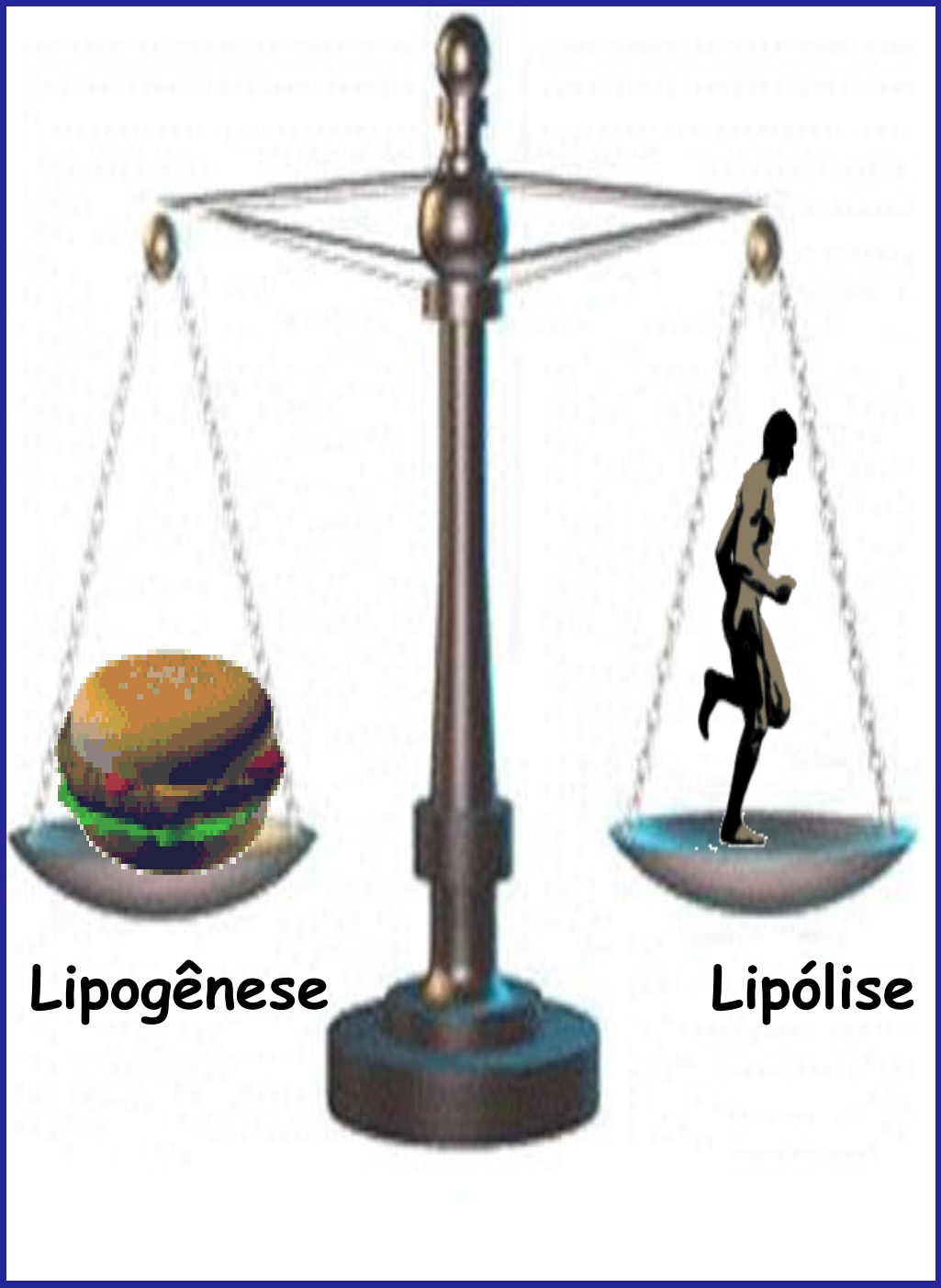
- isolamento e proteção mecânica

- estoque de energia (síntese e degradação de TAG)

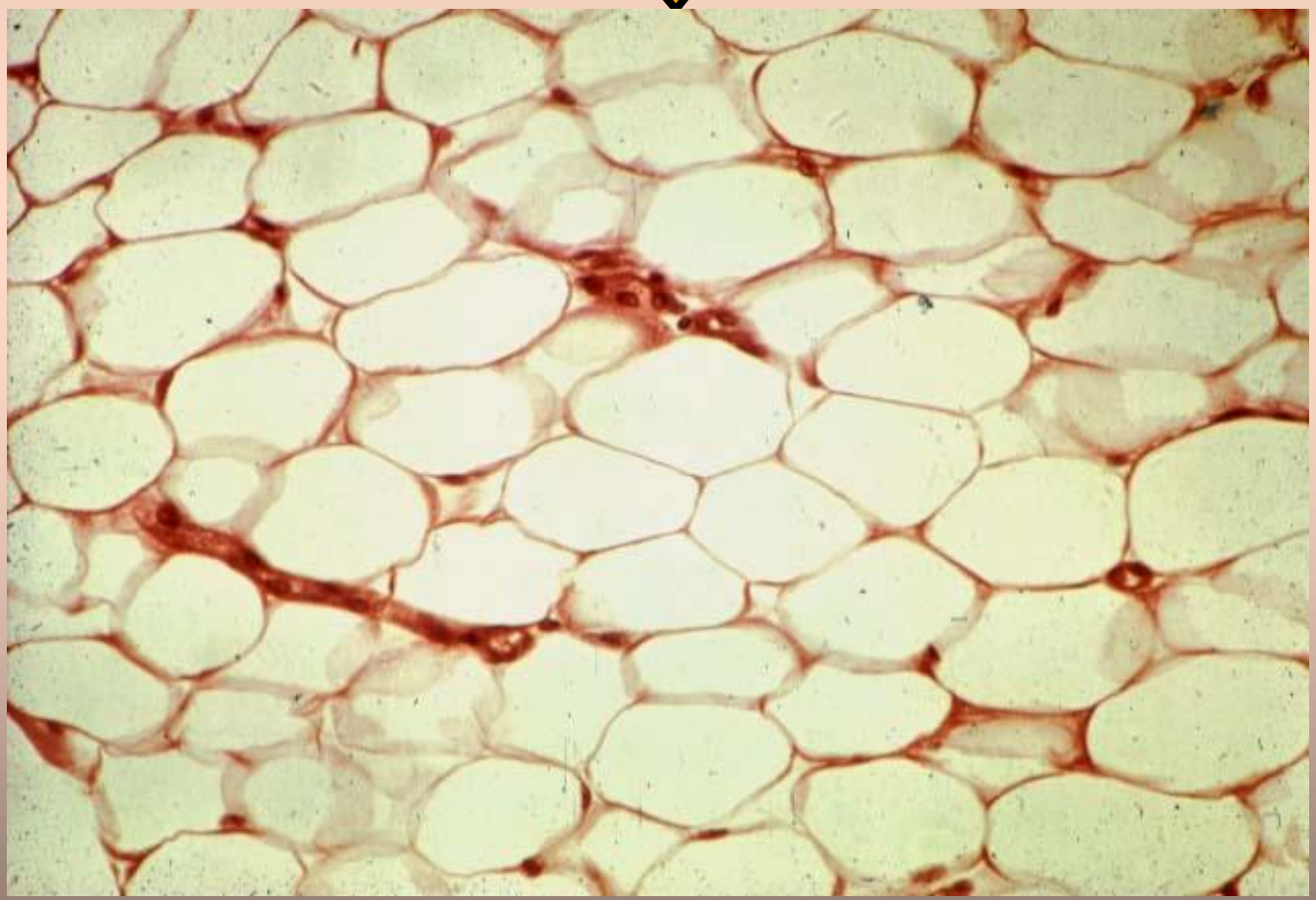
- órgão endócrino

- vários tipos de células e várias localizações

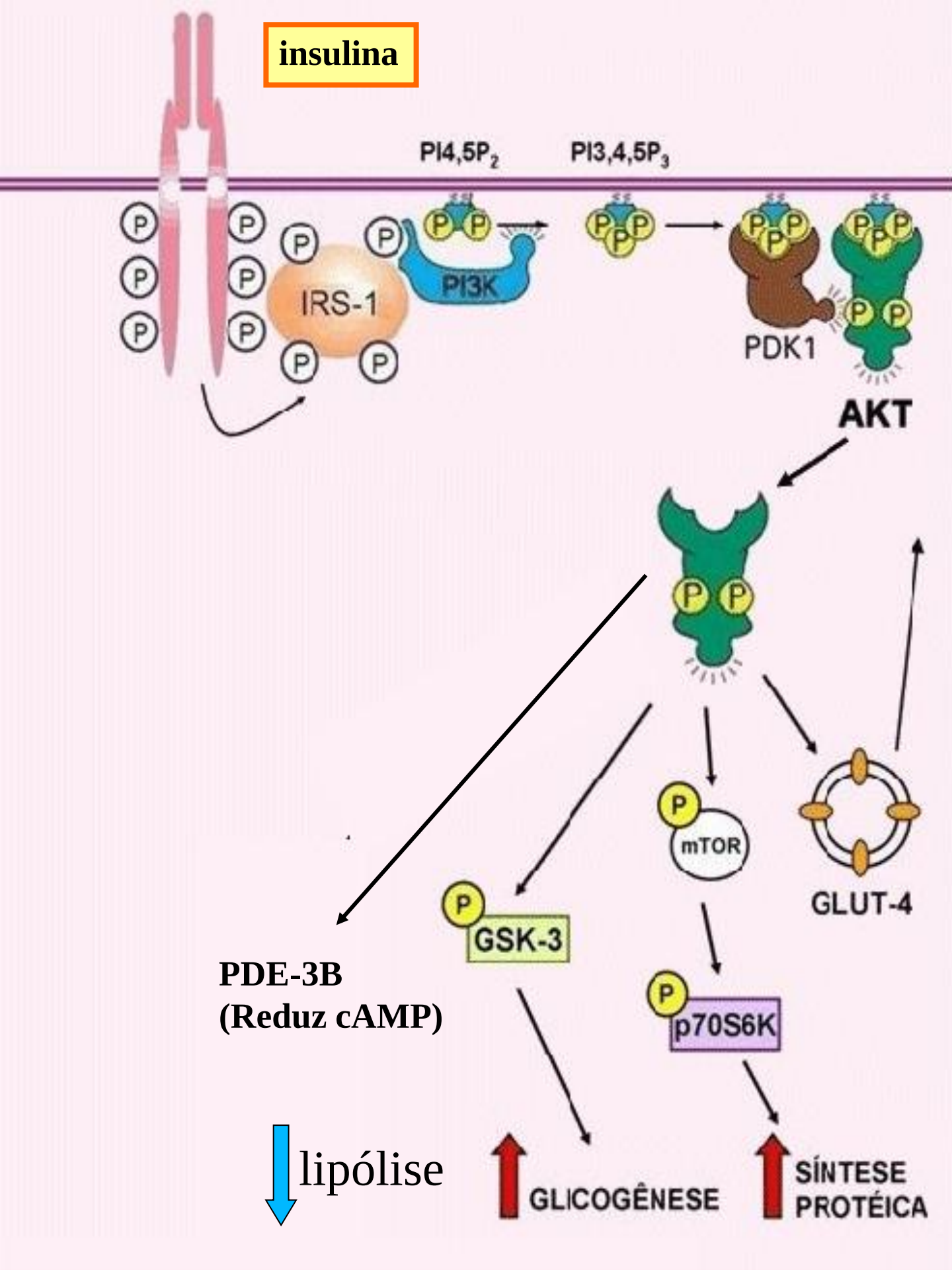
Conteúdo de TAG

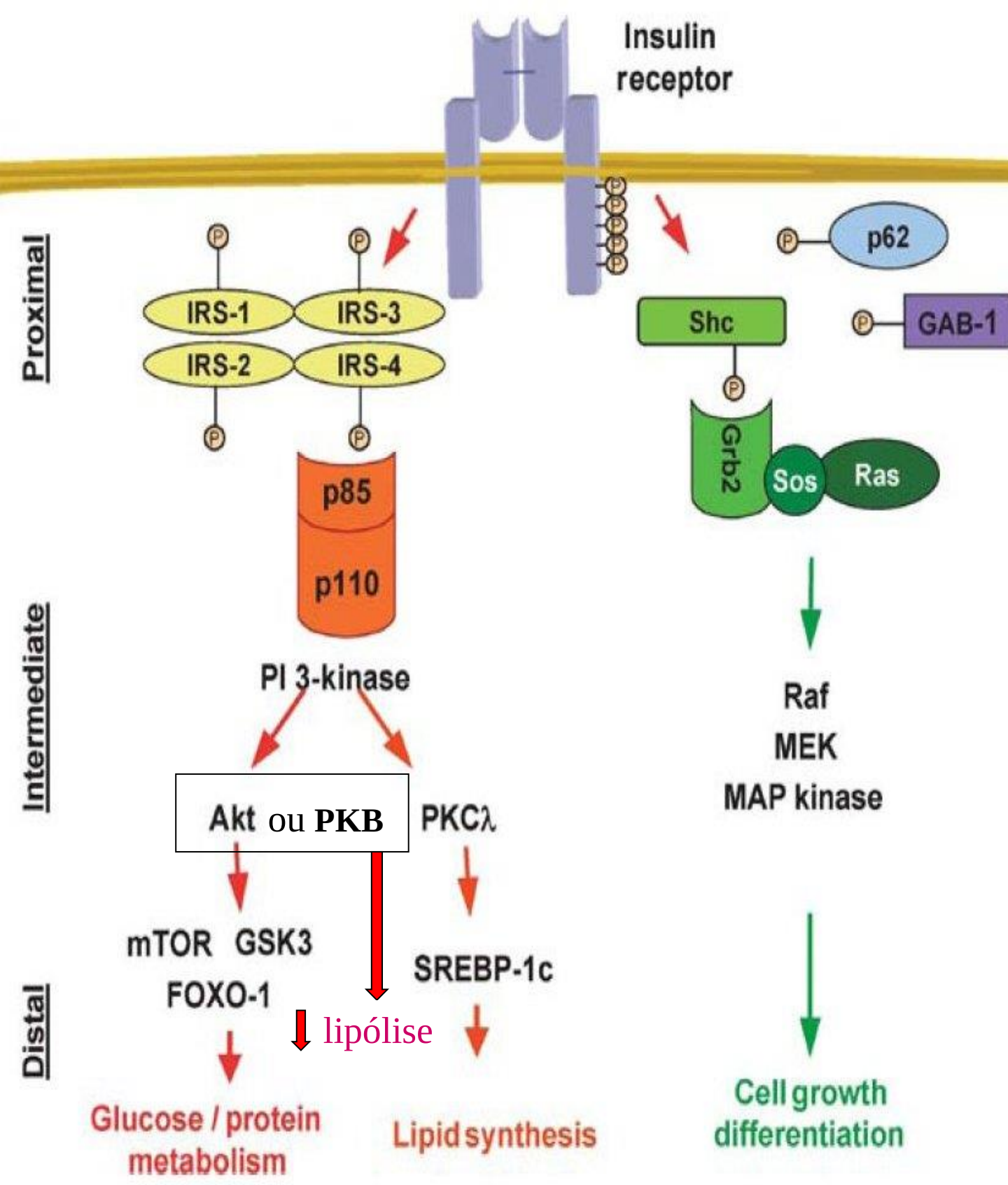


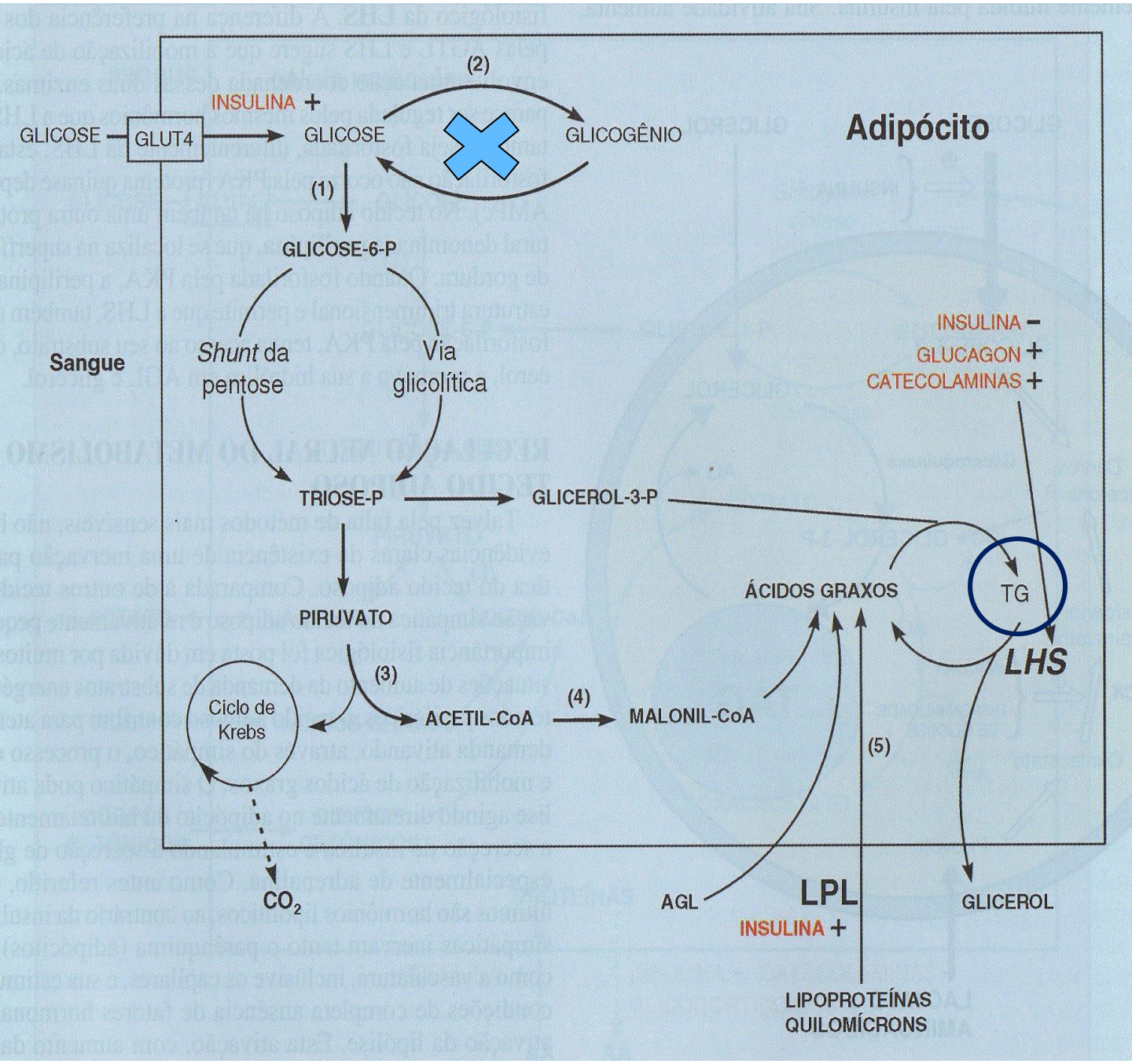
INSULINA: principal hormônio anabólico e anti-catabólico

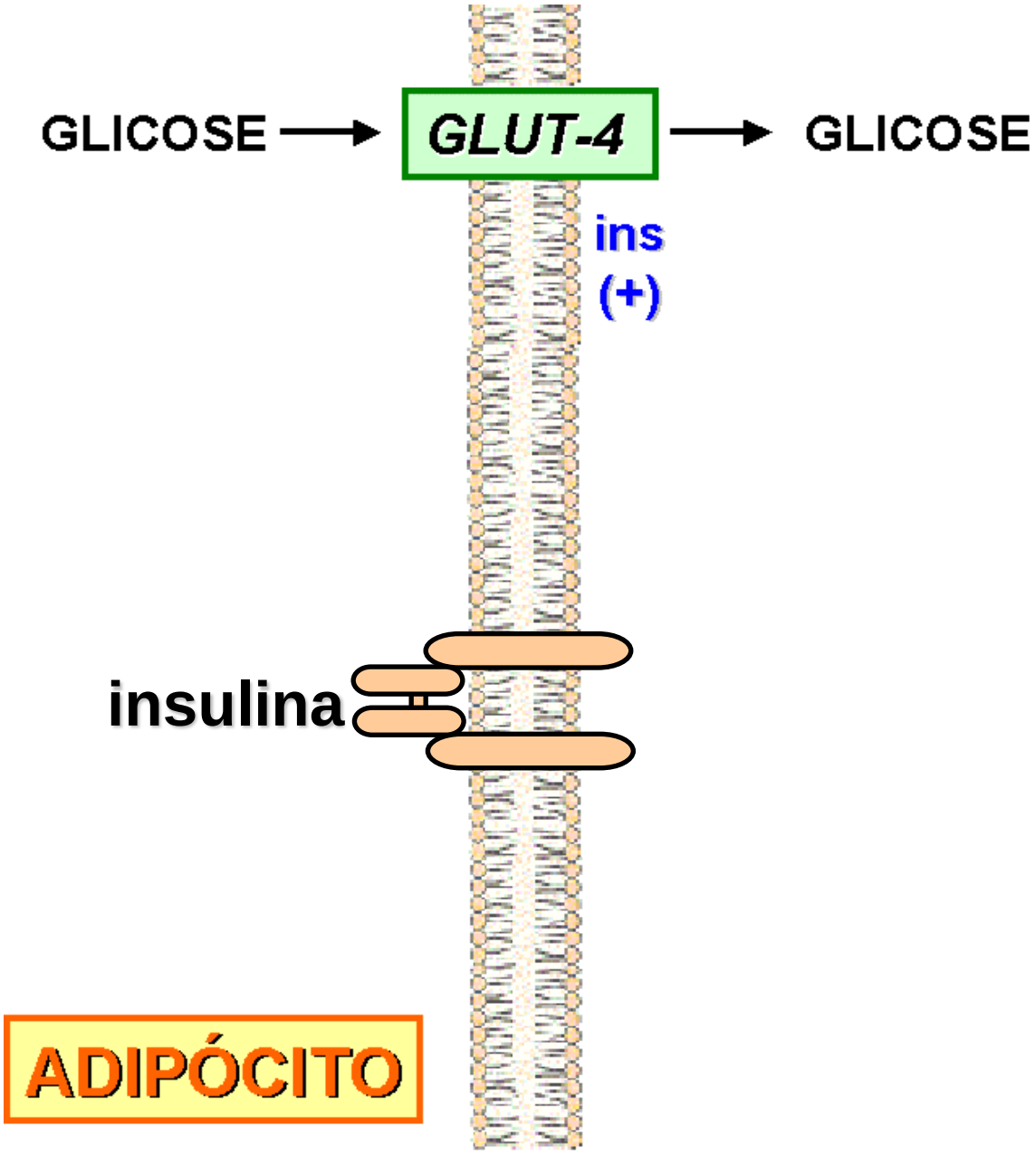


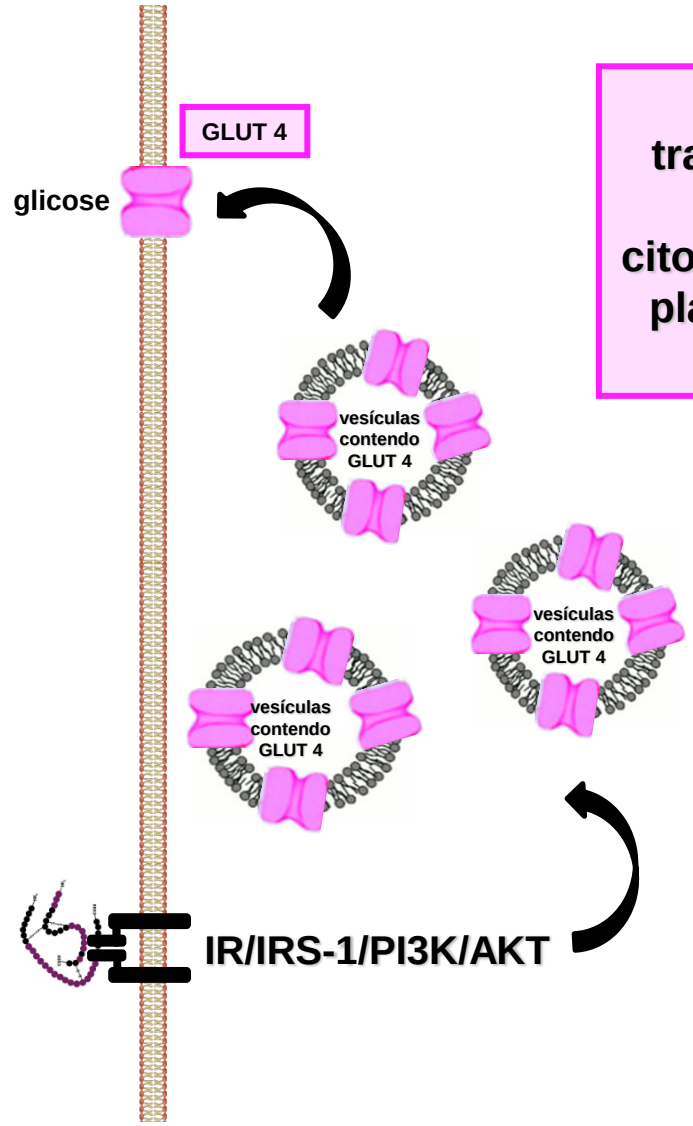
ADIPÓCITO


insulina
PI4,5P2
PI3,4,5P3
IRS-1
PI3K
PDK1
AKT
mTOR
GLUT-4
GSK-3
PDE-3B
(Reduz cAMP)
p70S6K
lipólise
GLICOGÊNESE
SÍNTESE
PROTÉICA

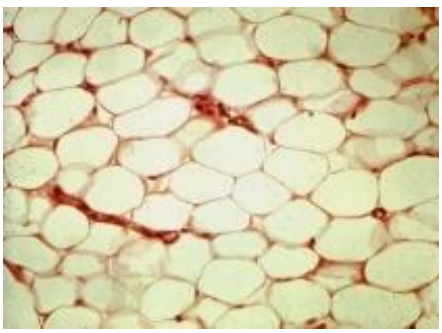

Insulin
receptor
Proximal
IRS-1
IRS-3
IRS-2
IRS-4
p85
p110
PI 3-kinase
p62
Shc
GAB-1
Grb2
Sos
Ras
Raf
MEK
MAP kinase
Intermediate
Akt ou PKB
PKCλ
mTOR GSK3
FOXO-1
SREBP-1c
lipólise
Distal
Glucose / protein
metabolism
Lipid synthesis
Cell growth
differentiation

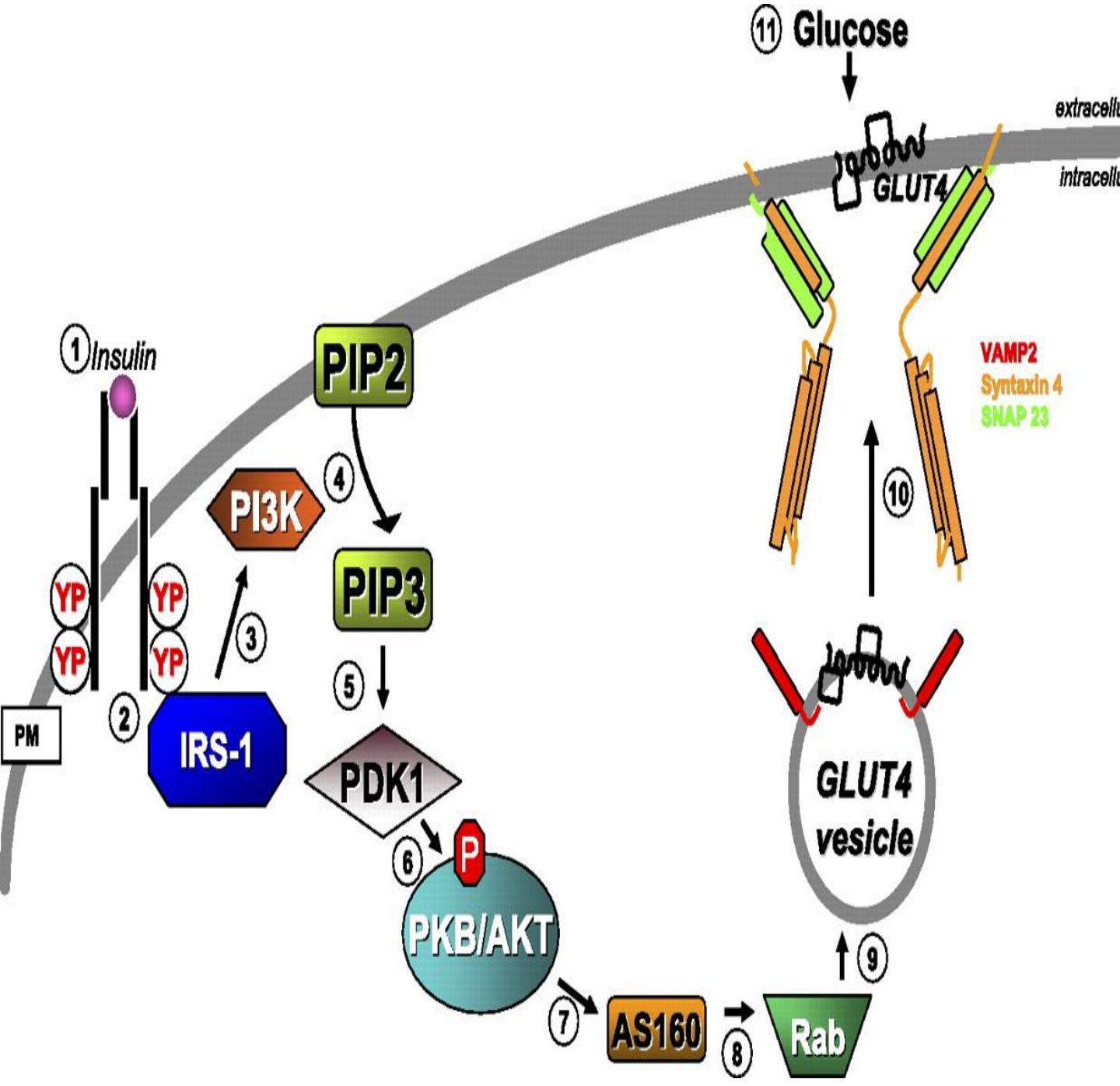

Adipócito
Sangue
GLICOSE
GLUT4
GLICOSE
INSULINA +
(2)
GLICOGÊNIO
(1)
GLICOSE-6-P
Shunt da pentose
Via glicolítica
TRIOSE-P
GLICEROL-3-P
PIRUVATO
(3)
Ciclo de Krebs
ACETIL-CoA
(4)
MALONIL-CoA
ÁCIDOS GRAXOS
TG
LHS
INSULINA −
GLUCAGON +
CATECOLAMINAS +
(5)
CO2
AGL
LPL
INSULINA +
GLICEROL
LIPOPROTEÍNAS
QUILOMÍCRONS

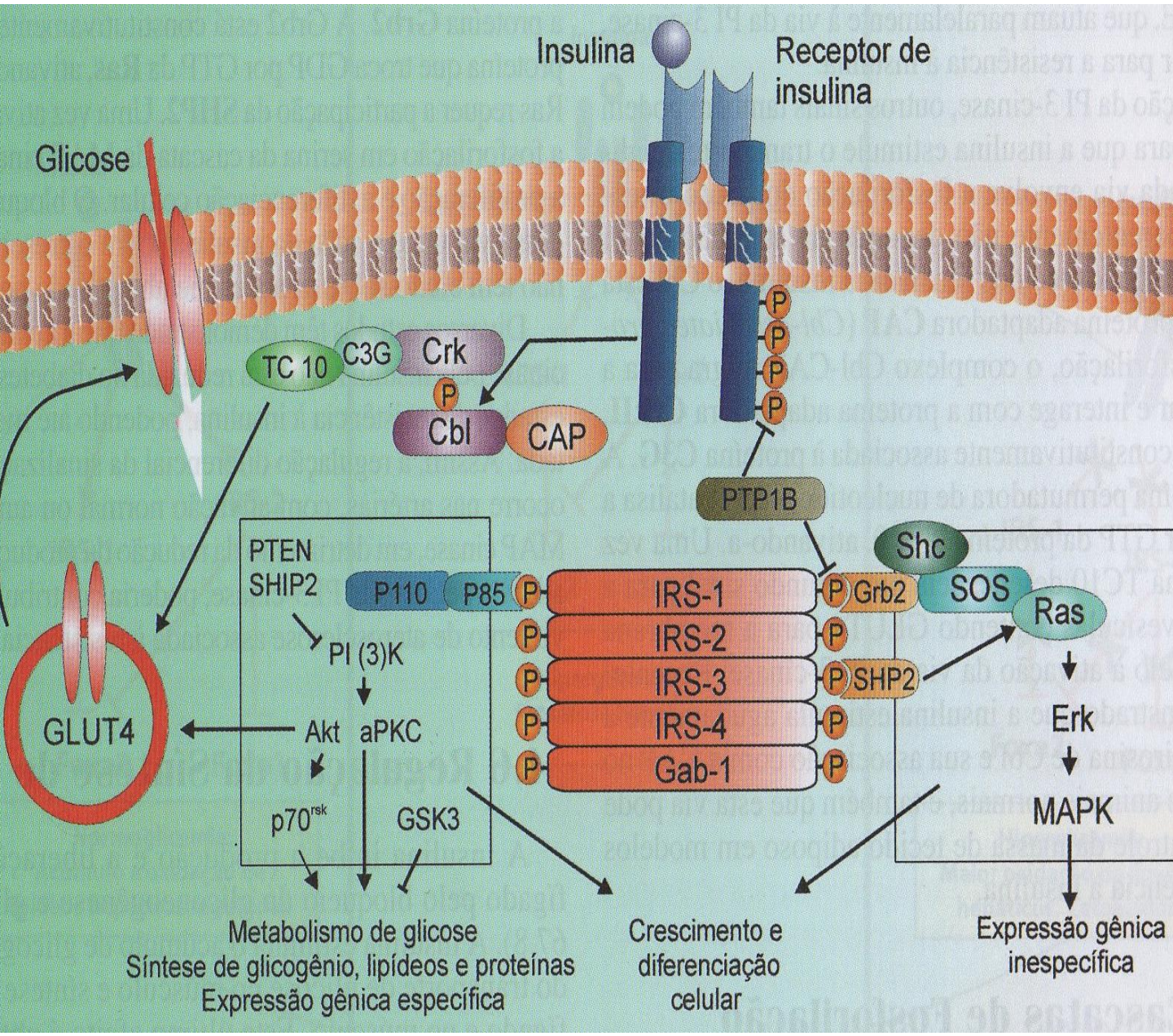

GLICOSE
GLUT-4
GLICOSE
ins
(+)
insulina
ADIPÓCITO

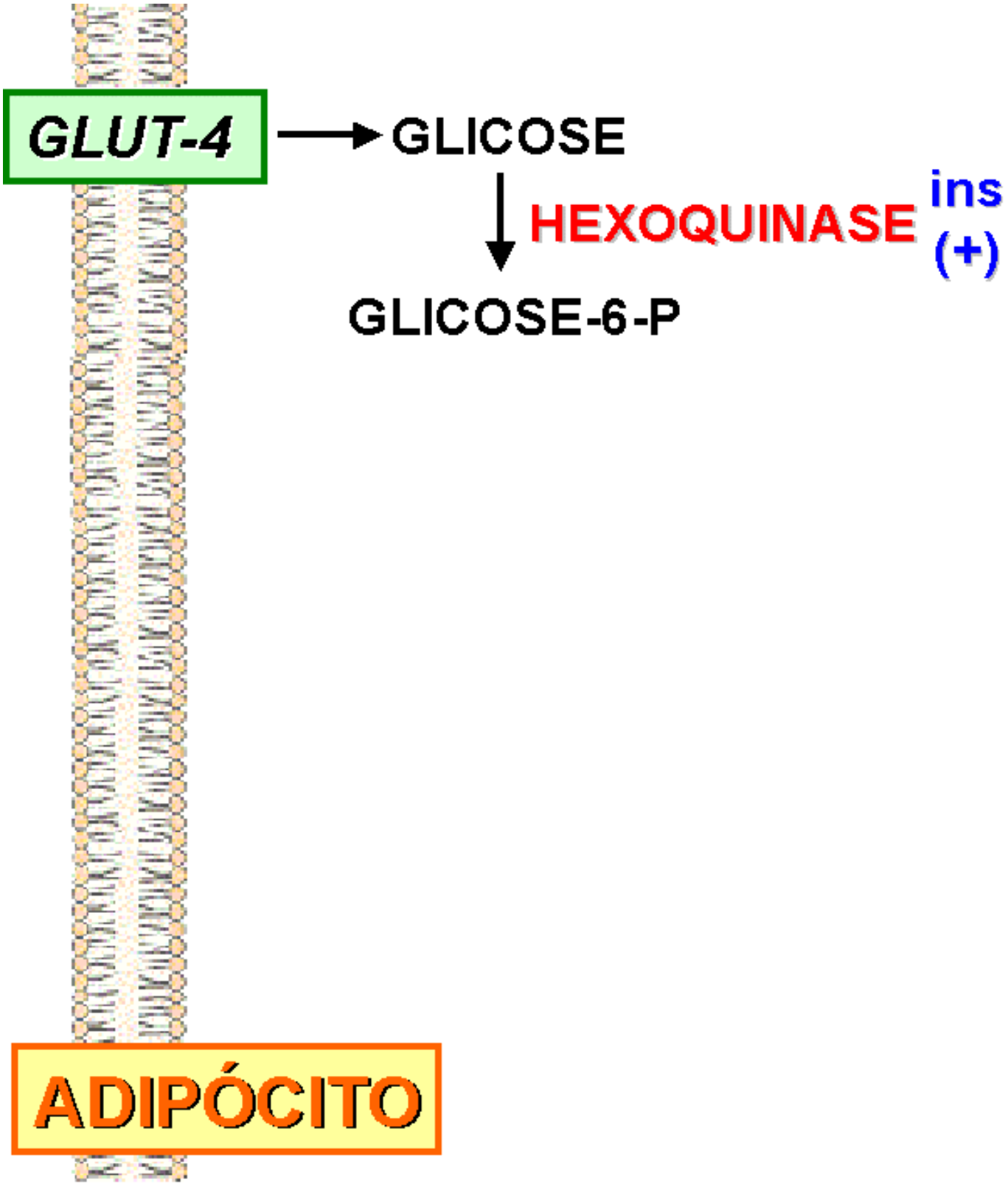


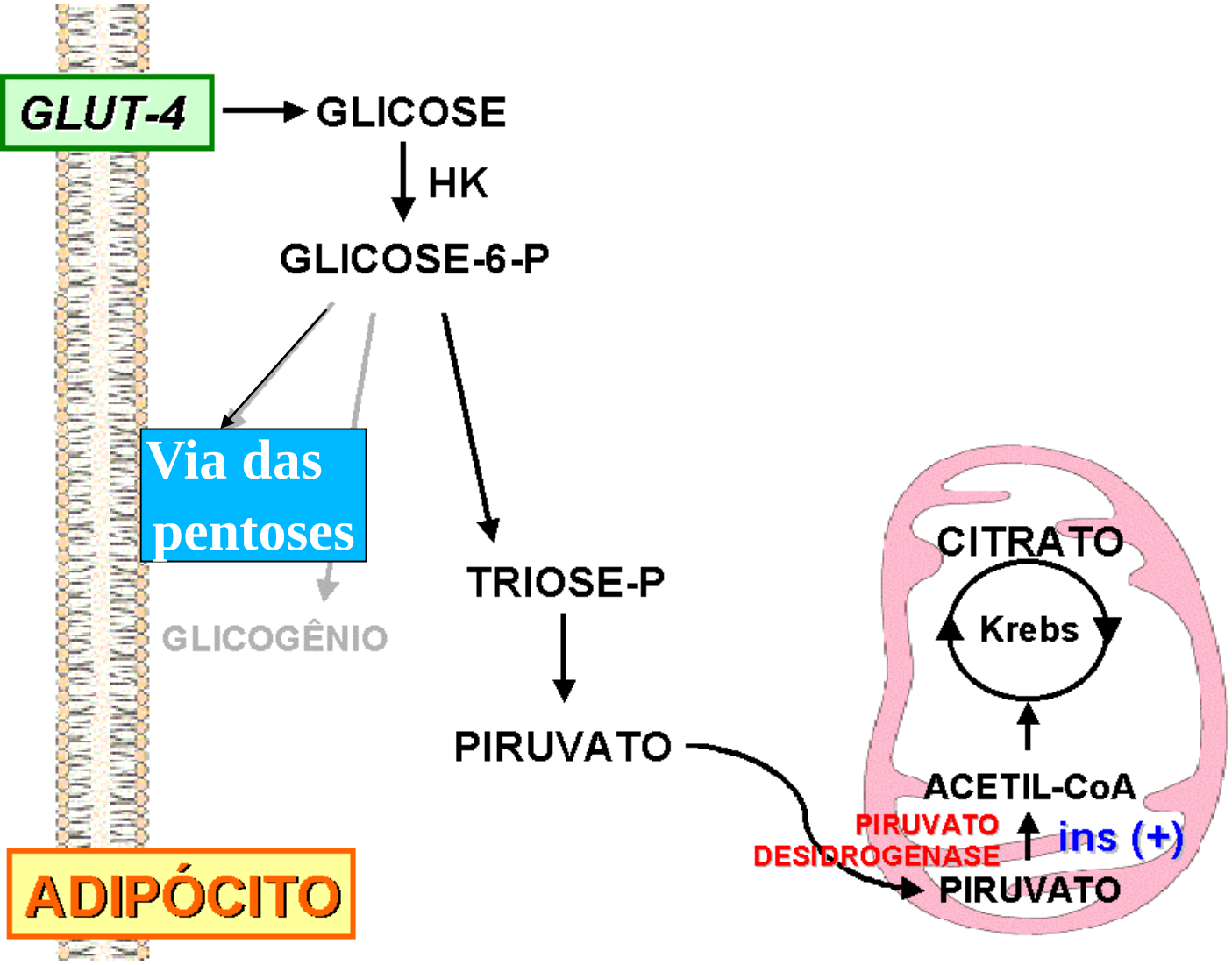
A insulina estimula a translocação de vesículas contendo GLUT 4 do citoplasma para a membrana plasmática, estimulando a captação de glicose

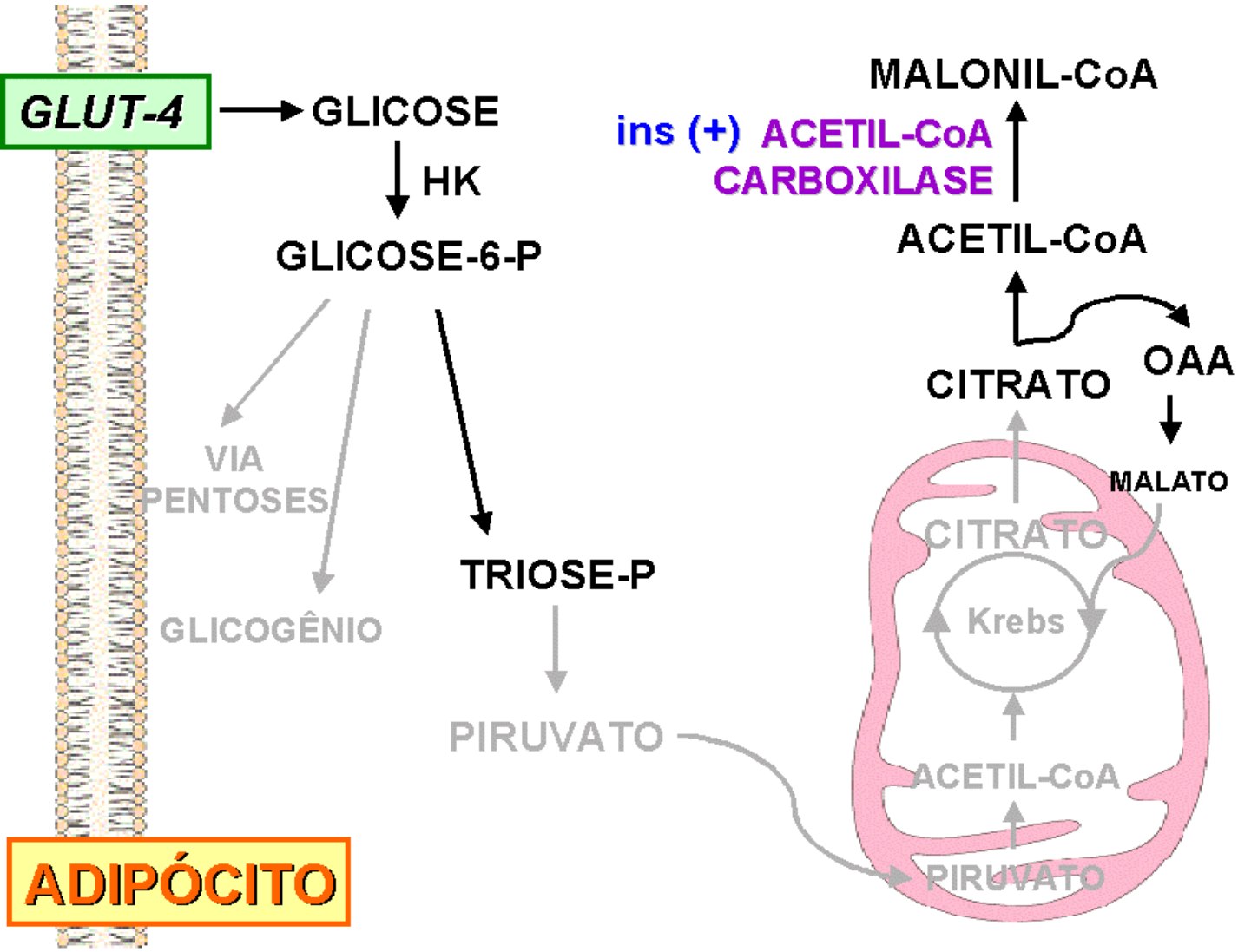


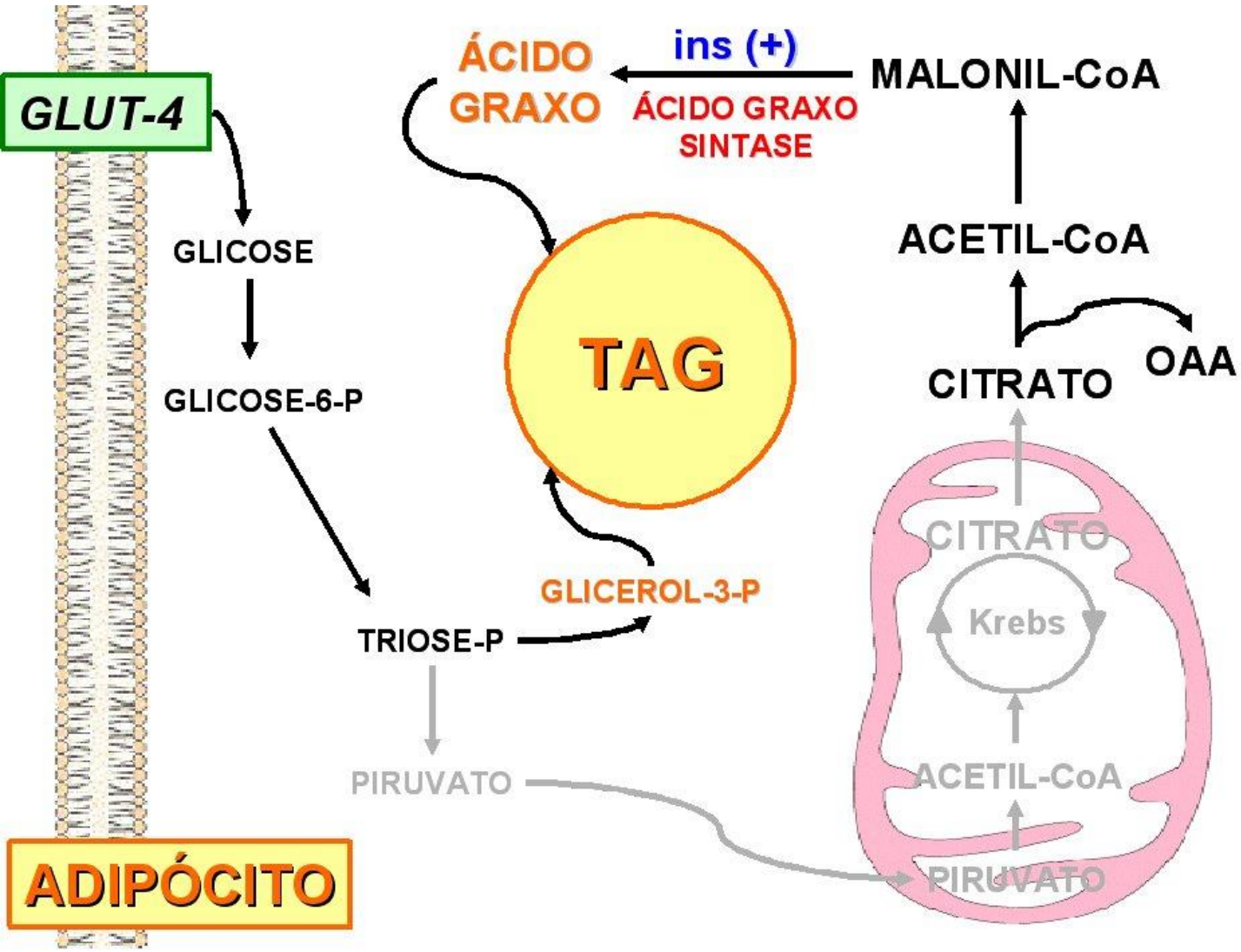

11 Glucose
extracellu
intracellu
GLUT4
VAMP2
Syntaxin 4
SNAP 23
1 Insulin
PIP2
PI3K
4
PIP3
YP
YP
YP
YP
3
5
PM
2
IRS-1
PDK1
6
P
PKB/AKT
7
AS160
8
Rab
9
10
GLUT4
vesicle


Insulina
Receptor de insulina
Glicose
TC 10
C3G
Crk
P
Cbl
CAP
PTP1B
PTEN
SHIP2
P110
P85
PI (3)K
Akt
aPKC
p70rsk
GSK3
GLUT4
IRS-1
IRS-2
IRS-3
IRS-4
Gab-1
Shc
Grb2
SOS
Ras
SHP2
Erk
MAPK
Metabolismo de glicose
Síntese de glicogênio, lipídeos e proteínas
Expressão gênica específica
Crescimento e diferenciação celular
Expressão gênica inespecífica

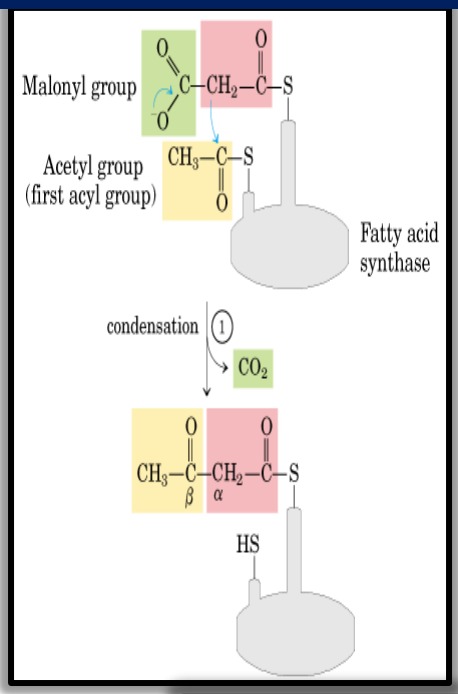

GLUT-4
GLICOSE
HEXOQUINASE
ins
(+)
GLICOSE-6-P
ADIPÓCITO

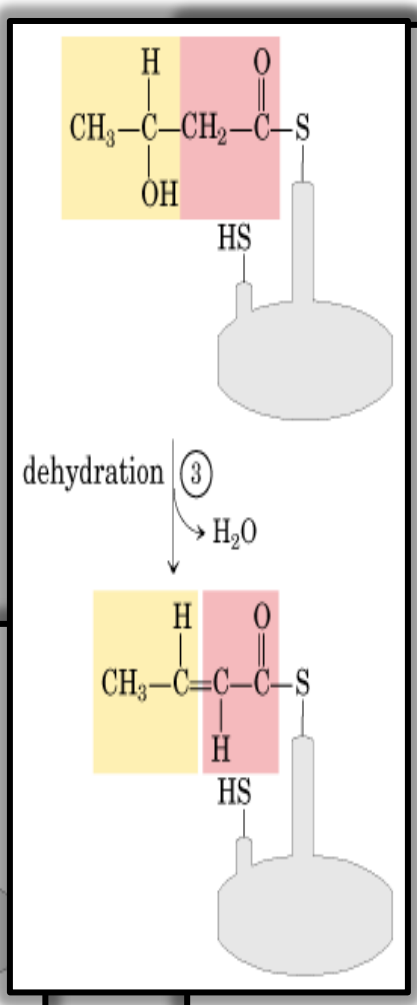

GLUT-4
GLICOSE
HK
GLICOSE-6-P
Via das pentoses
GLICOGÊNIO
TRIOSE-P
PIRUVATO
CITRATO
Krebs
ACETIL-CoA
PIRUVATO DESIDROGENASE
ins (+)
PIRUVATO
ADIPÓCITO

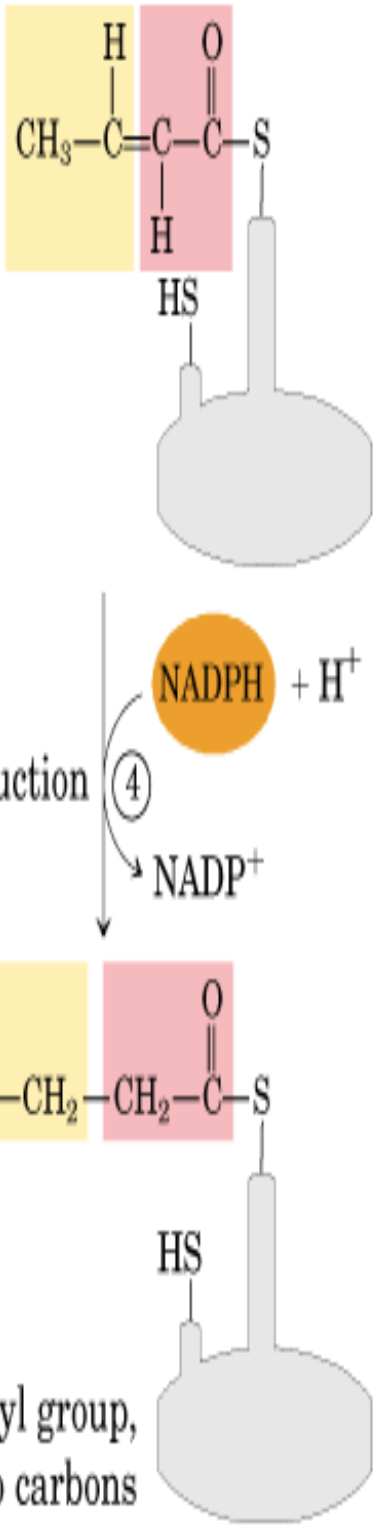

GLUT-4
GLICOSE
HK
GLICOSE-6-P
VIA PENTOSES
GLICOGÊNIO
TRIOSE-P
PIRUVATO
ADIPÓCITO
MALONIL-CoA
ins (+) ACETIL-CoA CARBOXILASE
ACETIL-CoA
CITRATO
OAA
MALATO
CITRATO
Krebs
ACETIL-CoA
PIRUVATO

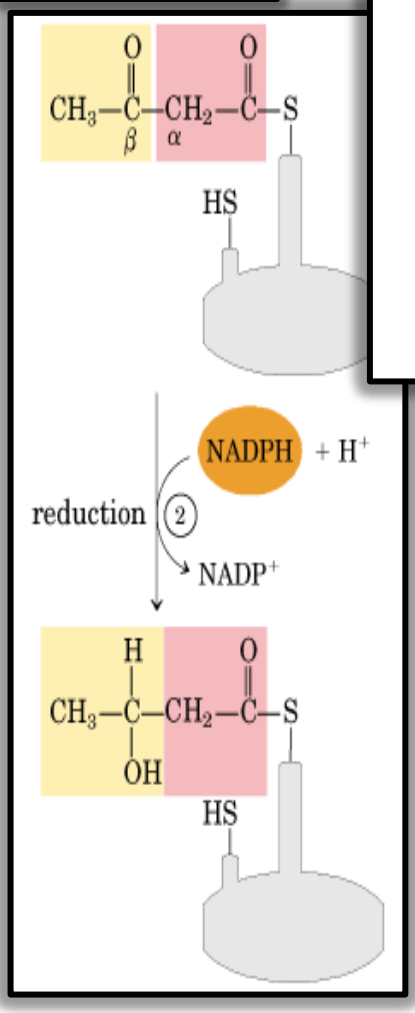

GLUT-4
GLICOSE
GLICOSE-6-P
TRIOSE-P
PIRUVATO
ADIPÓCITO
ÁCIDO GRAXO
ins (+)
ÁCIDO GRAXO SINTASE
MALONIL-CoA
ACETIL-CoA
CITRATO
OAA
TAG
GLICEROL-3-P
CITRATO
Krebs
ACETIL-CoA
PIRUVATO

Síntese de ácidos graxos

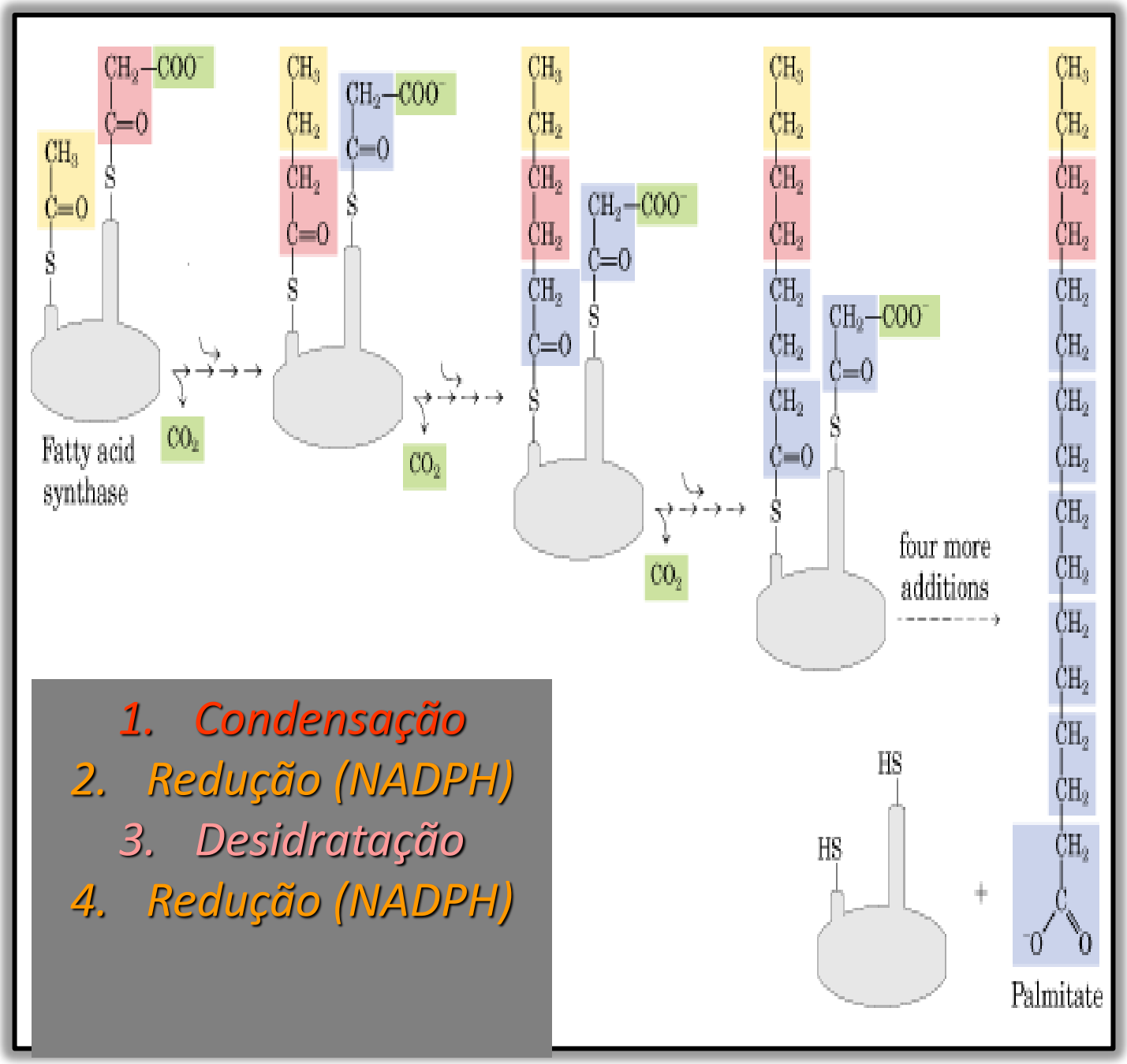




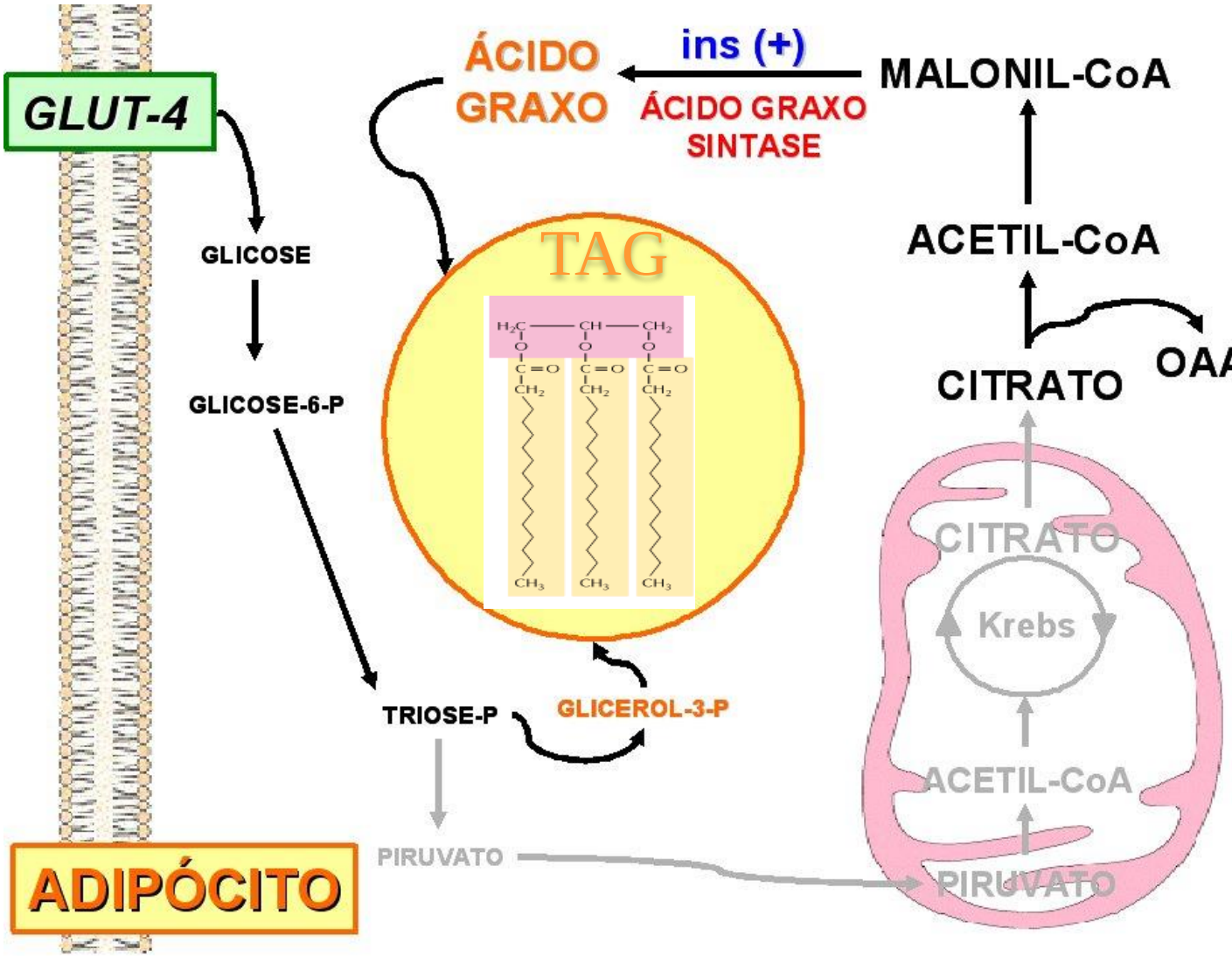


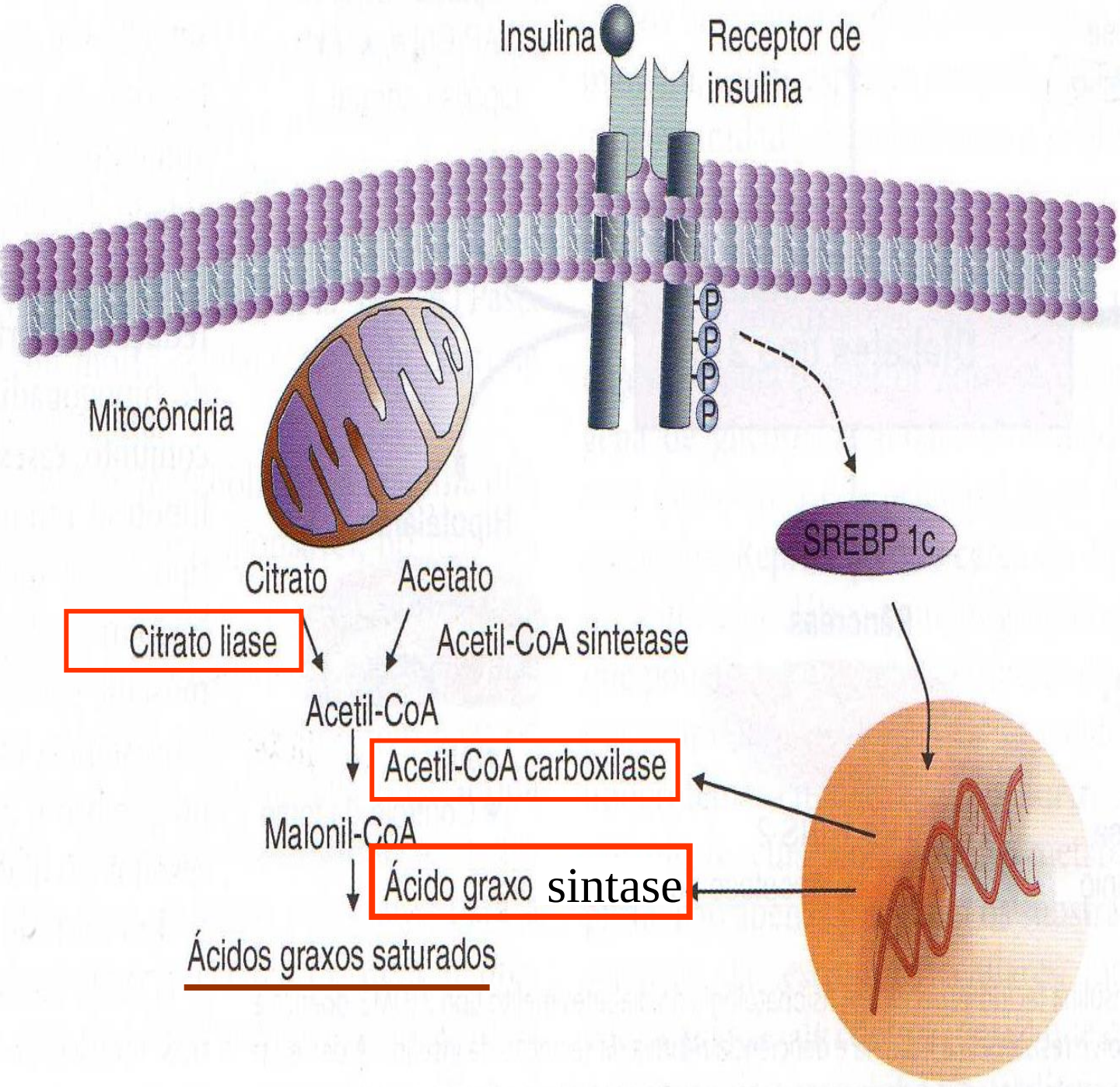


Síntese de ácidos graxos

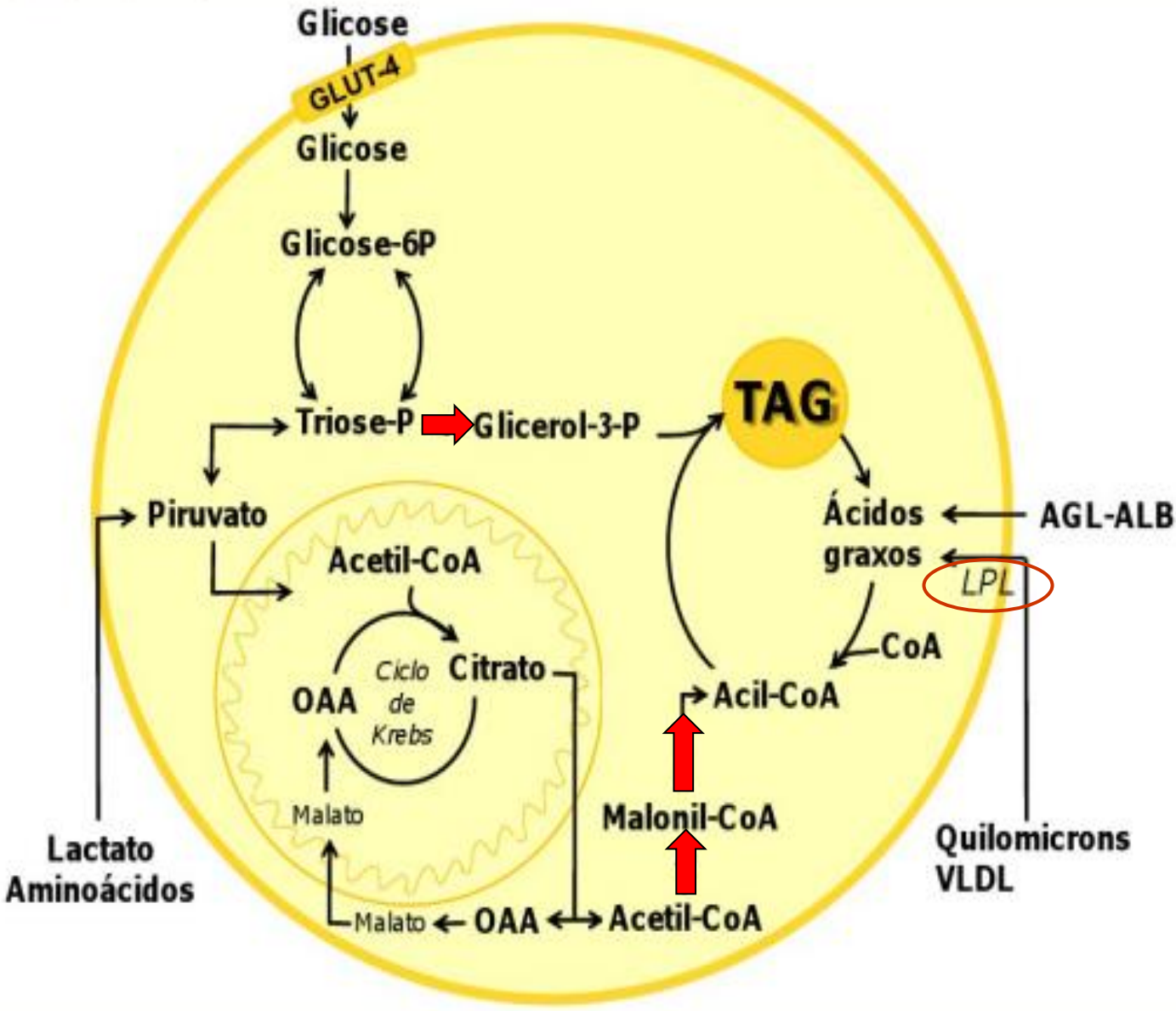


1. Condensação
2. Redução (NADPH)
3. Desidratação
4. Redução (NADPH)

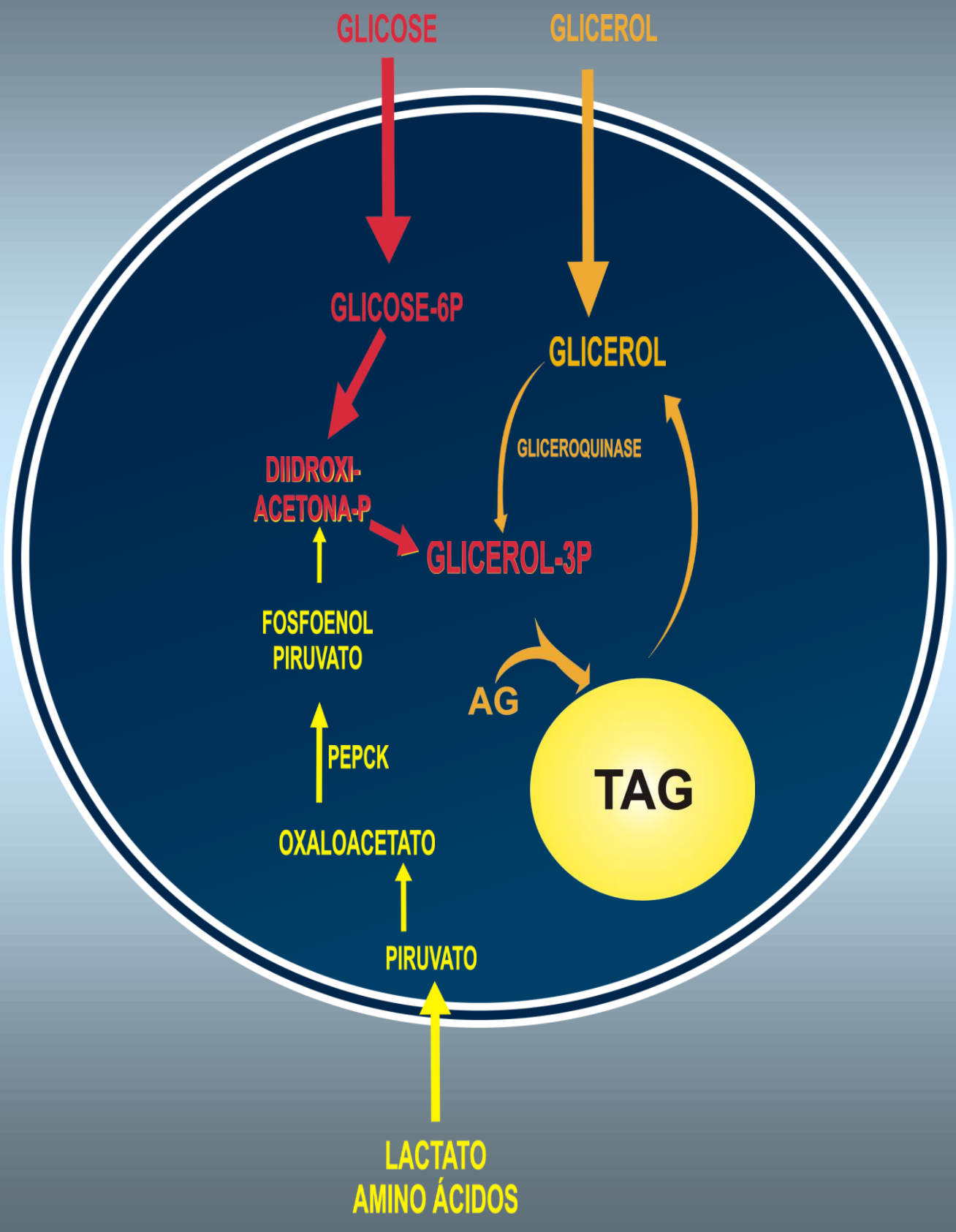

GLUT-4
GLICOSE
GLICOSE-6-P
ÁCIDO GRAXO
ins (+)
ÁCIDO GRAXO SINTASE
MALONIL-CoA
ACETIL-CoA
CITRATO
OAA
TAG
TRIOSE-P
GLICEROL-3-P
PIRUVATO
CITRATO
Krebs
ACETIL-CoA
PIRUVATO
ADIPÓCITO


Insulina
Receptor de insulina
P
P
P
P
Mitocôndria
SREBP 1c
Citrato
Acetato
Citrato liase
Acetil-CoA sintetase
Acetil-CoA
Acetil-CoA carboxilase
Malonil-CoA
Ácido graxo sintase
Ácidos graxos saturados

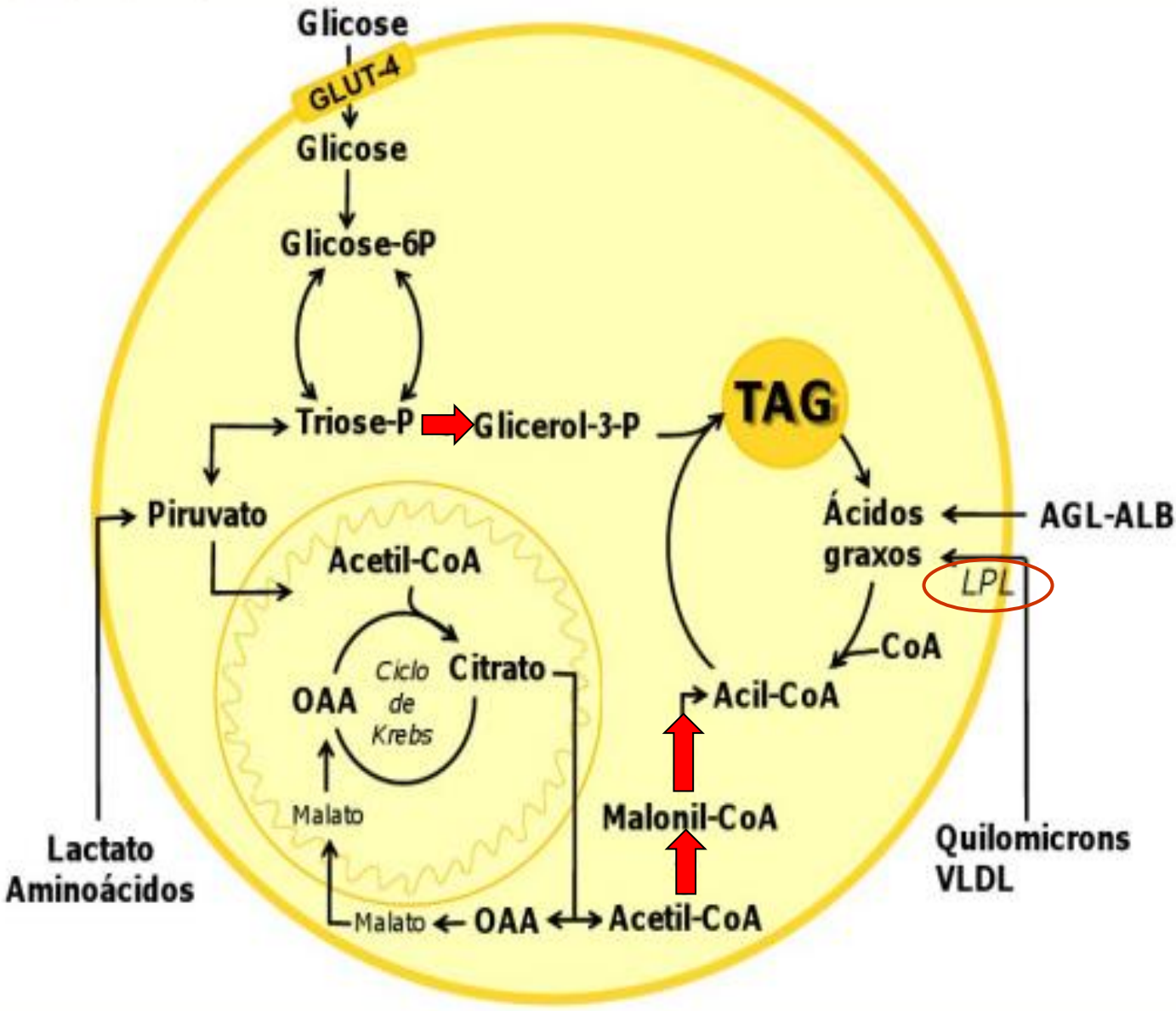
Insulina estimula a síntese de ácidos graxos e de glicerol-3-P



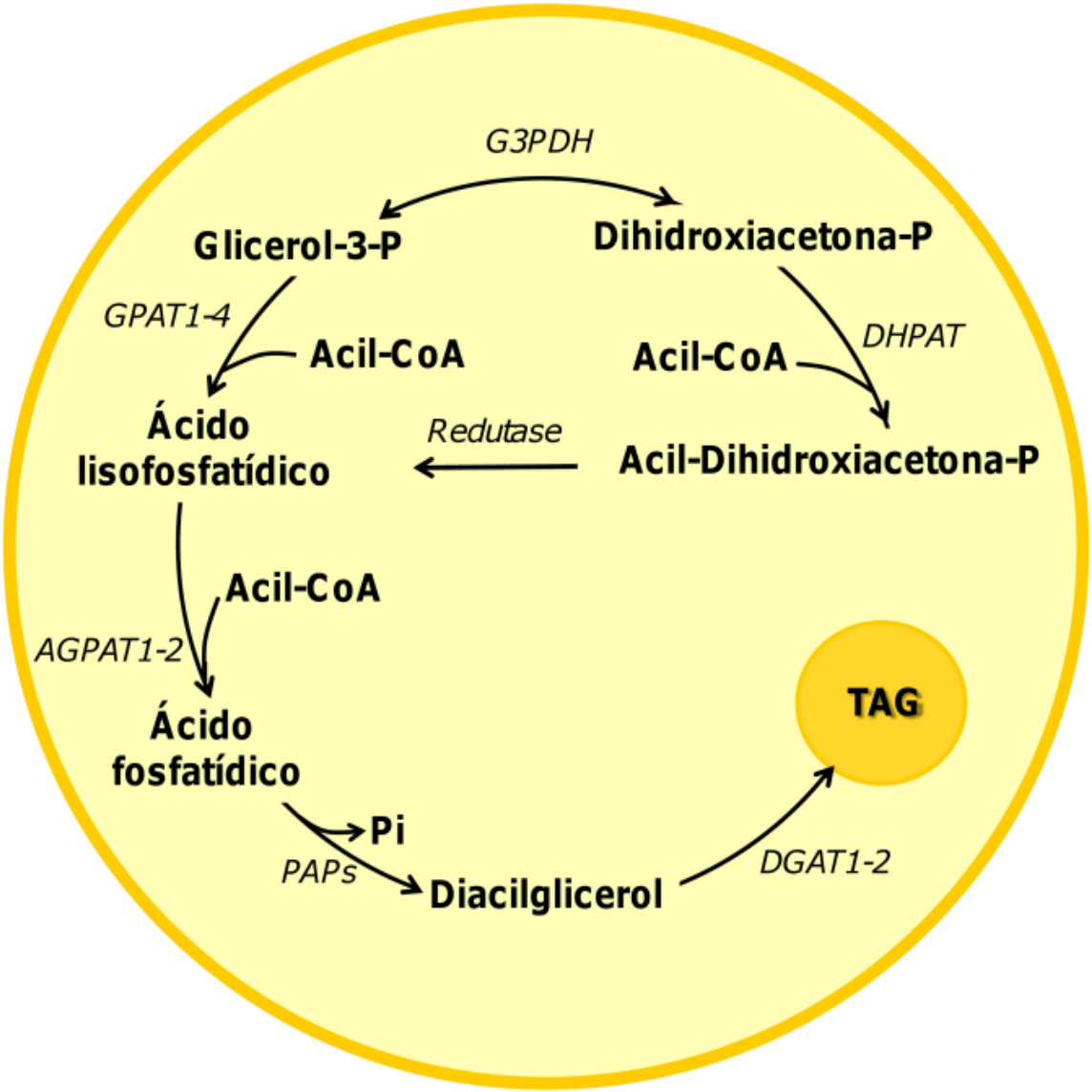
Vias de geração de glicerol-3-P

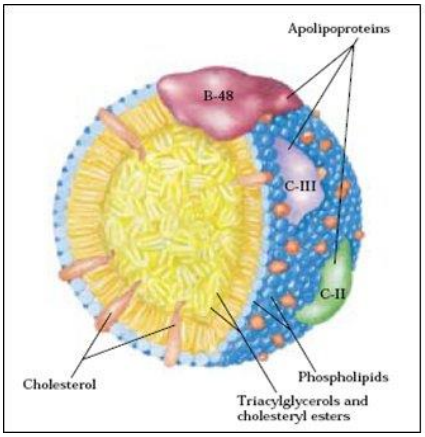


Insulina estimula a síntese de ácidos graxos e de glicerol-3-P



Formação do TAG





GLUT-4

GLICOSE

GLICOSE 6-P

TAG

ÁCIDOS GRAXOS

LHS ins (-)

glicerol

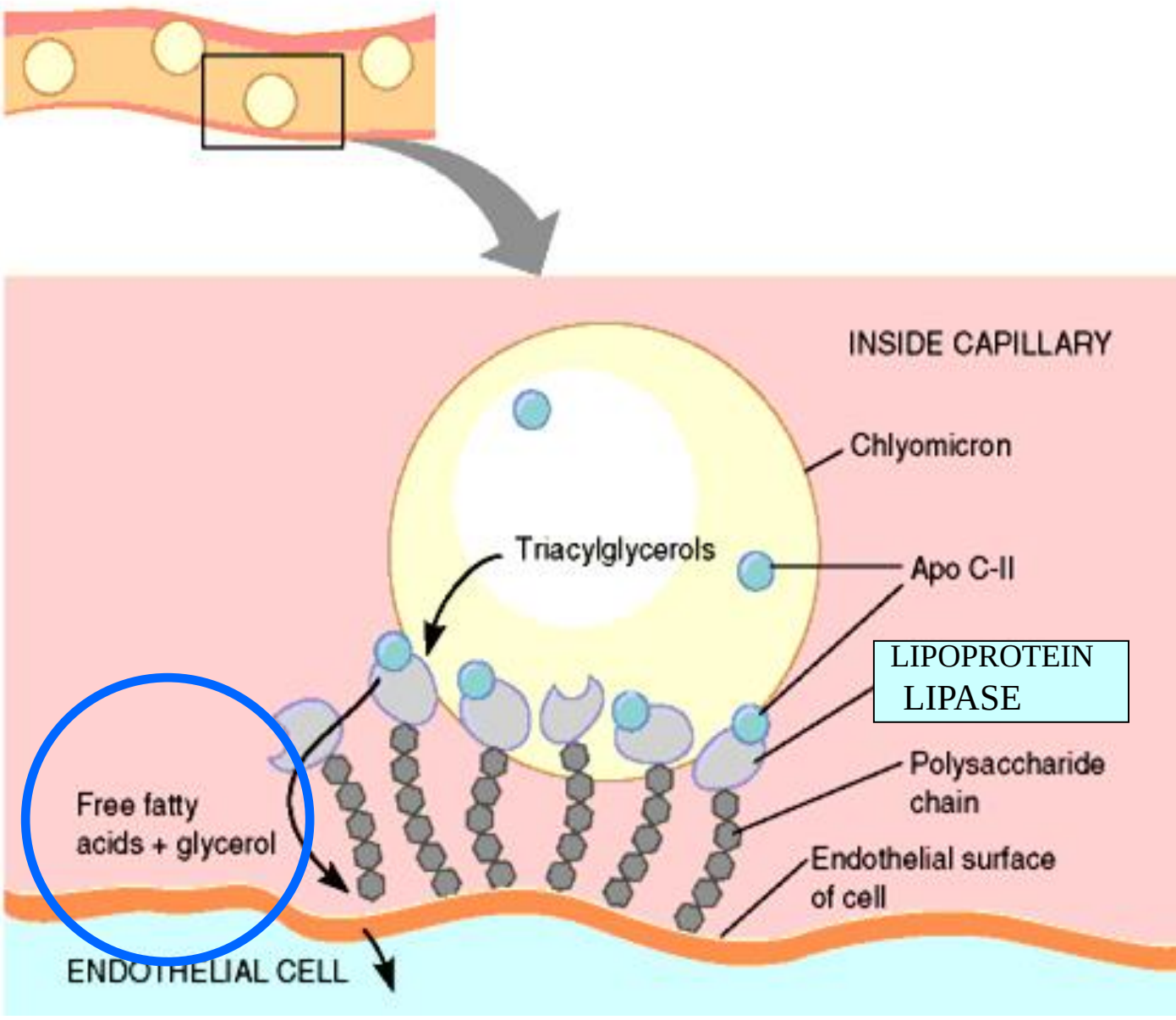
ADIPÓCITO

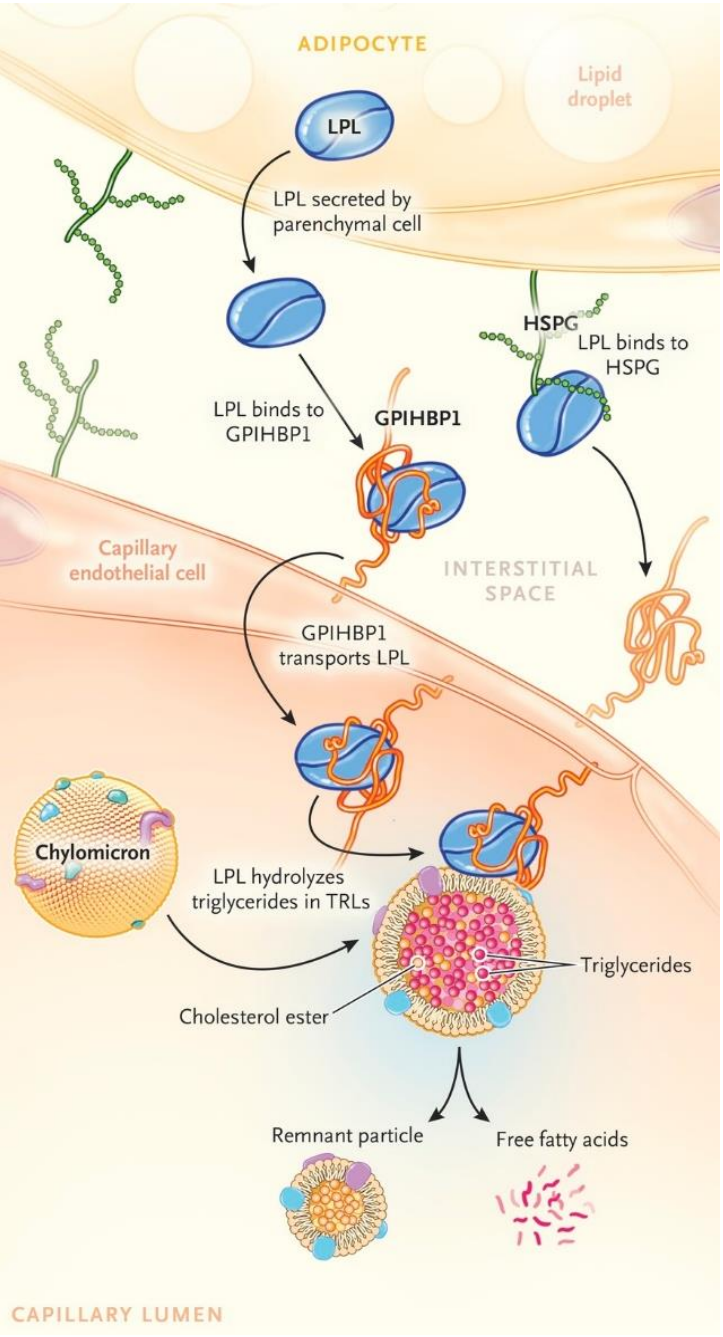
ins (+)

LPL

quilomícrons

VLDL


INSIDE CAPILLARY
Chlyomicron
Triacylglycerols
Apo C-II
LIPOPROTEIN
LIPASE
Polysaccharide
chain
Endothelial surface
of cell
Free fatty
acids + glycerol
ENDOTHELIAL CELL



HSPG: Heparan sulfate proteoglucano

A lipase lipoproteica (LPL) é <u>secretada</u> pelas células **dos tecidos adiposos** e musculares.

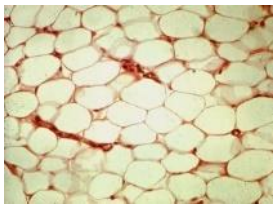
Em seguida, no espaço intersticial, a lipase lipoproteica é capturada por GPIHBP1 na superfície basolateral das células endoteliais.

GPIHBP1 (*glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1*)

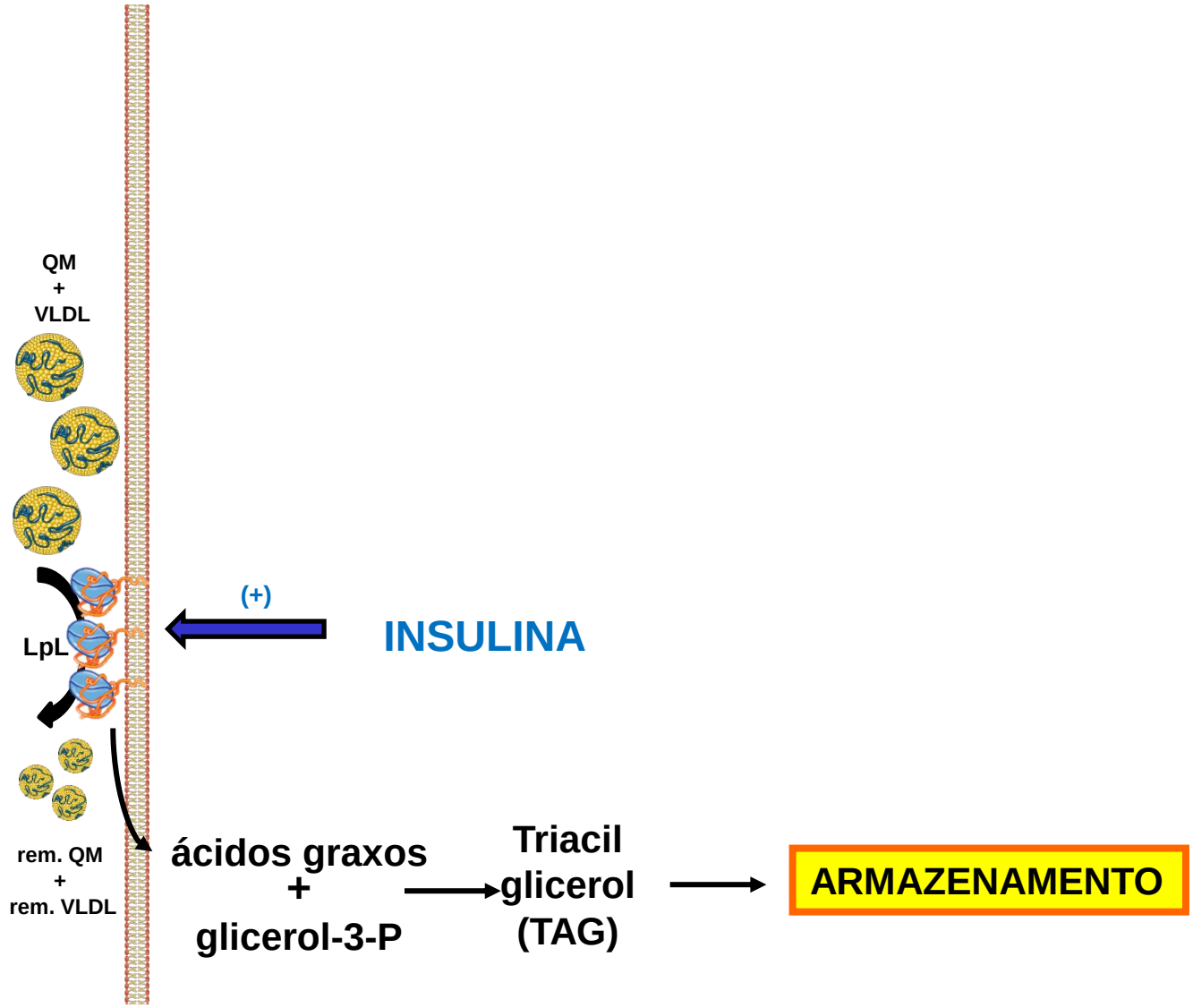
GPIHBP1 é expressa na superfície das células endoteliais capilares

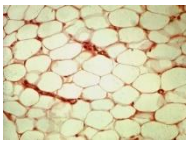
GPIHBP1 se liga à lipase lipoproteica nos espaços intersticiais e a transporta através das células endoteliais para o lúmen capilar

A lipase lipoproteica hidrolisa os triglicerídeos presentes nas lipoproteínas VLDL e quilomícrons

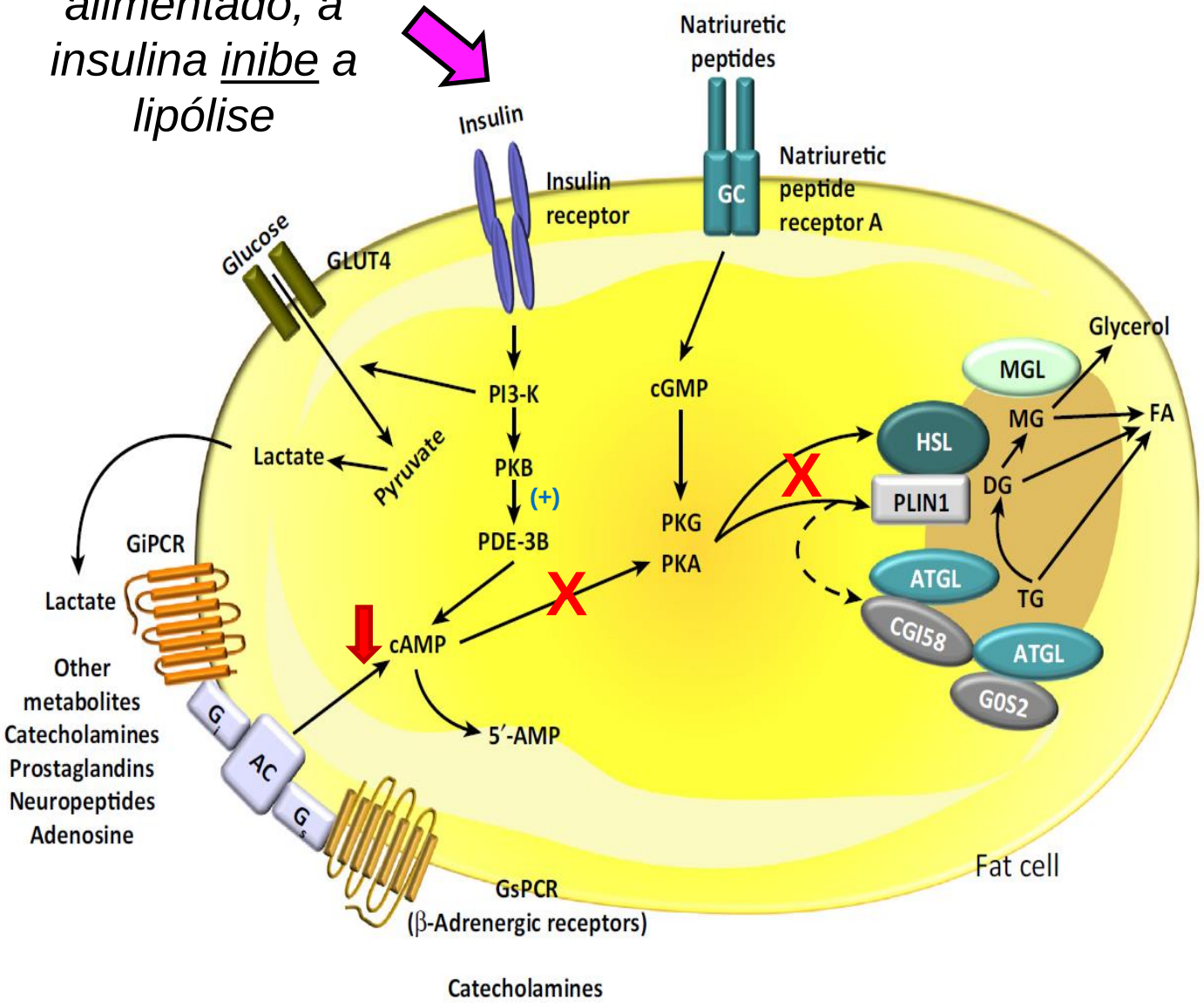


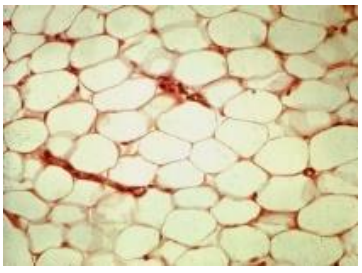
N Engl J Med 2017; 376:1647-1658


QM
+
VLDL
LpL
(+)
INSULINA
rem. QM
+
rem. VLDL
ácidos graxos
+
glicerol-3-P
Triacil
glicerol
(TAG)
ARMAZENAMENTO



No estado alimentado, a insulina inibe a lipólise





TECIDO ADIPOSO

Ações da insulina

↑ **LIPOGÊNESE:** ↑ **acetil-CoA carboxilase**
ácido graxo sintase

↓ **LIPÓLISE:** ↓ **Lipase hormônio-sensível**
↑ **Fosfodiesterase do cAMP**

↓ gliceroneogênese

↑ Formação do glicerol-3-P pela via glicolítica

dieta → abs.intestinal → QM

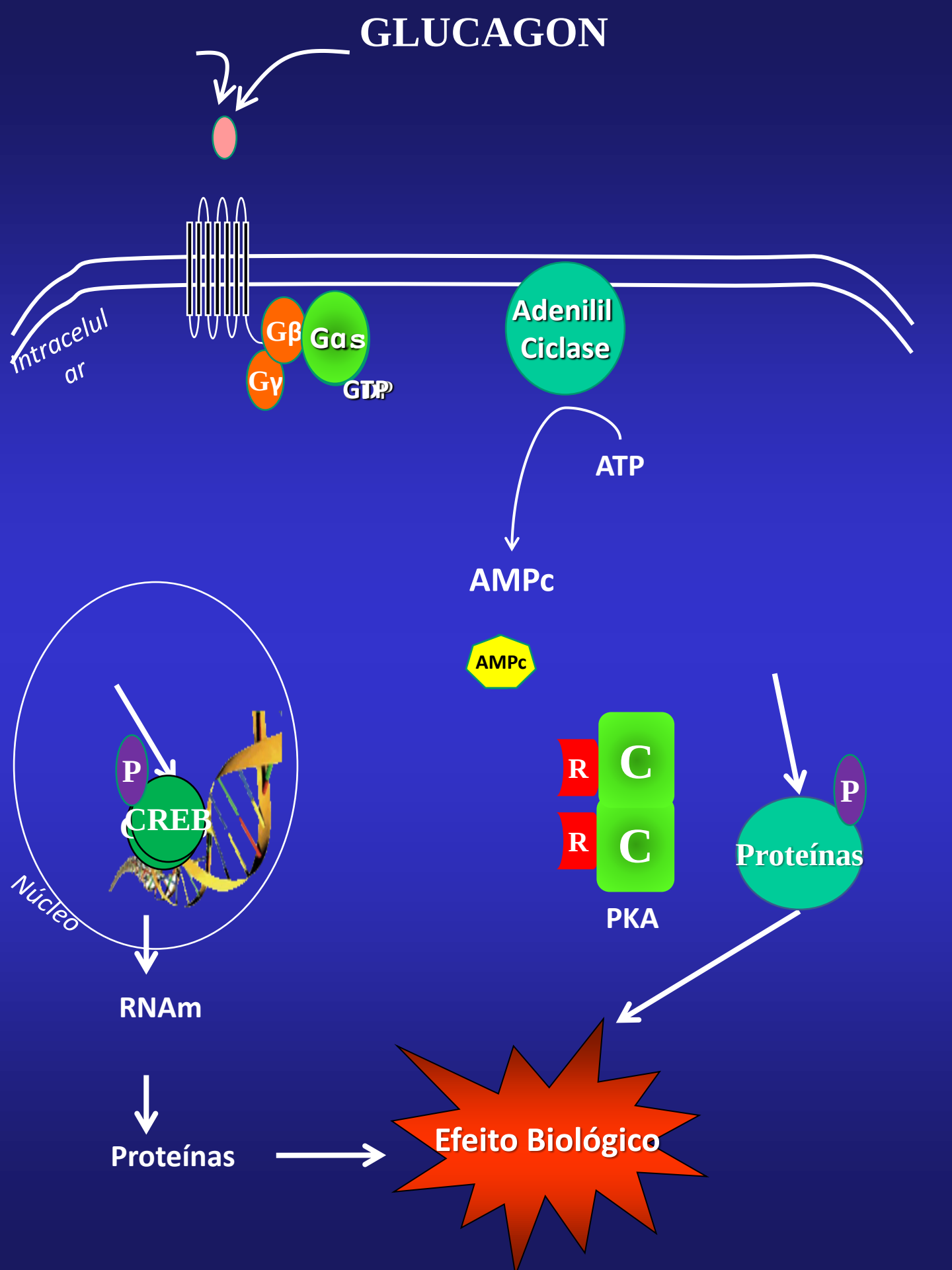
TG

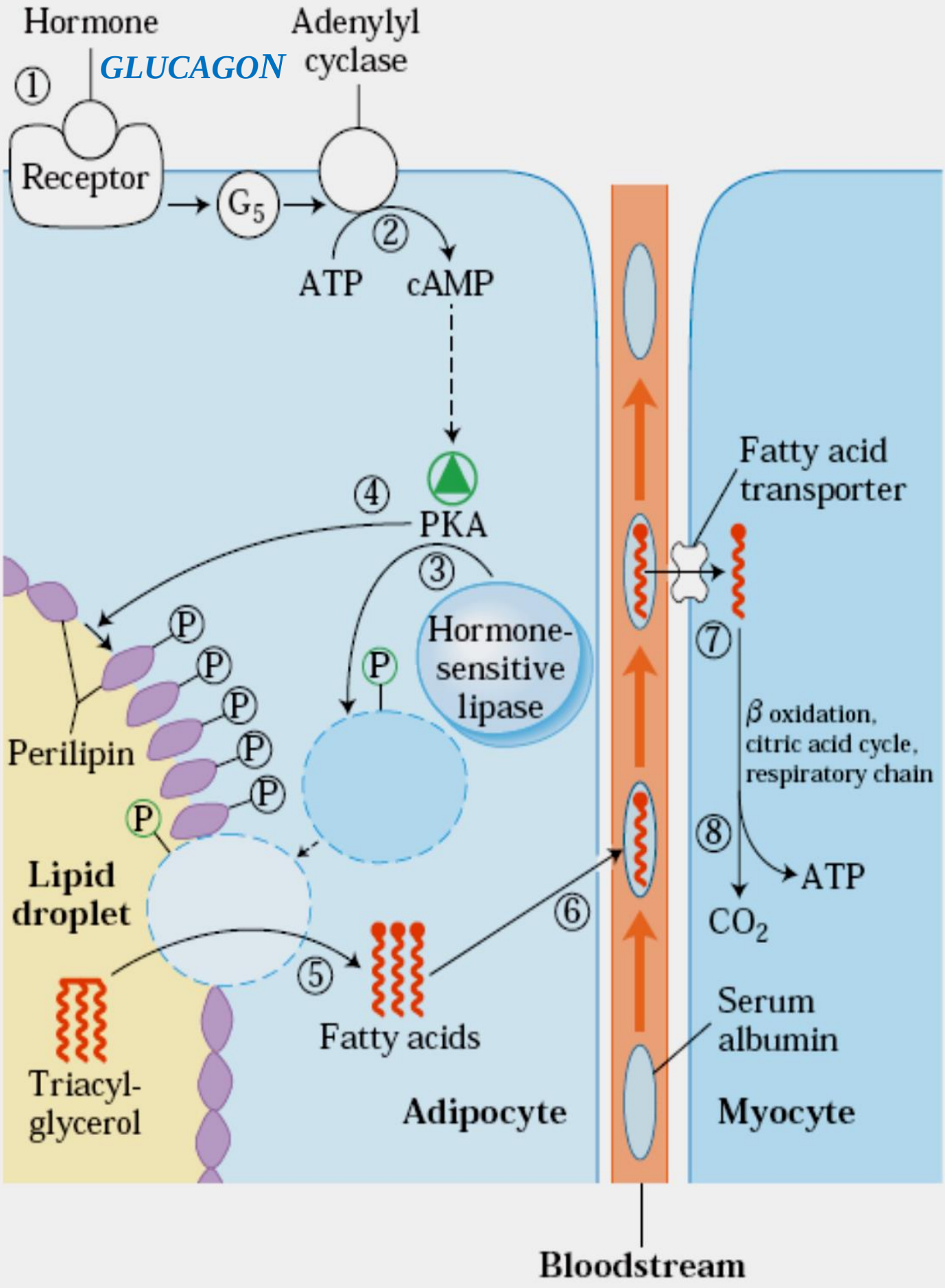
LPL(adipócito) ← circulação

↑ (Lipase lipoprotéica)

AG

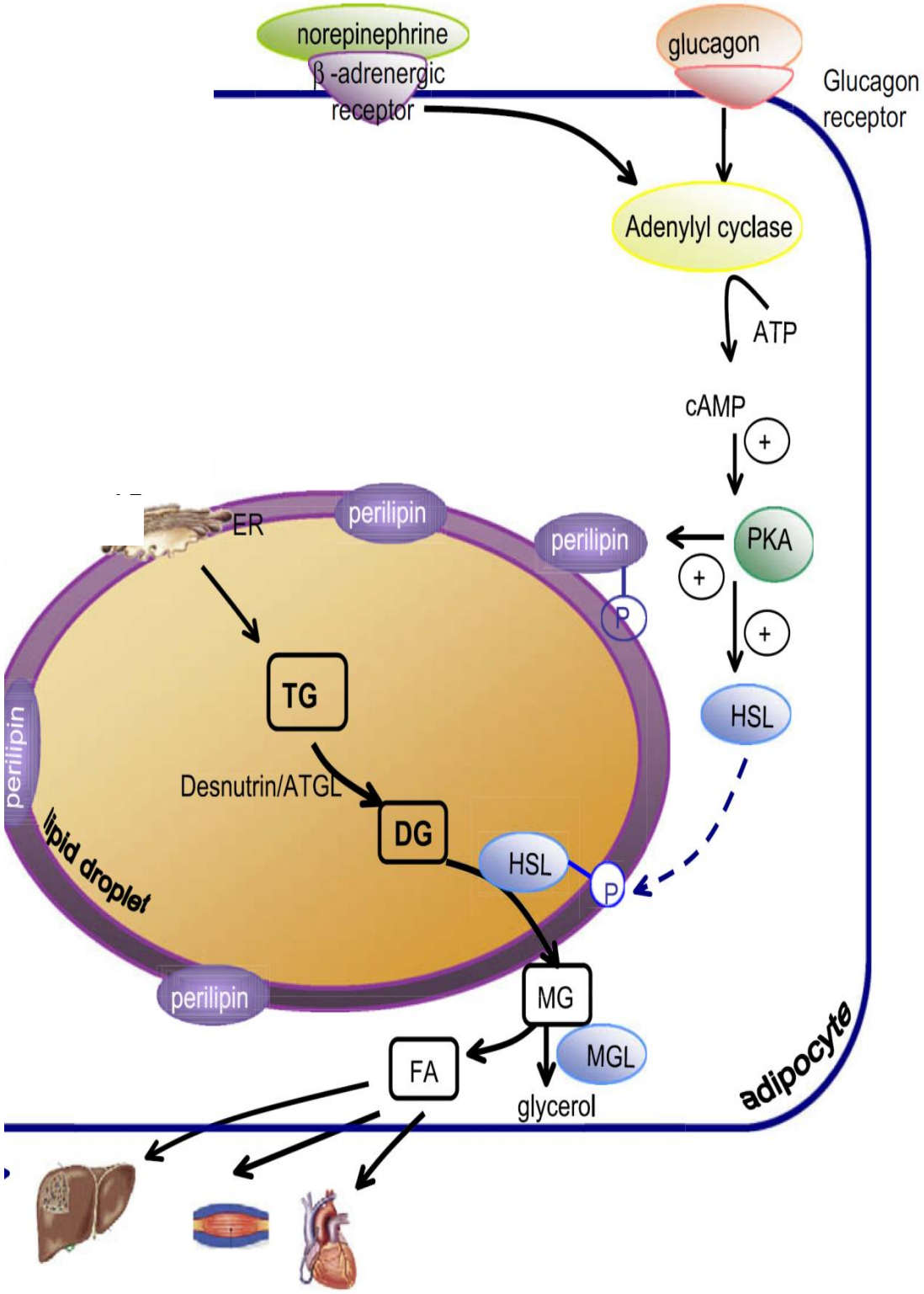
→ *ARMAZENAMENTO*


GLUCAGON
Intracelul
ar
Gβ
Gαs
Gγ
GTP
Adenilil
Ciclase
ATP
AMPc
AMPc
P
CREB
Núcleo
R
C
R
C
PKA
P
Proteínas
RNAm
Proteínas
Efeito Biológico

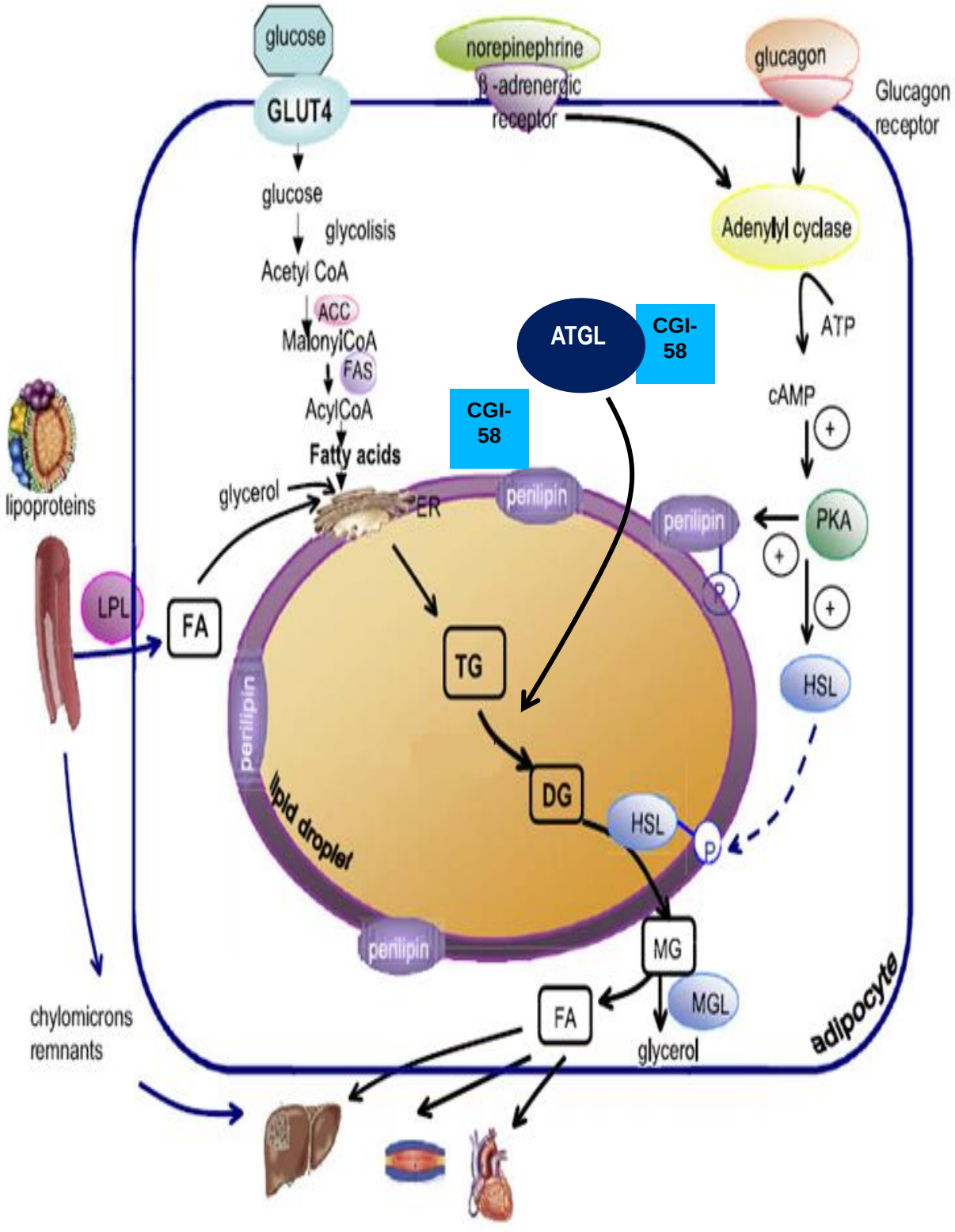

Hormone
GLUCAGON
Adenylyl cyclase
1
Receptor
G5
2
ATP
cAMP
4
PKA
3
Hormone-sensitive lipase
P
Perilipin
Lipid droplet
5
Fatty acids
Triacyl-glycerol
6
Fatty acid transporter
7
β oxidation, citric acid cycle, respiratory chain
8
ATP
CO2
Serum albumin
Adipocyte
Myocyte
Bloodstream

Lipólise : Mecanismo mais detalhado

Hidrólise do Triacilglicerol

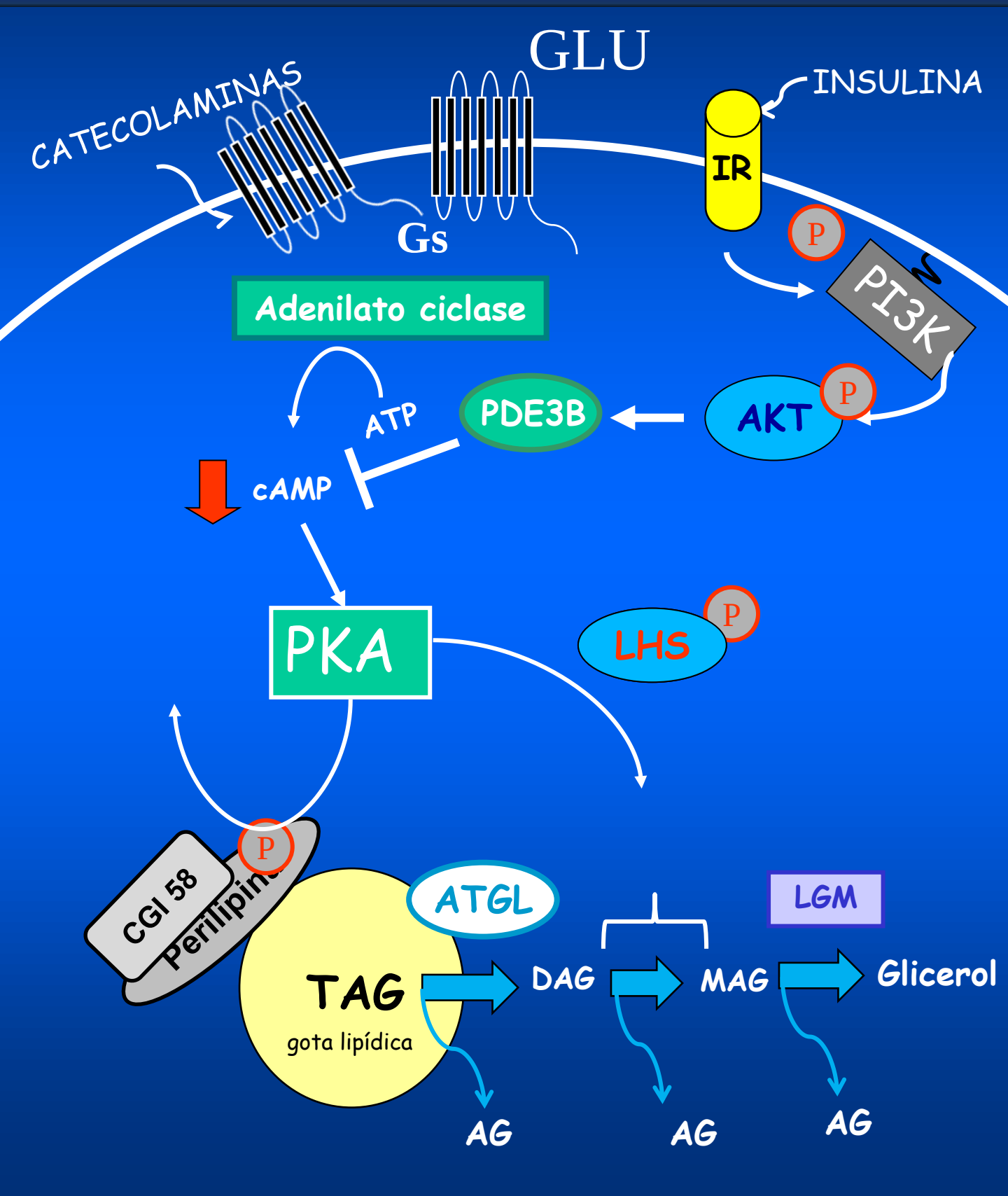


Vázquez-Vela ME, Torres N, Tovar AR. *Arch Med Res.* 2008 Nov;39(8):715-28. Review

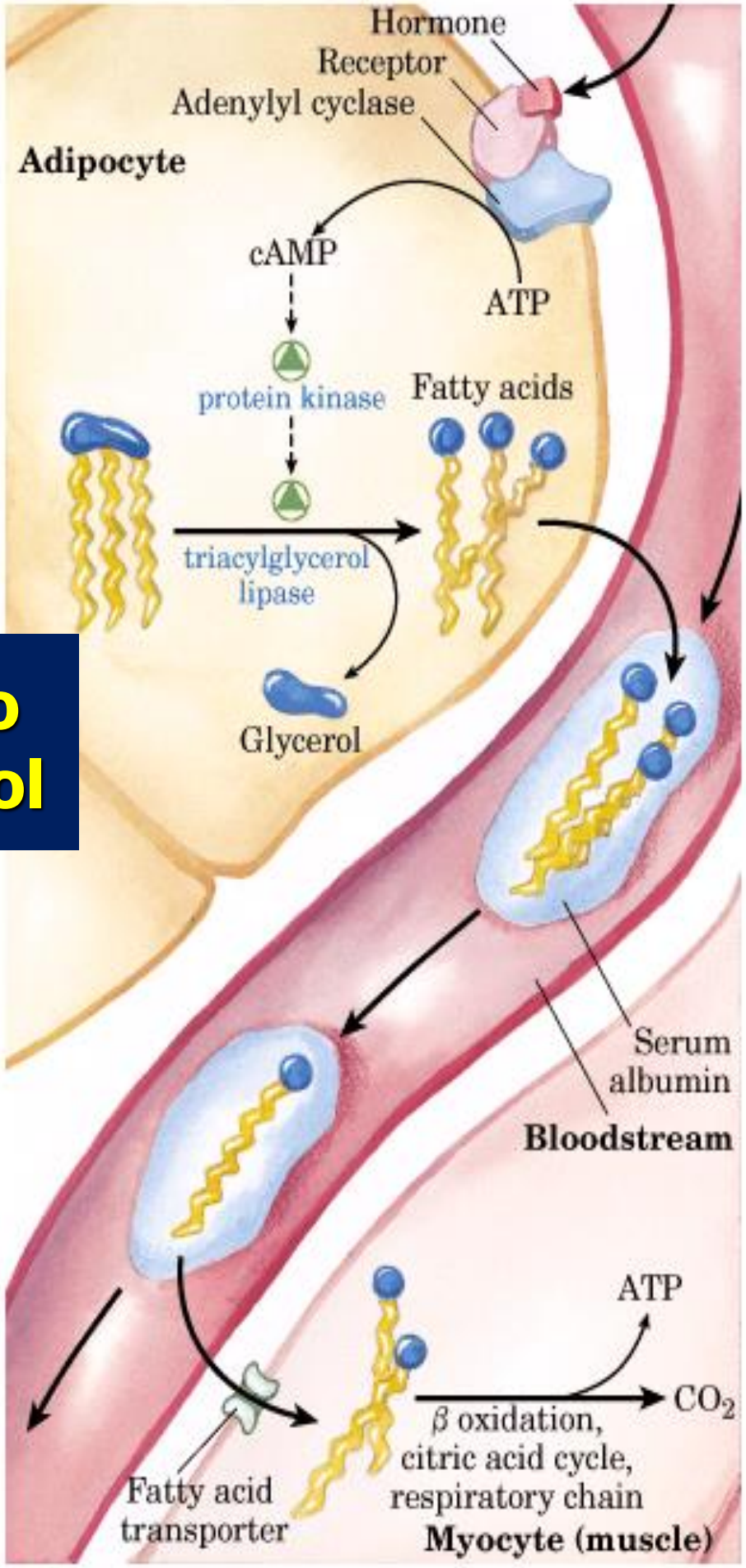


Vazquez-Vela et al., Arch. Med. Res. 39: 715-28, 2008

CONTROLE HORMONAL



Hidrólise do Triacilglicerol



TECIDO ADIPOSO

Ações do Glucagon

↑ LIPÓLISE:

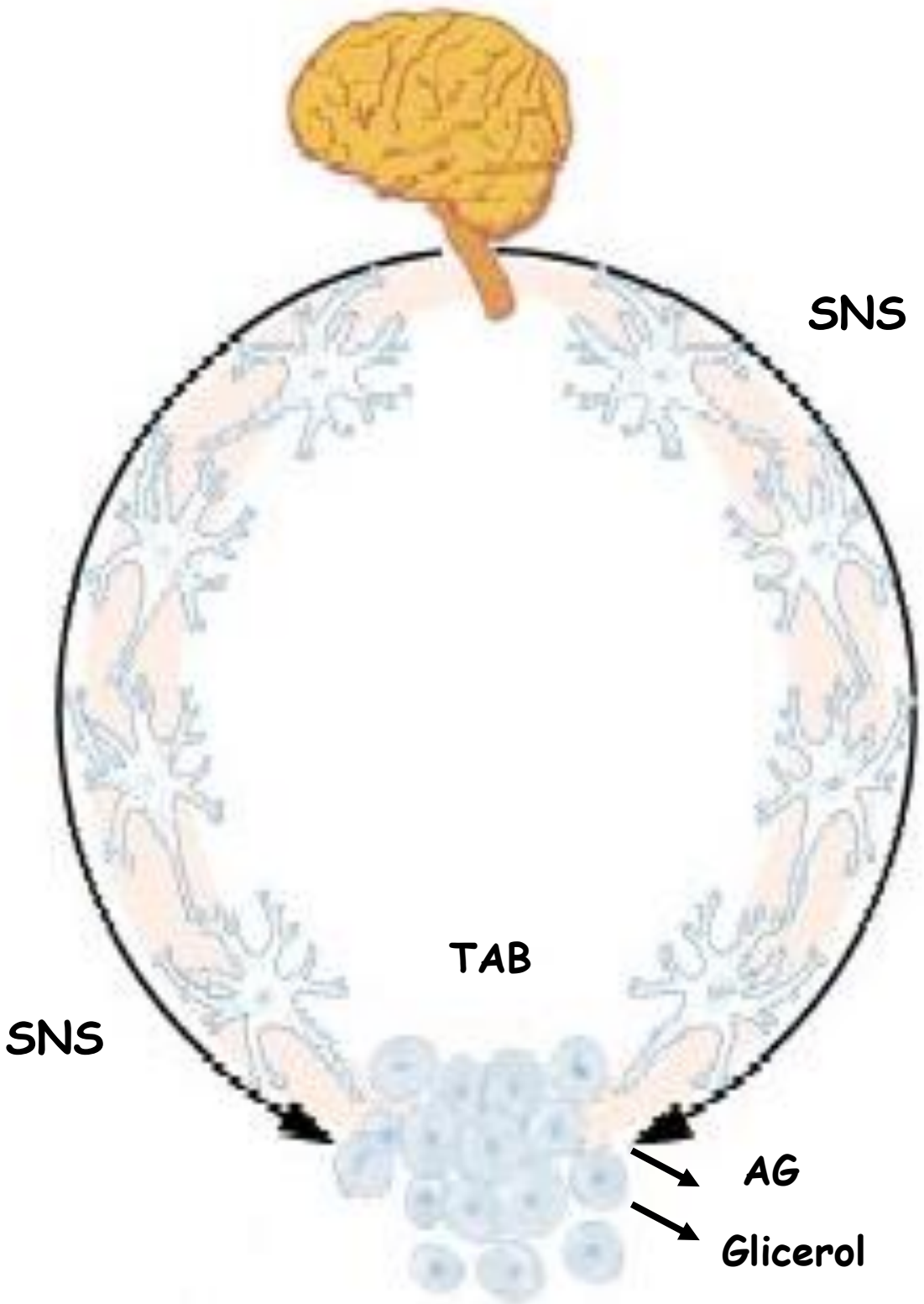
Aumenta a liberação de ácidos graxos e glicerol

PKA fosforila e estimula :

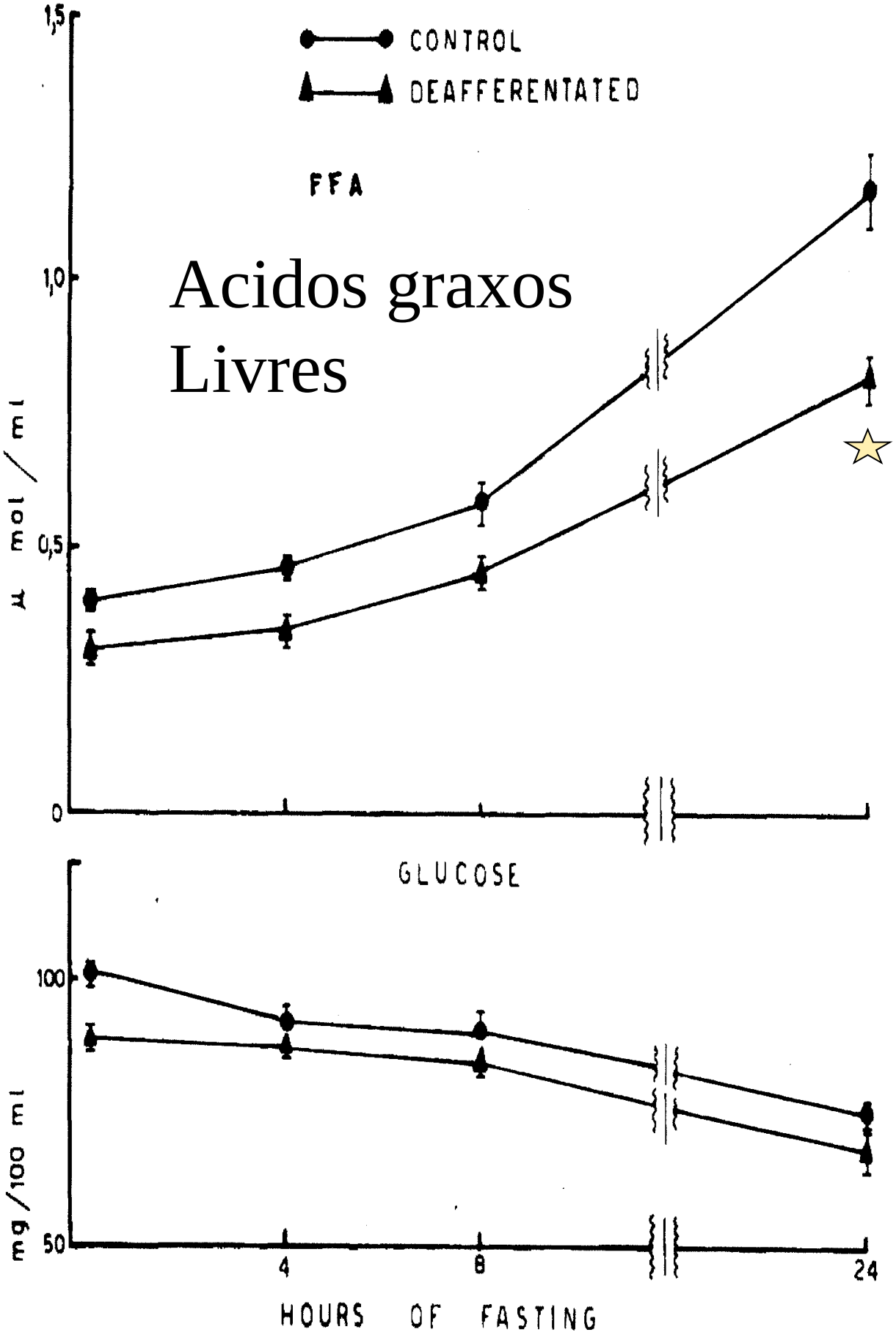
- **Lipase Hormônio-Sensível**
- **Perilipina**

↓ Lipogênese

Inervação Simpática no TAB



*Alterado de Bartness, J.C. Invest.*110: 1235 – 1237 (2002)


CONTROL
DEAFFERENTATED
FFA
Acidos graxos Livres
1,5
1,0
0,5
0
μ mol / ml
GLUCOSE
100
50
mg /100 ml
4
8
24
HOURS OF FASTING

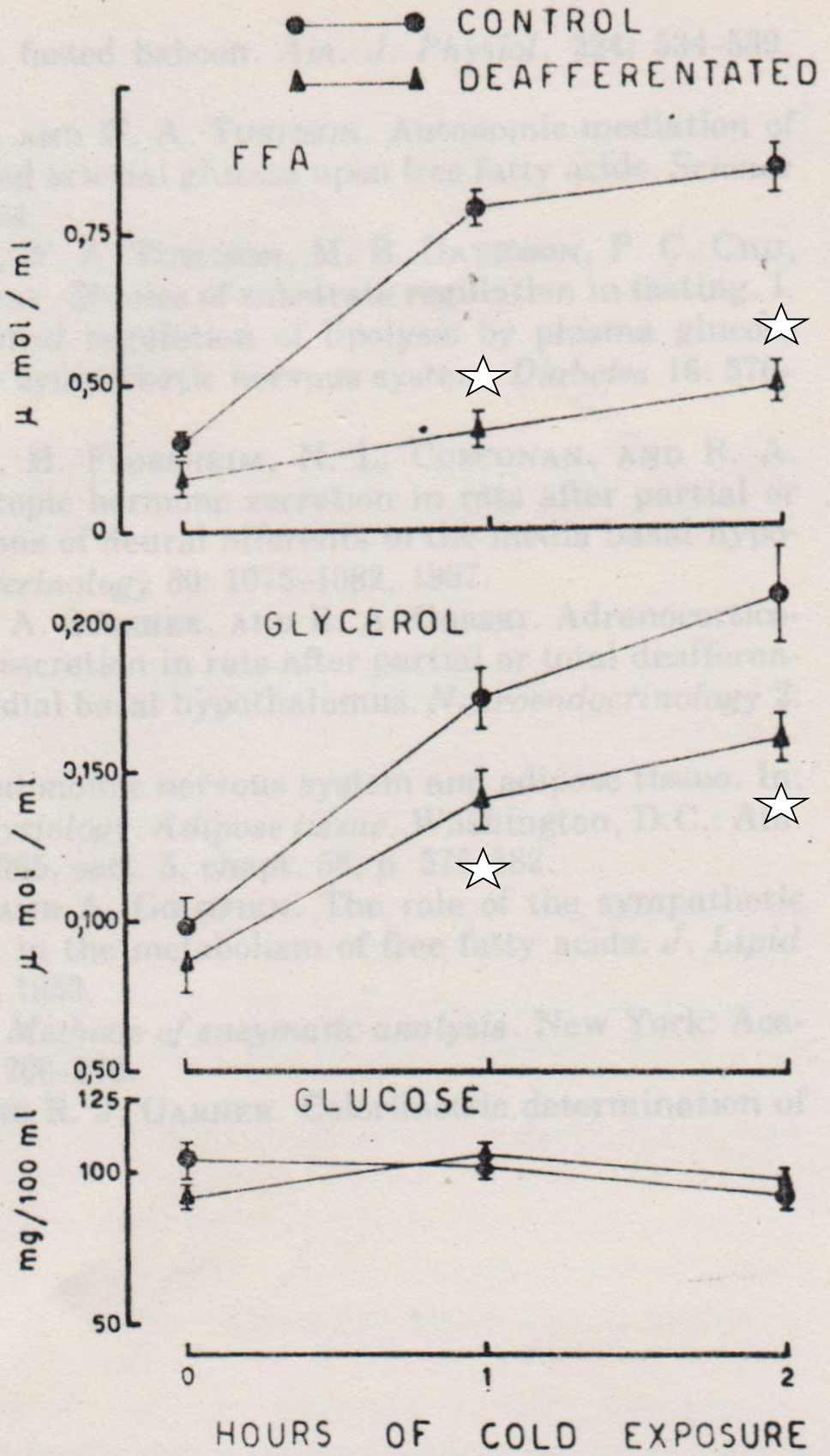
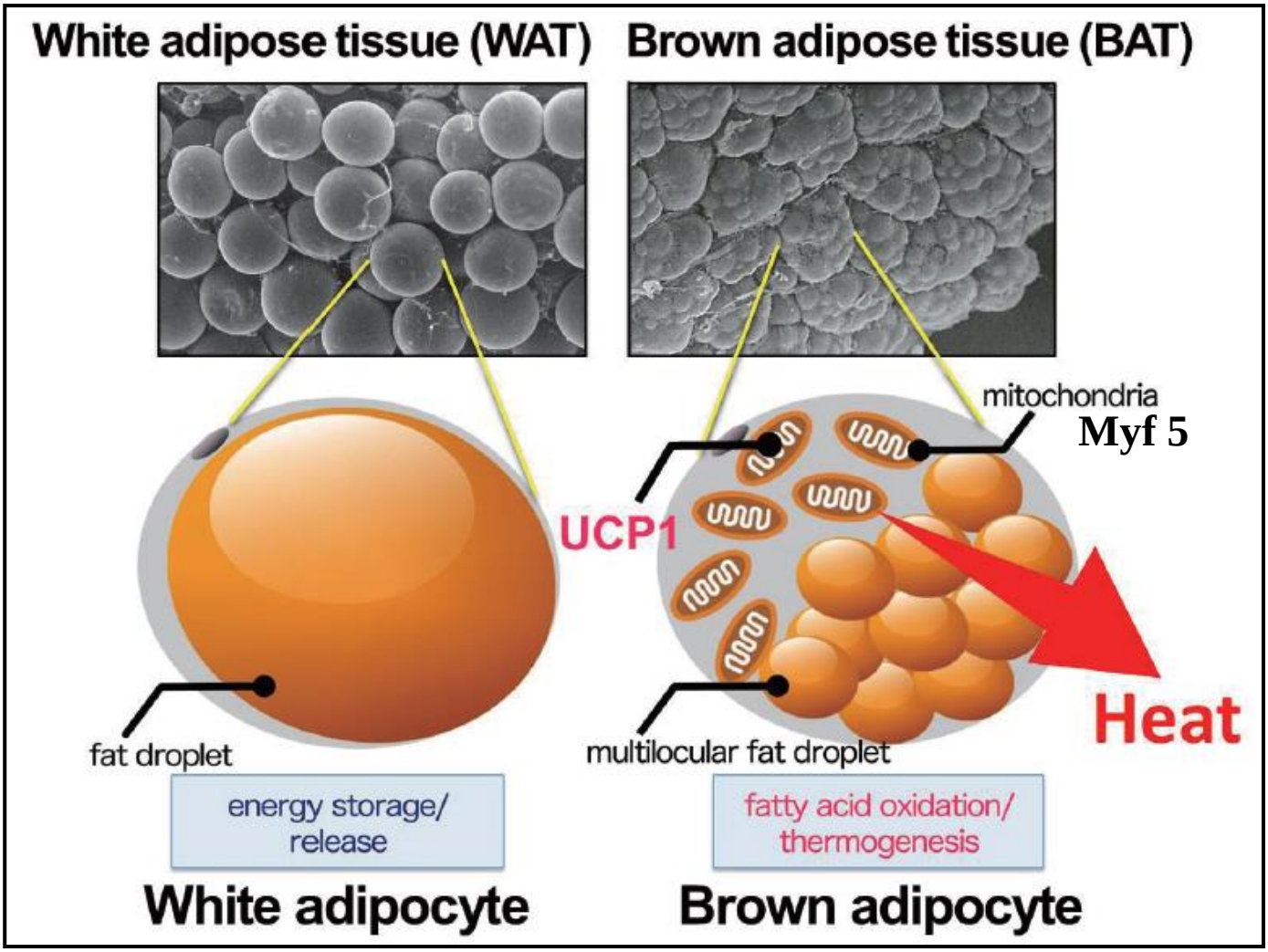


FIG. 4. Effect of cold (4°C) exposure on concentration of plasma FFA, plasma glycerol, and blood glucose in control and deafferented rats. Each point is average of 8–18 observations. Vertical brackets represent standard error.

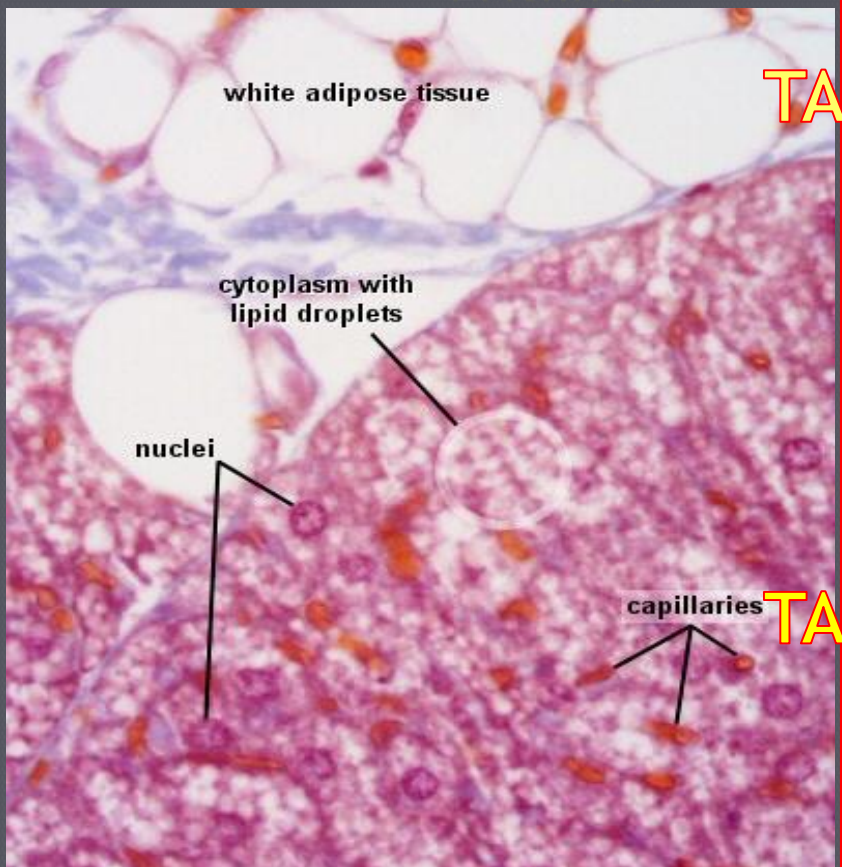
Além do tecido adiposo branco, existe também o tecido adiposo marrom, o qual apresenta características peculiares, como muitas mitocôndrias , múltiplas gotículas de gordura e a presença da proteína UCP1 (ou termogenina) na membrana interna das mitocôndrias, conferindo a este tecido a capacidade de produzir calor (capacidade termogênica).

Morfologia: tamanho das células, vascularização e inervação simpática

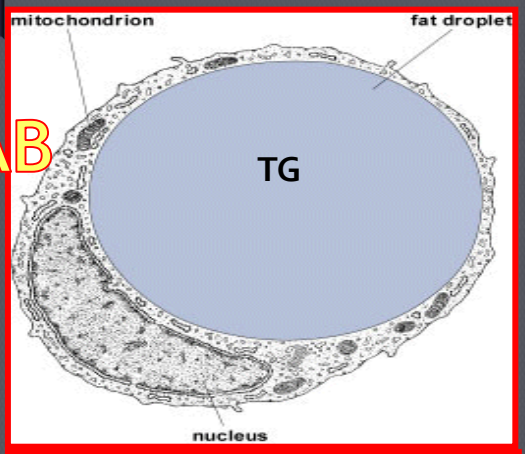


GOTO et al., 2016

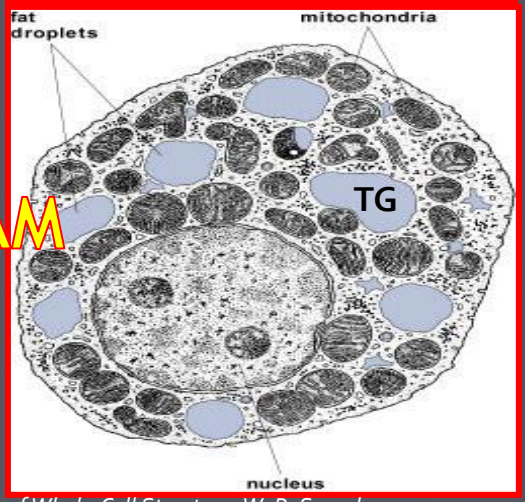
Estrutura



TAB



TAM



http://www.lab.anhb.uwa.edu.au; Lentz, ATL. *Cell Fine Structure: An Atlas of Drawings of Whole-Cell Structure, W. B. Saunders, 1971*

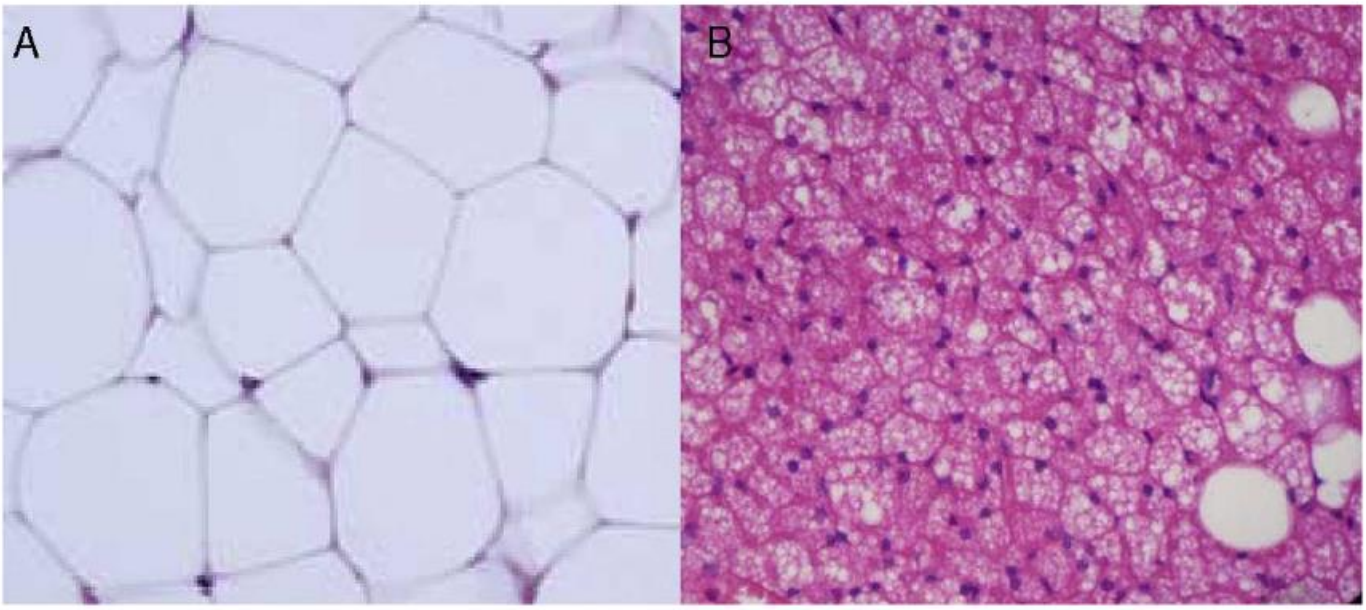
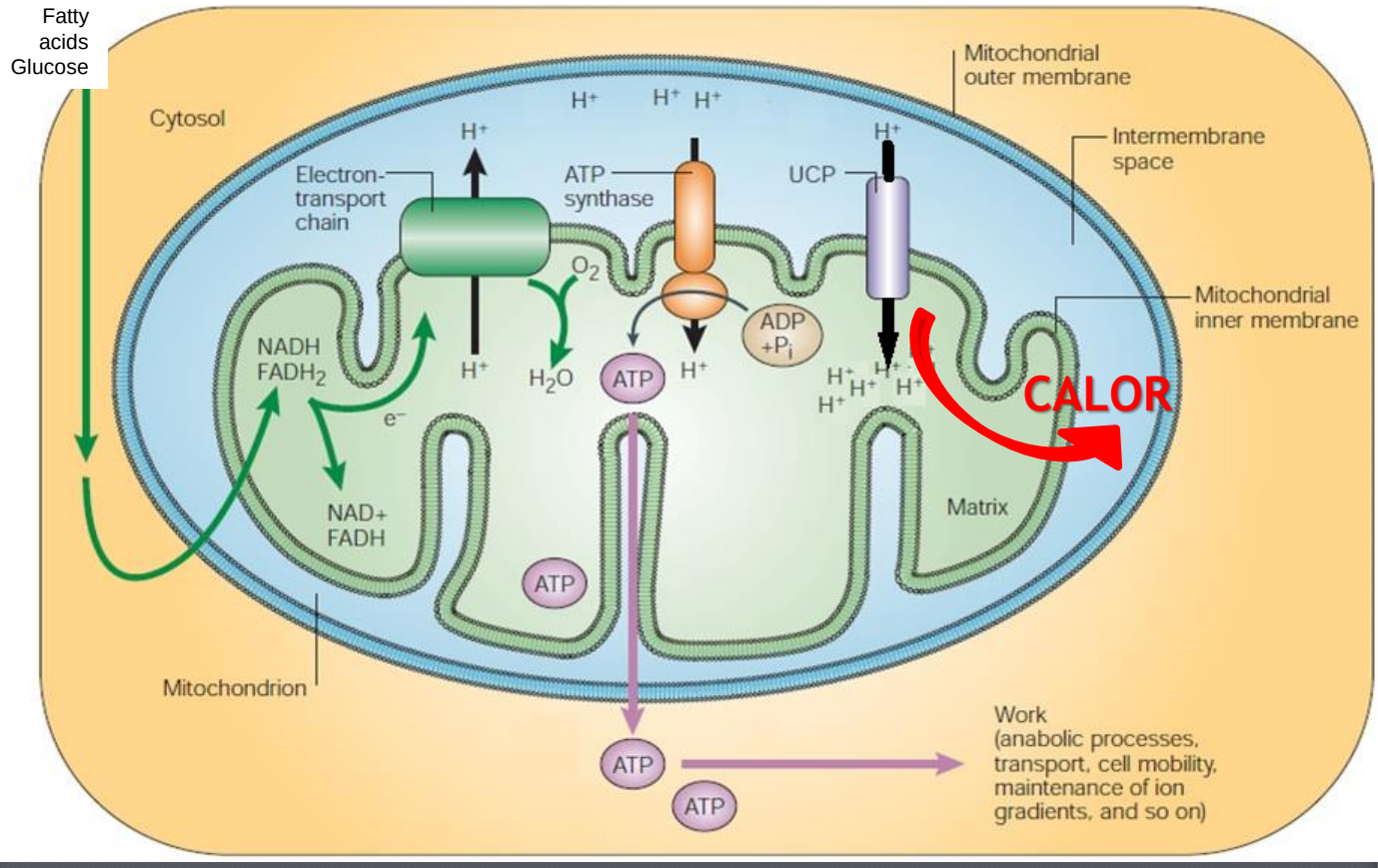


Figure 5 Light microscope image of white adipose tissue (A) and brown adipose tissue (B).

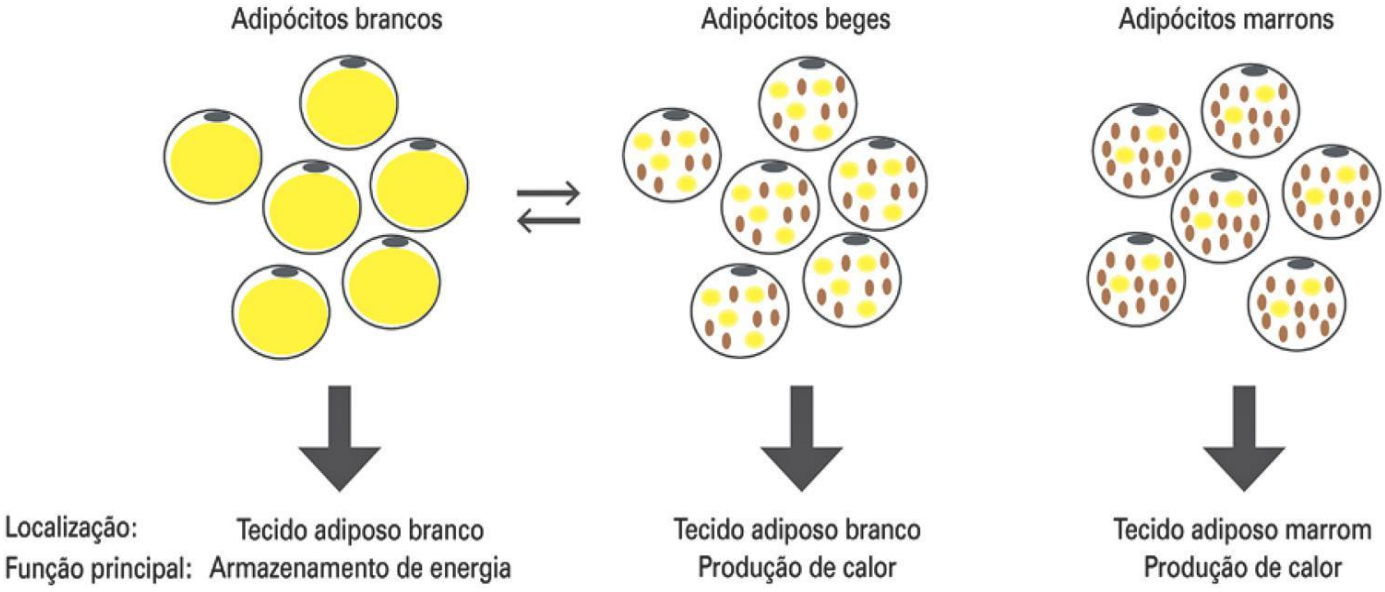
Mecanismo de ação das UCPs

UCP

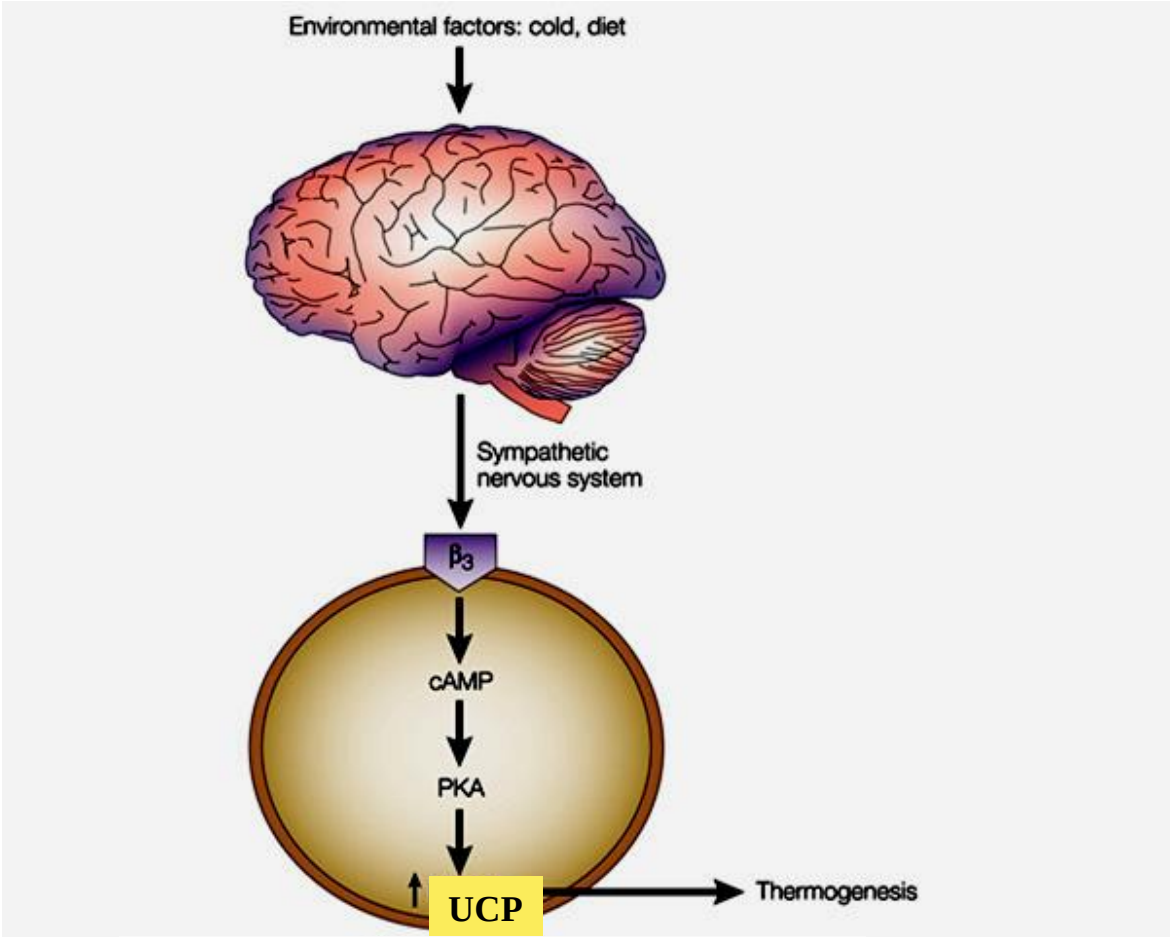


Krauss *et al. Nature Reviews*, 2005 (figura adaptada)

O processo de “Browning”

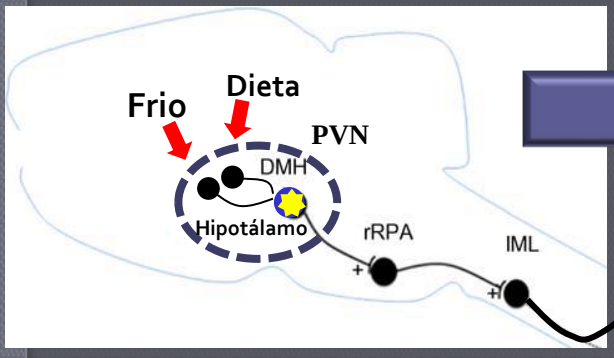


Como o sistema nervoso regula a função Termogênica do TAM ?

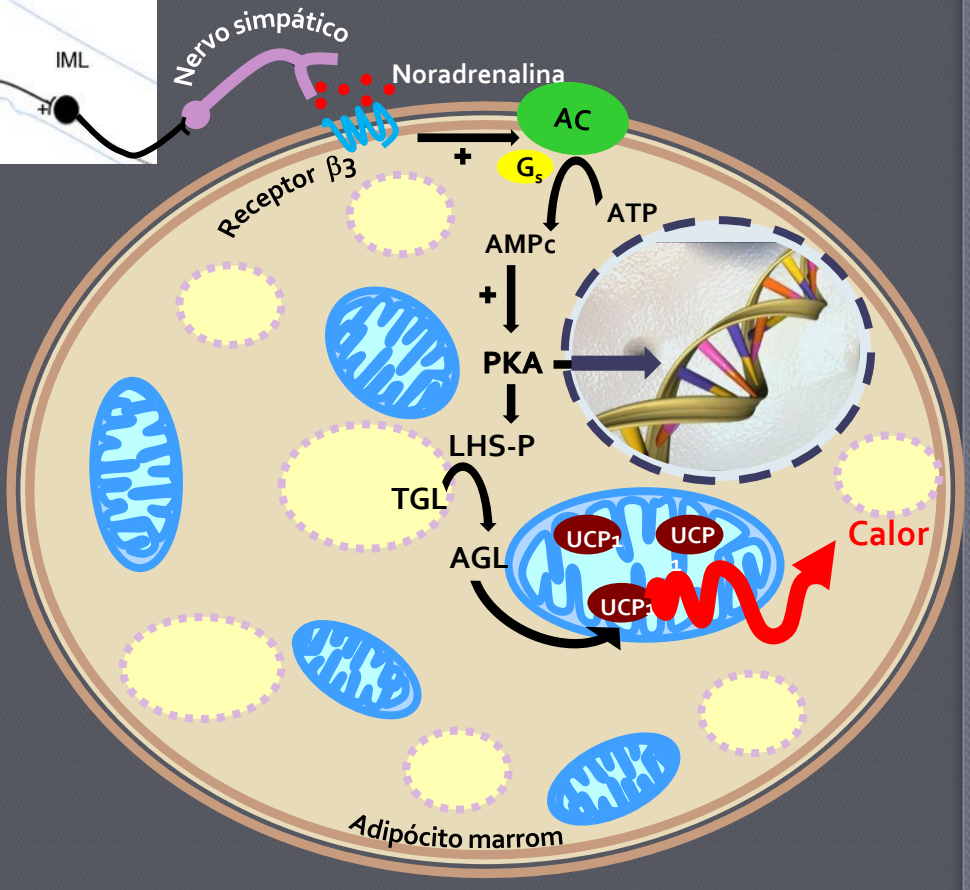


brown adipocyte

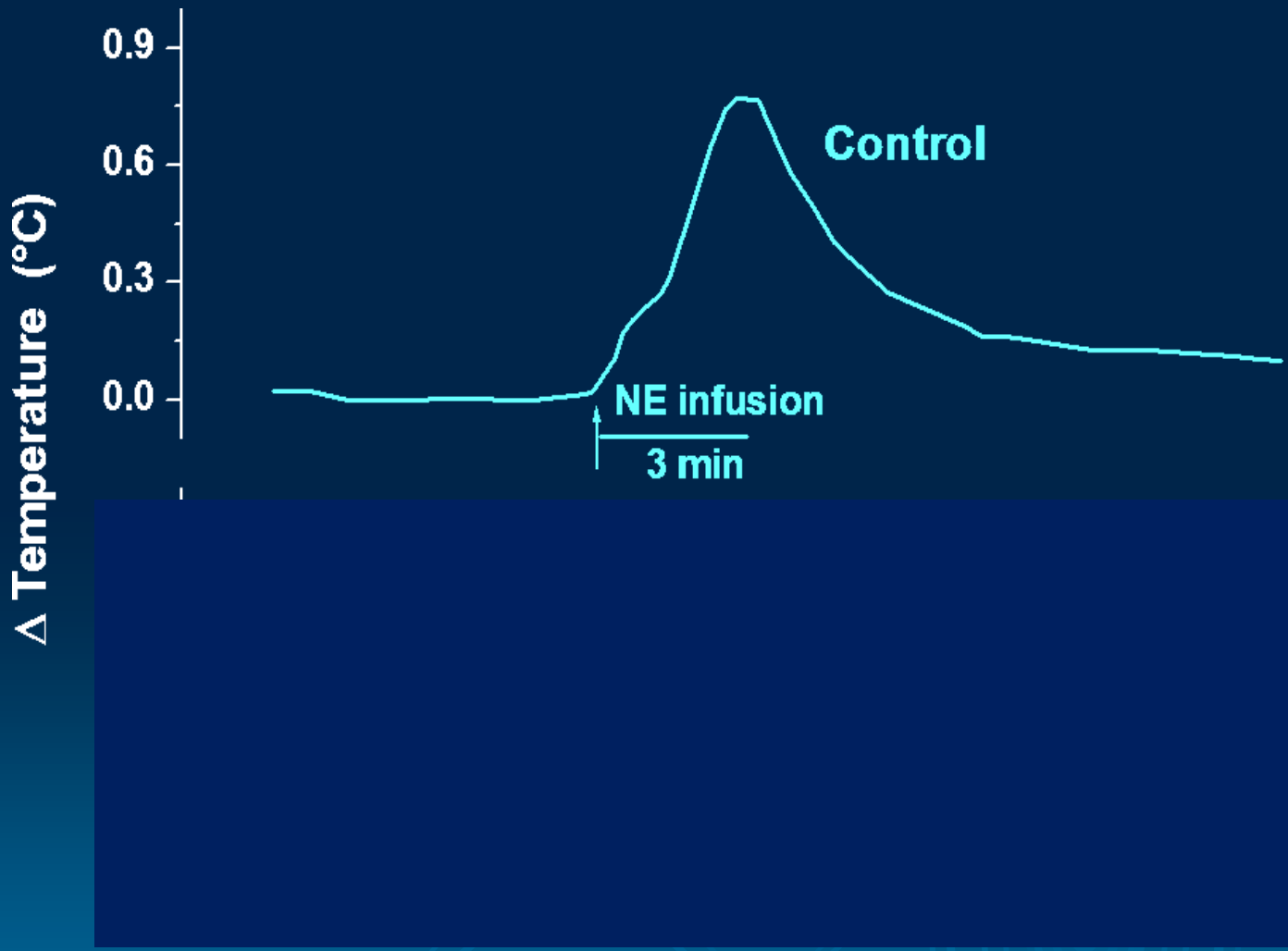
Tecido adiposo marrom: Qual a sua função?



Função



Tecido adiposo marrom de rato

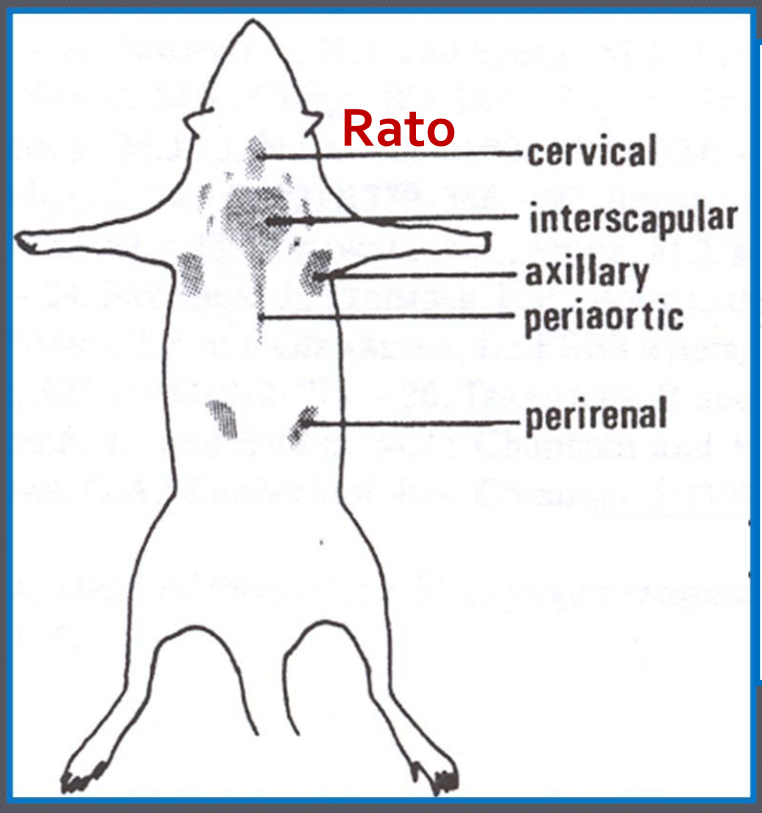


Brito, M.N. *et al. J. Nut. 122: 2081-2086, 1992.*

Tecido adiposo marrom: Onde fica? Quem tem?

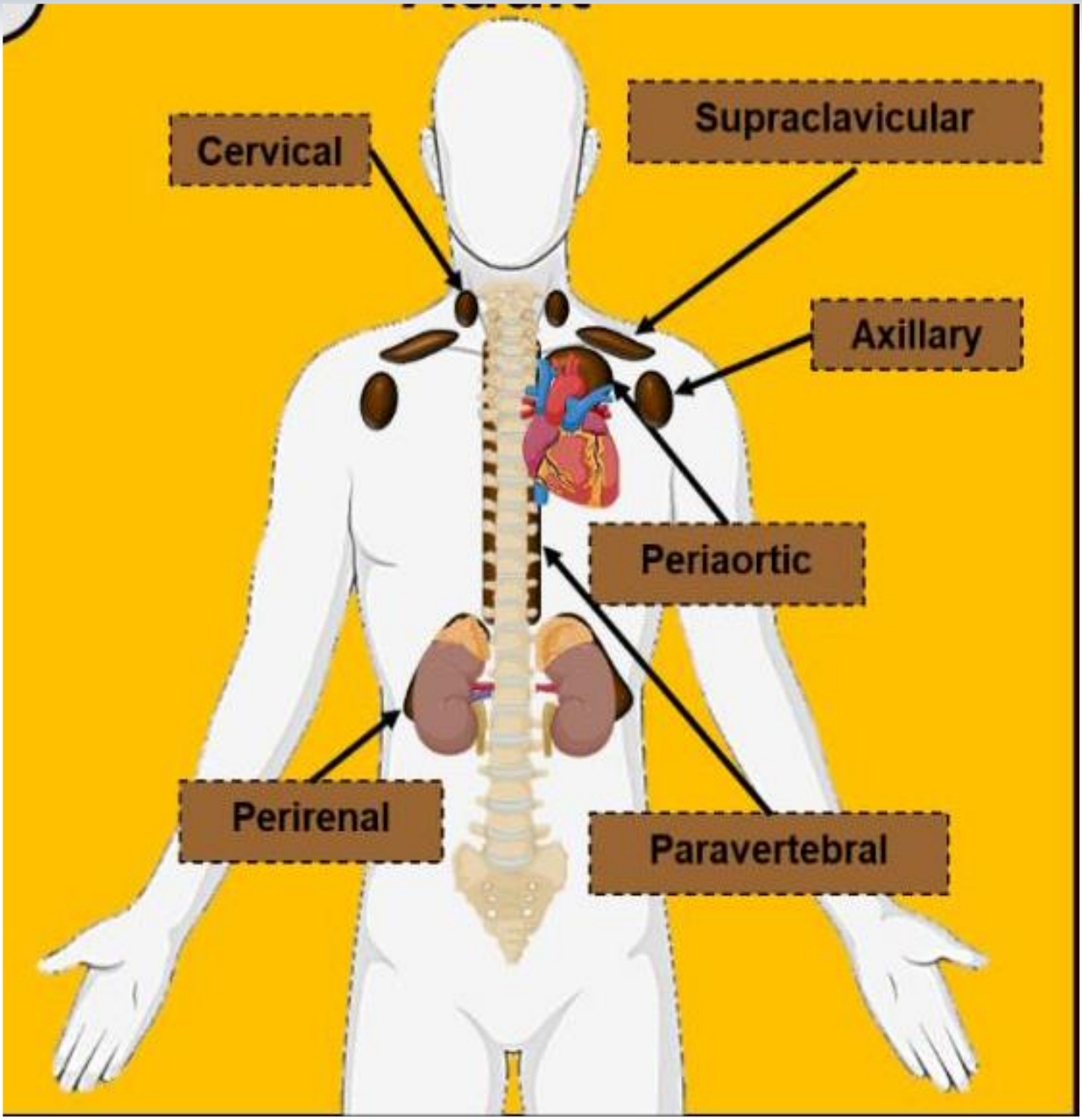
Localização

Próximo do coração, dos grandes vasos e dos rins.



pbmo.wordpress.com

Localização do Tecido Adiposo Marrom



TAM no homem adulto

The NEW ENGLAND JOURNAL of MEDICINE
N ENGL J MED 360;15 NEJM.ORG APRIL 9, 2009

ORIGINAL ARTICLE

Identification and Importance of Brown Adipose Tissue in Adult Humans

Aaron M. Cypess, M.D., Ph.D., M.M.Sc., Sanaz Lehman, M.B., B.S., Gethin Williams, M.B., B.S., Ph.D., Ilan Tal, Ph.D., Dean Rodman, M.D., Allison B. Goldfine, M.D., Frank C. Kuo, M.D., Ph.D., Edwin L. Palmer, M.D., Yu-Hua Tseng, Ph.D., Alessandro Doria, M.D., Ph.D., M.P.H., Gerald M. Kolodny, M.D., and C. Ronald Kahn, M.D.

OURNAL of MEDICINE
NEJM.ORG APRIL 9, 2009

BRIEF REPORT

Functional Brown Adipose Tissue in Healthy Adults

Kirsi A. Virtanen, M.D., Ph.D., Martin E. Lidell, Ph.D., Janne Orava, B.S., Mikael Heglind, M.S., Rickard Westergren, M.S., Tarja Niemi, M.D., Markku Taittonen, M.D., Ph.D., Jukka Laine, M.D., Ph.D., Nina-Johanna Savisto, M.S., Sven Enerbäck, M.D., Ph.D., and Pirjo Nuutila, M.D., Ph.D.

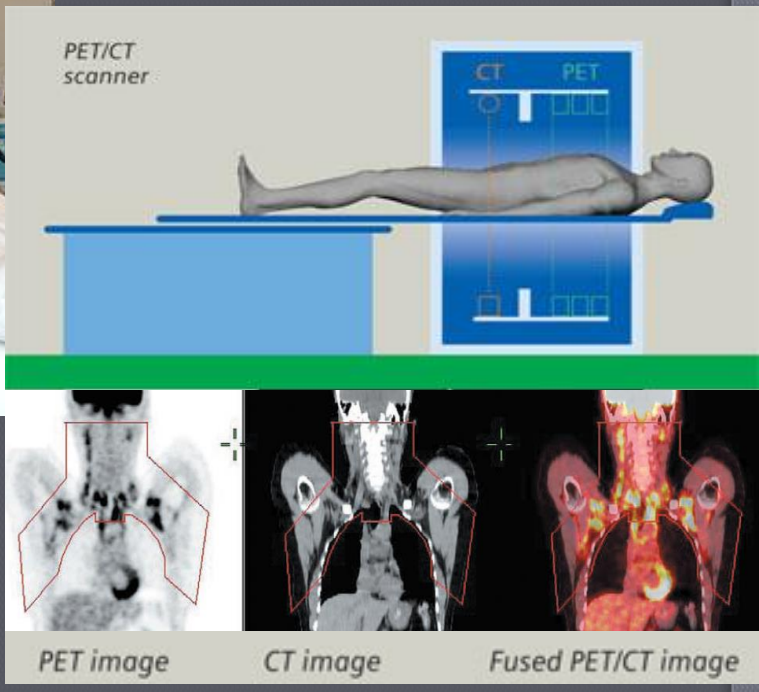
The NEW ENGLAND JOURNAL of MEDICINE
N ENGL J MED 360;15 NEJM.ORG APRIL 9, 2009

ORIGINAL ARTICLE

Cold-Activated Brown Adipose Tissue in Healthy Men

Wouter D. van Marken Lichtenbelt, Ph.D., Joost W. Vanhommerig, M.S., Nanda M. Smulders, M.D., Jamie M.A.F.L. Drossaerts, B.S., Gerrit J. Kemerink, Ph.D., Nicole D. Bouvy, M.D., Ph.D., Patrick Schrauwen, Ph.D., and G.J. Jaap Teule, M.D., Ph.D.

PET + CT



Tomografia por emissão de pósitron (PET)
(atividade)

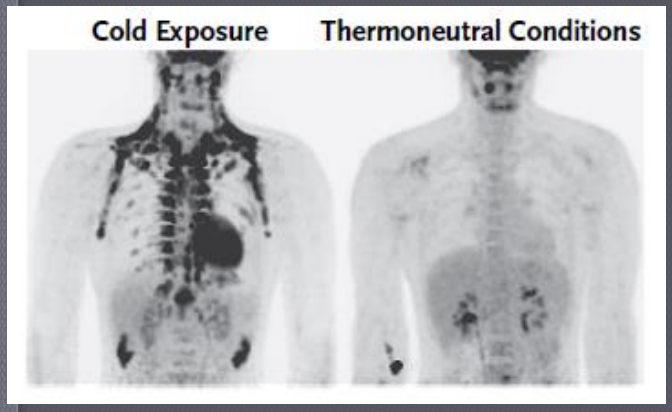
+

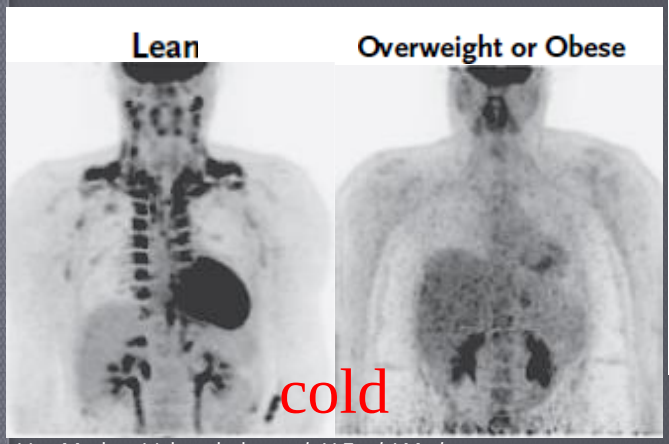
Tomografia computadorizada (CT)
(anatomia)

http://www.nepetimaging.com; http://nuclearmedicine.stanford.edu; Cypess *et al. N Engl J Med.*, 2009

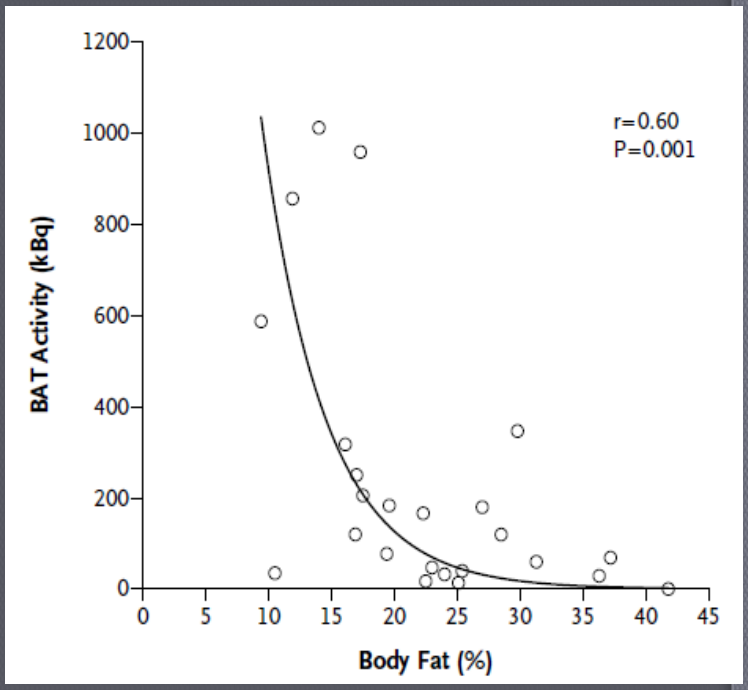
Tecido adiposo marrom: Qual a sua função?

Função

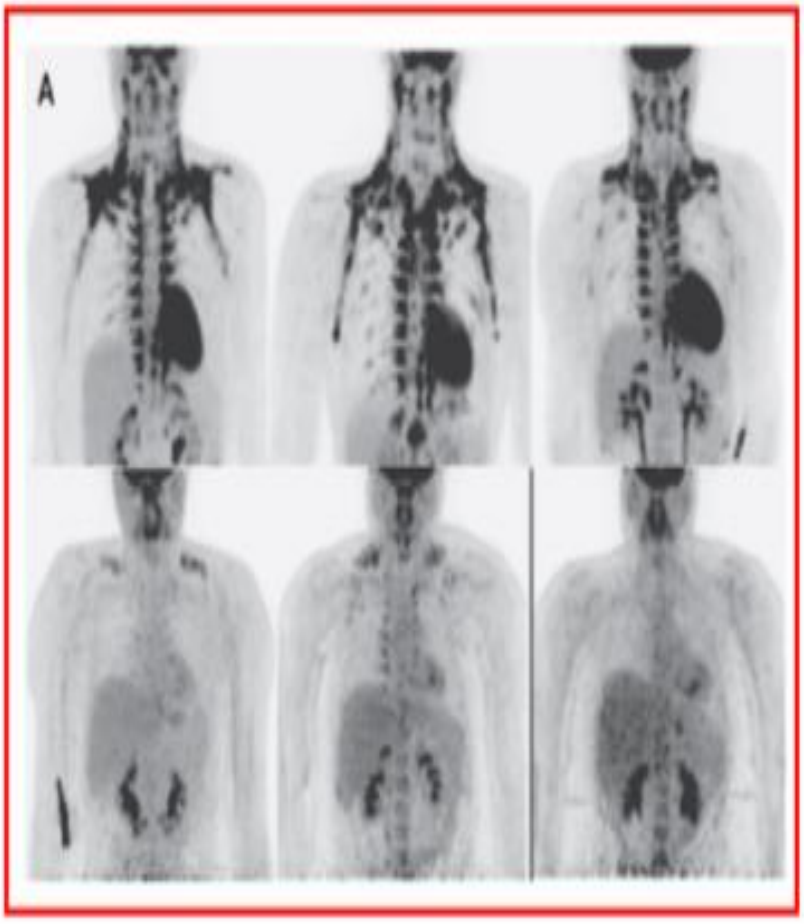




Van Marken Lichtenbelt, *et al. N Engl J Med,* 2009



Exposição ao frio



Indivíduos magros

Indivíduos sobrepeso ou obesos

Novo alvo terapêutico no tratamento da obesidade

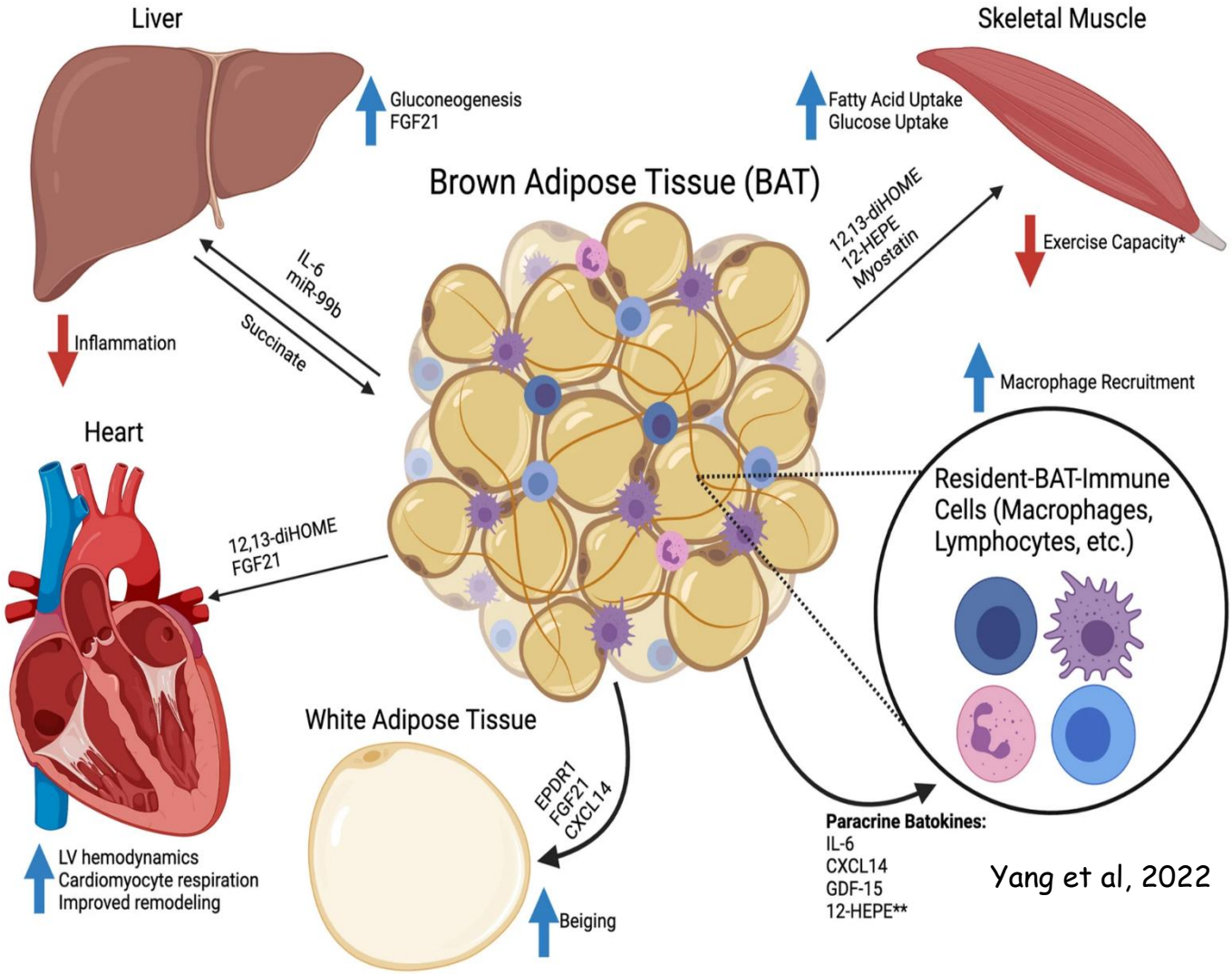
Fatores que aumentam a atividade do TAM

- Dieta hipercalórica (“cafeteria”)
- Frio
- T3
- Insulina
- Agonistas beta-3 adrenérgicos (aumento da atividade do SNS)

Fatores que inibem a atividade do TAM

- Dieta rica em proteínas e pobre em carboidrato
- Jejum
- Desnutrição
- Beta-bloqueadores
- Glicocorticóides
- Gestação e lactação

BATocinas
Mediadores da comunicação inter-orgãos



Yang et al, 2022

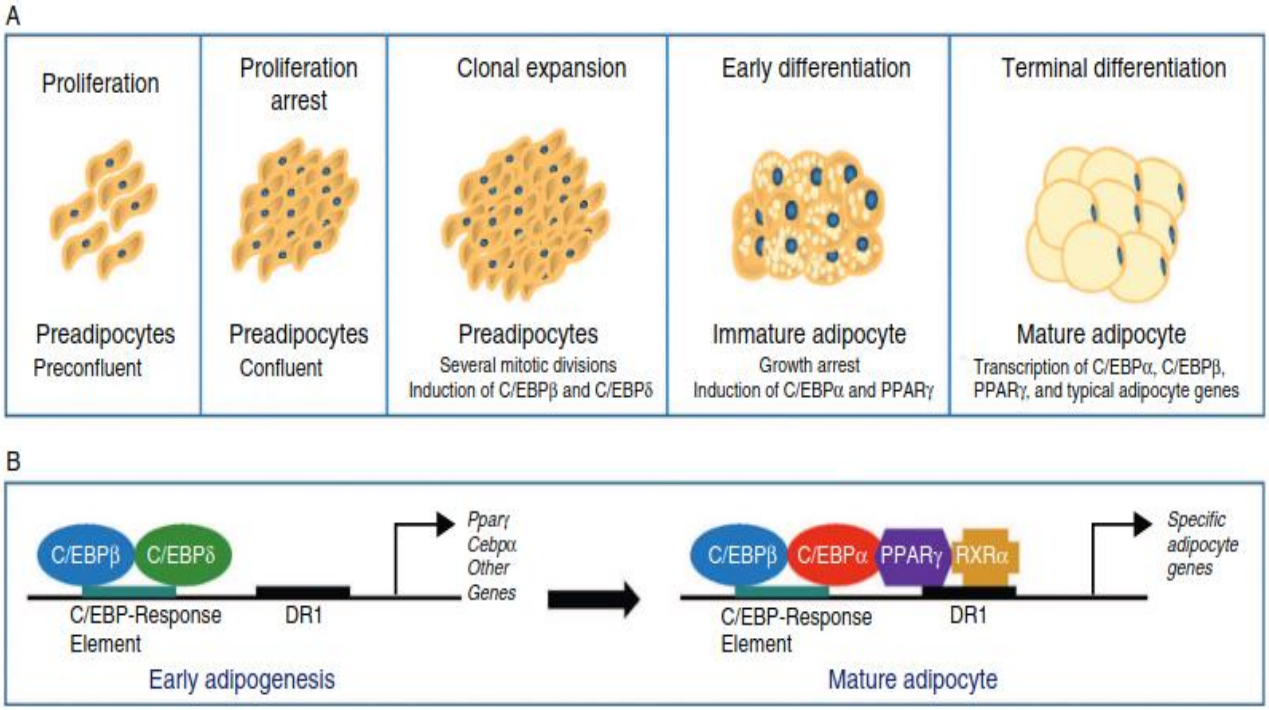


Figure 6 Differentiation of preadipocytes into adipocytes. (A) Scheme of the transition process from preadipocyte to mature adipocyte including the different stages. (B) Sequential model of transcriptional control during adipogenesis.