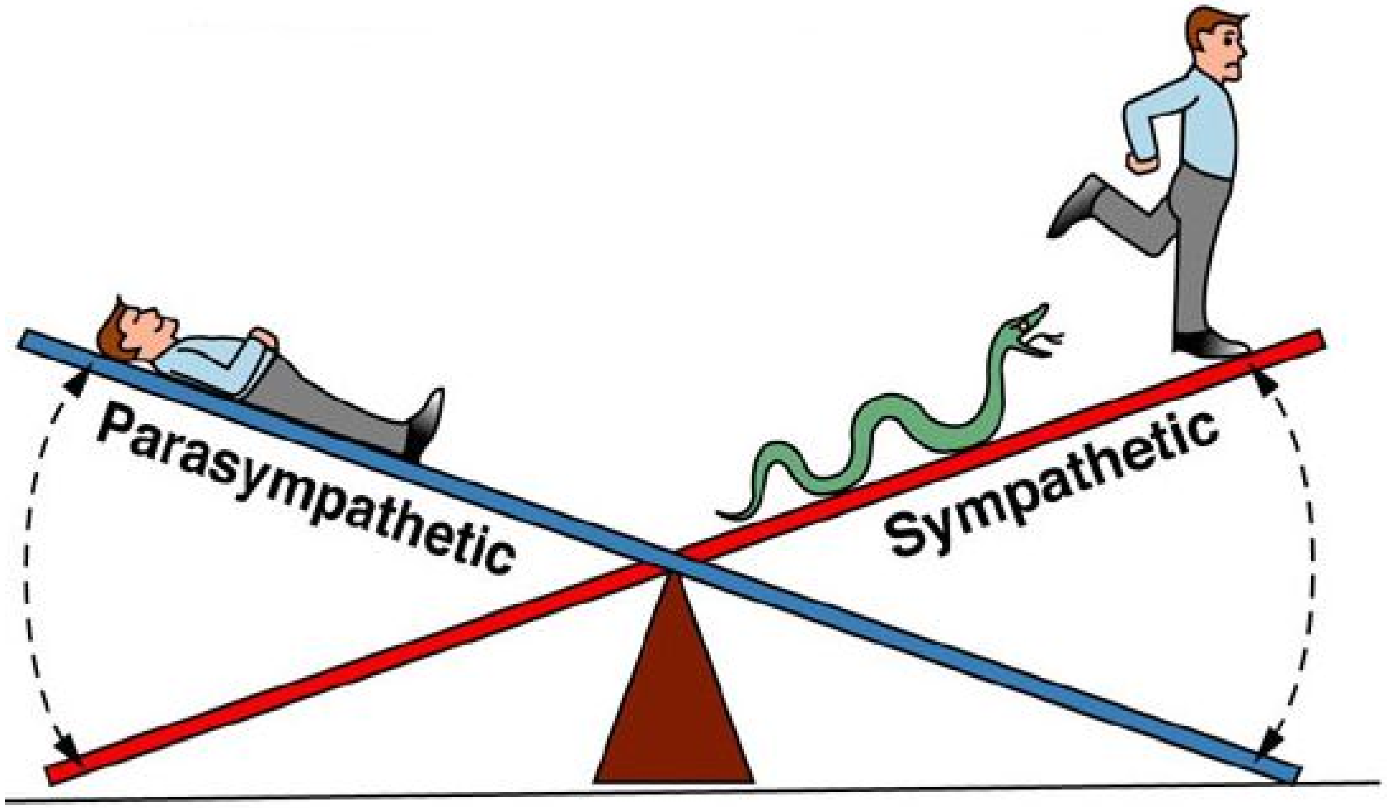
Ação do Sistema Nervoso Autônomo sobre a fibra muscular

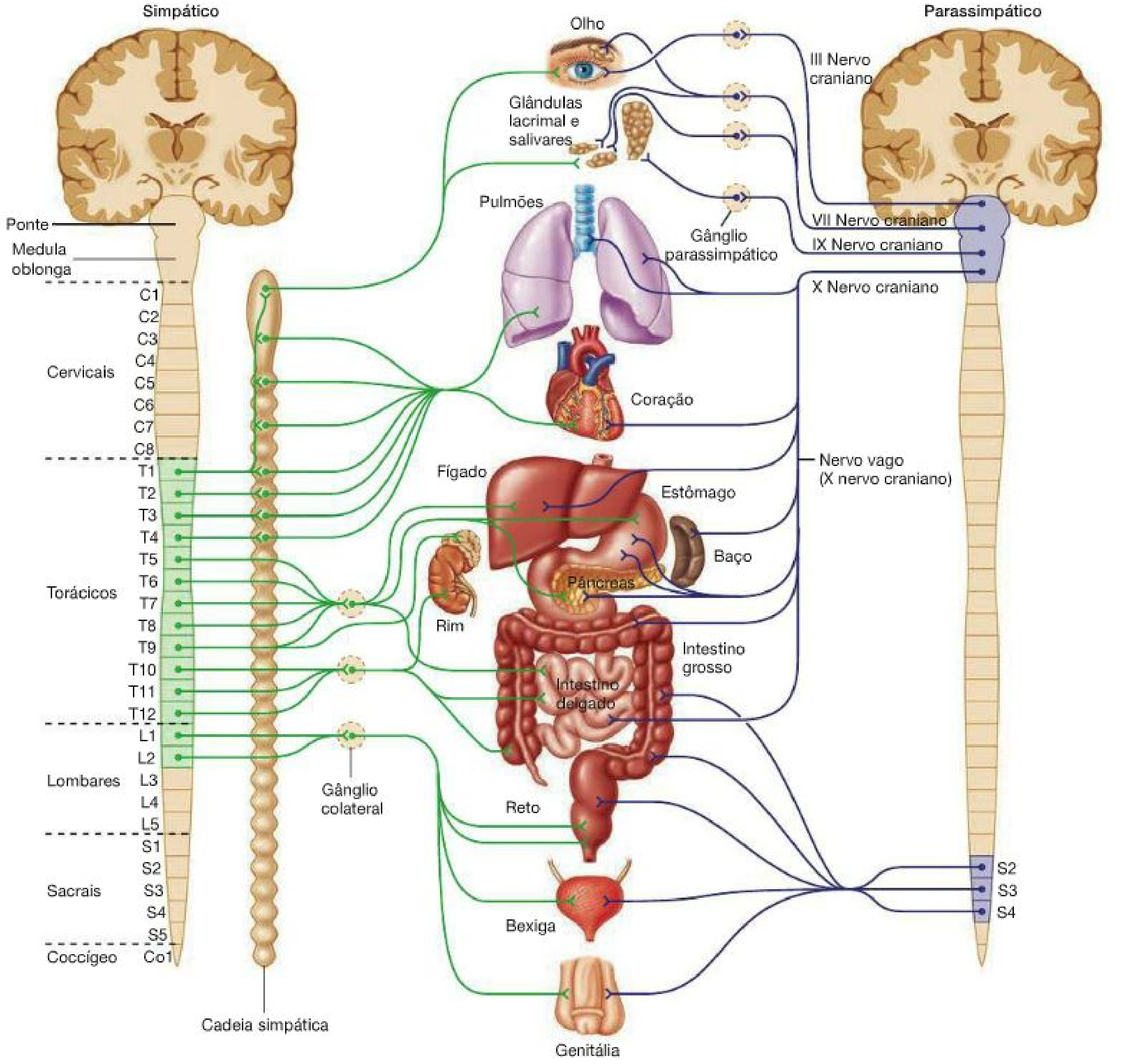
Tanes Imamura de Lima
Departamento de Bioquímica e Imunologia
Faculdade de Medicina de Ribeirão Preto-FMRP
Universidade de São Paulo-USP
Obesity and Comorbidities Research Center-OCRC
Universidade de Campinas-Unicamp

Papel do Sistema Nervoso Autônomo

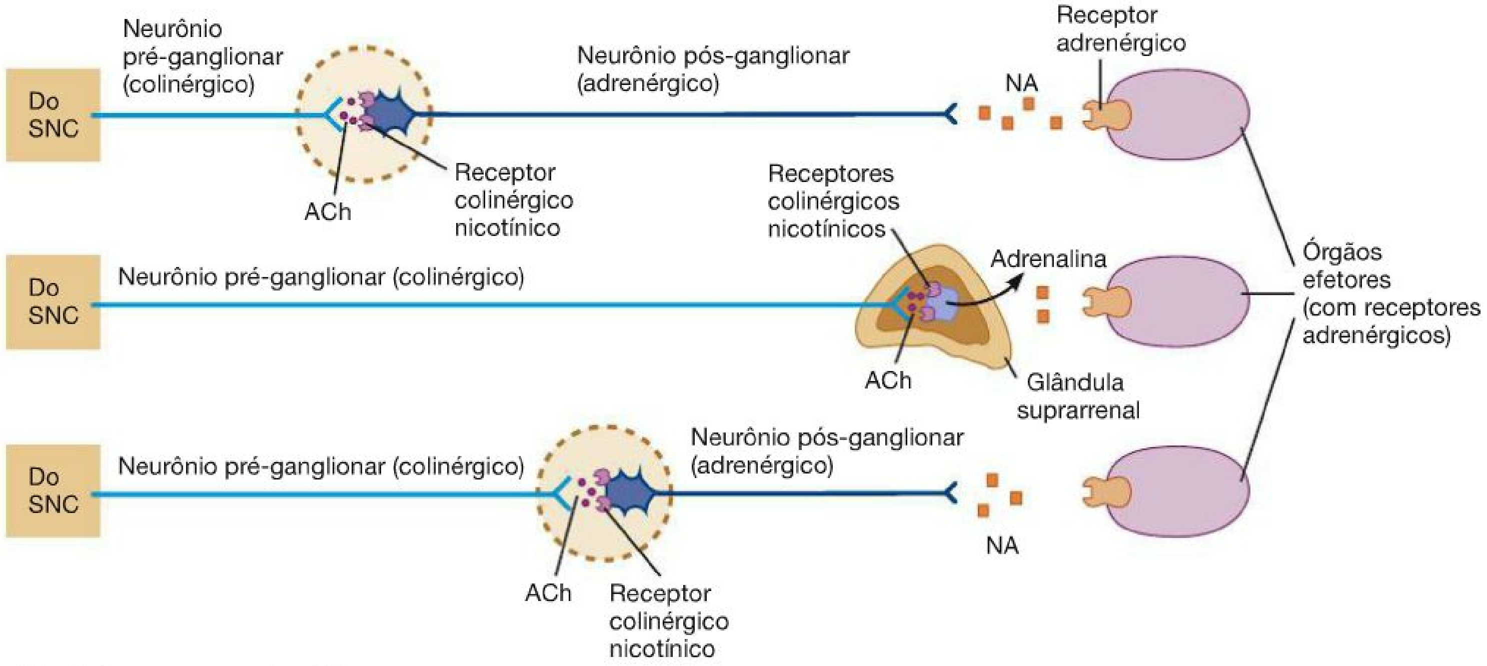

Parasympathetic
Sympathetic

https://bodypoets.wordpress.com/tag/parasympathetic-nervous-system/

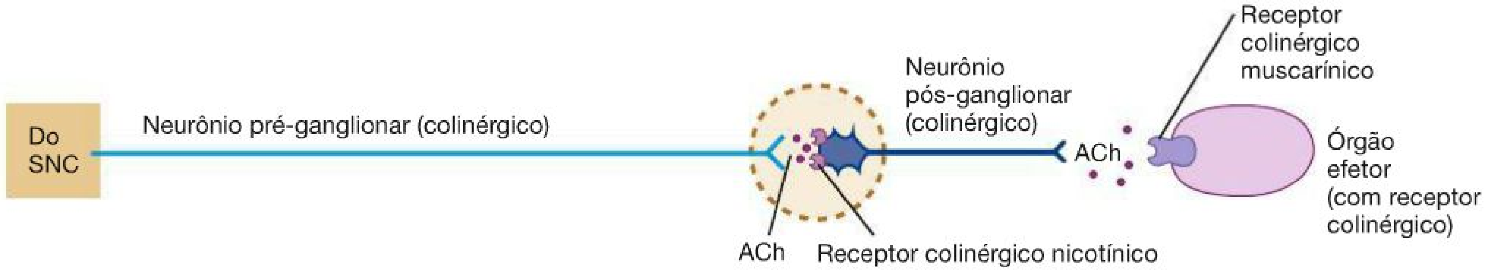
Dupla Inervação do Sistema Nervoso Autônomo


Simpático
Parassimpático
Ponte
Medula oblonga
C1
C2
C3
C4
Cervicais
C5
C6
C7
C8
T1
T2
T3
T4
T5
T6
Torácicos
T7
T8
T9
T10
T11
T12
L1
L2
Lombares
L3
L4
L5
S1
S2
Sacrais
S3
S4
S5
Coccígeo
Co1
Cadeia simpática
Gânglio colateral
Olho
Glândulas lacrimal e salivares
Pulmões
Gânglio parassimpático
Coração
Fígado
Estômago
Baço
Pâncreas
Rim
Intestino grosso
Intestino delgado
Reto
Bexiga
Genitália
III Nervo craniano
VII Nervo craniano
IX Nervo craniano
X Nervo craniano
Nervo vago (X nervo craniano)
S2
S3
S4

Neuroransmissores e Receptores do Sistema Nervoso Autônomo

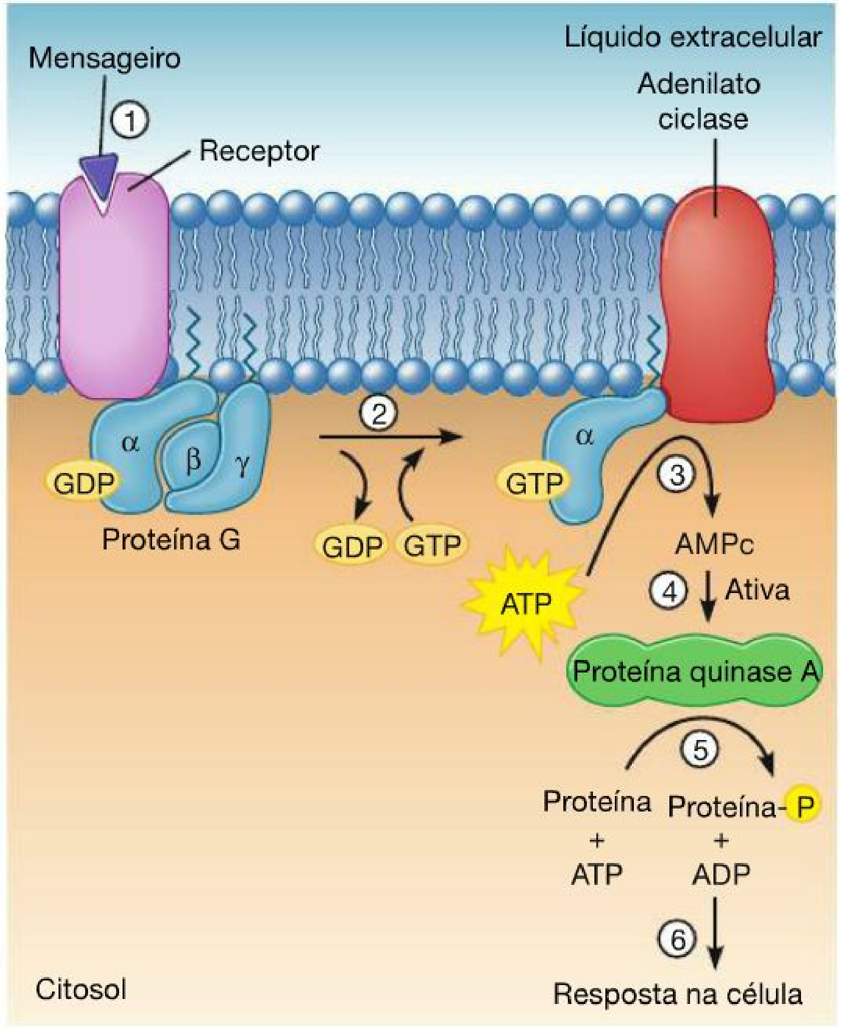

Do SNC
Neurônio pré-ganglionar (colinérgico)
ACh
Receptor colinérgico nicotínico
Neurônio pós-ganglionar (adrenérgico)
NA
Receptor adrenérgico
Do SNC
Neurônio pré-ganglionar (colinérgico)
Receptores colinérgicos nicotínicos
Adrenalina
ACh
Glândula suprarrenal
Órgãos efetores (com receptores adrenérgicos)
Do SNC
Neurônio pré-ganglionar (colinérgico)
Neurônio pós-ganglionar (adrenérgico)
NA
ACh
Receptor colinérgico nicotínico

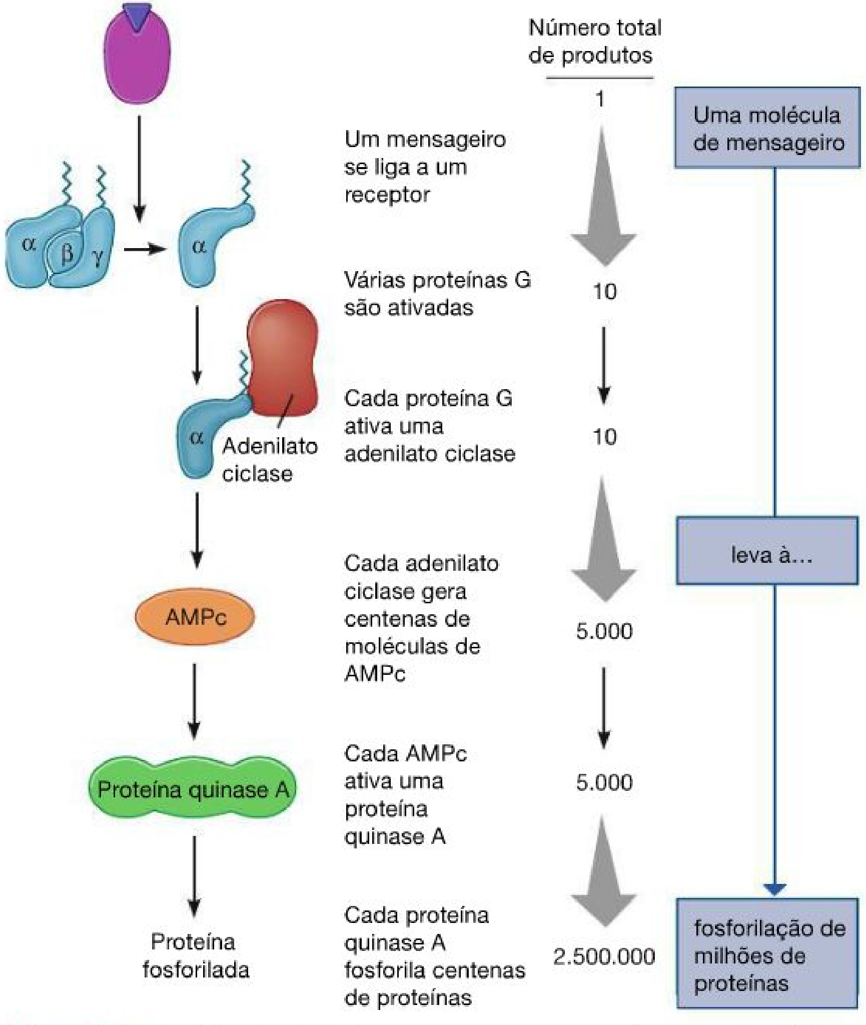
(a) Sistema nervoso simpático


Do SNC
Neurônio pré-ganglionar (colinérgico)
Neurônio pós-ganglionar (colinérgico)
Receptor colinérgico muscarínico
ACh
Órgão efetor (com receptor colinérgico)
ACh
Receptor colinérgico nicotínico

(b) Sistema nervoso parassimpático

Mecanismo de transdução de sinal por proteína G


Líquido extracelular
Mensageiro
①
Receptor
Adenilato ciclase
α
β
γ
GDP
Proteína G
②
GDP
GTP
α
GTP
③
AMPc
ATP
④
Ativa
Proteína quinase A
⑤
Proteína
+
ATP
Proteína-P
+
ADP
⑥
Resposta na célula
Citosol


α
β
γ
α
α
Adenilato ciclase
AMPc
Proteína quinase A
Proteína fosforilada

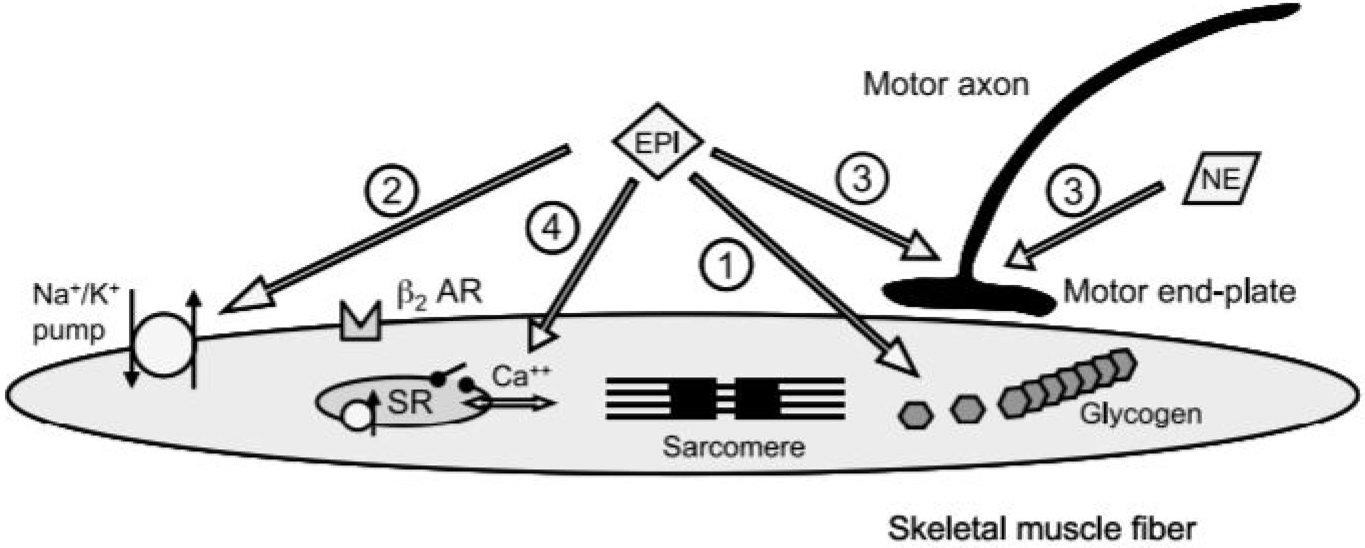
	Número total de produtos
	1
Um mensageiro se liga a um receptor	
Várias proteínas G são ativadas	10
Cada proteína G ativa uma adenilato ciclase	10
Cada adenilato ciclase gera centenas de moléculas de AMPc	5.000
Cada AMPc ativa uma proteína quinase A	5.000
Cada proteína quinase A fosforila centenas de proteínas	2.500.000

Uma molécula de mensageiro

leva à...

fosforilação de milhões de proteínas

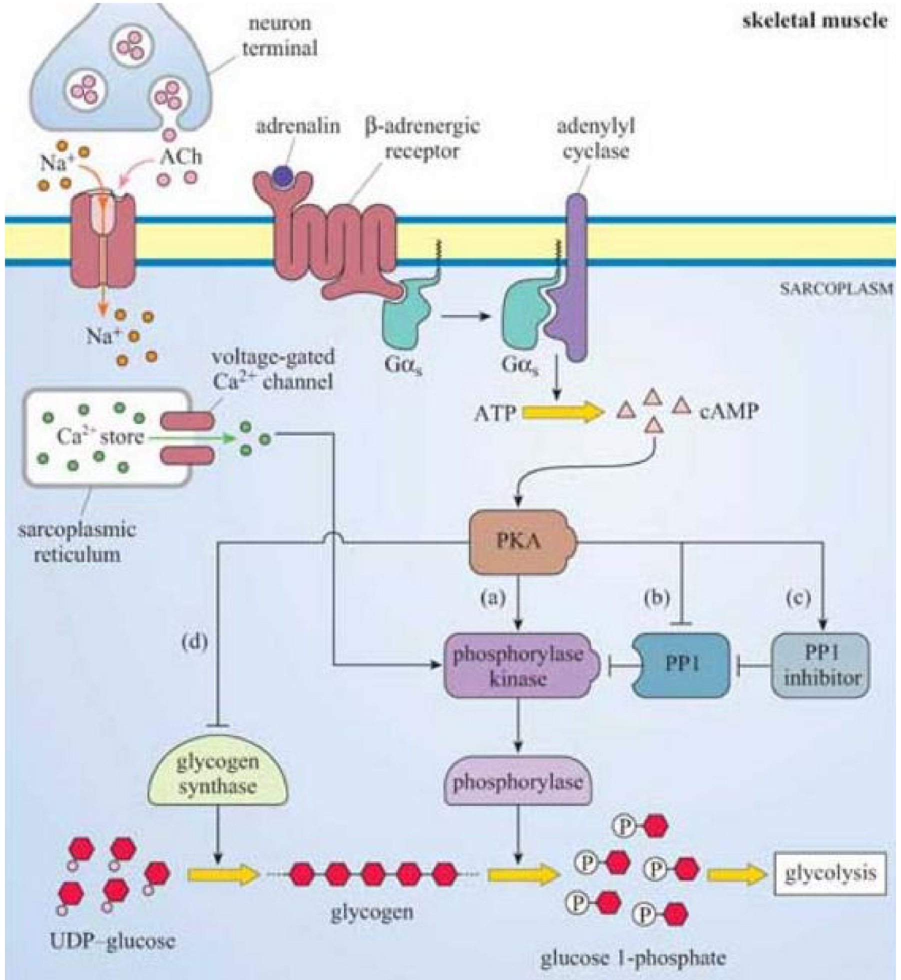
O Sistema Nervoso Simpático regula uma série de funções no músculo esquelético


Motor axon
EPI
NE
②
④
①
③
③
Na⁺/K⁺ pump
β₂ AR
Motor end-plate
Ca⁺⁺
SR
Sarcomere
Glycogen
Skeletal muscle fiber

1. **Metabolismo de proteína e glicose**
2. **Aumento da atividade da bomba de Na+/K+**
3. **Aumento da liberação de acetilcolina na sinapse**
4. **Modulação da captação e liberação de cálcio do retículo sarcoplasmático**

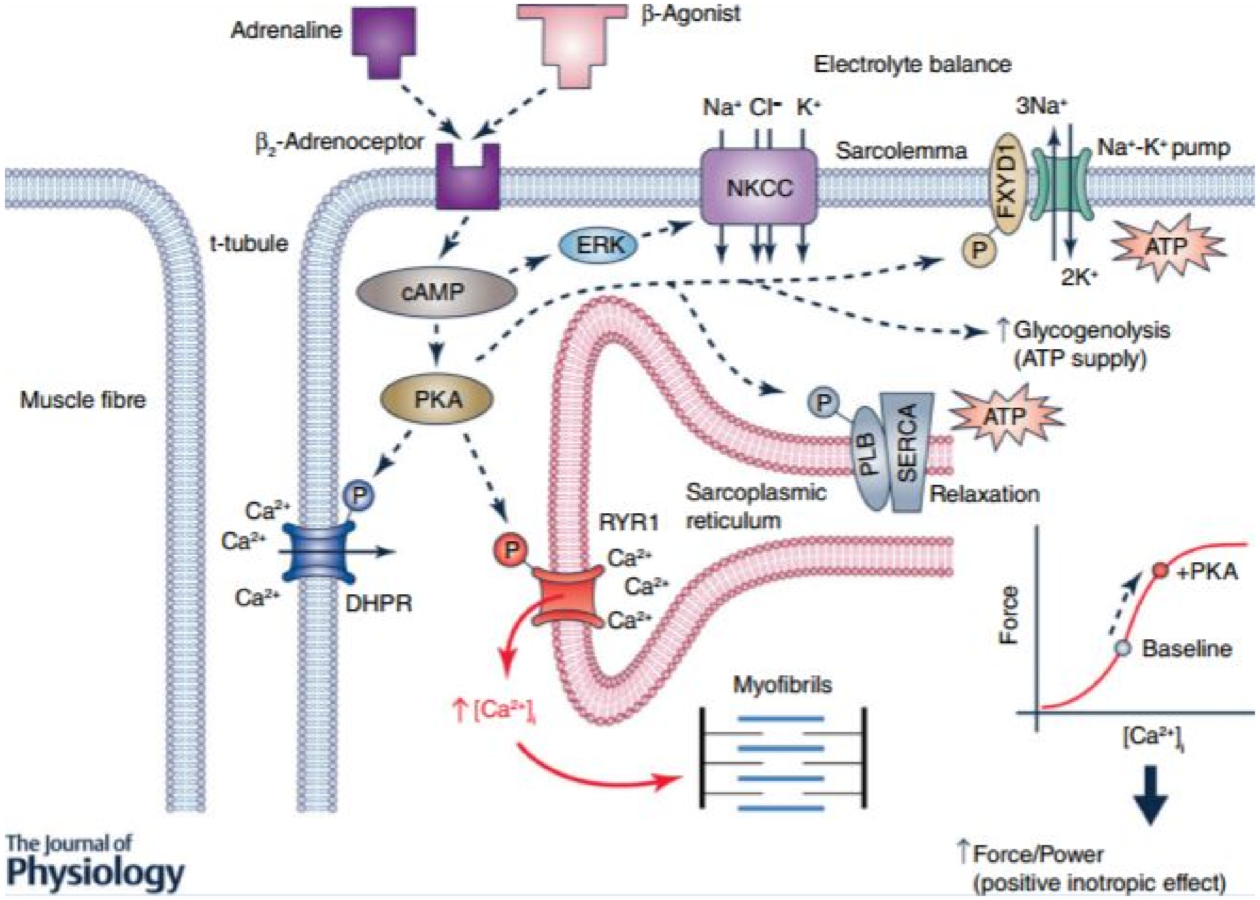
Roatta and Farina. Sympathetic actions on the skeletal muscle. Exerc Sport Sci Rev. 2010 Jan;38(1):31-5

Modulação do metabolismo de glicose


neuron terminal
skeletal muscle
adrenalin
β-adrenergic receptor
adenylyl cyclase
Na^+
ACh
SARCOPLASM
Na^+
voltage-gated Ca^{2+} channel
$G\alpha_s$
$G\alpha_s$
ATP
cAMP
Ca^{2+} store
sarcoplasmic reticulum
PKA
(a)
(b)
(c)
(d)
phosphorylase kinase
PP1
PP1 inhibitor
glycogen synthase
phosphorylase
P
glycolysis
UDP–glucose
glycogen
glucose 1-phosphate

1. **Ativação do receptor β2**
2. **Ativação da via cAMP/PKA**
3. **PKA ativa a fosforilase quinase e inibe a glicogênio sintase**
4. **Redução da glicogênese e aumento da glicogenólise**

Modulação da atividade da bomba de Na+/K+

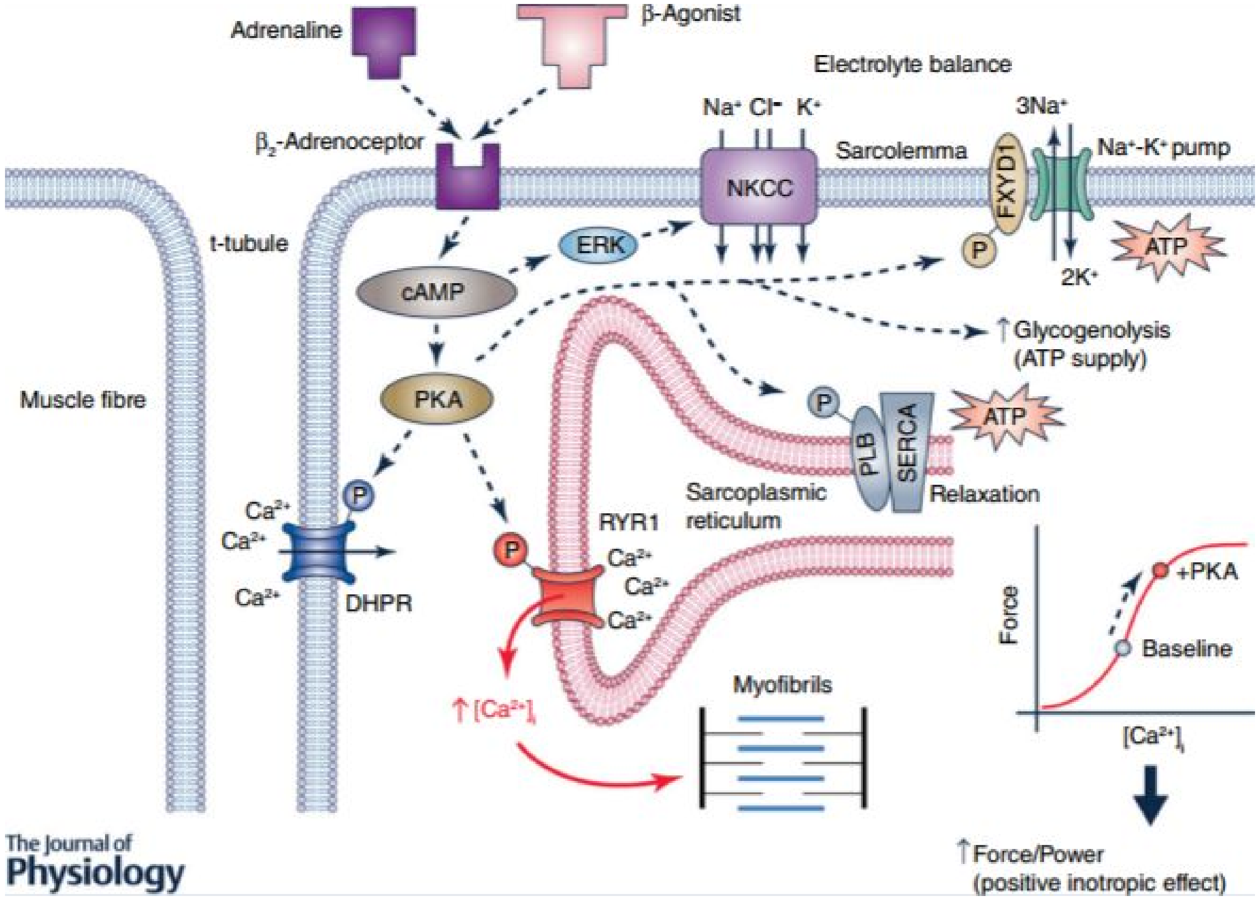


Adrenaline
β-Agonist
Electrolyte balance
β2-Adrenoceptor
Na+ Cl- K+
3Na+
Sarcolemma
Na+-K+ pump
NKCC
FXYD1
t-tubule
ERK
P
ATP
2K+
cAMP
↑Glycogenolysis
(ATP supply)
Muscle fibre
PKA
P
ATP
PLB
SERCA
Ca2+
Ca2+
Ca2+
P
DHPR
P
RYR1
Ca2+
Ca2+
Ca2+
Sarcoplasmic reticulum
Relaxation
Force
+PKA
Baseline
↑[Ca2+]i
Myofibrils
[Ca2+]i
↑Force/Power
(positive inotropic effect)

The Journal of Physiology

1. **Ativação do receptor β2**
2. **Ativação da via cAMP/PKA**
3. **PKA fosforila FXYD1 e estimula a atividade da bomba Na+/K+**
4. **Aumento do potencial de membrana e amplitude de potencial de ação**
5. **Atenuação da fadiga**

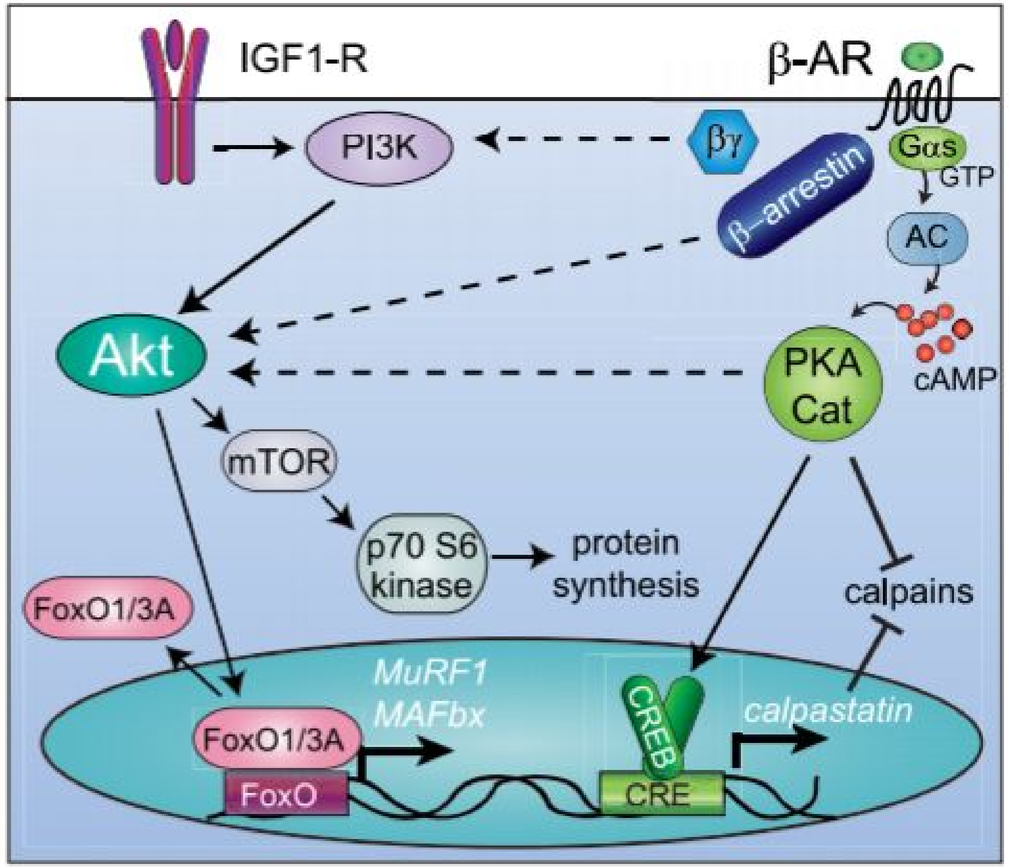
Modulação no fluxo de cálcio


Adrenaline
β-Agonist
Electrolyte balance
β_2-Adrenoceptor
Na⁺ Cl⁻ K⁺
3Na⁺
Sarcolemma
Na⁺-K⁺ pump
NKCC
FXYD1
t-tubule
ERK
P
ATP
2K⁺
cAMP
↑Glycogenolysis
(ATP supply)
Muscle fibre
PKA
P
PLB
SERCA
ATP
Sarcoplasmic
reticulum
Relaxation
Ca²⁺
Ca²⁺
Ca²⁺
P
DHPR
RYR1
P
Ca²⁺
Ca²⁺
Ca²⁺
Force
+PKA
Baseline
↑[Ca²⁺]ᵢ
Myofibrils
[Ca²⁺]ᵢ
↑Force/Power
(positive inotropic effect)

The Journal of Physiology

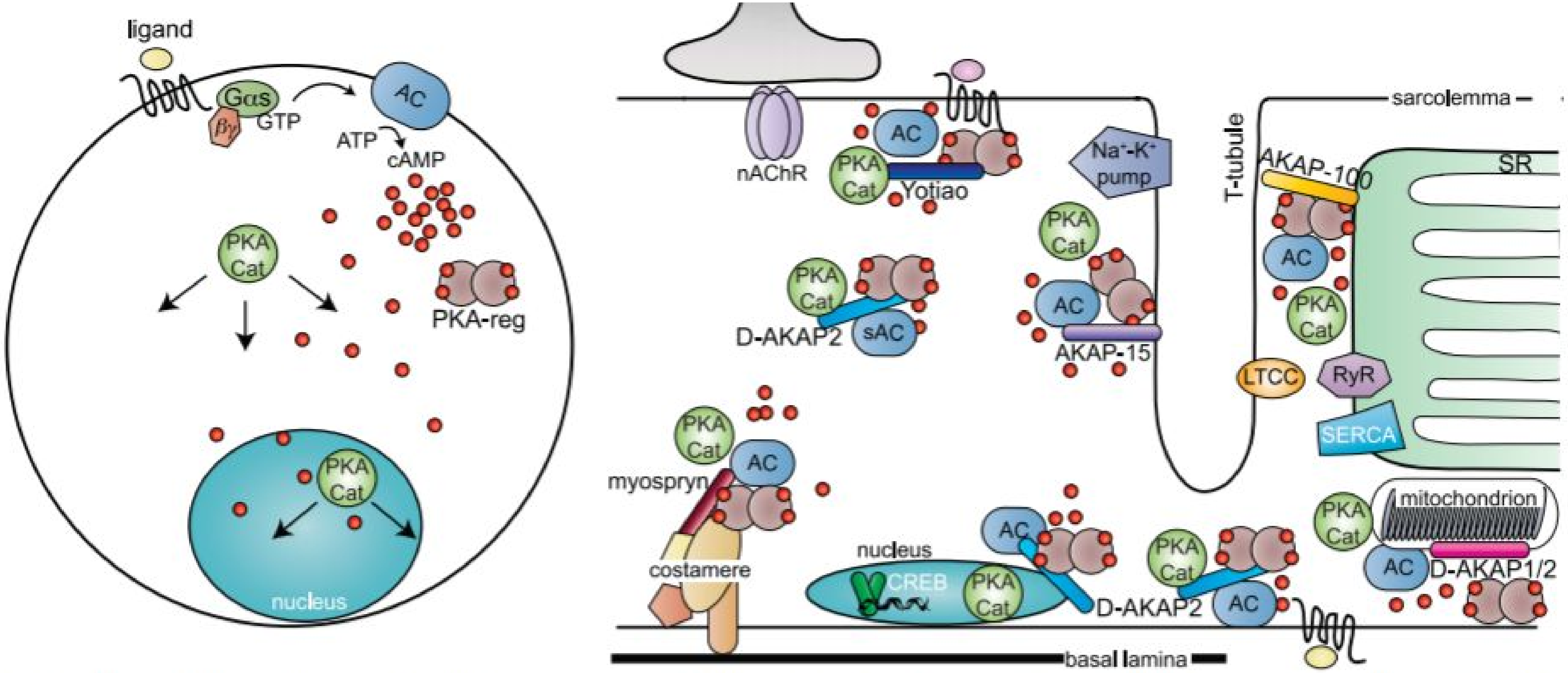
1. **Ativação do receptor β2**
2. **Ativação da via cAMP/PKA**
3. **PKA fosforila o canal de DHPR, RYR1 e PLB**
4. **Aumento do fluxo de cálcio**
5. **Aumento na força contrátil**

Modulação do metabolismo de proteína


IGF1-R
β-AR
PI3K
βγ
Gαs
GTP
β-arrestin
AC
Akt
cAMP
PKA
Cat
mTOR
p70 S6
kinase
protein
synthesis
calpains
FoxO1/3A
MuRF1
MAFbx
CREB
calpastatin
FoxO1/3A
FoxO
CRE

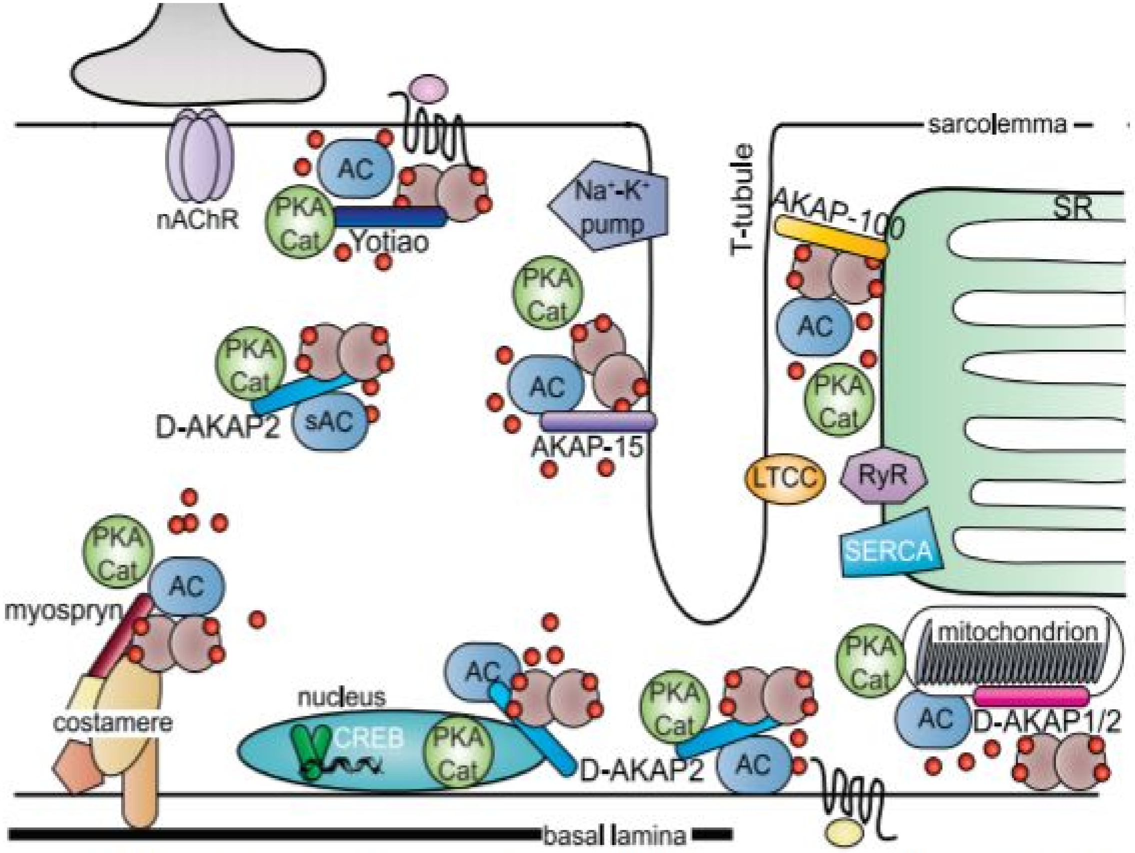
1. **Ativação do receptor β2**
2. **Ativação da via cAMP/PKA e PI3k**
3. **Ativação de Akt**
4. **Fosforilação e inativação de FoxO1 e subsequente inativação da expressão de genes atróficos**
5. **PKA também aumenta a expressão de calpastatina que inibe calpaínas (protease)**
6. **Aumento de síntese e redução da degradação de proteínas**

Vias de sinalização cAMP/PKA em fibras musculares esqueléticas


ligand
Gαs
βγ
GTP
AC
ATP
cAMP
PKA Cat
PKA-reg
PKA Cat
nucleus
nAChR
AC
PKA Cat
Yotiao
Na⁺-K⁺ pump
T-tubule
sarcolemma
SR
AKAP-100
AC
PKA Cat
PKA Cat
D-AKAP2
sAC
PKA Cat
AC
AKAP-15
LTCC
RyR
SERCA
PKA Cat
AC
myospryn
costamere
nucleus
CREB
PKA Cat
AC
D-AKAP2
PKA Cat
AC
PKA Cat
mitochondrion
AC
D-AKAP1/2
basal lamina

Berdeux R, Stwart R. cAMP signaling in skeletal muscle adaptation: hypertrophy, metabolism, and regeneration. Am J Physiol Endocrinol Metab 303: E1–E17, 2012

Localização intracelular de PKA em fibras musculares esqueléticas


nAChR
AC
PKA
Cat
Yotiao
Na^+-K^+ pump
T-tubule
sarcolemma
AKAP-100
SR
PKA
Cat
D-AKAP2
sAC
AC
AKAP-15
LTCC
RyR
SERCA
PKA
Cat
AC
myospryn
costamere
nucleus
CREB
PKA
Cat
AC
D-AKAP2
PKA
Cat
AC
mitochondrion
D-AKAP1/2
basal lamina

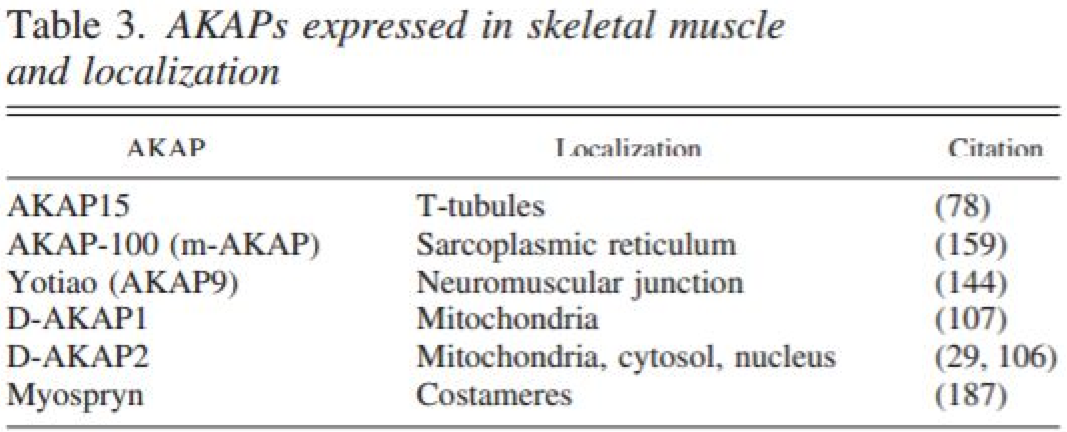
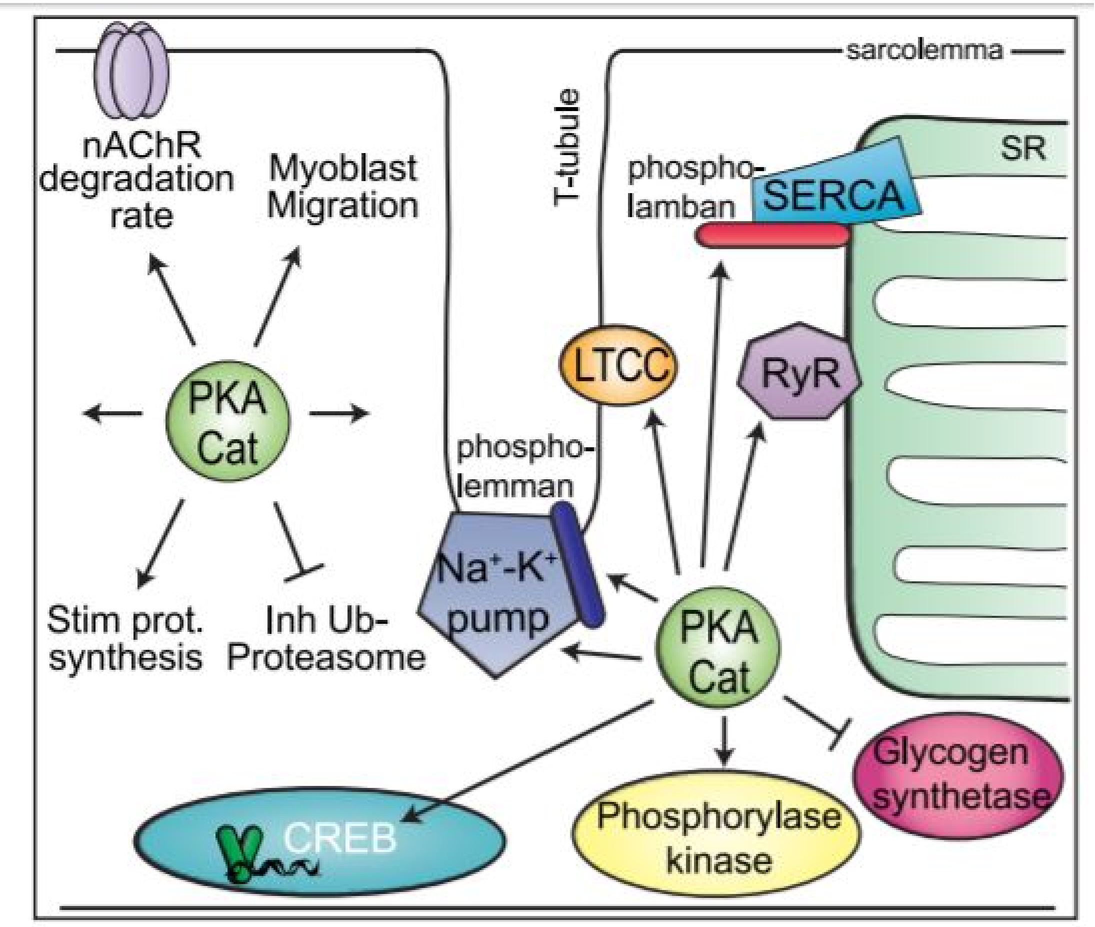


Table 3. *AKAPs expressed in skeletal muscle and localization*

AKAP	Localization	Citation
AKAP15	T-tubules	(78)
AKAP-100 (m-AKAP)	Sarcoplasmic reticulum	(159)
Yotiao (AKAP9)	Neuromuscular junction	(144)
D-AKAP1	Mitochondria	(107)
D-AKAP2	Mitochondria, cytosol, nucleus	(29, 106)
Myospryn	Costameres	(187)

Berdeux R, Stwart R. cAMP signaling in skeletal muscle adaptation: hypertrophy, metabolism, and regeneration. Am J Physiol Endocrinol Metab 303: E1–E17, 2012

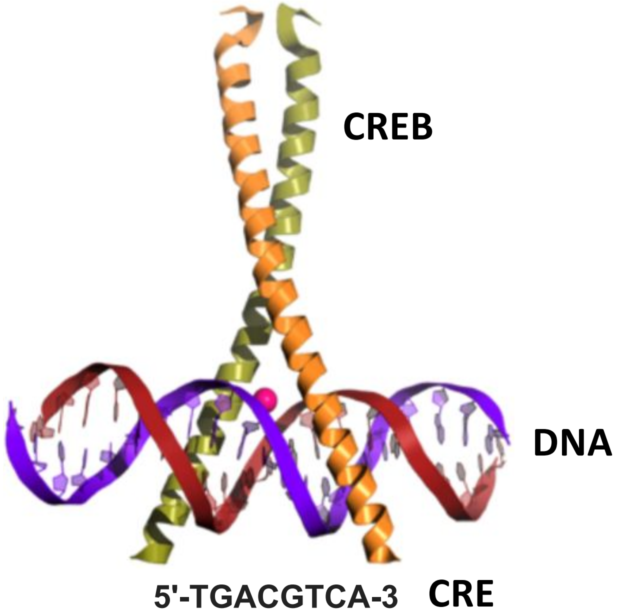
Substratos cAMP/PKA em fibras musculares esqueléticas


sarcolemma
nAChR degradation rate
Myoblast Migration
T-tubule
phospho-lamban
SERCA
SR
LTCC
RyR
PKA Cat
phospho-lemman
Na^+-K^+ pump
Stim prot. synthesis
Inh Ub-Proteasome
PKA Cat
Glycogen synthetase
Phosphorylase kinase
CREB

- **Substratos de PKA**
  - Bomba de Na+/k+
  - Fosfolambam
  - Glicogênio sintase
  - Fosforilase quinase
  - Receptor de rianodina
  - Proteína de ligação ao elemento de resposta do cAMP (CREB)

Berdeux R, Stwart R. cAMP signaling in skeletal muscle adaptation: hypertrophy, metabolism, and regeneration. Am J Physiol Endocrinol Metab 303: E1–E17, 2012

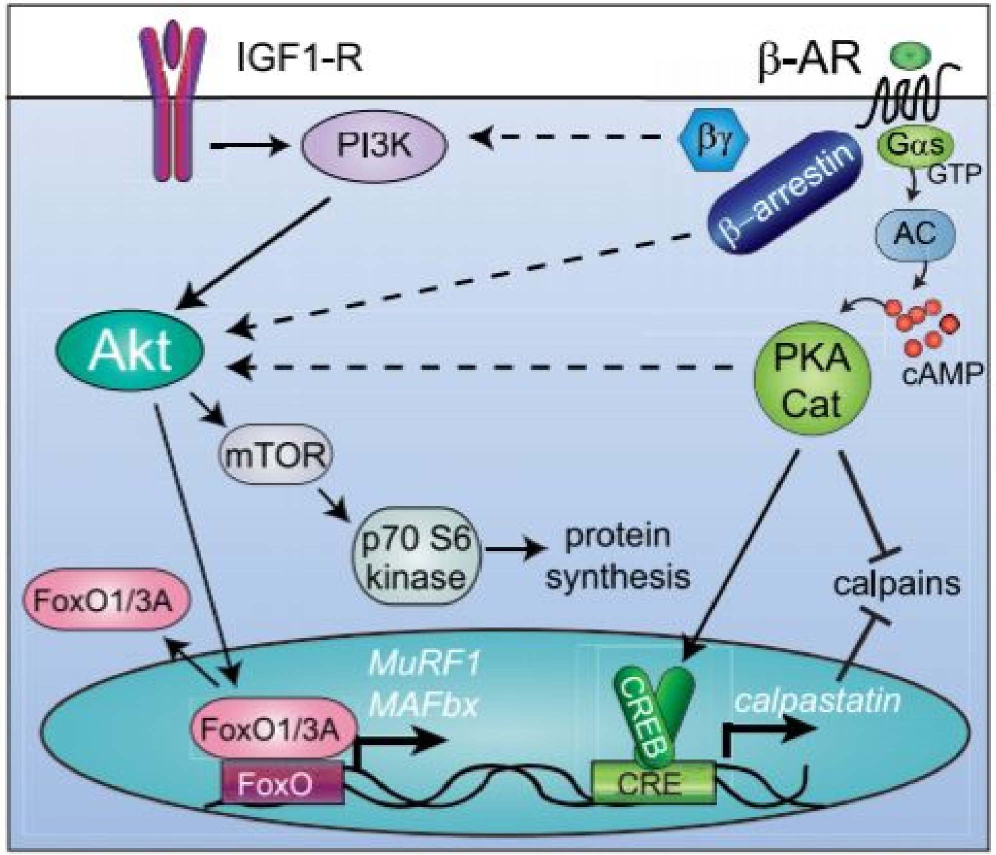
Proteína de ligação ao elemento de resposta do cAMP (CREB)



- **Características do CREB**
  - Fator de transcrição
  - É ativado por fosforilação (PKA e Camk)
  - Regulação por cofatores (ex: CRTC2, NCoR1)
  - Se liga em elementos responsivos à AMPc (CRE)
  - Importante para a maioria dos efeitos da ativação do PKA
  - Em células musculares esqueléticas controla:
    - Biogênese mitocondrial
    - Metabolismo oxidativo
    - Hipertrofia
    - Miogênese

Berdeux R, Stwart R. cAMP signaling in skeletal muscle adaptation: hypertrophy, metabolism, and regeneration. Am J Physiol Endocrinol Metab 303: E1–E17, 2012
Scarpula paper

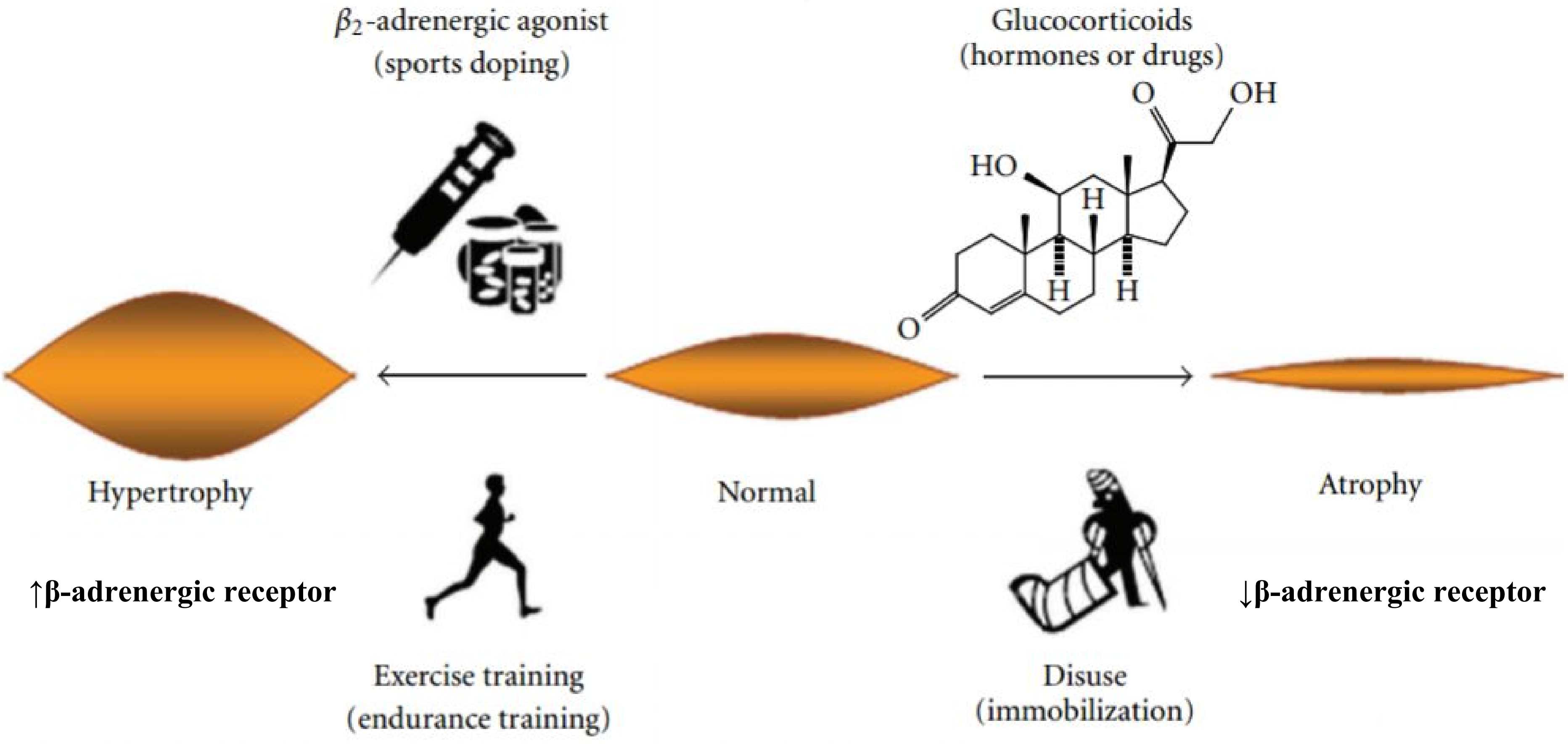
Via PKA/CREB controla o trofismo da fibra muscular


IGF1-R
β-AR
PI3K
βγ
Gαs
GTP
β-arrestin
AC
Akt
PKA
Cat
cAMP
mTOR
p70 S6
kinase
protein
synthesis
calpains
FoxO1/3A
MuRF1
MAFbx
FoxO1/3A
FoxO
CREB
CRE
calpastatin

1. **Ativação do receptor β2**
2. **Ativação da via PKA/CREB e PI3k**
3. **Ativação de Akt e inativação de genes atróficos**
4. **PKC fosforila CREB e aumenta a expressão de calpastatina**
5. **Aumento de síntese e redução da degradação de proteínas**
6. **Hipertrofia muscular**

Berdeux R, Stwart R. cAMP signaling in skeletal muscle adaptation: hypertrophy, metabolism, and regeneration. Am J Physiol Endocrinol Metab 303: E1–E17, 2012

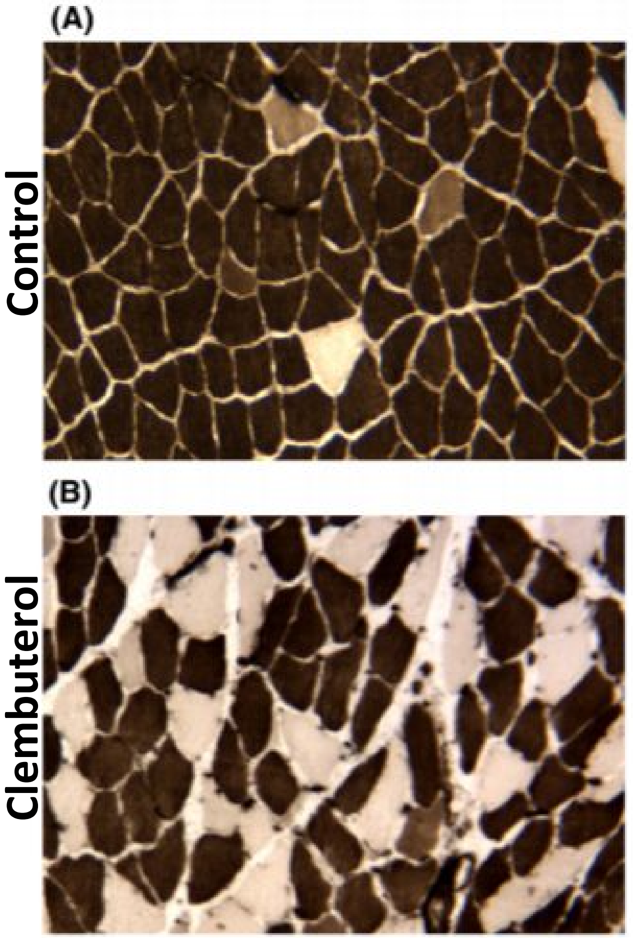
Agonista-β adrenérgico controla o trofismo da fibra muscular

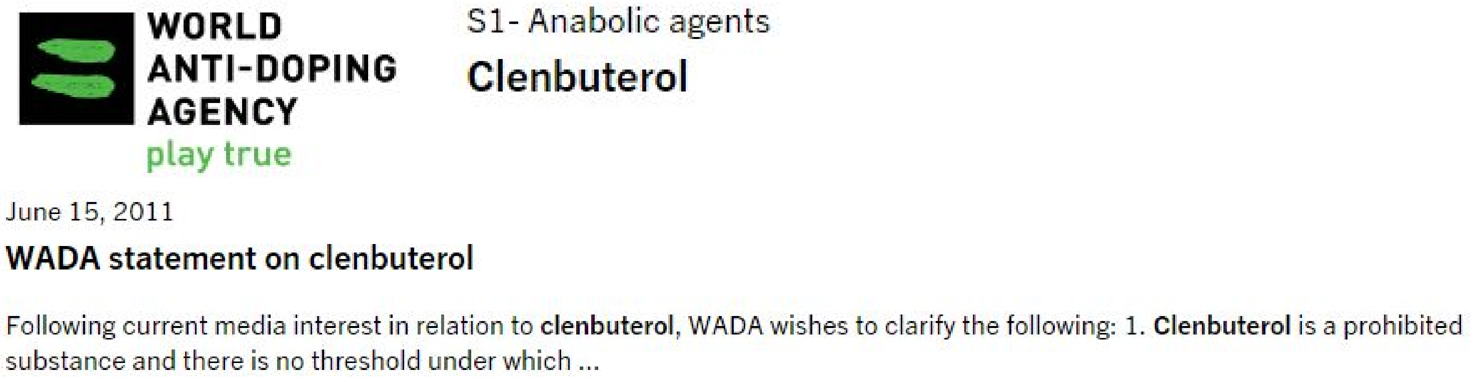

β_2-adrenergic agonist
(sports doping)
Glucocorticoids
(hormones or drugs)
O
OH
HO
H
H
H
O
Hypertrophy
Normal
Atrophy
Exercise training
(endurance training)
Disuse
(immobilization)

↑β-adrenergic receptor

↓β-adrenergic receptor

Agonista-β adrenérgico controla o trofismo da fibra muscular


(A)
Control
(B)
Clembuterol


WORLD ANTI-DOPING AGENCY
play true

S1- Anabolic agents

Clenbuterol

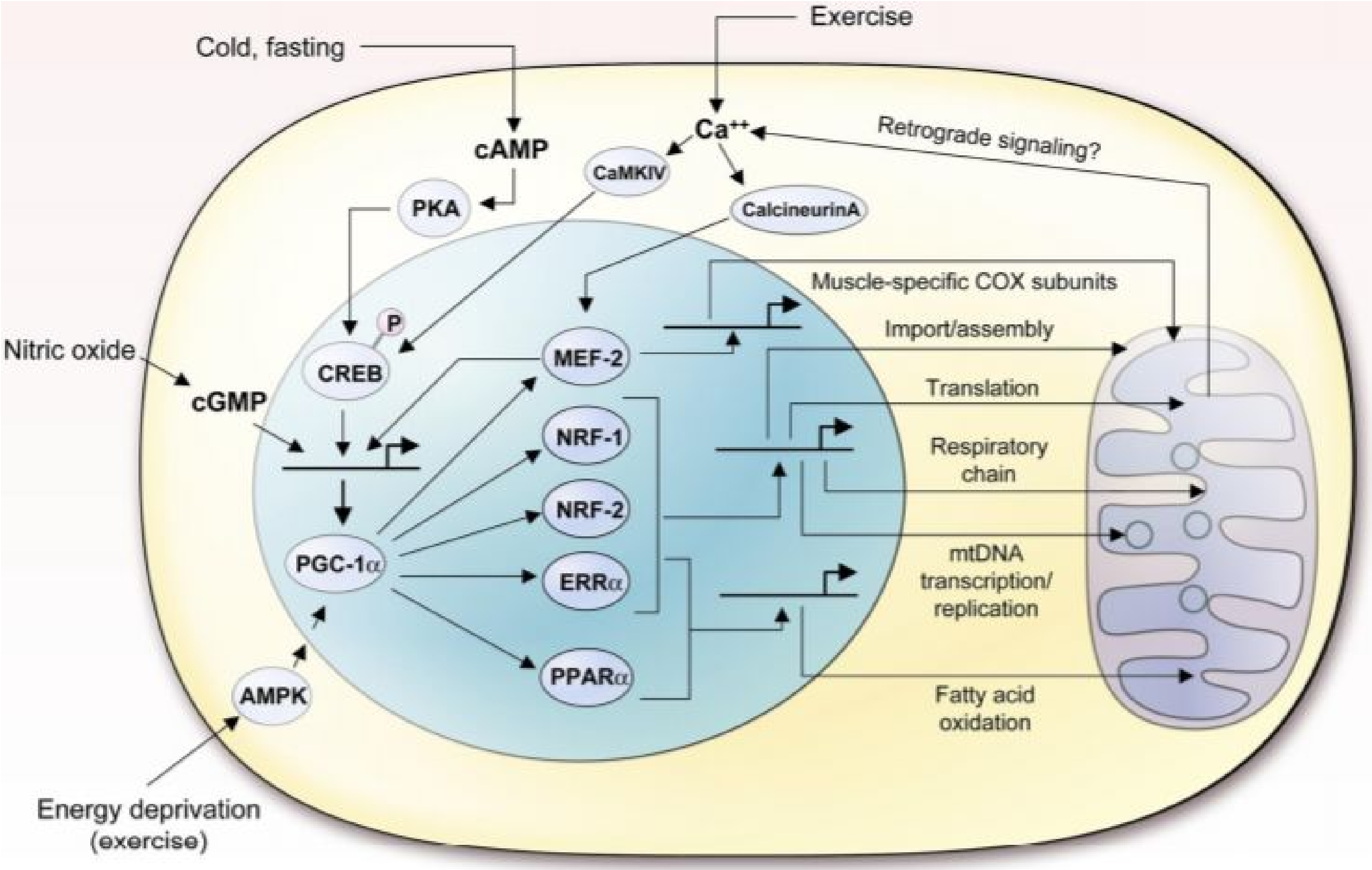
June 15, 2011

WADA statement on clenbuterol

Following current media interest in relation to **clenbuterol**, WADA wishes to clarify the following: 1. **Clenbuterol** is a prohibited substance and there is no threshold under which ...

UWORKFIT
CRAZY BULK
EPHEDRINE-FREE FAT BURNER
CLENBUTROL
CLENBUTEROL ALTERNATIVE
MASS SERIES
90 CAPSULES

Via PKA/CREB/PGC-1α controla a biogênese mitocondrial da fibra muscular


Exercise
Cold, fasting
cAMP
Ca++
Retrograde signaling?
CaMKIV
PKA
CalcineurinA
Muscle-specific COX subunits
P
Import/assembly
Nitric oxide
CREB
MEF-2
cGMP
Translation
NRF-1
Respiratory chain
NRF-2
mtDNA transcription/ replication
PGC-1α
ERRα
PPARα
AMPK
Fatty acid oxidation
Energy deprivation (exercise)

1. **Ativação do receptor β2**
2. **Ativação da via PKA/CREB**
3. **Expressão de PGC-1α**
4. **Ativação de MEF-2, PPARs, ERRs e NRFs**
5. **Expressão de genes mitocôndrias**
6. **↑Biogênese mitocondrial**
7. **↑Metabolismo oxidativo**

Berdeux R, Stwart R. cAMP signaling in skeletal muscle adaptation: hypertrophy, metabolism, and regeneration. Am J Physiol Endocrinol Metab 303: E1–E17, 2012

Agonista-β adrenérgico modula genes do metabolismo oxidativo

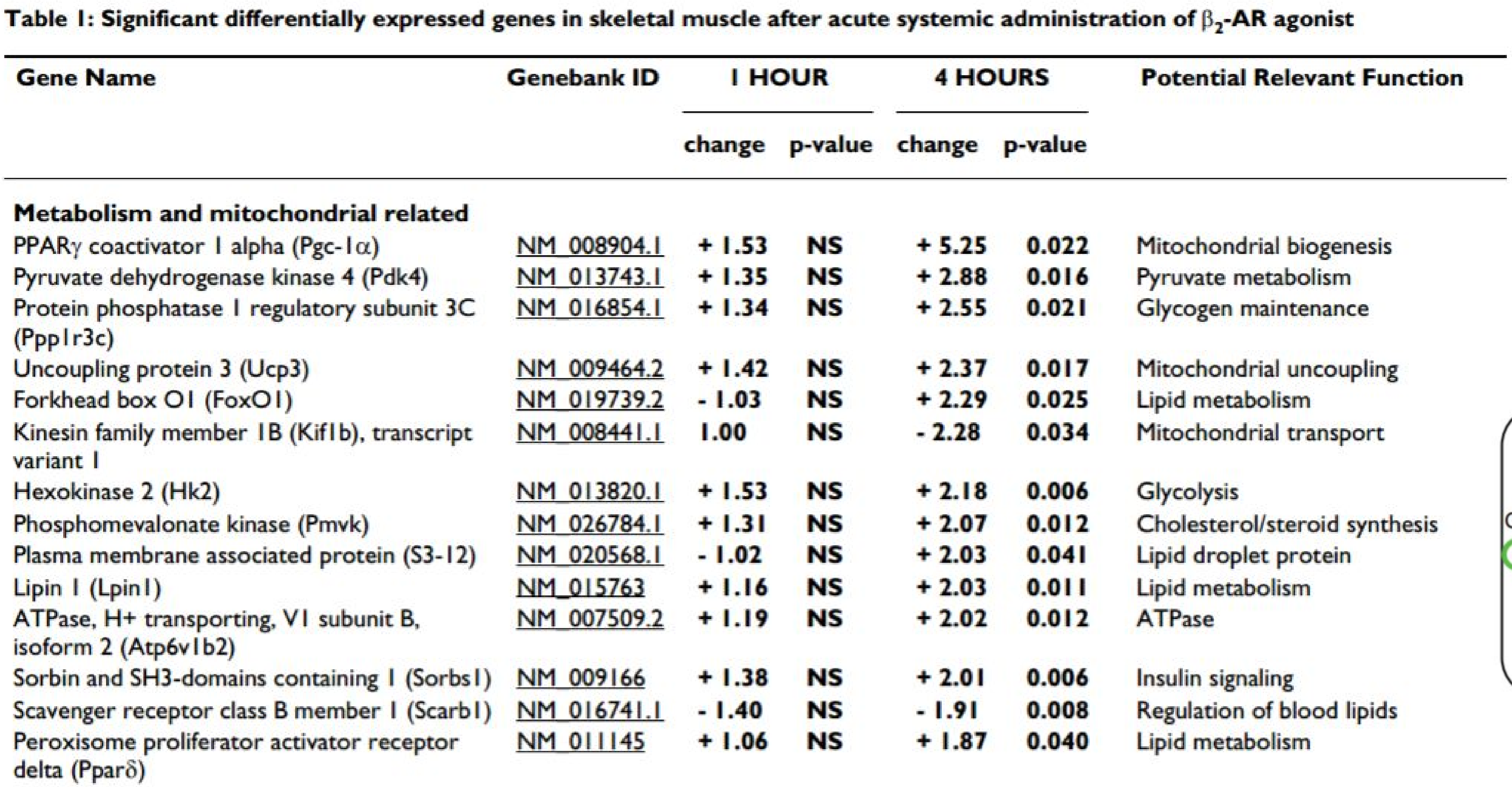
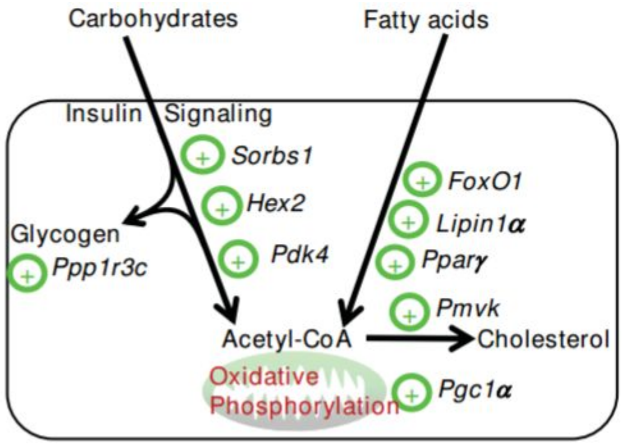


Table 1: Significant differentially expressed genes in skeletal muscle after acute systemic administration of β_2-AR agonist

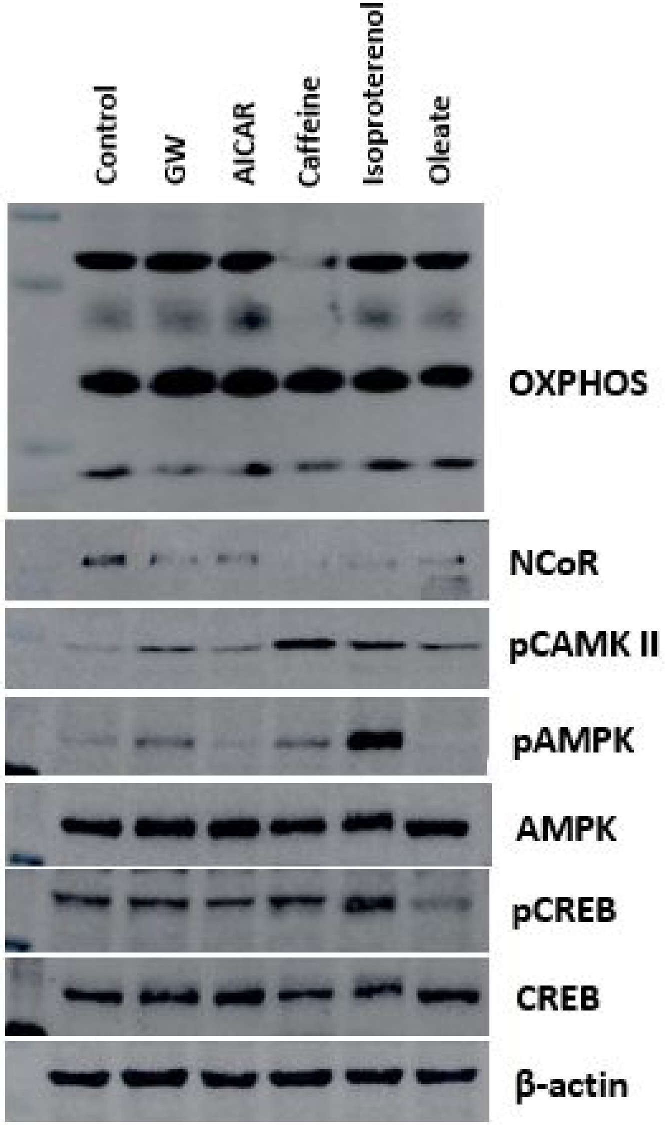
Gene Name	Genebank ID	1 HOUR		4 HOURS		Potential Relevant Function
		change	p-value	change	p-value	
Metabolism and mitochondrial related						
PPARγ coactivator 1 alpha (Pgc-1α)	NM_008904.1	+ 1.53	NS	+ 5.25	0.022	Mitochondrial biogenesis
Pyruvate dehydrogenase kinase 4 (Pdk4)	NM_013743.1	+ 1.35	NS	+ 2.88	0.016	Pyruvate metabolism
Protein phosphatase 1 regulatory subunit 3C (Ppp1r3c)	NM_016854.1	+ 1.34	NS	+ 2.55	0.021	Glycogen maintenance
Uncoupling protein 3 (Ucp3)	NM_009464.2	+ 1.42	NS	+ 2.37	0.017	Mitochondrial uncoupling
Forkhead box O1 (FoxO1)	NM_019739.2	- 1.03	NS	+ 2.29	0.025	Lipid metabolism
Kinesin family member 1B (Kif1b), transcript variant 1	NM_008441.1	1.00	NS	- 2.28	0.034	Mitochondrial transport
Hexokinase 2 (Hk2)	NM_013820.1	+ 1.53	NS	+ 2.18	0.006	Glycolysis
Phosphomevalonate kinase (Pmvk)	NM_026784.1	+ 1.31	NS	+ 2.07	0.012	Cholesterol/steroid synthesis
Plasma membrane associated protein (S3-12)	NM_020568.1	- 1.02	NS	+ 2.03	0.041	Lipid droplet protein
Lipin 1 (Lpin1)	NM_015763	+ 1.16	NS	+ 2.03	0.011	Lipid metabolism
ATPase, H+ transporting, V1 subunit B, isoform 2 (Atp6v1b2)	NM_007509.2	+ 1.19	NS	+ 2.02	0.012	ATPase
Sorbin and SH3-domains containing 1 (Sorbs1)	NM_009166	+ 1.38	NS	+ 2.01	0.006	Insulin signaling
Scavenger receptor class B member 1 (Scarb1)	NM_016741.1	- 1.40	NS	- 1.91	0.008	Regulation of blood lipids
Peroxisome proliferator activator receptor delta (Pparδ)	NM_011145	+ 1.06	NS	+ 1.87	0.040	Lipid metabolism

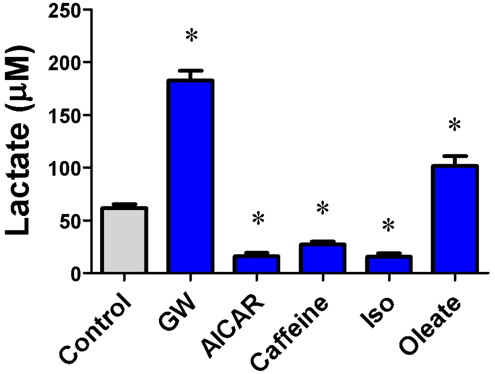
Administração aguda de Formoterol

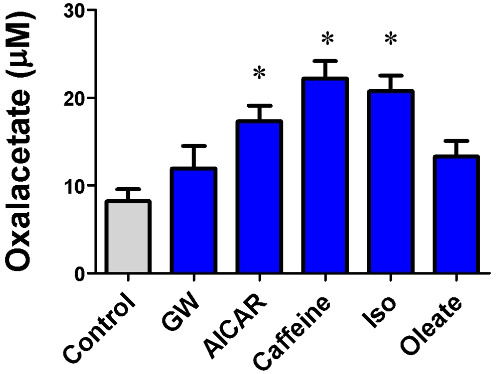


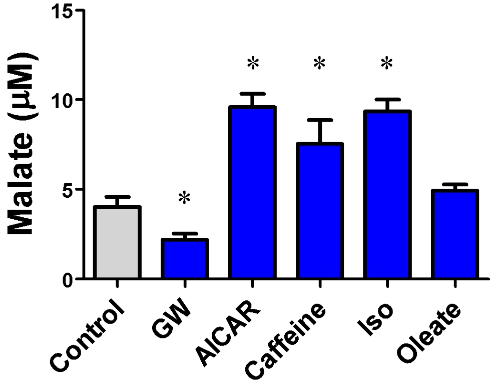
Expression profiling of skeletal muscle following acute and chronic β_2-adrenergic stimulation: implications for hypertrophy, metabolism and circadian rhythm

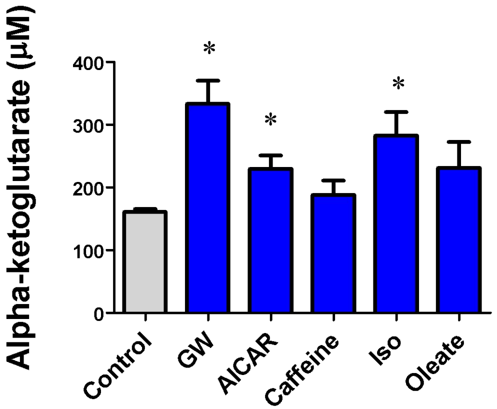
Agonista β-adrenérgico ativa o metabolismo oxidativo

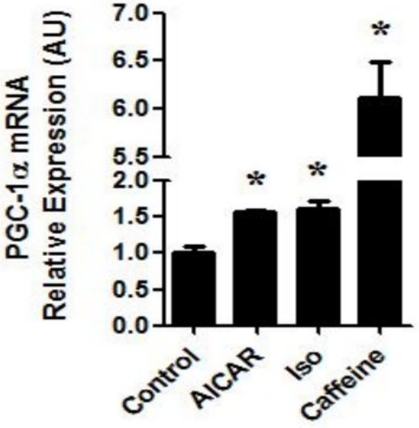

Control
GW
AICAR
Caffeine
Isoproterenol
Oleate
OXPHOS
NCoR
pCAMK II
pAMPK
AMPK
pCREB
CREB
β-actin





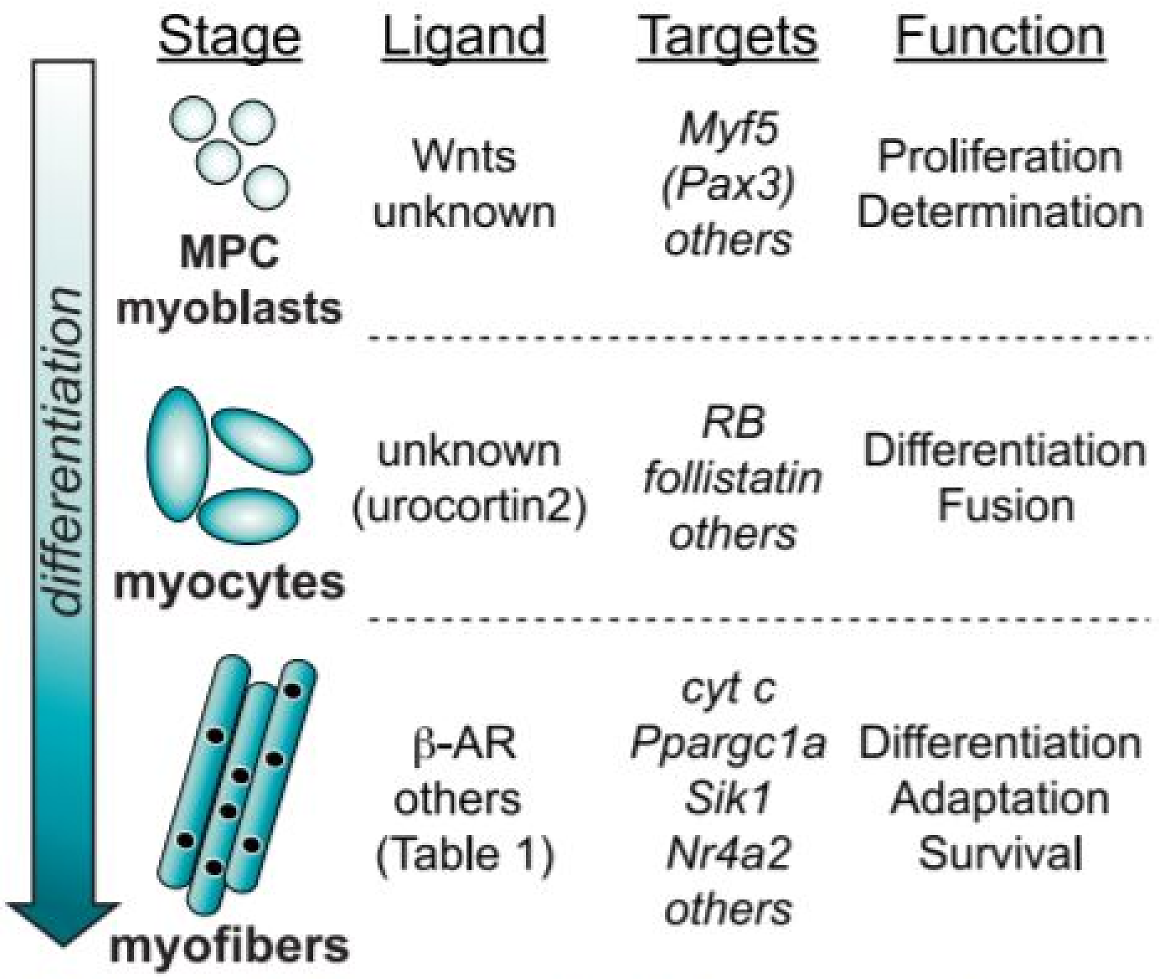






Lima *et al*. dados não publicados

Papel da via β-adrenérgica/CREB no controle da diferenciação da fibra muscular

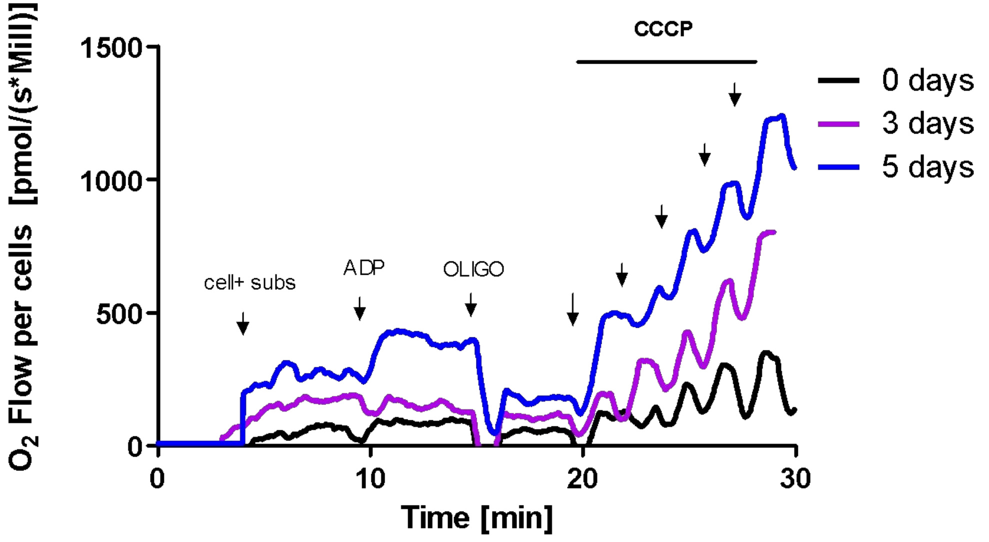


Stage	Ligand	Targets	Function
MPC myoblasts	Wnts unknown	*Myf5* *(Pax3)* *others*	Proliferation Determination
myocytes	unknown (urocortin2)	*RB* *follistatin* *others*	Differentiation Fusion
myofibers	β-AR others (Table 1)	*cyt c* *Ppargc1a* *Sik1* *Nr4a2* *others*	Differentiation Adaptation Survival

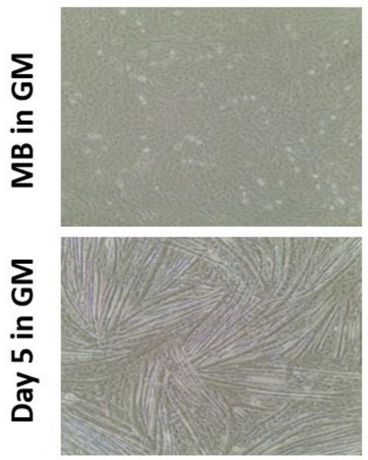
Berdeux R, Stwart R. cAMP signaling in skeletal muscle adaptation: hypertrophy, metabolism, and regeneration. Am J Physiol Endocrinol Metab 303: E1–E17, 2012

Biogênese mitocondrial durante a diferenciação da fibra muscular

A

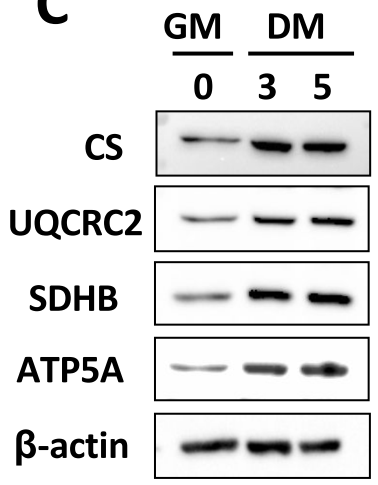


B



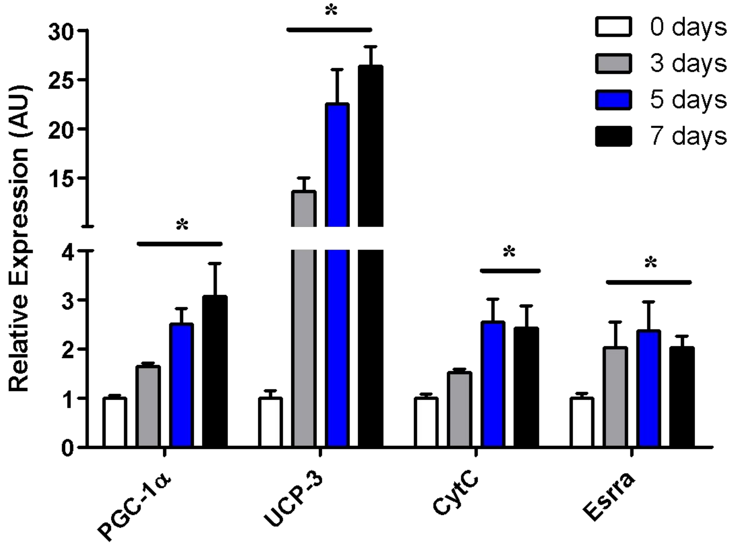
MB in GM
Day 5 in GM

C

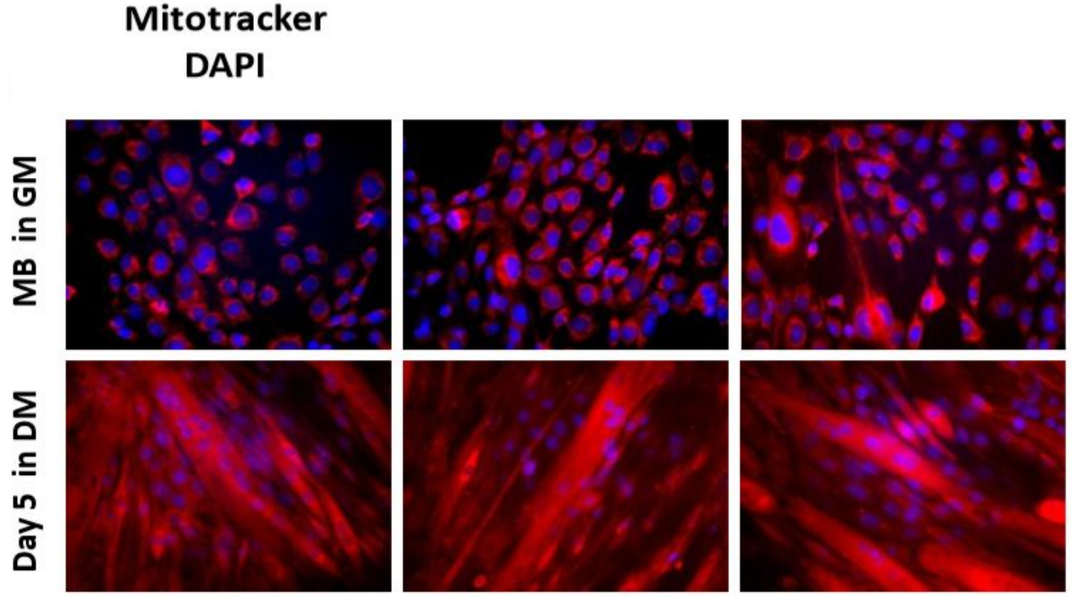


GM
DM
0
3
5
CS
UQCRC2
SDHB
ATP5A
β-actin

D



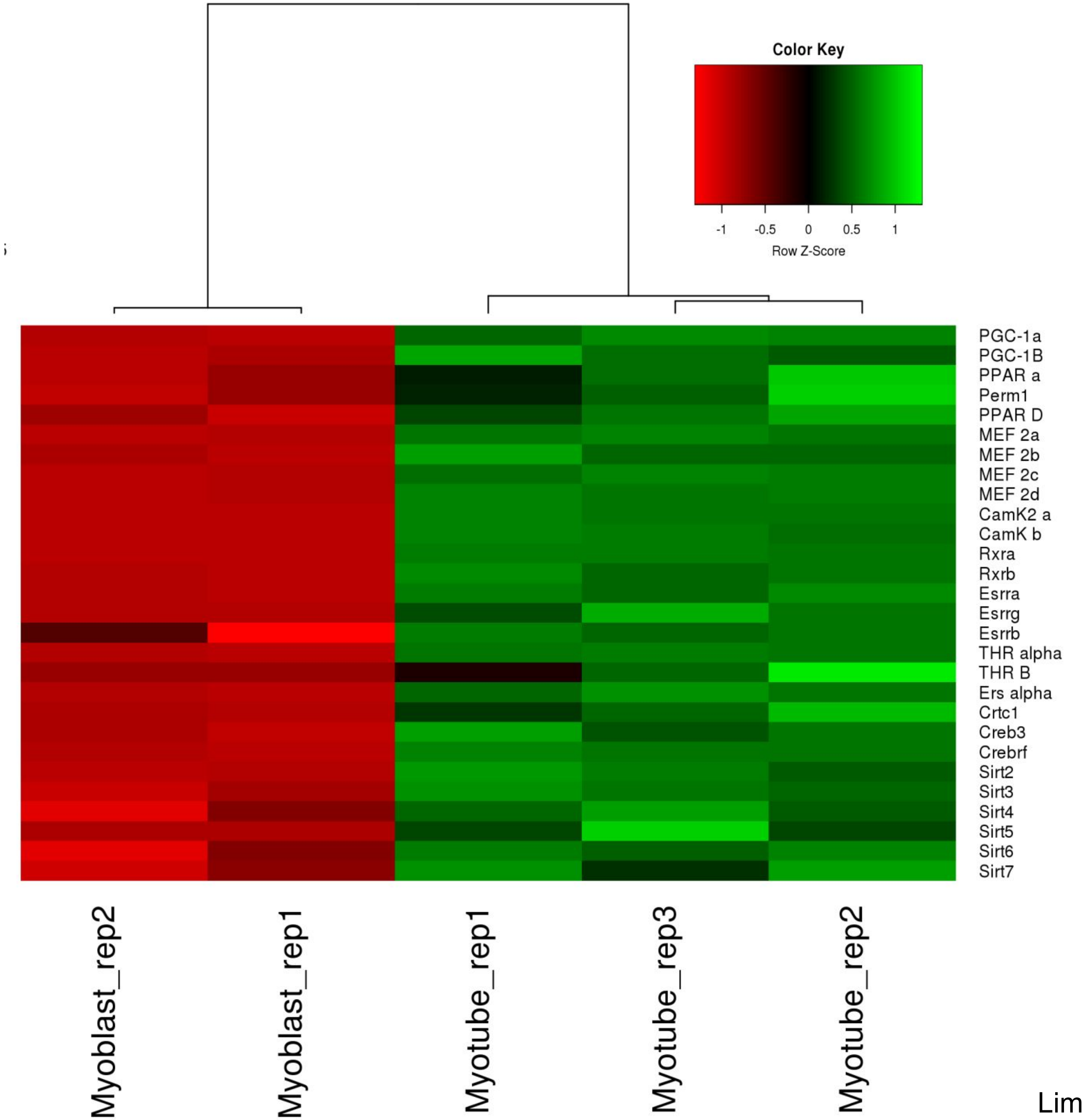
E

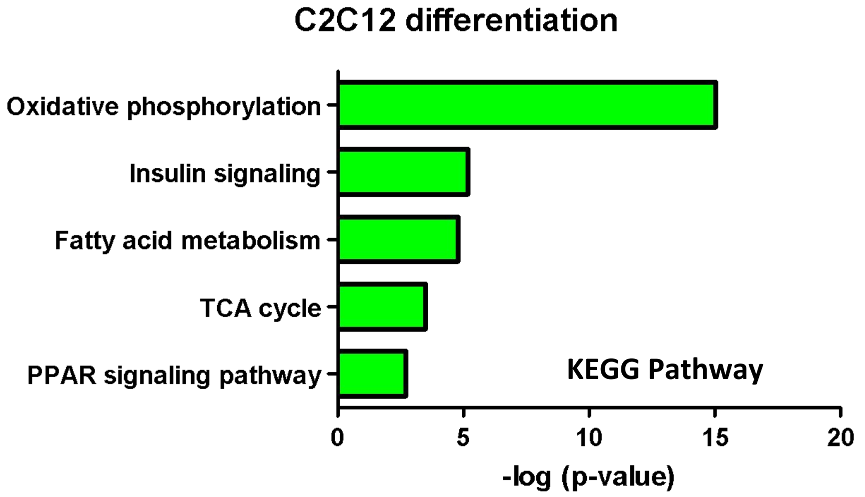


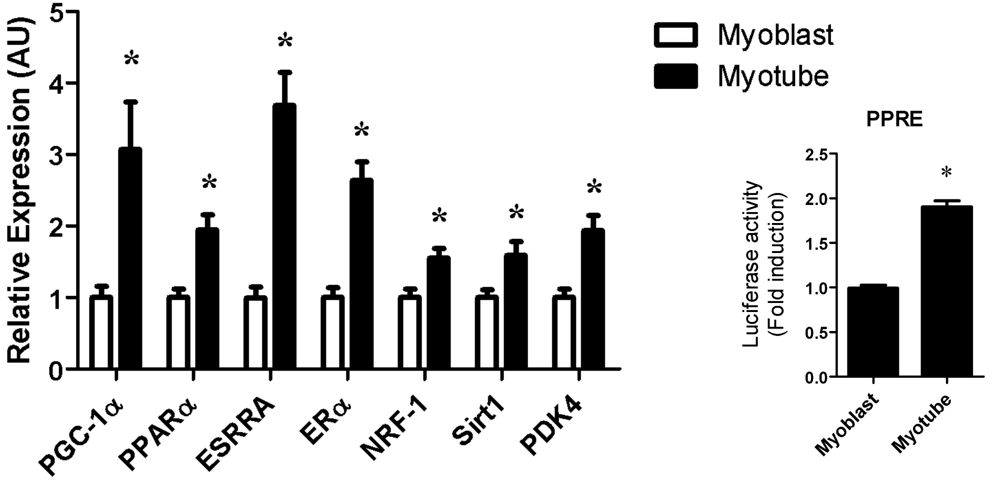
Mitotracker
DAPI
MB in GM
Day 5 in DM

Lima *et al*. dados não publicados

Vias enriquecidas durante a diferenciação da fibra muscular

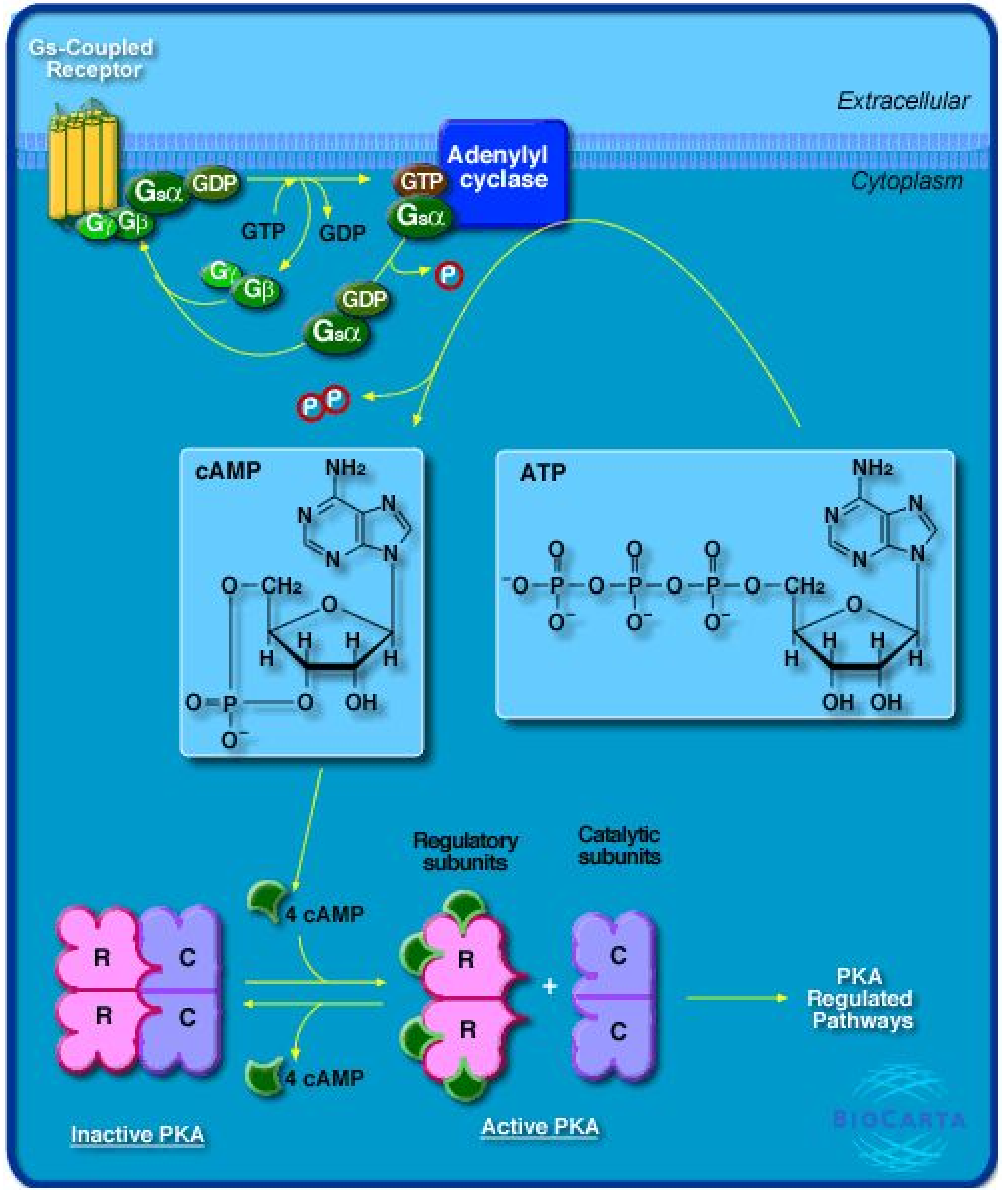




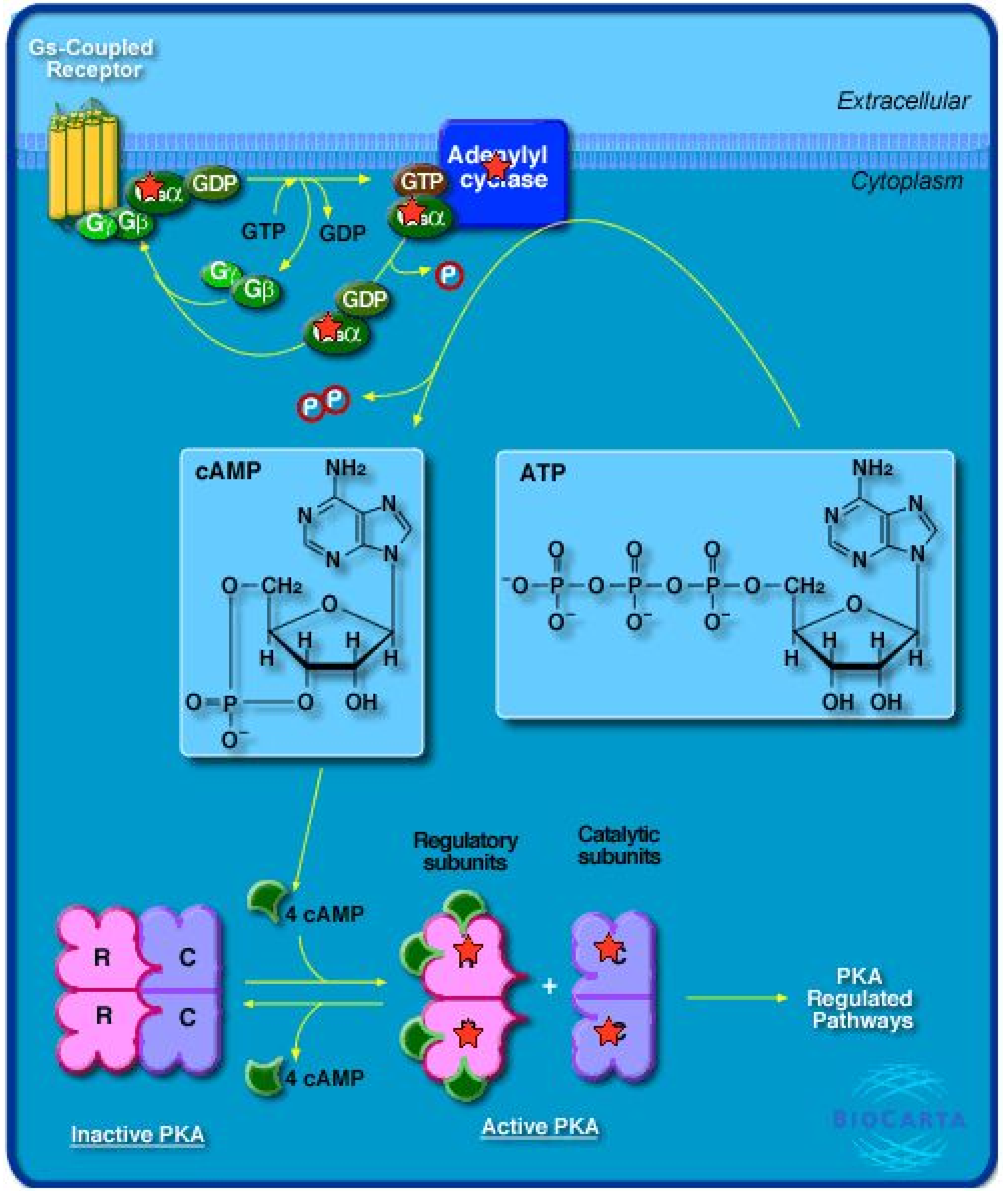


Lima *et al*. dados não publicados

Ativação da via cAMP/PKA durante a diferenciação

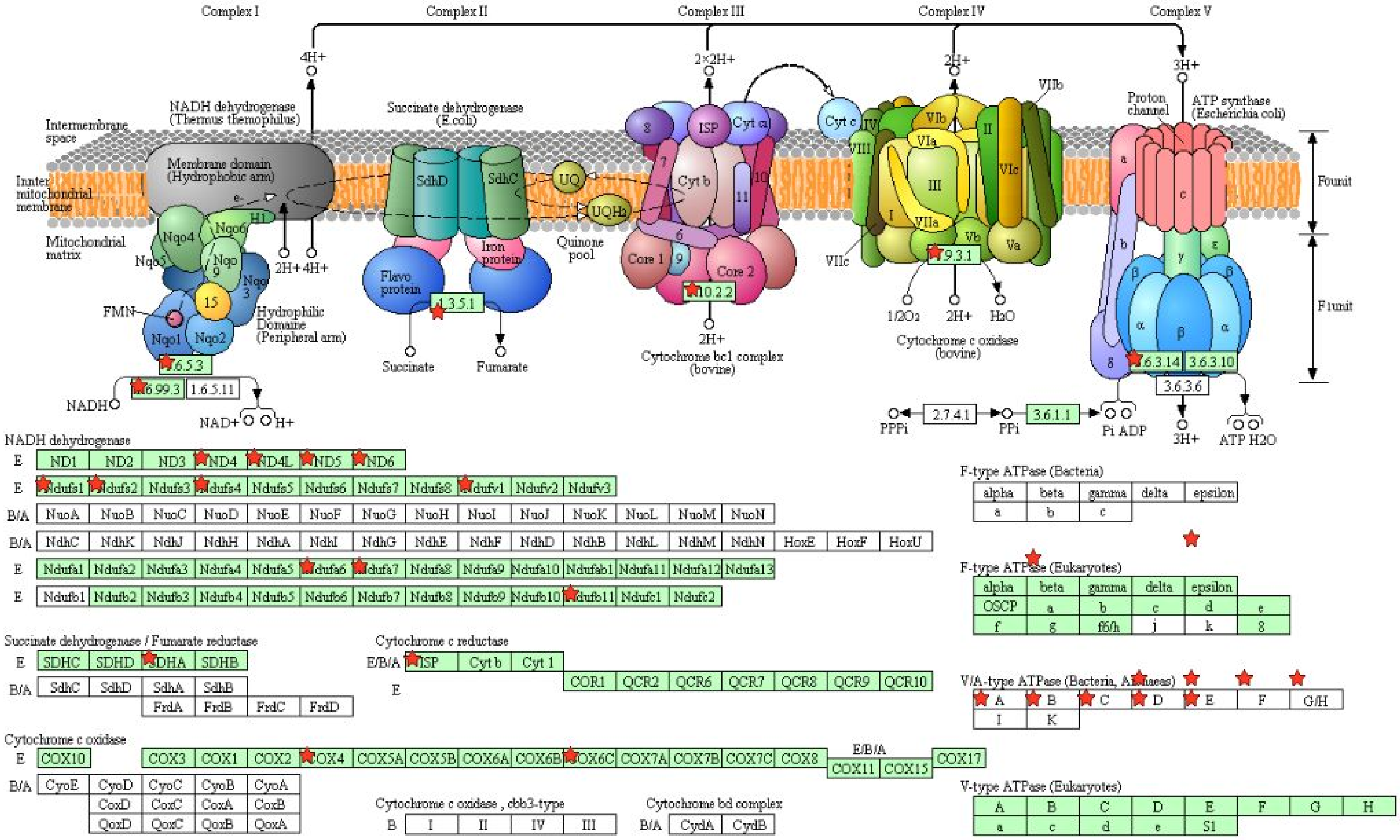

Gs-Coupled Receptor
Extracellular
Cytoplasm
Adenylyl cyclase
GTP
GDP
Gsα
Gγ
Gβ
GTP
GDP
GDP
Gsα
P
P P
cAMP
NH2
ATP
NH2
Regulatory subunits
Catalytic subunits
4 cAMP
R
C
R
C
R
R
C
C
4 cAMP
PKA Regulated Pathways
Inactive PKA
Active PKA
BIOCARTA

DAVID Bioinformatics Resources 6.7


Gs-Coupled Receptor
Extracellular
Cytoplasm
Adenylyl cyclase
GTP
GDP
Gsα
Gγ
Gβ
GTP
GDP
GDP
Gsα
P
P P
cAMP
NH2
ATP
NH2
Regulatory subunits
Catalytic subunits
4 cAMP
R
C
R
C
R
R
C
C
4 cAMP
PKA Regulated Pathways
Inactive PKA
Active PKA
BIOCARTA

Lima *et al*. dados não publicados

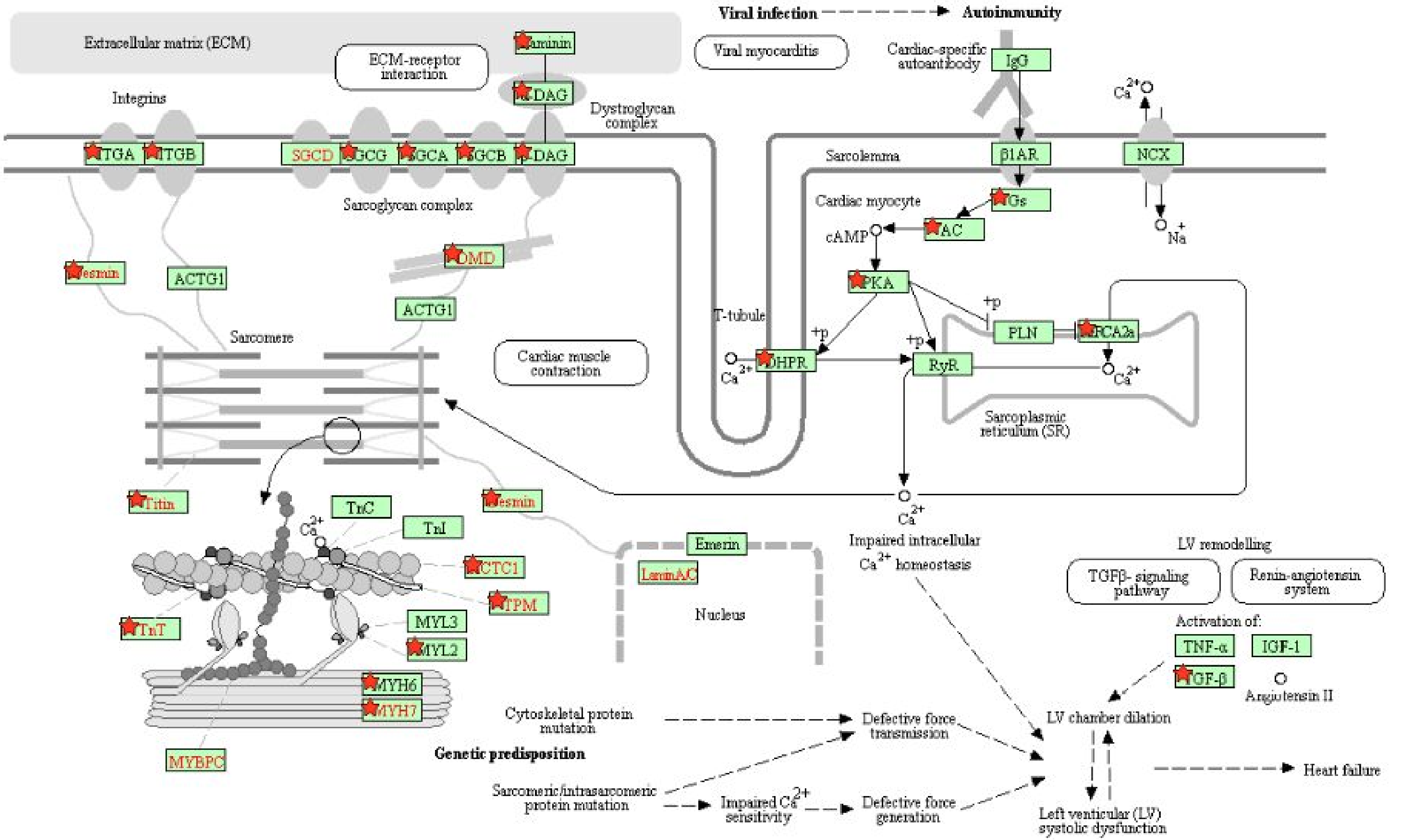
Ativação da fosforilação oxidativa durante a diferenciação


Complex I
Complex II
Complex III
Complex IV
Complex V
4H+
2×2H+
2H+
3H+
NADH dehydrogenase (Thermus themophilus)
Intermembrane space
Inner mitochondrial membrane
Mitochondrial matrix
Membrane domain (Hydrophobic arm)
e-
H1
Nqo4
Nqo6
Nqo5
Nqo 9
Nqo 3
15
FMN
Nqo1
Nqo2
Hydrophilic Domain (Peripheral arm)
2H+ 4H+
1.6.5.3
1.6.99.3
1.6.5.11
NADH
NAD+
H+
Succinate dehydrogenase (E.coli)
SdhD
SdhC
Iron protein
Flavo protein
1.3.5.1
Succinate
Fumarate
UQ
UQH2
Quinone pool
8
ISP
Cyt c1
Cyt b
7
10
11
6
9
Core 1
Core 2
1.10.2.2
2H+
Cytochrome bc1 complex (bovine)
Cyt c
VIIb
IV
VIII
VIb
VIa
II
III
VIc
I
VIIa
Vb
Va
VIIc
1.9.3.1
1/2O2
2H+
H2O
Cytochrome c oxidase (bovine)
Proton channel
ATP synthase (Escherichia coli)
a
c
b
ε
γ
β
α
δ
Fo unit
F1 unit
3.6.3.14
3.6.3.10
3.6.3.6
2.7.4.1
3.6.1.1
PPPi
PPi
Pi ADP
3H+
ATP H2O
NADH dehydrogenase
E ND1 ND2 ND3 ND4 ND4L ND5 ND6
E Ndufs1 Ndufs2 Ndufs3 Ndufs4 Ndufs5 Ndufs6 Ndufs7 Ndufs8 Ndufv1 Ndufv2 Ndufv3
B/A NuoA NuoB NuoC NuoD NuoE NuoF NuoG NuoH NuoI NuoJ NuoK NuoL NuoM NuoN
B/A NdhC NdhK NdhJ NdhH NdhA NdhI NdhG NdhE NdhF NdhD NdhB NdhL NdhM NdhN HoxE HoxF HoxU
E Ndufa1 Ndufa2 Ndufa3 Ndufa4 Ndufa5 Ndufa6 Ndufa7 Ndufa8 Ndufa9 Ndufa10 Ndufab1 Ndufa11 Ndufa12 Ndufa13
E Ndufb1 Ndufb2 Ndufb3 Ndufb4 Ndufb5 Ndufb6 Ndufb7 Ndufb8 Ndufb9 Ndufb10 Ndufb11 Ndufc1 Ndufc2
Succinate dehydrogenase / Fumarate reductase
E SDHC SDHD SDHA SDHB
B/A SdhC SdhD SdhA SdhB
FrdA FrdB FrdC FrdD
Cytochrome c reductase
E/B/A ISP Cyt b Cyt 1
E COR1 QCR2 QCR6 QCR7 QCR8 QCR9 QCR10
Cytochrome c oxidase
E COX10 COX3 COX1 COX2 COX4 COX5A COX5B COX6A COX6B COX6C COX7A COX7B COX7C COX8
E/B/A COX11 COX15 COX17
B/A CyoE CyoD CyoC CyoB CyoA
CoxD CoxC CoxA CoxB
QoxD QoxC QoxB QoxA
Cytochrome c oxidase , cbb3-type
B I II IV III
Cytochrome bd complex
B/A CydA CydB
F-type ATPase (Bacteria)
alpha beta gamma delta epsilon
a b c
F-type ATPase (Eukaryotes)
alpha beta gamma delta epsilon
OSCP a b c d e
f g f6/h j k 8
V/A-type ATPase (Bacteria, Archaeas)
A B C D E F G/H
I K
V-type ATPase (Eukaryotes)
A B C D E F G H
a c d e S1

DAVID Bioinformatics Resources 6.7

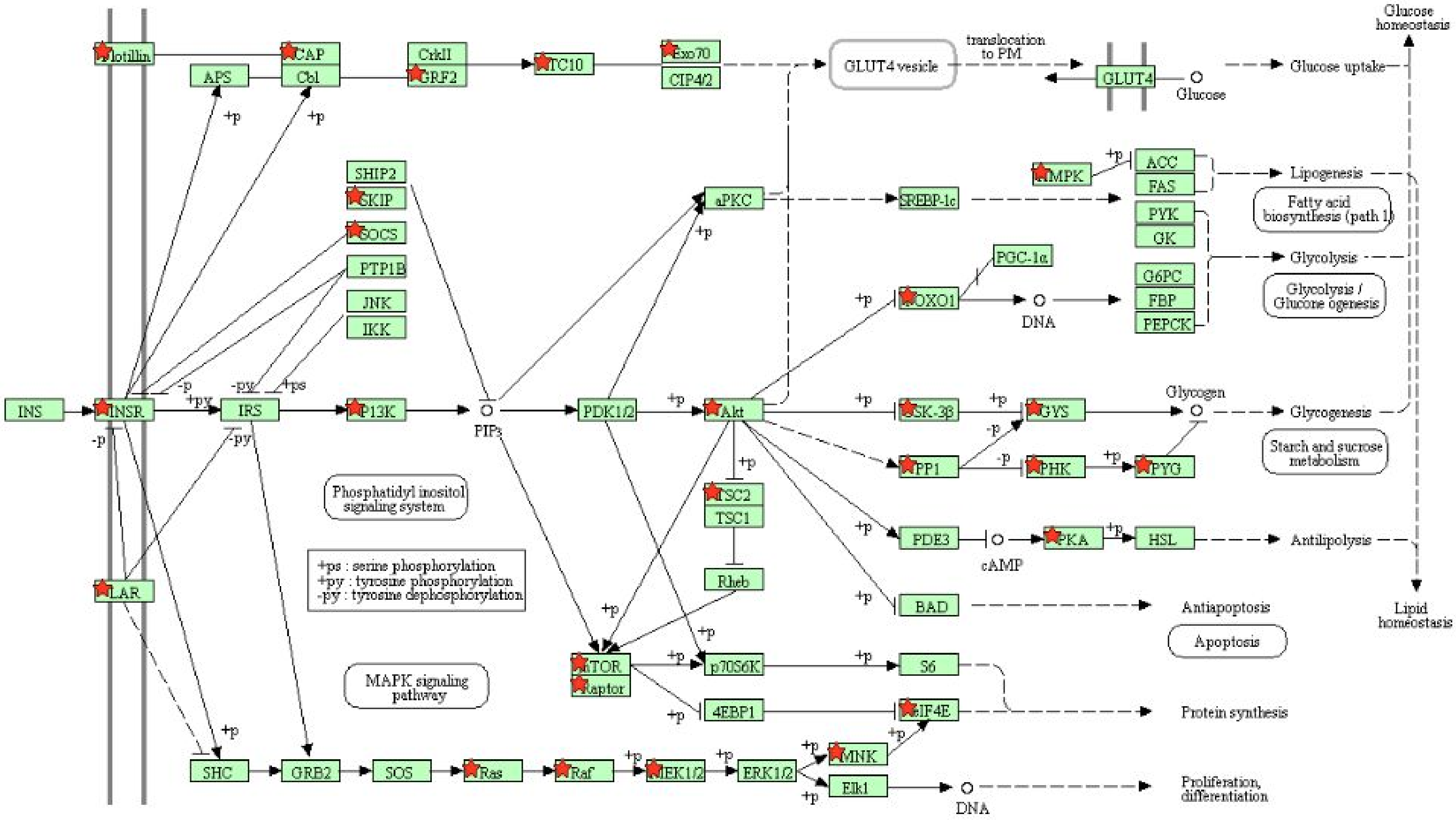
Lima *et al*. dados não publicados

Ativação da hipertrofia muscular durante a diferenciação


Extracellular matrix (ECM)
ECM-receptor interaction
aminin
Viral infection
Autoimmunity
Viral myocarditis
Cardiac-specific autoantibody
IgG
Integrins
DAG
Dystroglycan complex
Ca^{2+}
TGA
ITGB
SGCD
GCG
GCA
GCB
DAG
Sarcolemma
β1AR
NCX
Sarcoglycan complex
Cardiac myocyte
Gs
cAMP
AC
Na^{+}
esmin
ACTG1
DMD
PKA
ACTG1
+p
PLN
RCA2a
Sarcomere
T-tubule
+p
+p
DHPR
RyR
Ca^{2+}
Ca^{2+}
Cardiac muscle contraction
Sarcoplasmic reticulum (SR)
Titin
TnC
Ca^{2+}
esmin
TnI
Emerin
Ca^{2+}
Impaired intracellular Ca^{2+} homeostasis
LV remodelling
CTC1
LaminA/C
TGFβ- signaling pathway
Renin-angiotensin system
TPM
Nucleus
TnT
MYL3
Activation of:
MYL2
TNF-α
IGF-1
MYH6
GF-β
Angiotensin II
MYH7
Cytoskeletal protein mutation
Defective force transmission
LV chamber dilation
Genetic predisposition
MYBPC
Heart failure
Sarcomeric/intrasarcomeric protein mutation
Impaired Ca^{2+} sensitivity
Defective force generation
Left ventricular (LV) systolic dysfunction

DAVID Bioinformatics Resources 6.7 Lima *et al*. dados não publicados

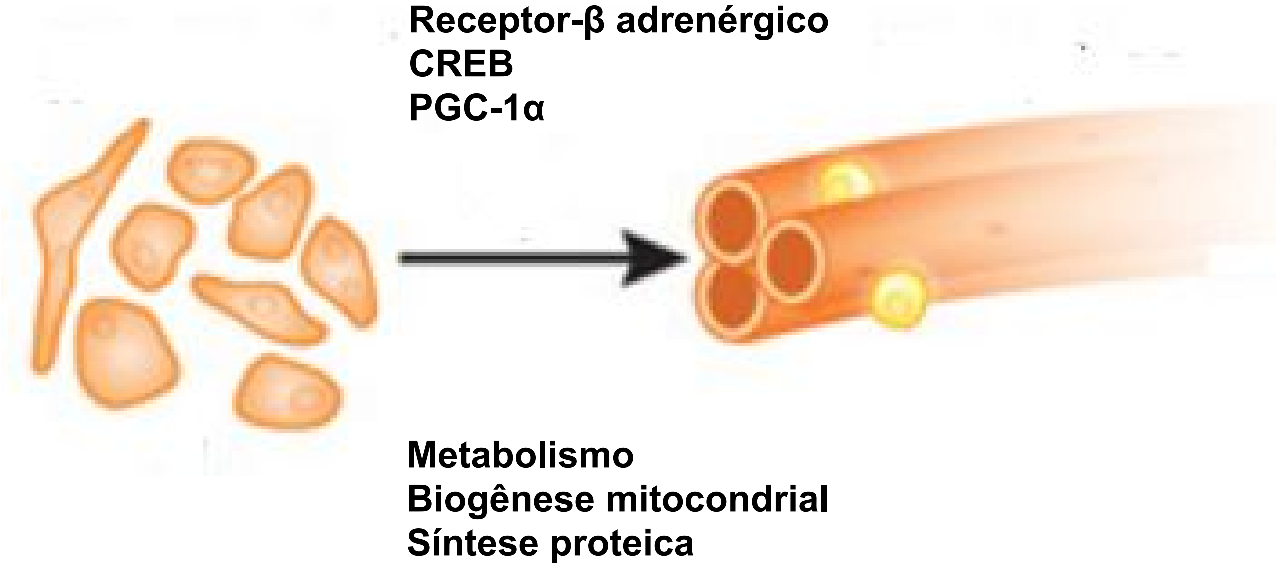
Sinalização da insulina e metabolismo de proteínas durante a diferenciação


lotillin
CAP
APS
Cbl
CrkII
GRF2
TC10
Exo70
CIP4/2
GLUT4 vesicle
translocation to PM
GLUT4
Glucose
Glucose uptake
Glucose homeostasis
+p
SHIP2
SKIP
SOCS
PTP1B
JNK
IKK
aPKC
SREBP-1c
MPK
ACC
FAS
Lipogenesis
Fatty acid biosynthesis (path 1)
PYK
GK
Glycolysis
PGC-1α
OXO1
DNA
G6PC
FBP
PEPCK
Glycolysis / Gluconeogenesis
INS
INSR
-p
+py
-py
+ps
IRS
PI3K
PIP3
PDK1/2
Akt
SK-3β
GYS
Glycogen
Glycogenesis
PP1
PHK
PYG
Starch and sucrose metabolism
SC2
TSC1
PDE3
cAMP
PKA
HSL
Antilipolysis
Lipid homeostasis
Rheb
BAD
Antiapoptosis
Apoptosis
Phosphatidyl inositol signaling system
+ps : serine phosphorylation
+py : tyrosine phosphorylation
-py : tyrosine dephosphorylation
LAR
TOR
Raptor
p70S6K
S6
4EBP1
IF4E
Protein synthesis
MAPK signaling pathway
SHC
GRB2
SOS
Ras
Raf
EK1/2
ERK1/2
MNK
Elk1
Proliferation, differentiation

DAVID Bioinformatics Resources 6.7

Lima *et al*. dados não publicados

Vias enriquecidas durante a diferenciação

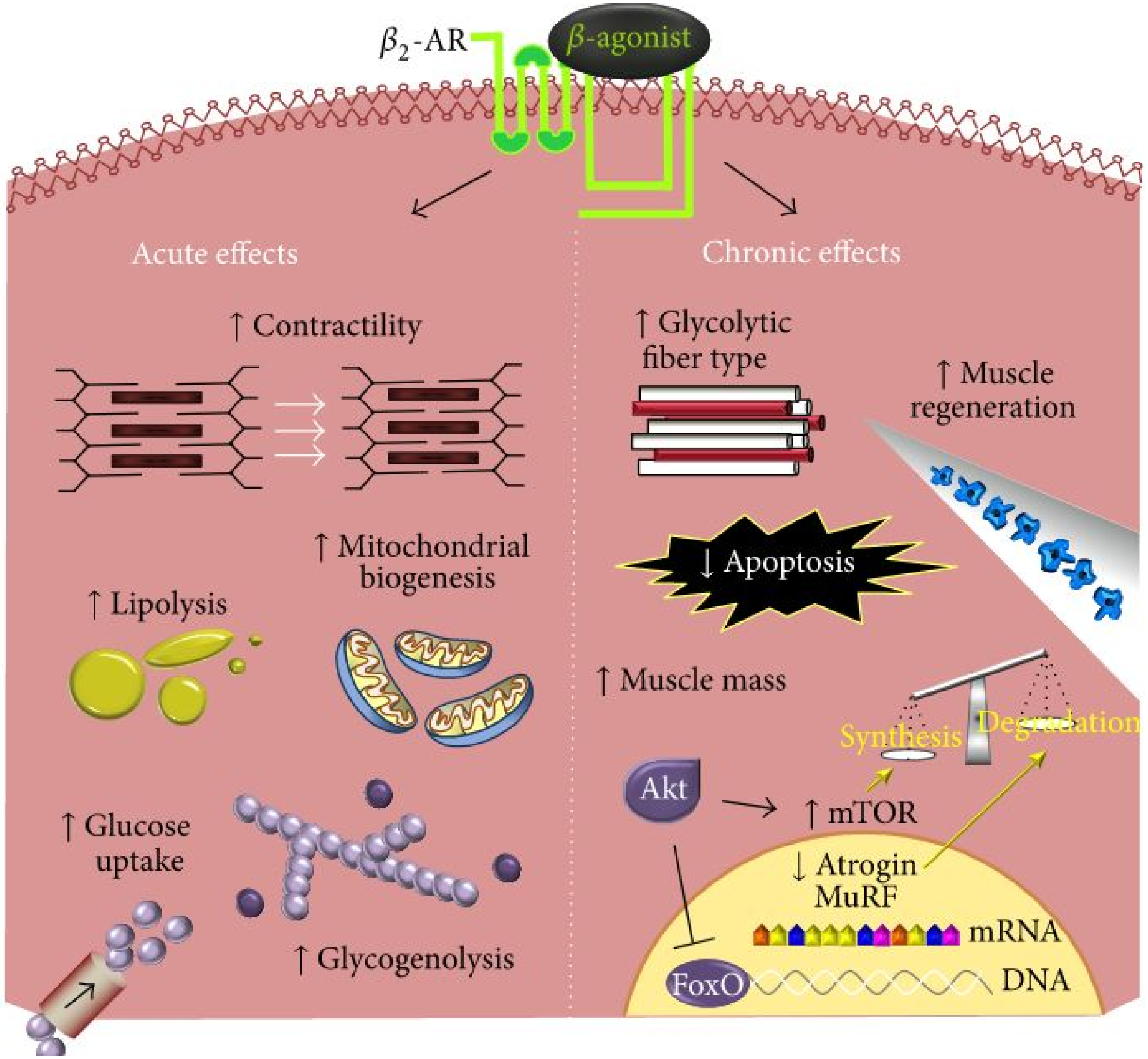


Receptor-β adrenérgico
CREB
PGC-1α

Metabolismo
Biogênese mitocondrial
Síntese proteica

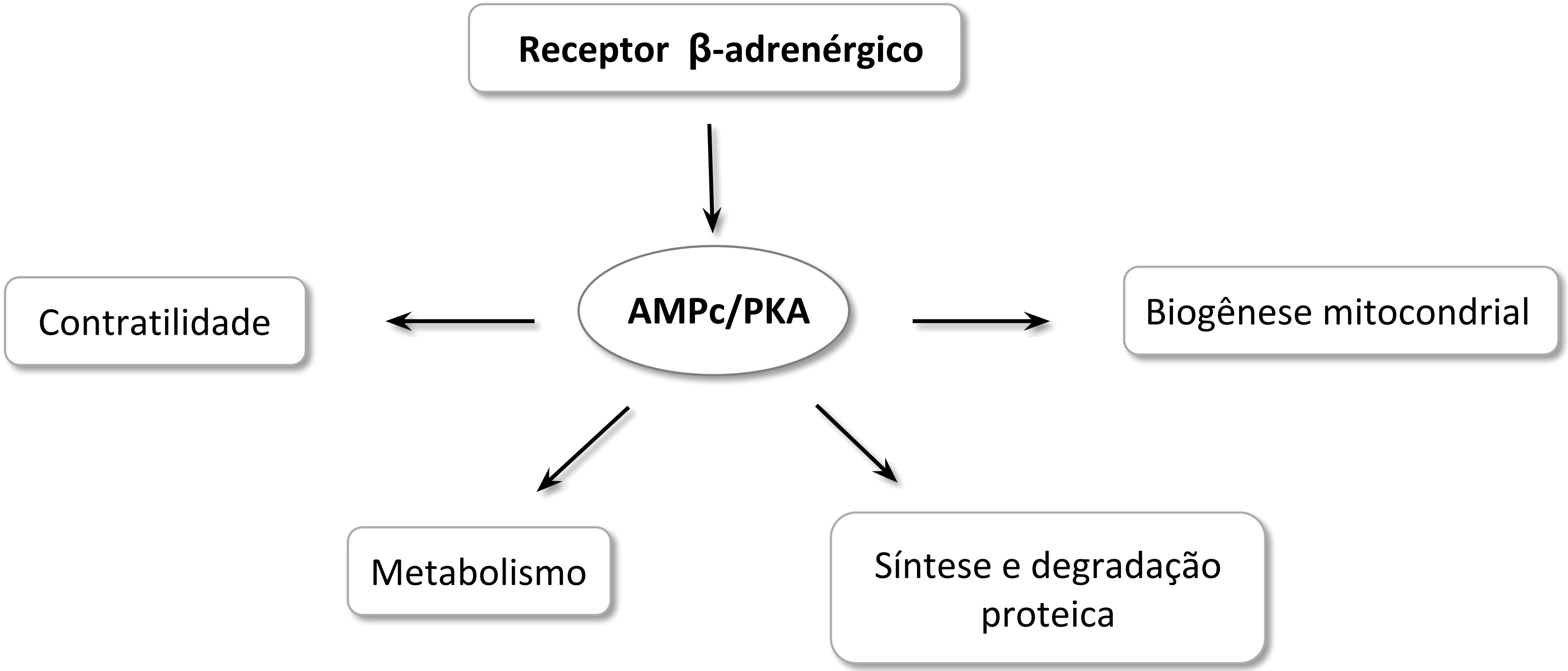
http://www.nature.com/nm/journal/v16/n2/fig_tab/nm0210-171_F1.html

Papel da ativação aguda e crônica da via PKA/CREB na fibra muscular



β_2-AR
β-agonist
Acute effects
Chronic effects
↑ Contractility
↑ Glycolytic fiber type
↑ Muscle regeneration
↓ Apoptosis
↑ Mitochondrial biogenesis
↑ Lipolysis
↑ Muscle mass
Synthesis
Degradation
Akt
↑ mTOR
↓ Atrogin MuRF
mRNA
FoxO
DNA
↑ Glucose uptake
↑ Glycogenolysis

Ação do Sistema Nervoso Simpático na fibra muscular



Receptor β-adrenérgico

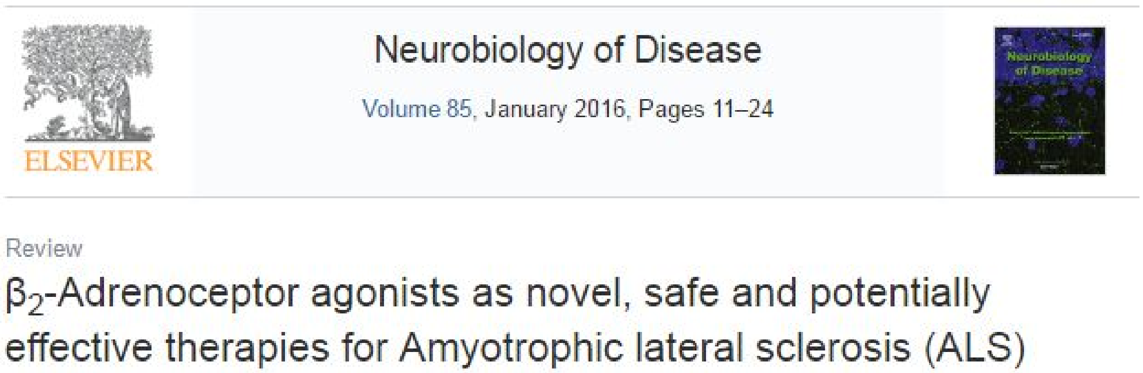
AMPc/PKA

Contratilidade

Biogênese mitocondrial

Metabolismo

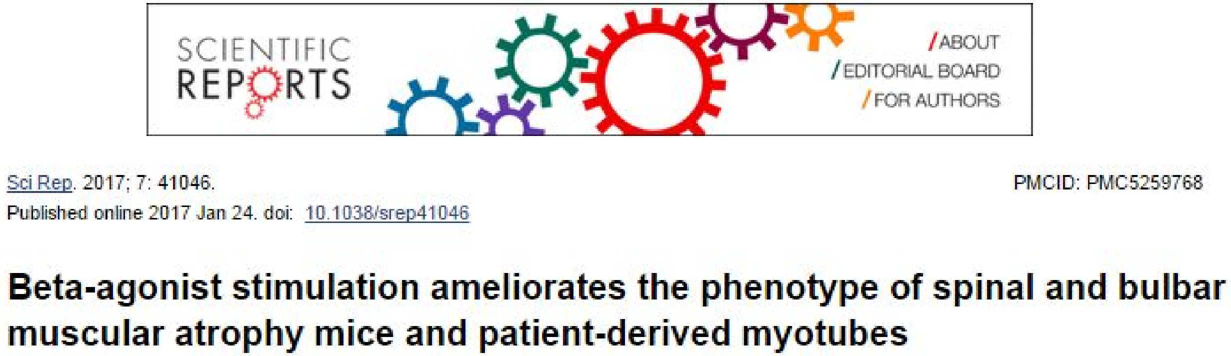
Síntese e degradação proteica


Neurobiology of Disease

Volume 85, January 2016, Pages 11–24

Review

β_2-Adrenoceptor agonists as novel, safe and potentially effective therapies for Amyotrophic lateral sclerosis (ALS)

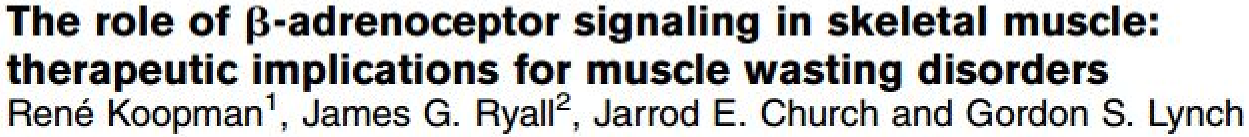


Sci Rep. 2017; 7: 41046.

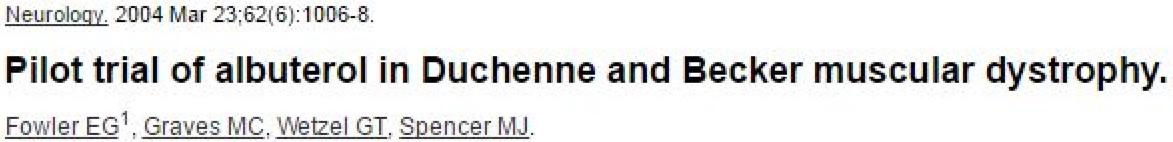
PMCID: PMC5259768

Published online 2017 Jan 24. doi: 10.1038/srep41046

Beta-agonist stimulation ameliorates the phenotype of spinal and bulbar muscular atrophy mice and patient-derived myotubes

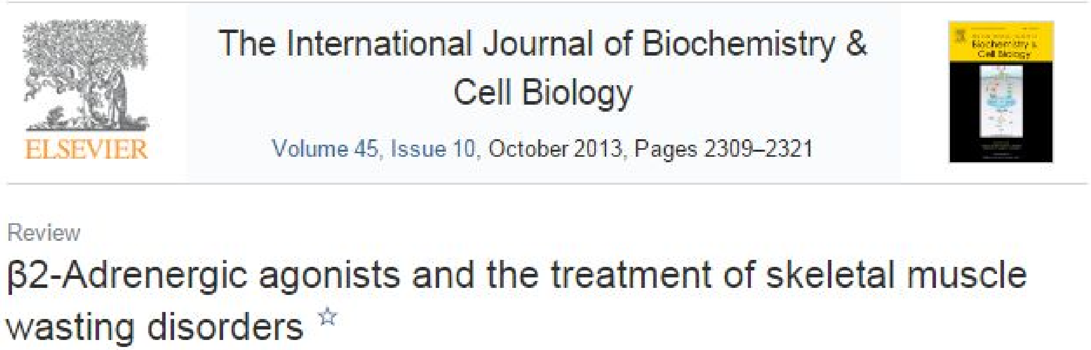

The role of β-adrenoceptor signaling in skeletal muscle: therapeutic implications for muscle wasting disorders

René Koopman[1], James G. Ryall[2], Jarrod E. Church and Gordon S. Lynch


Neurology. 2004 Mar 23;62(6):1006-8.

Pilot trial of albuterol in Duchenne and Becker muscular dystrophy.

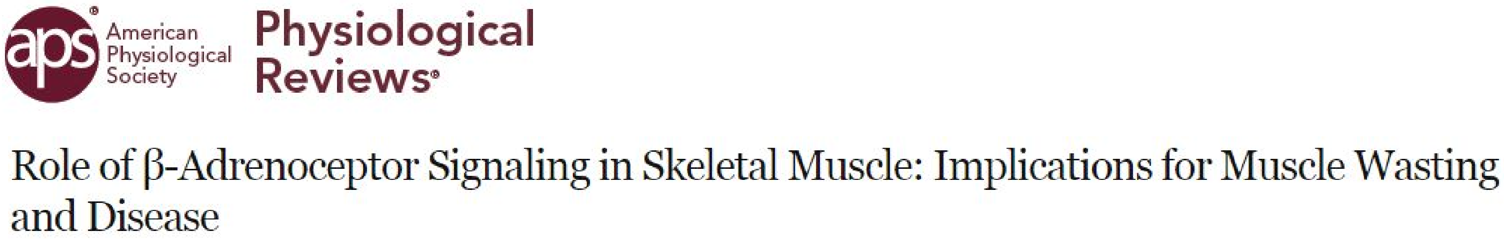
Fowler EG[1], Graves MC, Wetzel GT, Spencer MJ.


The International Journal of Biochemistry & Cell Biology

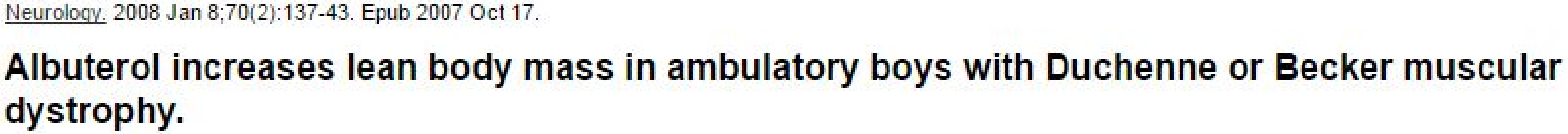
Volume 45, Issue 10, October 2013, Pages 2309–2321

Review

β2-Adrenergic agonists and the treatment of skeletal muscle wasting disorders ☆


aps American Physiological Society Physiological Reviews

Role of β-Adrenoceptor Signaling in Skeletal Muscle: Implications for Muscle Wasting and Disease


Neurology. 2008 Jan 8;70(2):137-43. Epub 2007 Oct 17.

Albuterol increases lean body mass in ambulatory boys with Duchenne or Becker muscular dystrophy.