Nutrigenômica e Exercício Físico

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Nutricionista
Mestre em Ciências - Faculdade de Medicina da USP

Diferentes perfis no consultório

Perfil 1

“Quero hipertrofia muscular.”
“Treino com intensidade, como bastante carboidrato e proteína, mas não consigo evoluir.”
“Sou muito ansioso.”

Perfil 2

“Quero definir, ganhar massa muscular.”
“Malho, faço dieta e não saio do lugar.”
“Sinto que falta energia para os treinos, preciso tomar termogênico.”

Perfil 3

“Quero mudar meu estilo de vida. Fiz exames e deu tudo alterado.”
“Vou começar a fazer exercícios regularmente”
“Sempre comi de tudo, gosto de beber e comer fora.”
“Meu maior problema é a noite.”
“Durmo pouco.”

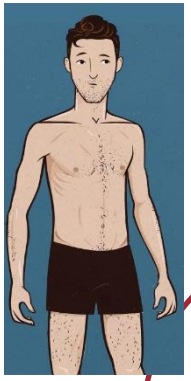
Mecanismos e Alvos Importantes

Emagrecimento:

1- Biogênese mitocondrial
2- Metabolismo Lipídico
3- Compulsão e desejo por açúcar/carboidrato

Hipertrofia Muscular:

1- Ciclo circadiano
2- Inflamação
3- Resposta anabólica



Perfil 1 e 2

- Ansiedade e estresse → reduz a ingestão
- Não consegue ingerir grandes volumes → saciedade precoce
- “Come de tudo e não engorda” → perfil inflamatório e sensibilidade à insulina
- Gordura localizada e fadiga para os treinos → mais comum nas mulheres
- Hipoglicemia de rebote

Perfil 1 e 2

Perfil de polimorfismos genéticos comuns:

- IL-6
- PPARGC1A → perfil benéfico para redução de gordura corporal
- MTHFR

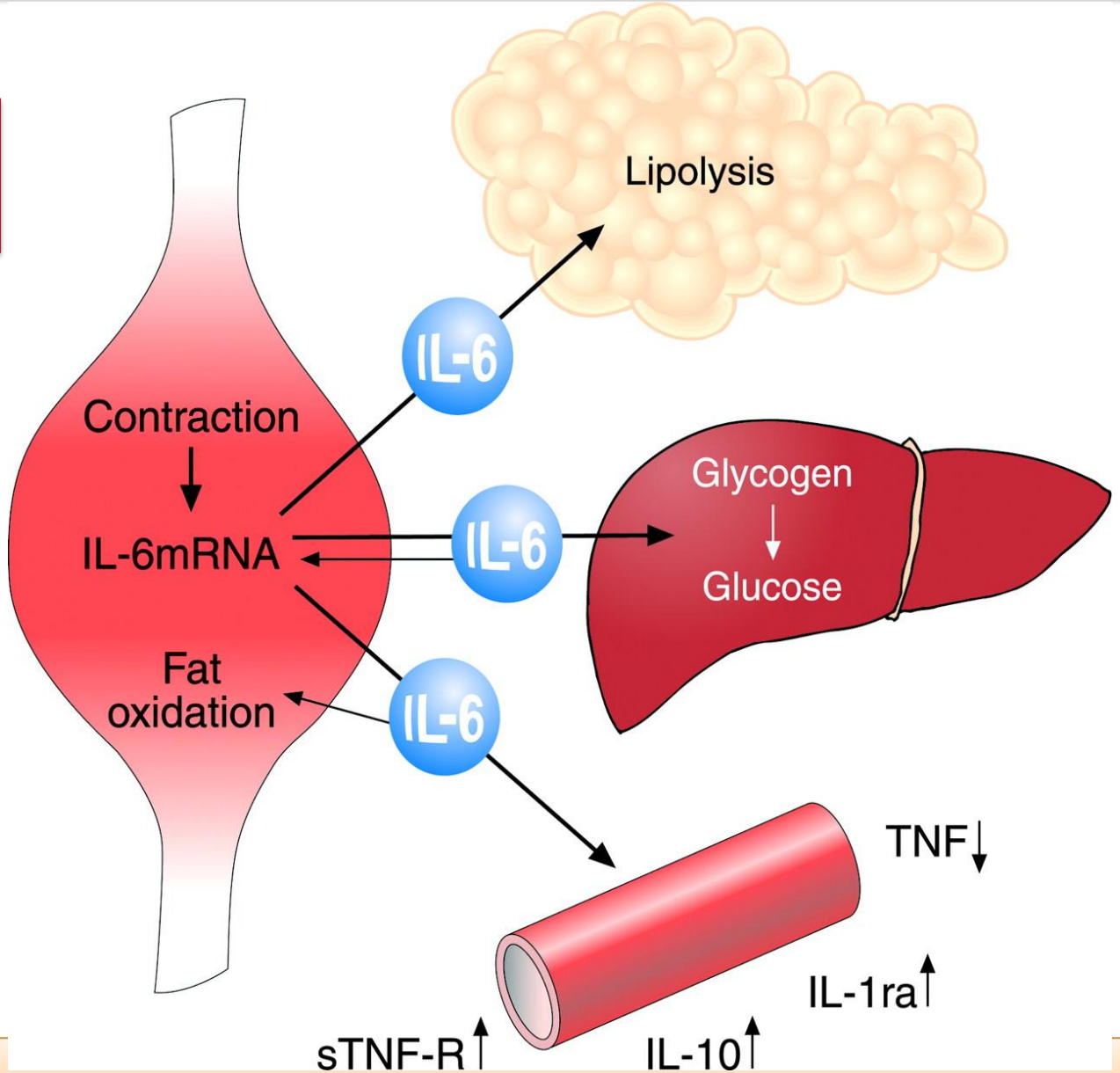
OUTROS:

- CLOCK
- ADRBs e UCP1 → especialmente mulheres

Polimorfismo IL-6

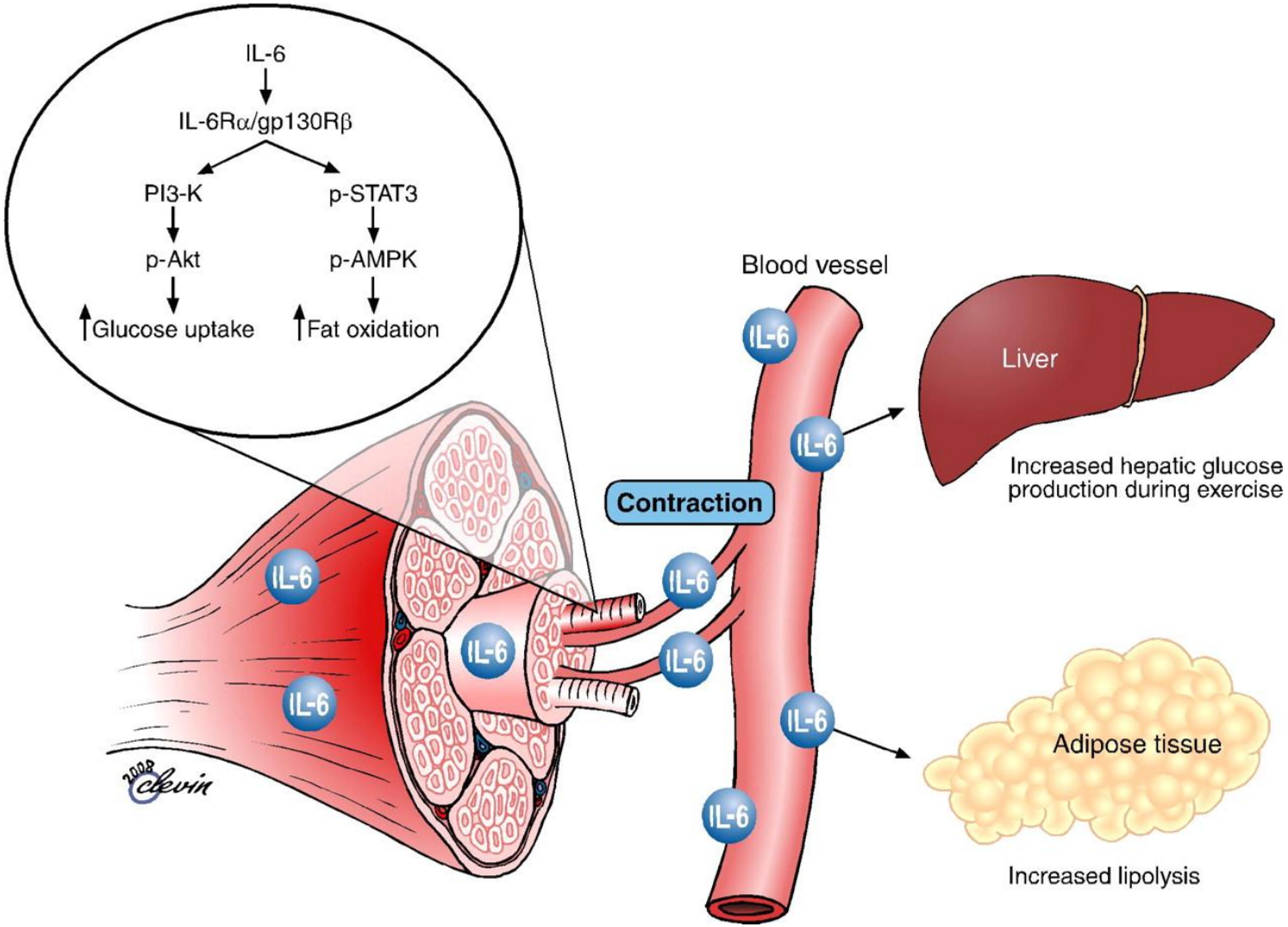
IL-6 (rs1800795)

Alelo de risco: G (maiores níveis)



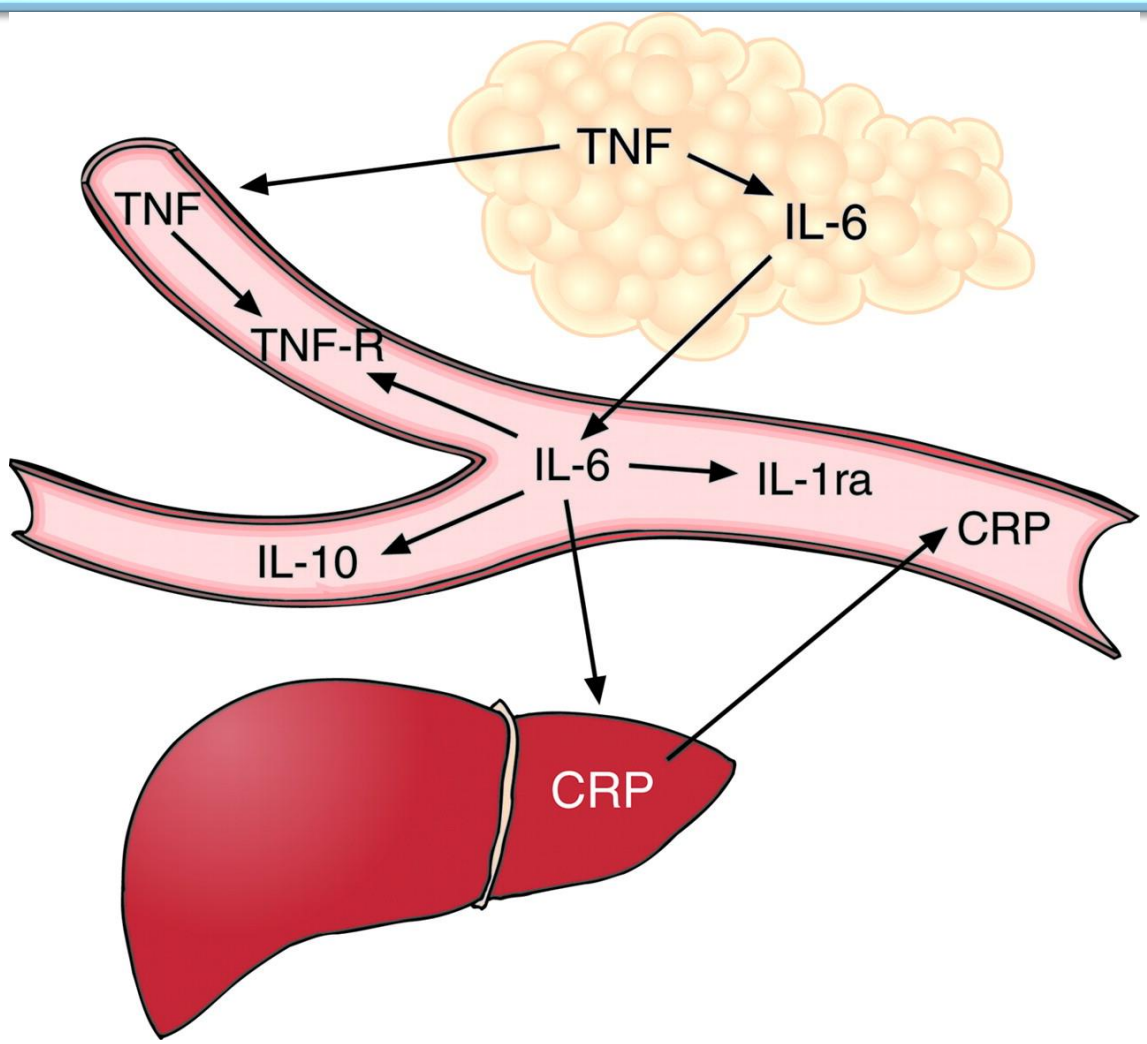
Journal of Applied Physiology. 2005 **Vol.** 98 **no.** 4, 1154-1162

Polimorfismo IL-6



Physiological Reviews Published 1 October 2008 **Vol.** 88 **no.** 4, 1379-1406

Chronic low-grade systemic inflammation.



Indicadores do polimorfismo:

NÍVEIS ALTOS

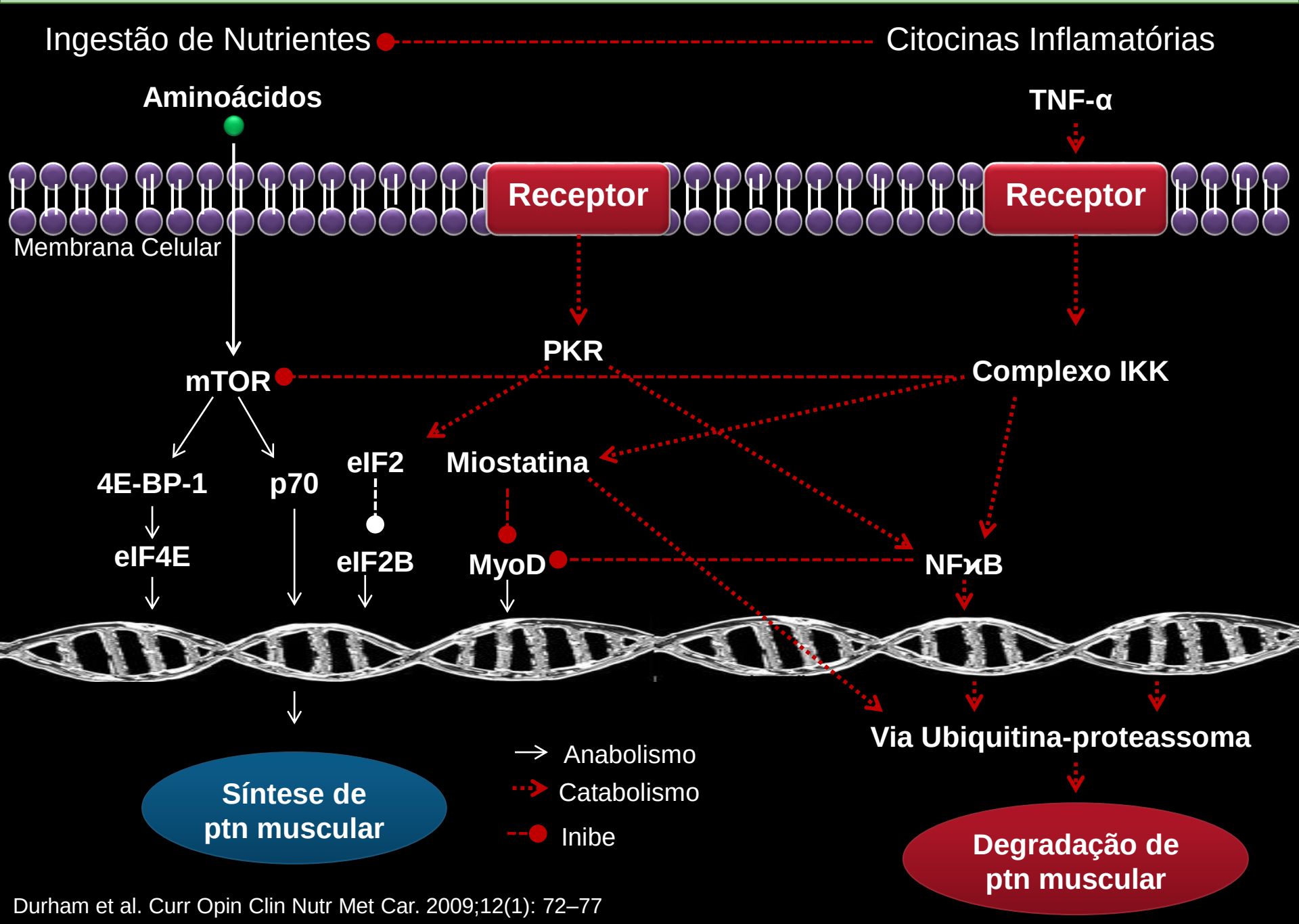
PCR
Hb1Ac

Anne Marie W. Petersen, and Bente Klarlund Pedersen J Appl Physiol 2005;98:1154-1162

Journal of Applied Physiology

©2005 by American Physiological Society

Anabolismo Proteico vs Catabolismo Proteico



Durham et al. Curr Opin Clin Nutr Met Car. 2009;12(1): 72–77

Sono e Hipertrofia

Melatonin feedback on clock genes: a theory involving the proteasome.

Vriend J[1], Reiter RJ.

Author information

Abstract

The expression of 'clock' genes occurs in all tissues, but especially in the suprachiasmatic nuclei (SCN) of the hypothalamus, groups of neurons in the brain that regulate circadian rhythms. Melatonin is secreted by the pineal gland in a circadian manner as influenced by the SCN. There is also considerable evidence that melatonin, in turn, acts on the SCN directly influencing the circadian 'clock' mechanisms. The most direct route by which melatonin could reach the SCN would be via the cerebrospinal fluid of the third ventricle. Melatonin could also reach the pars tuberalis (PT) of the pituitary, another melatonin-sensitive tissue, via this route. The major 'clock' genes include the period genes, Per1 and Per2, the cryptochrome genes, Cry1 and Cry2, the clock (circadian locomotor output cycles kaput) gene, and the Bmal1 (aryl hydrocarbon receptor nuclear translocator-like) gene. Clock and Bmal1 heterodimers act on E-box components of the promoters of the Per and Cry genes to stimulate transcription. A negative feedback loop between the cryptochrome proteins and the nucleus allows the Cry and Per proteins to regulate their own transcription. A cycle of ubiquitination and deubiquitination controls the levels of CRY protein degraded by the proteasome and, hence, the amount of protein available for feedback. Thus, it provides a post-translational component to the circadian clock mechanism. BMAL1 also stimulates transcription of REV-ERBα and, in turn, is also partially regulated by negative feedback by REV-ERBα. In the 'black widow' model of transcription, proteasomes destroy transcription factors that are needed only for a particular period of time. In the model proposed herein, the interaction of melatonin and the proteasome is required to adjust the SCN clock to changes in the environmental photoperiod. In particular, we predict that melatonin inhibition of the proteasome interferes with negative feedback loops (CRY/PER and REV-ERBα) on Bmal1 transcription genes in both the SCN and PT. Melatonin inhibition of the proteasome would also tend to stabilize BMAL1 protein itself in the SCN, particularly at night when melatonin is naturally elevated. Melatonin inhibition of the proteasome could account for the effects of melatonin on circadian rhythms associated with molecular timing genes. The interaction of melatonin with the proteasome in the hypothalamus also provides a model for explaining the dramatic 'time of day' effect of melatonin injections on reproductive status of seasonal breeders. Finally, the model predicts that a proteasome inhibitor such as bortezomib would modify circadian rhythms in a manner similar to melatonin.

Proantocianidinas e genes CLOCK

Mol Nutr Food Res. 2015 May;59(5):865-78. doi: 10.1002/mnfr.201400571. Epub 2015 Mar 23.

Dietary proanthocyanidins modulate melatonin levels in plasma and the expression pattern of clock genes in the hypothalamus of rats.

Ribas-Latre A[1], Del Bas JM, Baselga-Escudero L, Casanova E, Arola-Arnal A, Salvadó MJ, Arola L, Bladé C.

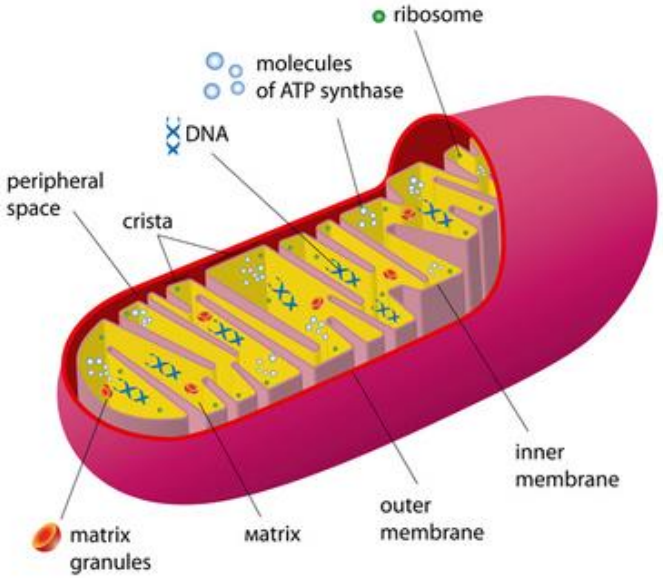
Sci Rep. 2015 Jun 8;5:10954. doi: 10.1038/srep10954.

Dietary proanthocyanidins modulate BMAL1 acetylation, Nampt expression and NAD levels in rat liver.

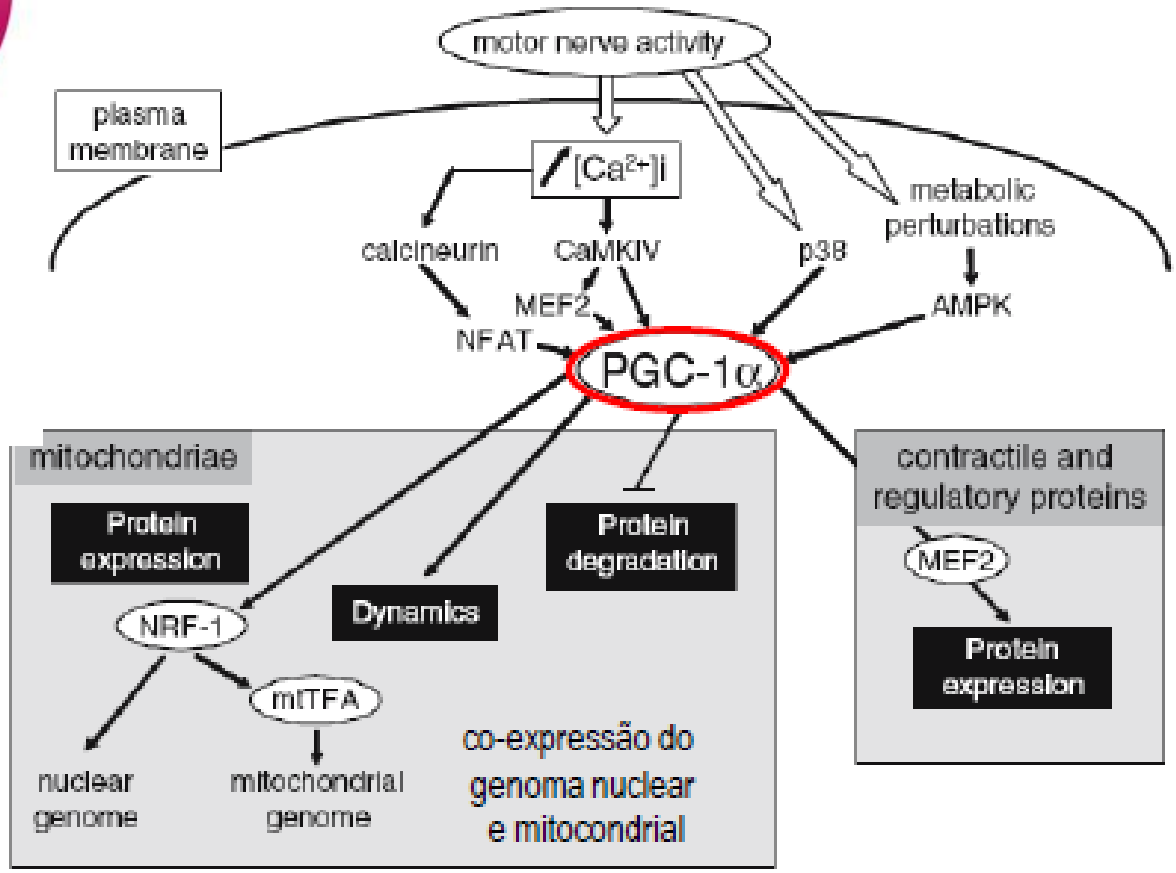
Ribas-Latre A[1], Baselga-Escudero L[1], Casanova E[1], Arola-Arnal A[1], Salvadó MJ[1], Bladé C[1], Arola L[1].

Fontes: canela, cacau, cranberry e frutas vermelhas

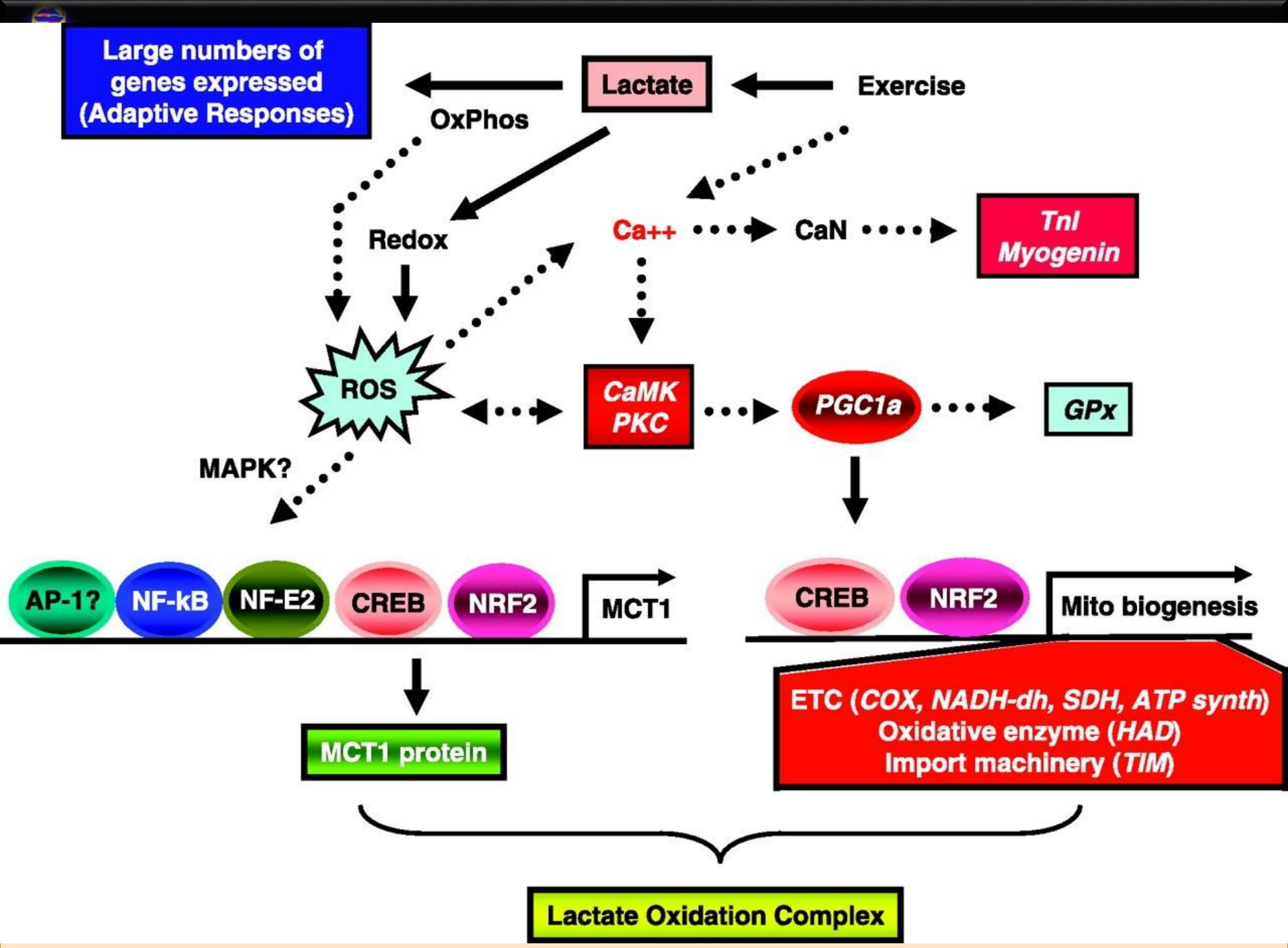
Mitocôndria



Mitochondrion



Koulmann N; Bigard AX. Pflugers Arch - Eur J Physiol., 452: 125–139, 2006


Large numbers of genes expressed (Adaptive Responses)
Lactate
Exercise
OxPhos
Redox
Ca++
CaN
TnI
Myogenin
ROS
CaMK
PKC
PGC1a
GPx
MAPK?
AP-1?
NF-kB
NF-E2
CREB
NRF2
MCT1
CREB
NRF2
Mito biogenesis
MCT1 protein
ETC (COX, NADH-dh, SDH, ATP synth)
Oxidative enzyme (HAD)
Import machinery (TIM)
Lactate Oxidation Complex

Polimorfismo GCK

GCK (rs4607517)

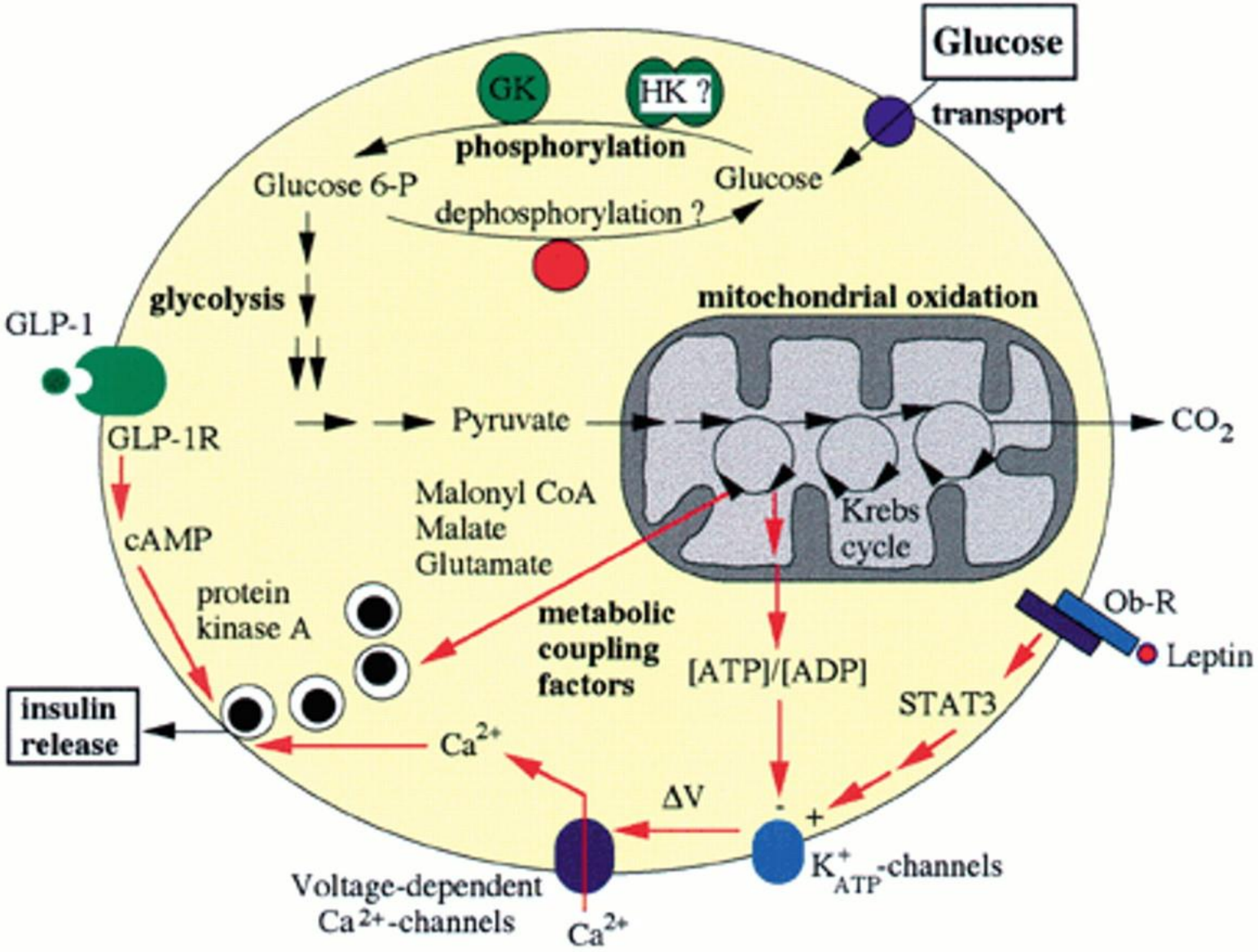
- **Alelo de risco: A (ALTA secreção de insulina)**

Diabete tipo Mody (maturity-onset diabetes of the Young)
Apoptose de células beta
Atenção: Hipoglicemia de rebote

Estratégias:

- Dieta: baixa carga glicêmica + fibras
- Suplementos: vitaminas e minerais reguladores + regulador da sensibilidade (com cuidado)

Polimorfismo GCK



PHYTOTHERAPY RESEARCH
Phytother. Res. **29**: 1032–1039 (2015)
Published online 21 April 2015 in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/ptr.5343

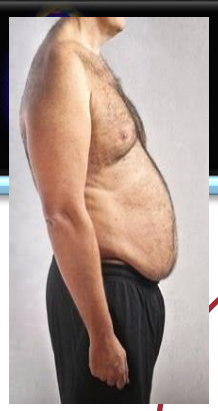
Effect of *Zingiber officinale* Supplementation on Obesity Management with Respect to the Uncoupling Protein 1 -3826A>G and ß3-adrenergic Receptor Trp64Arg Polymorphism

Vahideh Ebrahimzadeh Attari[1] Mohammad Asghari Jafarabadi,[2] Maryam Zemestani[1] and Alireza Ostadrahimi[1]*

[1]Nutrition Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Road Traffic Injury Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

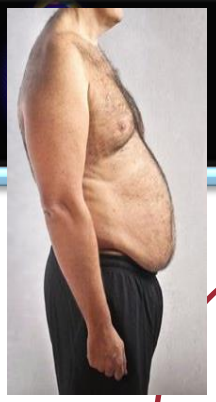
Suplementação: 2g durante 12 semanas

Modulou o polimorfismo em ADRB3 e UCP1



Perfil 3

- Ansiedade e estresse→ compulsão noturna
- Excesso de bebida alcoólica
- Viciado em massas e doces
- Não consegue se organizar para os horários das refeições e exercício físico
- Insônia → Acorda fadigado
- Condições clínicas: resistência à insulina, esteatose hepática, dislipidemia, hiperuricemia, refluxo gastroesofágico.



Caso 1 Perfil 3

Perfil de polimorfismos genéticos comuns:

- FTO
- PPARG
- ADRBs

OUTROS:

- CLOCK
- GST
- SOD

Curr Oncol Rep (2016) 18:43
DOI 10.1007/s11912-016-0529-6

INTEGRATIVE CARE (C LAMMERSFELD, SECTION EDITOR)

A Novel Approach to the Nutrigenetics and Nutrigenomics of Obesity and Weight Management

Yael T. Joffe[1,2] · Christine A. Houghton[3]

Genes que regulam a ingestão alimentar	Genes que regulam o metabolismo lipídico e adipogênese	Genes que regulam a termogênese	Genes relacionados com inflamação	Fatores de Transcrição
MC3R, MC4R, POMC, LEP, LEPR, FTO	**PLIN1, APOA5, LIPC, FABP2**	**ADBRs, UCPs**	**ADIPOQ, IL6**	PPARG, TCF7L2, CLOCK

FTO (*fat mass and obesity associated*)

Mais conhecido: rs9939609 (A/T)

FTO: alelo A

- Maior apetite
- Piores escolhas
- Perda de controle da ingestão
- Menor saciedade

Hum Mol Genet. 2014 Dec 20;23(25):6961-72

FTO (*fat mass and obesity associated*)

FTO:
alelo A

- Maior adipogênese: maior ativação de PPARG
- Redução de UCP1: menor termogênese
- Menos mitocôndrias
- Aumento da gliconeogênese
- Níveis altos de grelina = fome
- Tendência ao aumento de prolactina
- Alteração do ciclo circadiano

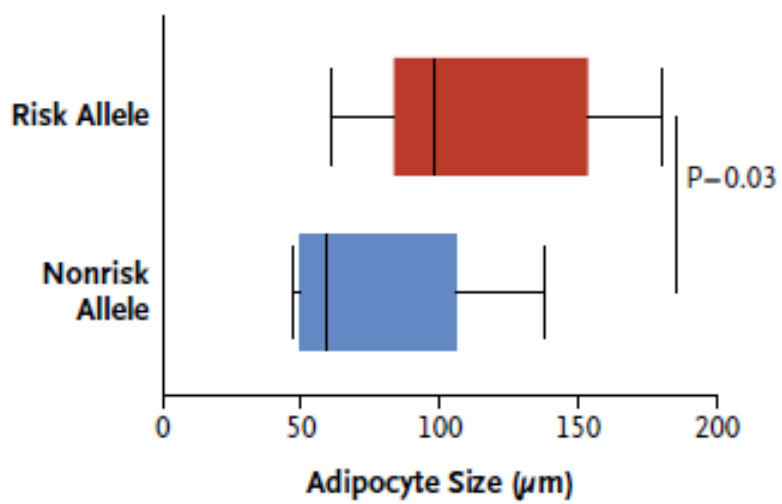
Zhao X, Yang Y, Sun BF, Zhao YL, Yang YG. FTO and obesity: mechanisms of association. Curr Diab Rep. 2014;14(5):486.

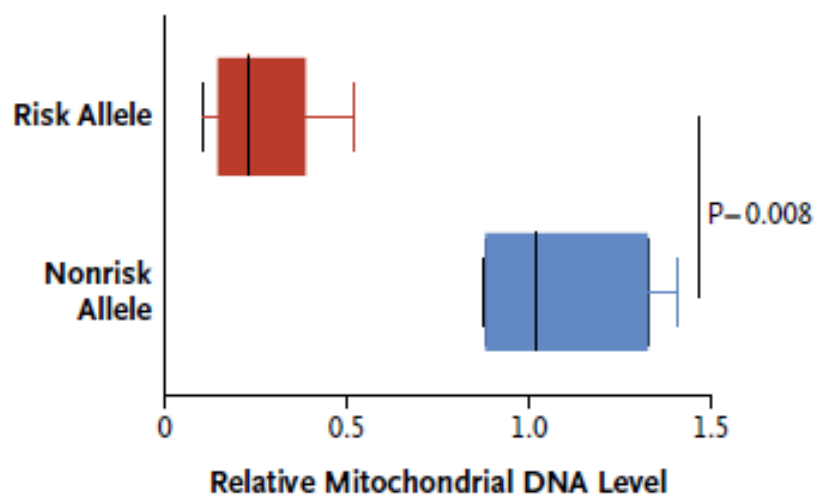
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 3, 2015 VOL. 373 NO. 10

FTO Obesity Variant Circuitry and Adipocyte Browning in Humans

Melina Claussnitzer, Ph.D., Simon N. Dankel, Ph.D., Kyoung-Han Kim, Ph.D., Gerald Quon, Ph.D., Wouter Meuleman, Ph.D., Christine Haugen, M.Sc., Viktoria Glunk, M.Sc., Isabel S. Sousa, M.Sc., Jacqueline L. Beaudry, Ph.D., Vijitha Puviindran, B.Sc., Nezar A. Abdennur, M.Sc., Jannel Liu, B.Sc., Per-Arne Svensson, Ph.D., Yi-Hsiang Hsu, Ph.D., Daniel J. Drucker, M.D., Gunnar Mellgren, M.D., Ph.D., Chi-Chung Hui, Ph.D., Hans Hauner, M.D., and Manolis Kellis, Ph.D.





E a resposta ao exercício?

Original Paper DOI: 10.5604/20831862.1198209 Biol. Sport 2016;33:117-126

A genetic-based algorithm for personalized resistance training

High genetic-risk individuals benefit less from resistance exercise intervention

Y C Klimentidis, J W Bea, T Lohman, P-S Hsieh, S Going, Z Chen

Cite this article as: Y C Klimentidis, J W Bea, T Lohman, P-S Hsieh, S Going, Z Chen, High genetic-risk individuals benefit less from resistance exercise intervention, *International Journal of Obesity* accepted article preview 30 April 2015; doi: 10.1038/ijo.2015.78.

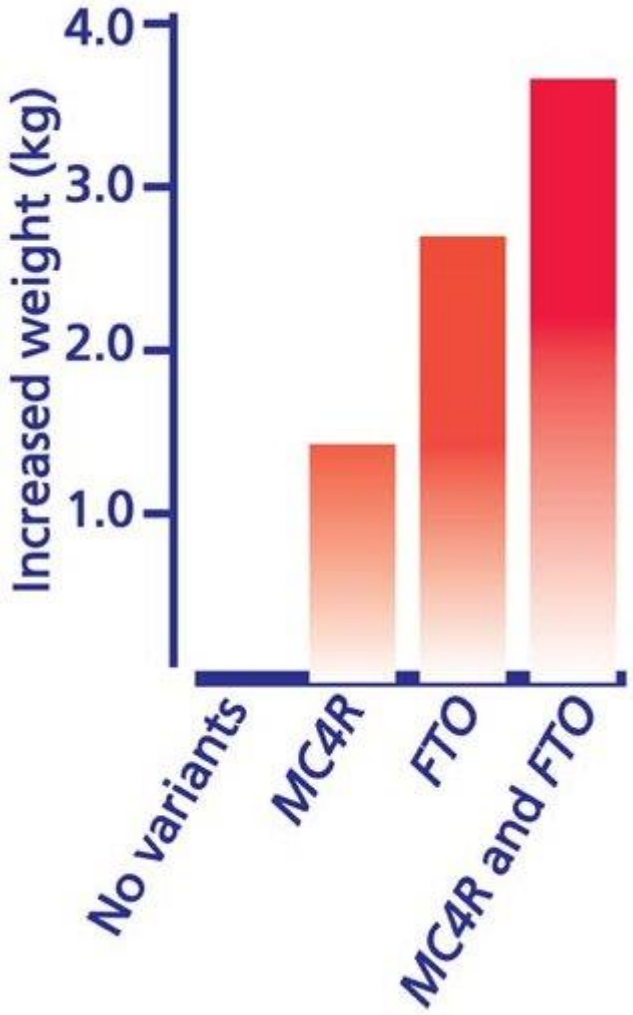
Table 1: List of single nucleotide polymorphisms (SNPs).

SNP	Nearest Gene	Minor Allele	Minor Allele Frequency	Other Allele	Risk allele	Weight*
rs10150332	*NRXN3*	C	0.25	T	C	0.13
rs10938397	*GNPDA2*	G	0.44	A	G	0.18
rs10968576	*LRRN6C*	G	0.32	A	G	0.11
rs11847697	*PRKD1*	T	0.04	C	T	0.17
rs12444979	*GPRC5B*	T	0.09	C	C	0.17
rs13107325	*SLC39A8*	T	0.06	C	T	0.19
rs1558902	*FTO*	A	0.38	T	A	0.39
rs2112347	*FLJ35779*	G	0.41	T	T	0.1
rs2241423	*MAP2K5*	A	0.27	G	G	0.13
rs2287019	*QPCTL-GIPR*	T	0.23	C	C	0.15
rs2815752	*NEGR1*	C	0.35	T	A	0.13
rs2890652	*LRP1B*	C	0.15	T	C	0.09
rs3817334	*MTCH2*	T	0.47	C	T	0.06
rs4771122	*MTIF3*	G	0.22	A	G	0.09
rs4836133	*ZNF608*	A	0.42	C	A	0.07
rs4929949	*RPL27A*	T	0.48	C	C	0.06
rs543874	*SEC16B*	G	0.19	A	G	0.22
rs7138803	*FAIM2*	A	0.35	G	A	0.12
rs887912	*FANCL*	A	0.28	G	T	0.1
rs9816226	*ETV5*	A	0.19	T	T	0.14
rs987237	*TFAP2B*	G	0.20	A	G	0.13

*weight refers to the SNP coefficient estimated in Speliotes et al. [8]

manuscript

Perfil Genético Desfavorável?



FTO: AA ou AT
MC4R: CC ou CT
PGC1A: AA ou AG
PPARG: CC (para risco de DM)

Características:
Efeito sanfona
Perda de motivação
Altos níveis de cortisol
Resistência à insulina
Compulsão alimentar

Nature Genetics [2008, 40(6):768-775]

Quais são as estratégias?

Ômega-3 e 9

Tratar intestino

Especiarias: canela, cúrcuma

Aumentar fibras: biomassa de banana verde, Psyllium (4-8g), batata yacon

Carboidratos de baixa carga glicêmica

Melhorar qualidade do sono: melatonina

Ciclo Circadiano e Gordura Corporal

Obesity (Silver Spring). 2017 May;25(5):873-880. doi: 10.1002/oby.21807.

Ability to adjust nocturnal fat oxidation in response to overfeeding predicts 5-year weight gain in adults.

Rynders CA[1], Bergouignan A[2,3], Kealey E[2], Bessesen DH[2,3,4].

Author information

Abstract

OBJECTIVE: To determine whether metabolic responses to short-term overfeeding predict longitudinal changes in body weight.

METHODS: Twenty-four-hour energy expenditure (EE) and substrate utilization were measured at baseline in a room calorimeter following 3 days of eucaloric and hypercaloric feeding (40% excess) in a sample of lean adults (n: 34; age: 28 ± 2 y; BMI: 22 ± 3 kg/m^2). Body mass and fat mass (dual-energy x-ray absorptiometry) were measured annually for 5 years. Regression analyses examined whether changes in EE and fuel use with overfeeding predicted body weight and composition changes over 5 years.

RESULTS: Overfeeding increased EE and reduced fat oxidation when examined over the 24-hour, waking, and nocturnal periods. Absolute change in body mass over 5 years was 3.0 ± 0.6 kg (average rate of change = 0.7 ± 0.1 kg/y, $P < 0.001$). Lower nocturnal (but not 24-hour or waking) fat oxidation ($r = -0.42$, $P = 0.01$) and EE ($r = -0.33$, $P = 0.05$) with overfeeding were the strongest predictors of 5-year weight gain. When adjusted for covariates, changes in nocturnal fat oxidation and EE with overfeeding predicted 41% of the variance in weight change ($P = 0.02$).

CONCLUSIONS: Failure to maintain fat oxidation at night following a period of overfeeding appears to be associated with a metabolic phenotype favoring weight gain.

EBioMedicine. 2016 May;7:100-11. doi: 10.1016/j.ebiom.2016.03.037. Epub 2016 Mar 31.

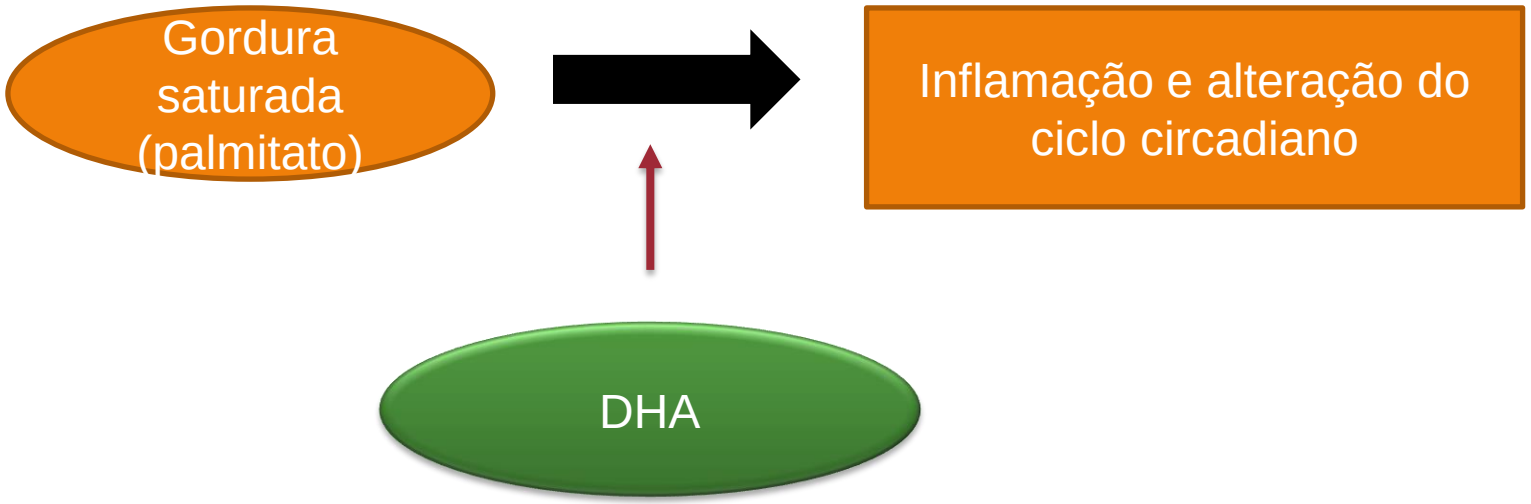
Role of Inflammatory Signaling in the Differential Effects of Saturated and Poly-unsaturated Fatty Acids on Peripheral Circadian Clocks.

Kim SM[1], Neuendorff N[2], Chapkin RS[3], Earnest DJ[4].

Author information

Abstract

Inflammatory signaling may play a role in high-fat diet (HFD)-related circadian clock disturbances that contribute to systemic metabolic dysregulation. Therefore, palmitate, the prevalent proinflammatory saturated fatty acid (SFA) in HFD and the anti-inflammatory, poly-unsaturated fatty acid (PUFA), docosahexaenoic acid (DHA), were analyzed for effects on circadian timekeeping and inflammatory responses in peripheral clocks. Prolonged palmitate, but not DHA, exposure increased the period of fibroblast Bmal1-dLuc rhythms. Acute palmitate treatment produced phase shifts of the Bmal1-dLuc rhythm that were larger in amplitude as compared to DHA. These phase-shifting effects were time-dependent and contemporaneous with rhythmic changes in palmitate-induced inflammatory responses. Fibroblast and differentiated adipocyte clocks exhibited cell-specific differences in the time-dependent nature of palmitate-induced shifts and inflammation. DHA and other inhibitors of inflammatory signaling (AICAR, cardamonin) repressed palmitate-induced proinflammatory responses and phase shifts of the fibroblast clock, suggesting that SFA-mediated inflammatory signaling may feed back to modulate circadian timekeeping in peripheral clocks.



Polimorfismos e desempenho esportivo

PPARD + PPARGC1A

T294C (rs2016520) e Gly482Ser (rs8192678)

PPARD + PPARGC1A

T294C → Alelo C: alta atividade transcricional do PPARD → conversão de fibras tipo II em tipo I

Physiol Genomics 43: 789–798, 2011.
First published May 3, 2011; doi:10.1152/physiolgenomics.00029.2011. Re

The champions' mitochondria: is it genetically determined? A review on mitochondrial DNA and elite athletic performance

Nir Eynon,[1]* María Morán,[2]* Ruth Birk,[1‡] and Alejandro Lucia[3‡]

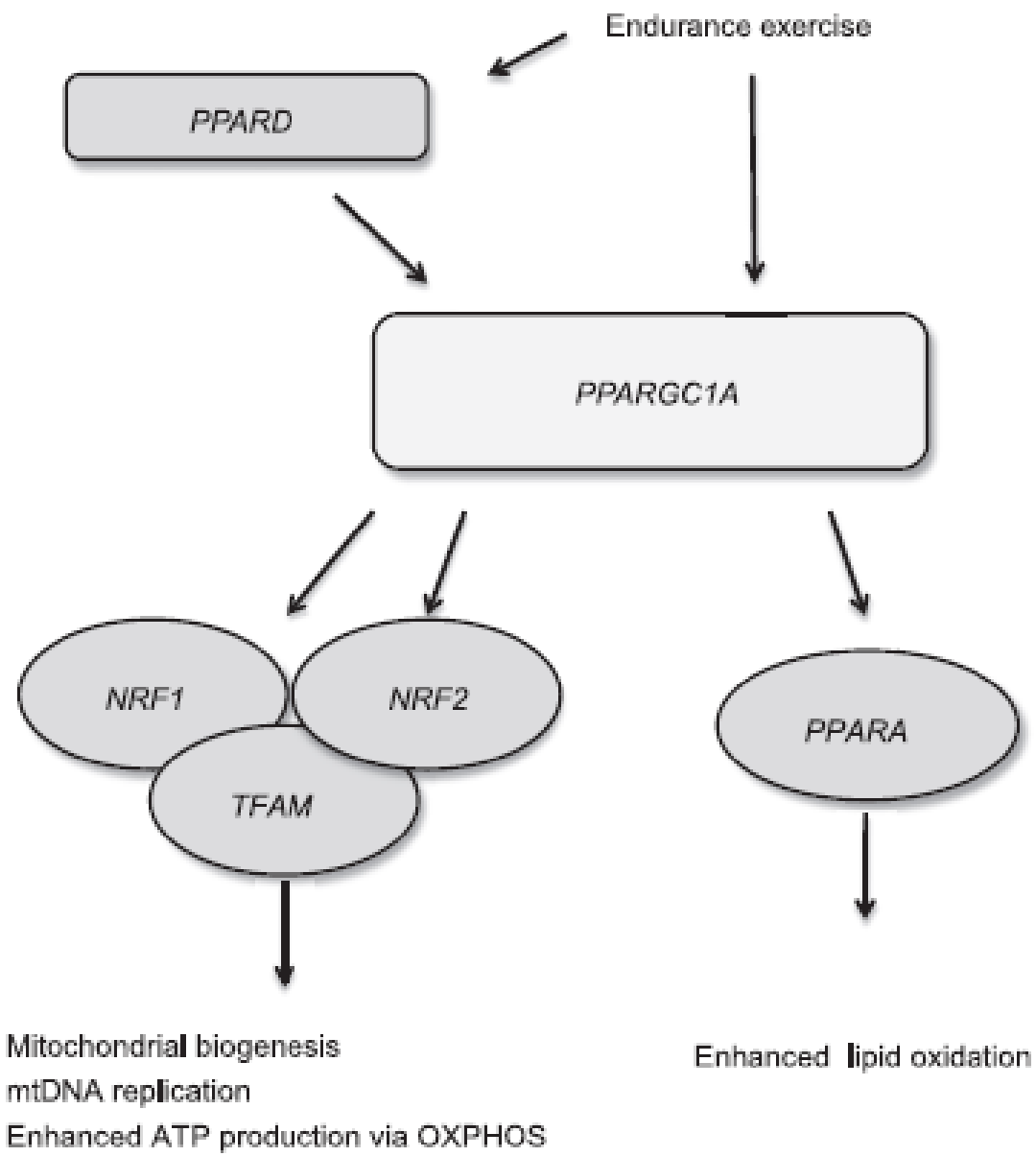
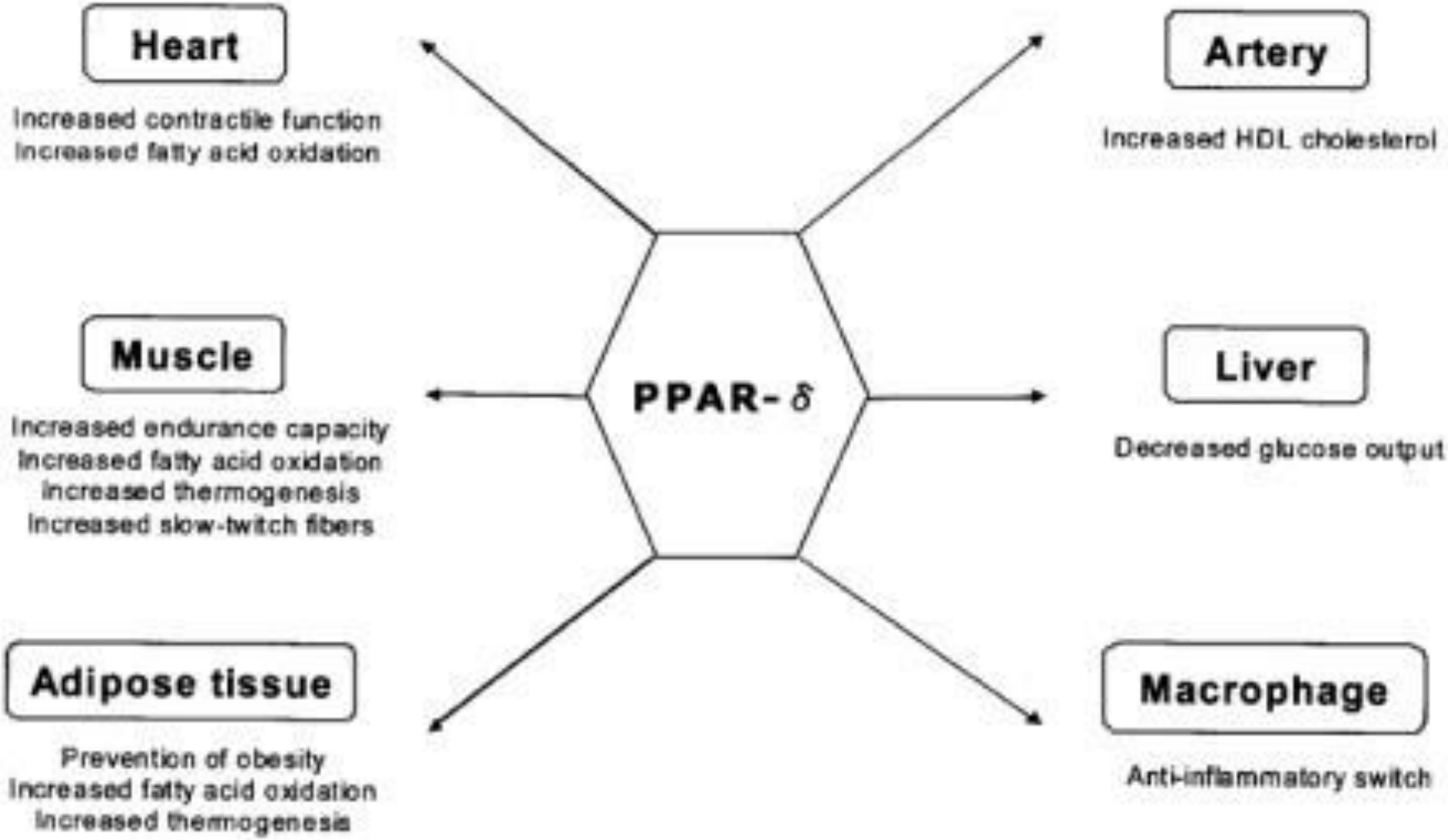


Fig. 1. Schematic representation of the main effects of the *PPARD-PPARGC1A-NRF-TFAM* pathway in endurance exercise phenotypes. mtDNA, mitochondrial DNA; OXPHOS, oxidative phosphorylation system.

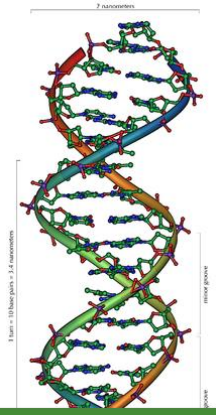

Heart
Increased contractile function
Increased fatty acid oxidation
Artery
Increased HDL cholesterol
Muscle
Increased endurance capacity
Increased fatty acid oxidation
Increased thermogenesis
Increased slow-twitch fibers
PPAR-δ
Liver
Decreased glucose output
Adipose tissue
Prevention of obesity
Increased fatty acid oxidation
Increased thermogenesis
Macrophage
Anti-inflammatory switch

Variação das necessidades nutricionais

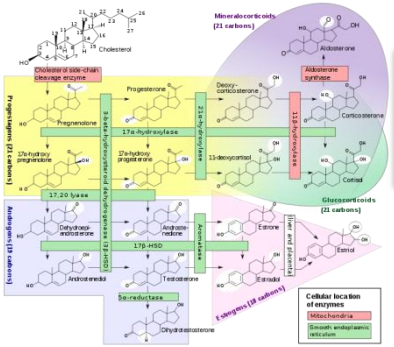
+

Interação dos nutrientes

+



Variações genéticas



Vias bioquímicas e metabólicas individualizadas

Diferentes necessidades para cada indivíduo

Simopoulos, A.P. Annu. Rev. Public Health 2010.

Raciocínio para a Prescrição Individualizada e Eficiente

Anamnese detalhada

- Histórico familiar
- Histórico de peso e “dietas”

Exames clínico, bioquímico e físico

Teste genético

- Identificar onde estão os “erros”

Quais estratégias diferentes devo tomar?
Primeiro passo: Estabelecer a prioridade!

ALVOS GENÉTICOS
E EPIGENÉTICOS:
ESTRATÉGIAS
NUTRICIONAIS
EFICIENTES
RITA CASTRO E LUCIANO BRUNO

Obrigada!

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