ENXAQUECA

Danielle Lodetti
NUTRICIONISTA

Fisiopatologia
Intervenção Nutricional e Fitoterápica

reViva
Alimente-se Bem. Viva Melhor.

A enxaqueca é um distúrbio de cefaléia **neurovascular** hereditária comum, multifatorial, incapacitante e recorrente.

Complexo distúrbio neurológico que ***afeta múltiplas áreas corticais, subcorticais e do tronco cerebral*** que regulam as funções autonômica, afetiva, cognitiva e sensorial

Curr Neurol Neurosci Rep. 2017 Feb;17(2):17. A Clinical Approach to Addressing Diet with Migraine Patients

The Journal of Neuroscience, April 29, 2015 35(17):6619–6629 • 6619

Critérios de diagnóstico IHS – indivíduos que tiveram pelo menos 2 episódios de enxaqueca com aura ou 5 episódios sem aura em 1 ano

Em média 15% da população entre 22- 55 anos. Maios prevalência em mulheres.

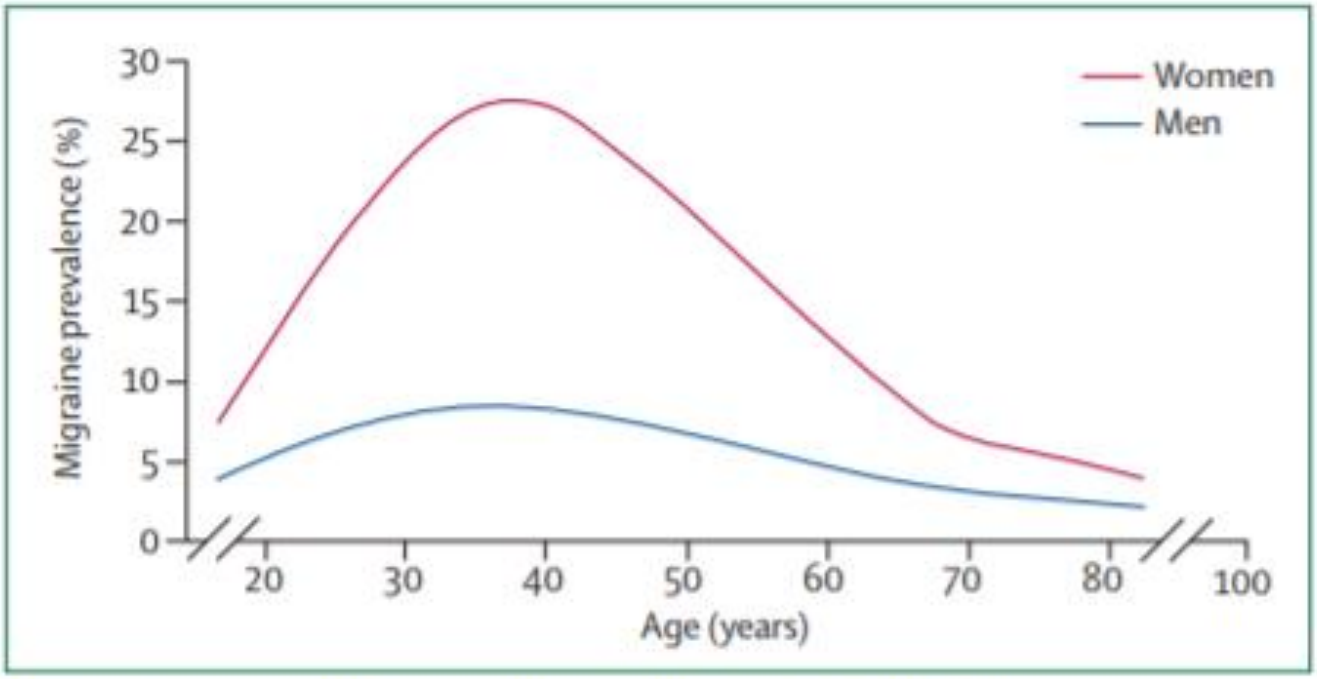


***Figure 5*: 1 year prevalence of migraine in the general population**

The Journal of Neuroscience, April 29, 2015 35(17):6619–6629 • 6619

Ferrari, M. D., Klever, R. R., Terwindt, G. M., Ayata, C., & van den Maagdenberg, A. M. J. M. (2015). *Migraine pathophysiology: lessons from mouse models and human genetics. The Lancet Neurology, 14(1), 65–80.* doi:10.1016/s1474-4422(14)70220-0

DISFUNÇÃO DE ***NERVOS E VASOS SANGUÍNEOS***

INCLUI VASODILATAÇÃO DAS ARTÉRIAS CEREBRAIS E MENINGEAIS

LIBERAÇÃO DE ***CGRP*** *PELO NERVO TRIGÊMEO*

(PEPTÍDEO RELACIONADO AO GENE DA CALCITONINA)

Nutrição Clínica Funcional: Neurologia. Bettina Moritz, Luana Meller Manosso. 2013

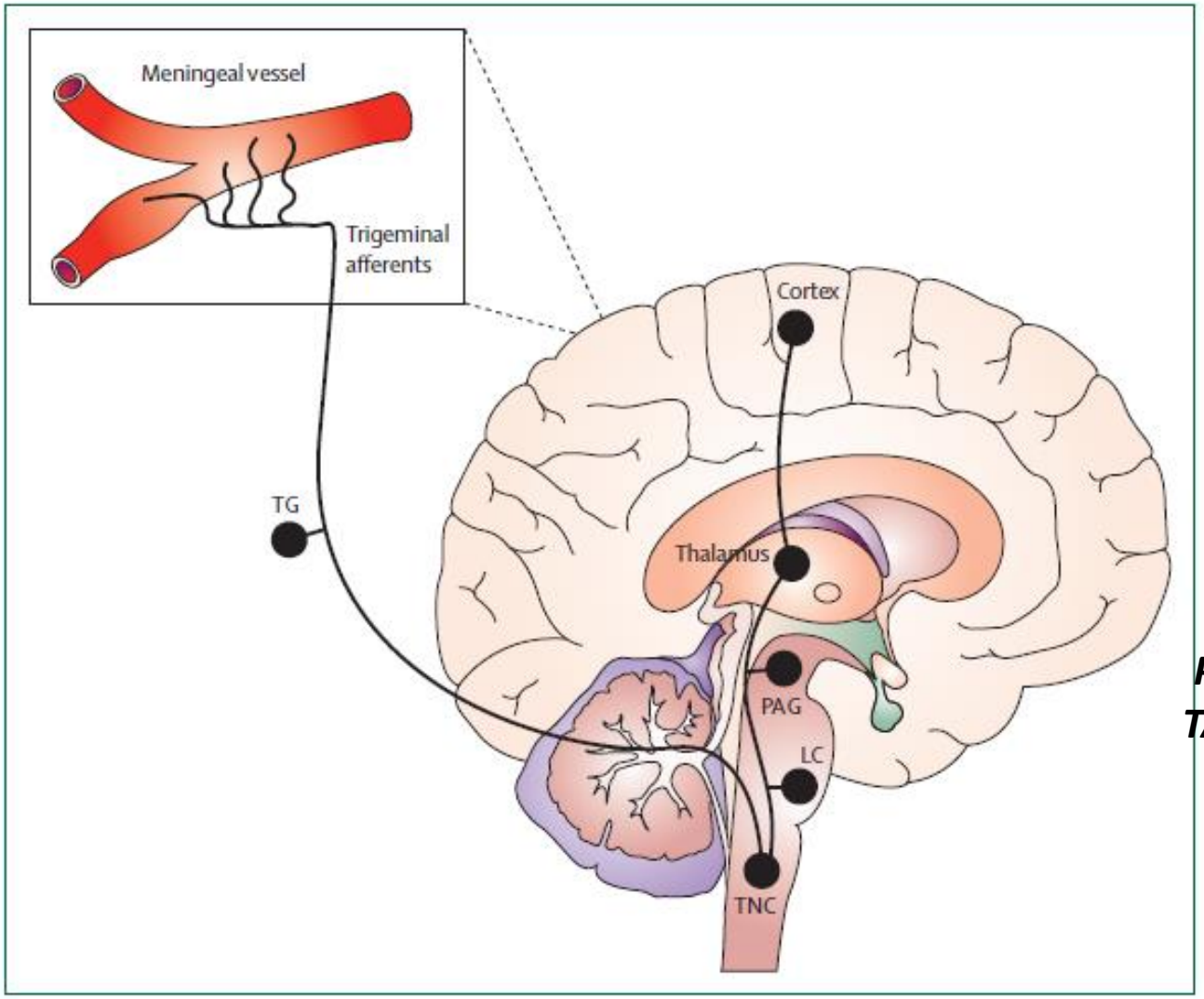


Figure 2: **Migraine headache is caused by activation of the trigeminovascular system**

SISTEMA TRIGEMINOVASCULAR

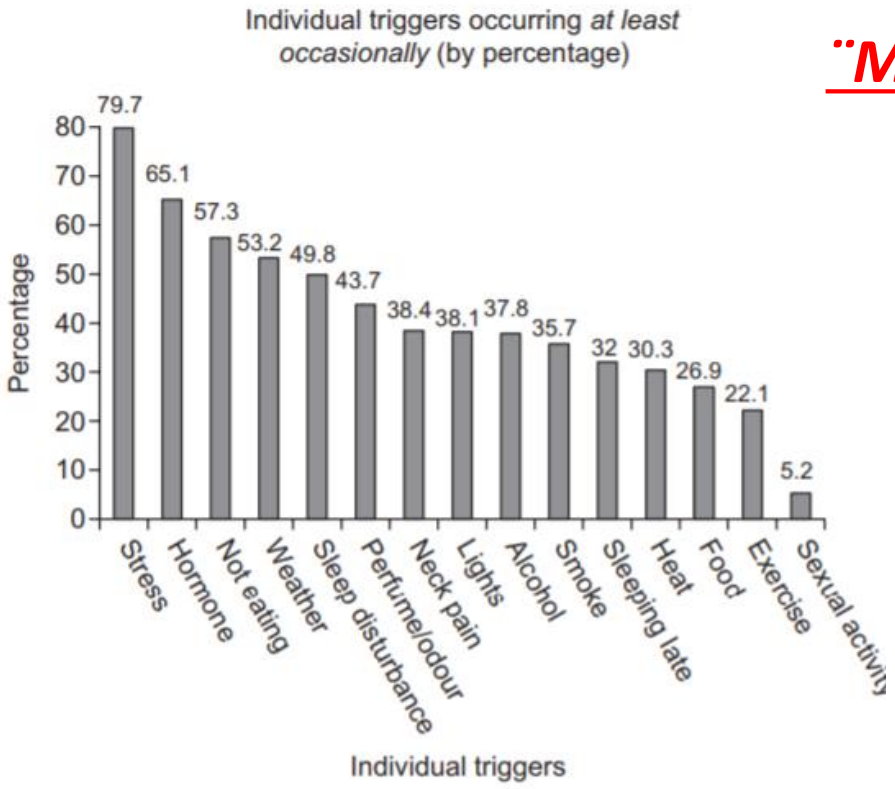
FIBRAS SENSORIAIS PRESENTES NOS VASOS SANGUÍNEOS CRANIANOS

PROJEÇÕES PARA O CÓRTEX, TÁLAMO , TRONCO CEREBRAL

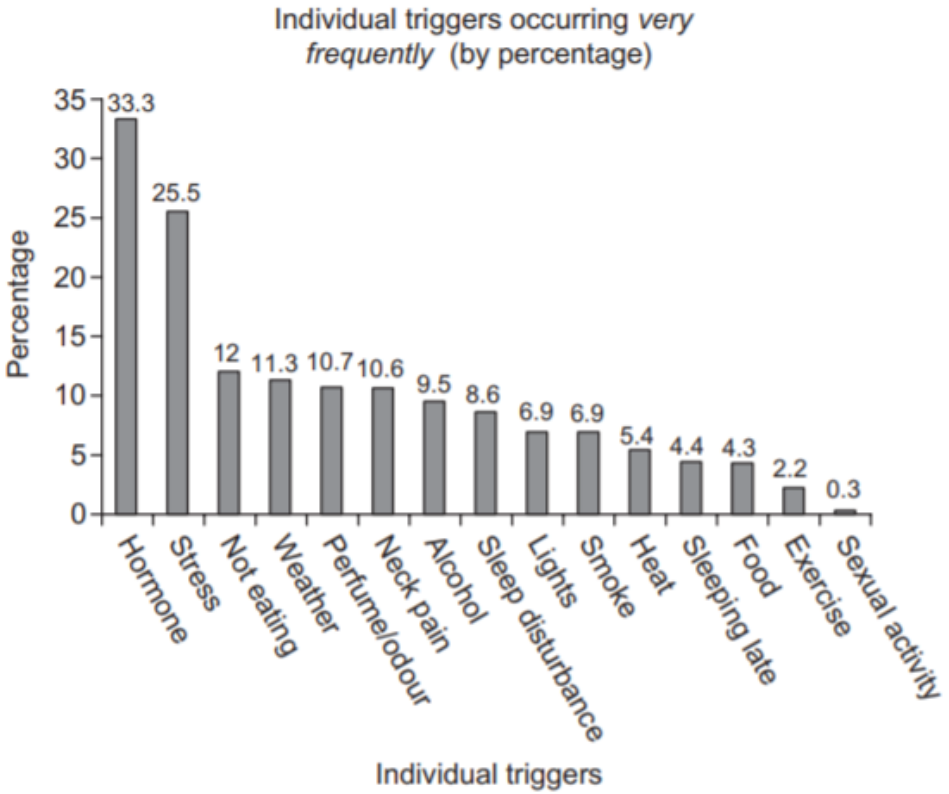
Ferrari, M. D., Klever, R. R., Terwindt, G. M., Ayata, C., & van den Maagdenberg, A. M. J. M. (2015). *Migraine pathophysiology: lessons from mouse models and human genetics. The Lancet Neurology, 14(1), 65–80.* doi:10.1016/s1474-4422(14)70220-0

A ENXAQUECA É CAUSADA PELA ATIVAÇÃO DO SISTEMA TRIGEMINAL

N = 1207 pacientes com Enxaqueca diagnosticada avaliados



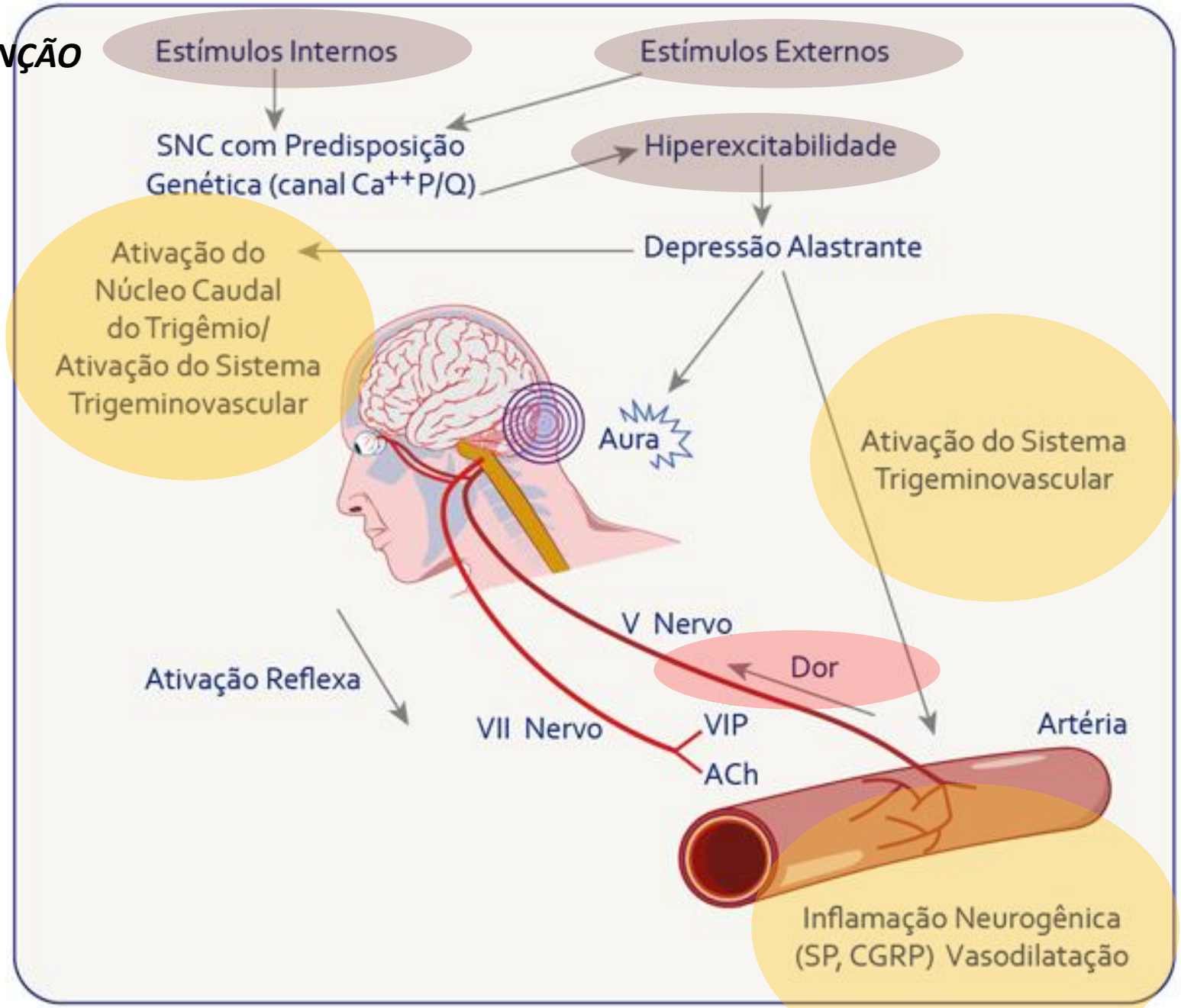
¨Management of triggers may be an important aspect of migraine management.¨



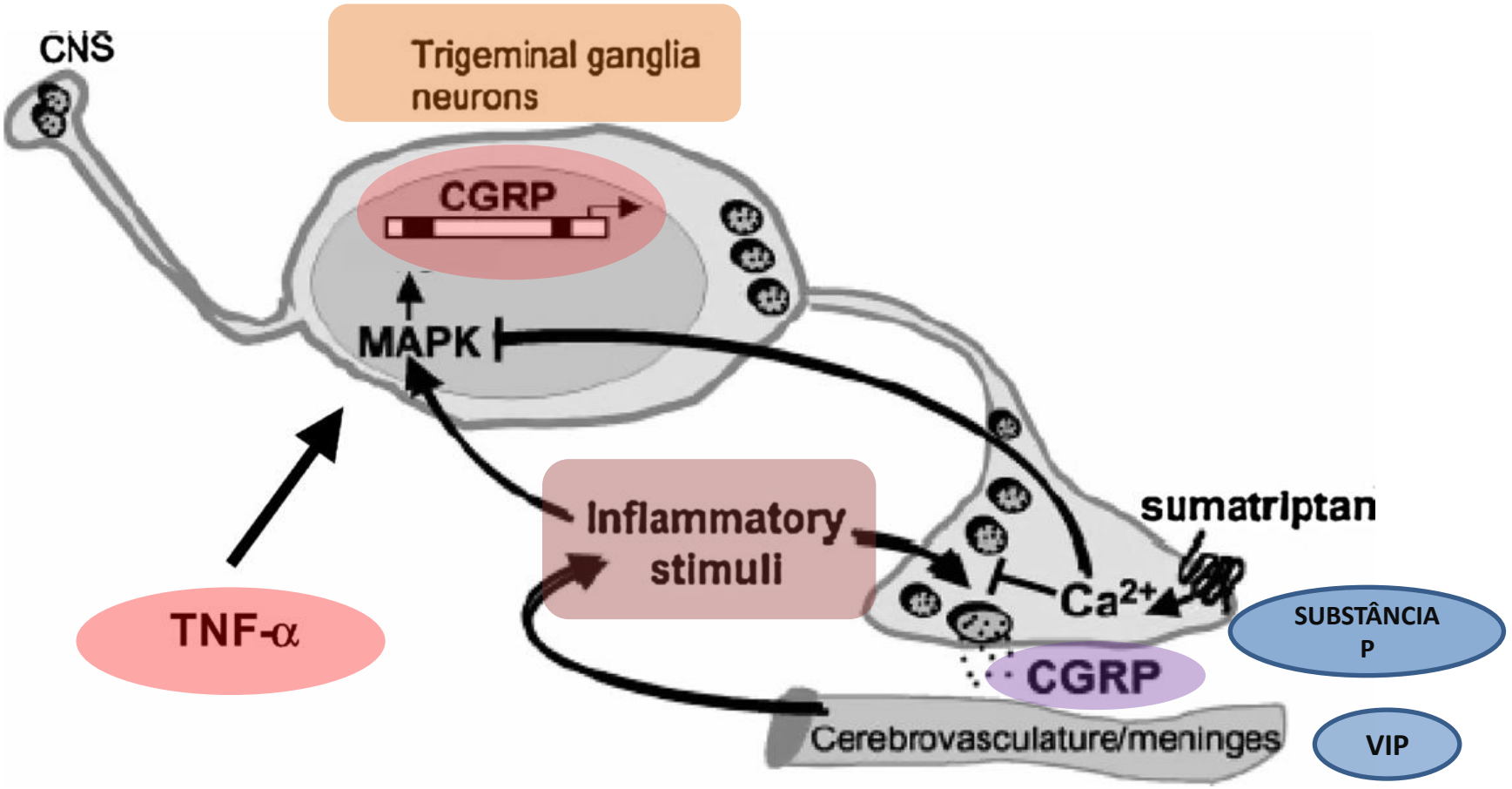
**** Hormônios – apenas mulheres***

Kelman, L. (2007). *The Triggers or Precipitants of the Ac*

DISFUNÇÃO


Estímulos Internos
Estímulos Externos
SNC com Predisposição Genética (canal Ca++P/Q)
Hiperexcitabilidade
Depressão Alastrante
Ativação do Núcleo Caudal do Trigêmio/ Ativação do Sistema Trigeminovascular
Aura
Ativação do Sistema Trigeminovascular
V Nervo
Dor
Ativação Reflexa
VII Nervo
VIP
ACh
Artéria
Inflamação Neurogênica (SP, CGRP) Vasodilatação

INFLAMAÇÃO ⇄ ENXAQUECA



Headache. 2006 Jun;46 Suppl 1:S3-8.
Calcitonin gene-related peptide (CGRP) and migraine.

CGRP

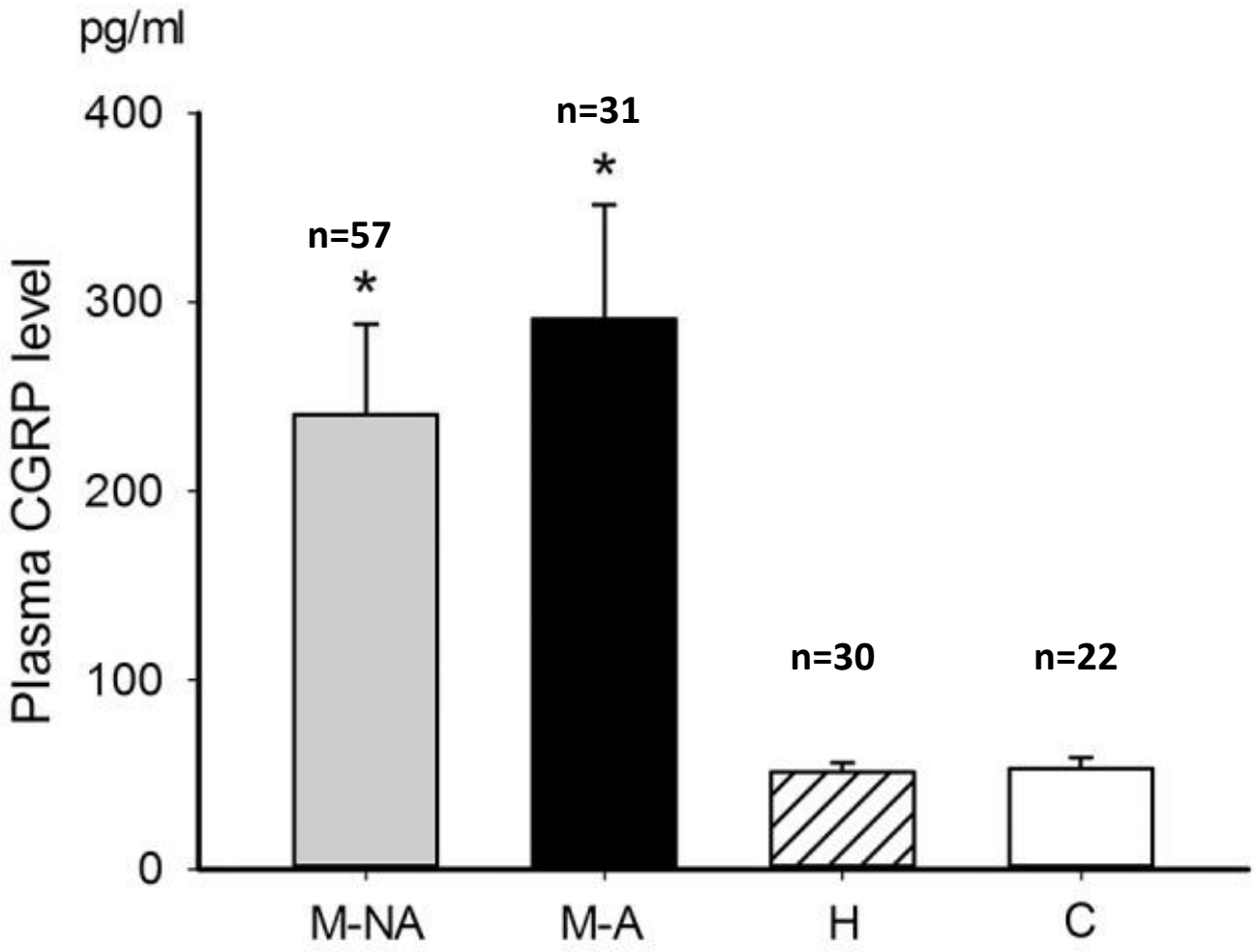
- NEUROPEPTÍDEO

- ***Activation of the trigeminal nerve causes CGRP to be released from perivascular nerve endings***

DUAS CATEGORIAS DE DROGAS ESTÃO SENDO DESENVOLVIDAS: ANTAGONISTAS DE CGRP E ANTICORPOS MONOCLONAIS COM ALVO NO CGRP OU EM SEUS RECEPTORES.

J Headache Pain. 2017; 18(1): 96.
Blocking CGRP in migraine patients – a review of pros and cons

Headache . 2006 June ; 46(Suppl 1): S3–S8.



Front Neurol. 2019 Jan 24;10:10. **Plasma Calcitonin Gene-Related Peptide: A Potential Biomarker for Diagnosis and Therapeutic Responses in Pediatric Migraine.**

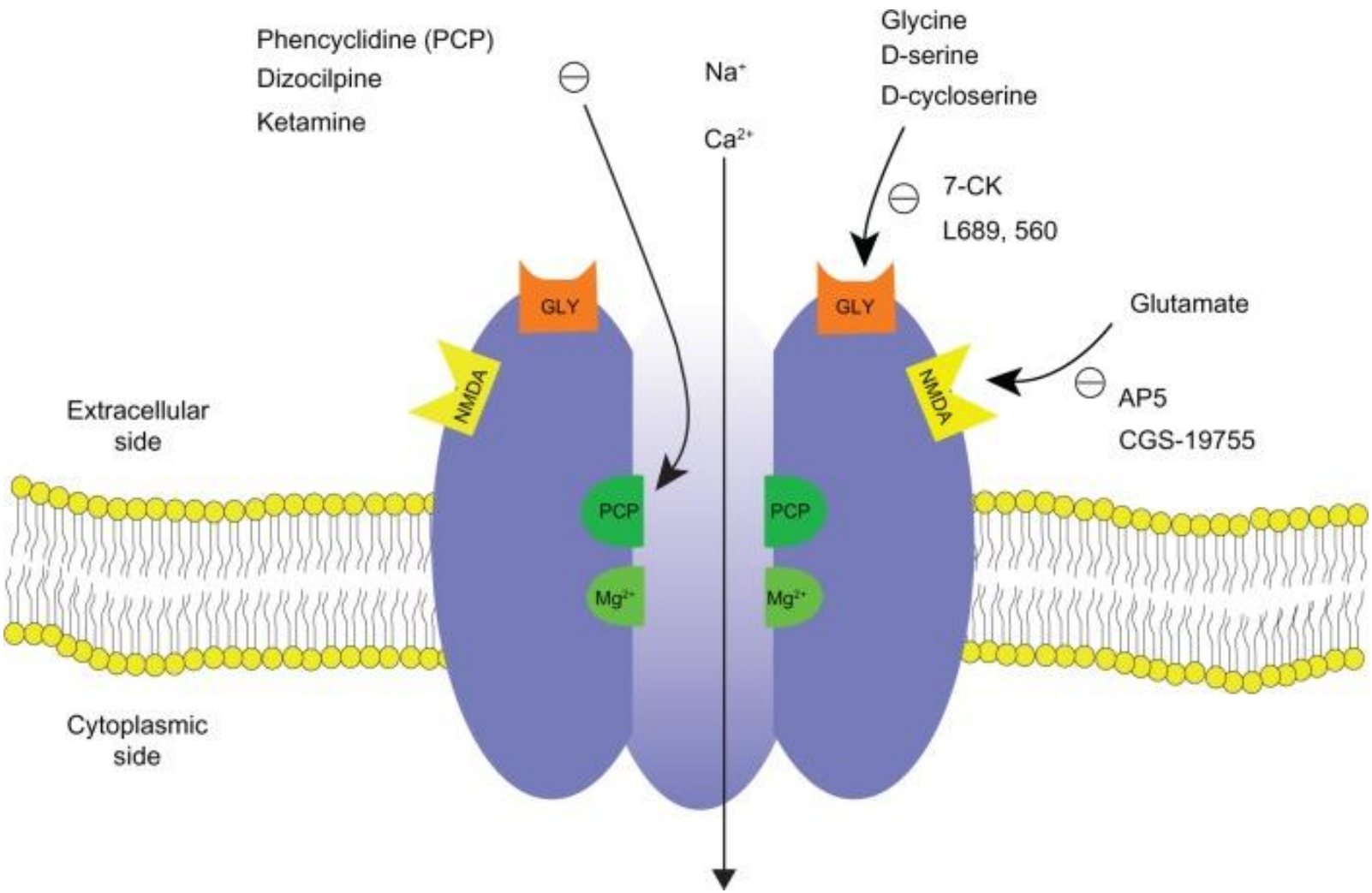
***Treatment for migraine can be divided into two broad categories: acute treatment for migraine attacks and prophylactic treatment to reduce the frequency of migraine attacks*.**

Magnesium as an Alternative or Adjunct to Opioids for Migraine and Chronic Pain: A Review of the Clinical Effectiveness and Guidelines [Internet]. : Canadian Agency for Drugs and Technologies in Health; 2017

1. HIPEREXCITABILIDADE NEURONAL

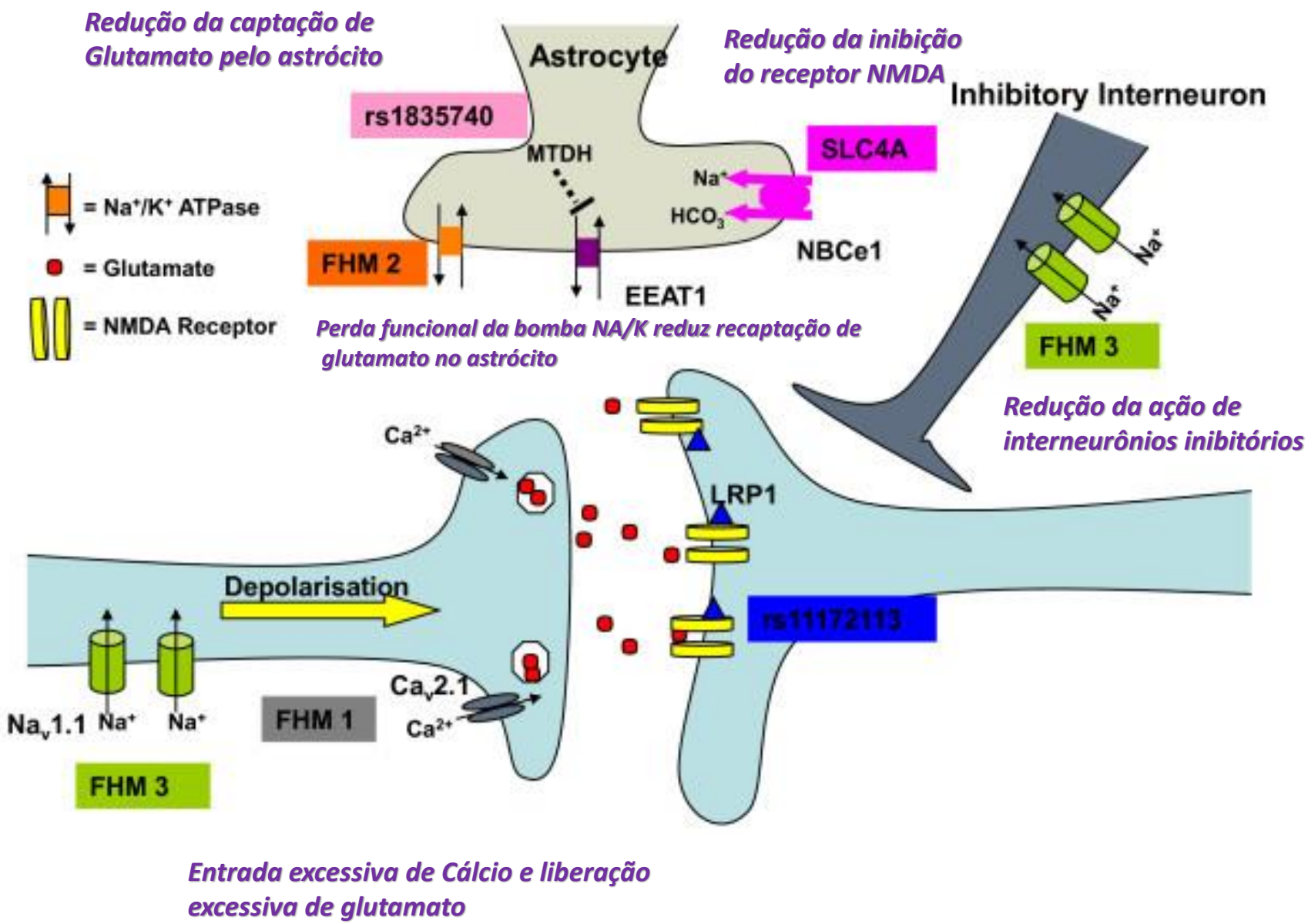
ATIVAÇÃO DOS NEURÔNIOS DO SISTEMA TRIGEMINAL

EXCESSO DE GLUTAMATO



Subst Abuse Rehabil. 2011; 2: 11–20.

To use or not to use: an update on licit and illicit ketamine use



BMC Med. 2011; 9: 116. 10.1186/1741-7015-9-116
Published online 2011 Oct New directions in migraine

RECEPTORES DE GLUTAMATO ESTÃO PRESENTES NOS NEURÔNIOS DO SISTEMA TRIGEMINAL

(2017). *Glutamate receptor antagonists with the potential for migraine treatment. Expert Opinion on Investigational Drugs, 26(12), 1321–1330.*

topiramate 50 mg/ day, five patients; amitriptyline 20 mg/day, seven patients; flunarizine 5 mg/day, seven patients; propranolol 80 mg/day, five patients

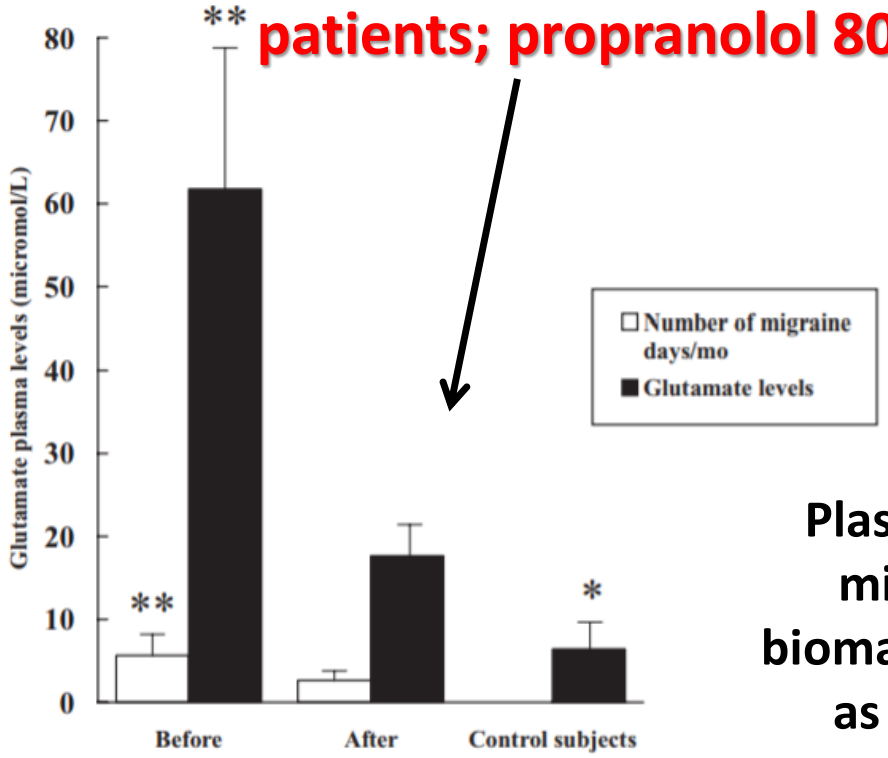
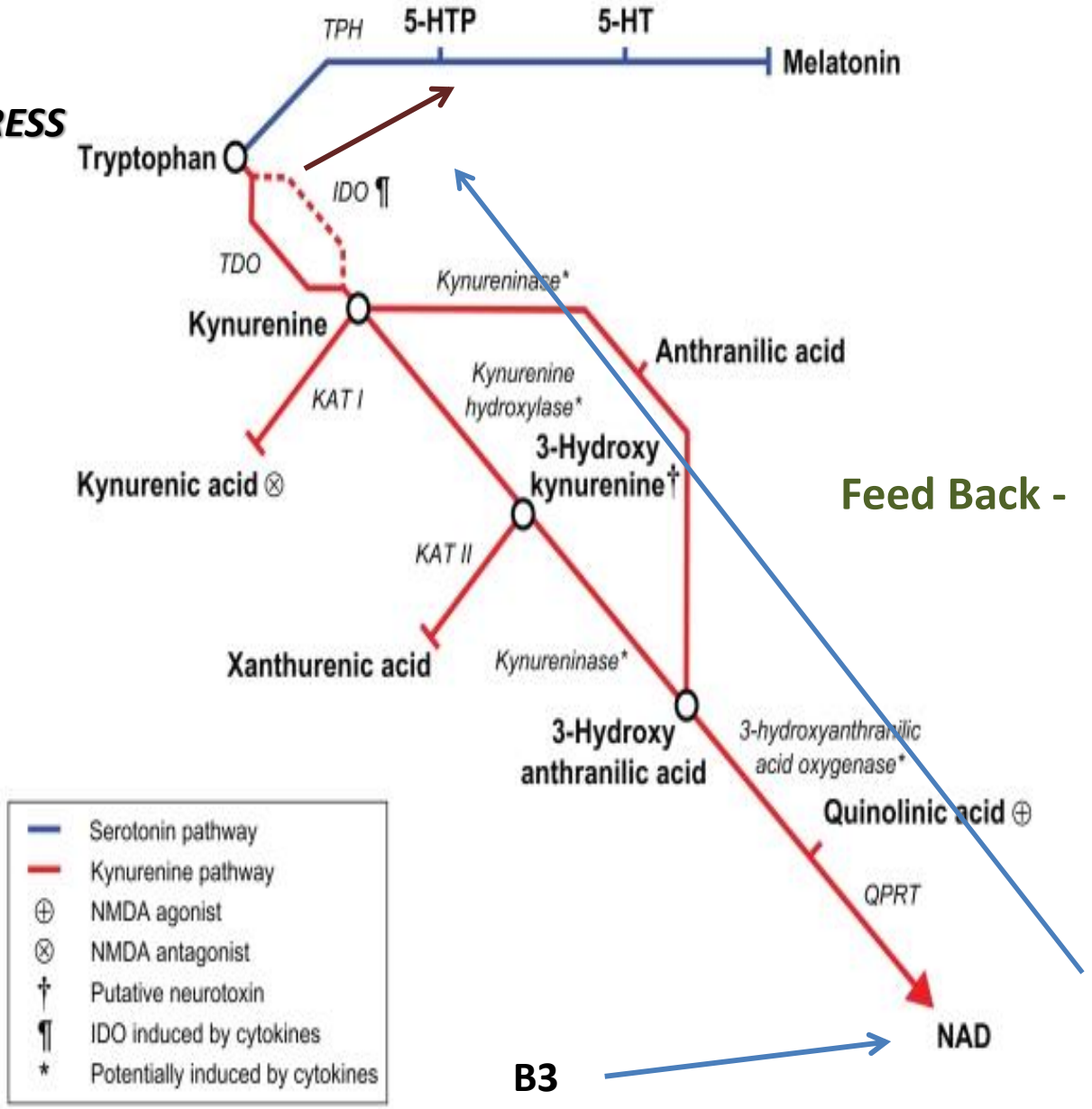


Figure 1 Plasma concentrations (mean ± S.D.) of glutamate (µmol/l) (black bar) in migraine patients, before and after 8 weeks of prophylactic treatment and in control subjects; number of migraine days per month (white bar) in migraine patients, before and after 8 weeks of prophylactic treatment (**Before vs. after: $P < 0.001$, Student's *t*-test for paired data; *Control subjects vs. migraine patients: $P < 0.05$, ANOVA followed by Newman–Keuls post hoc testing).

Plasma glutamate level monitoring in migraine patients might serve as a biomarker of response to treatments and as an objective measure of disease status.

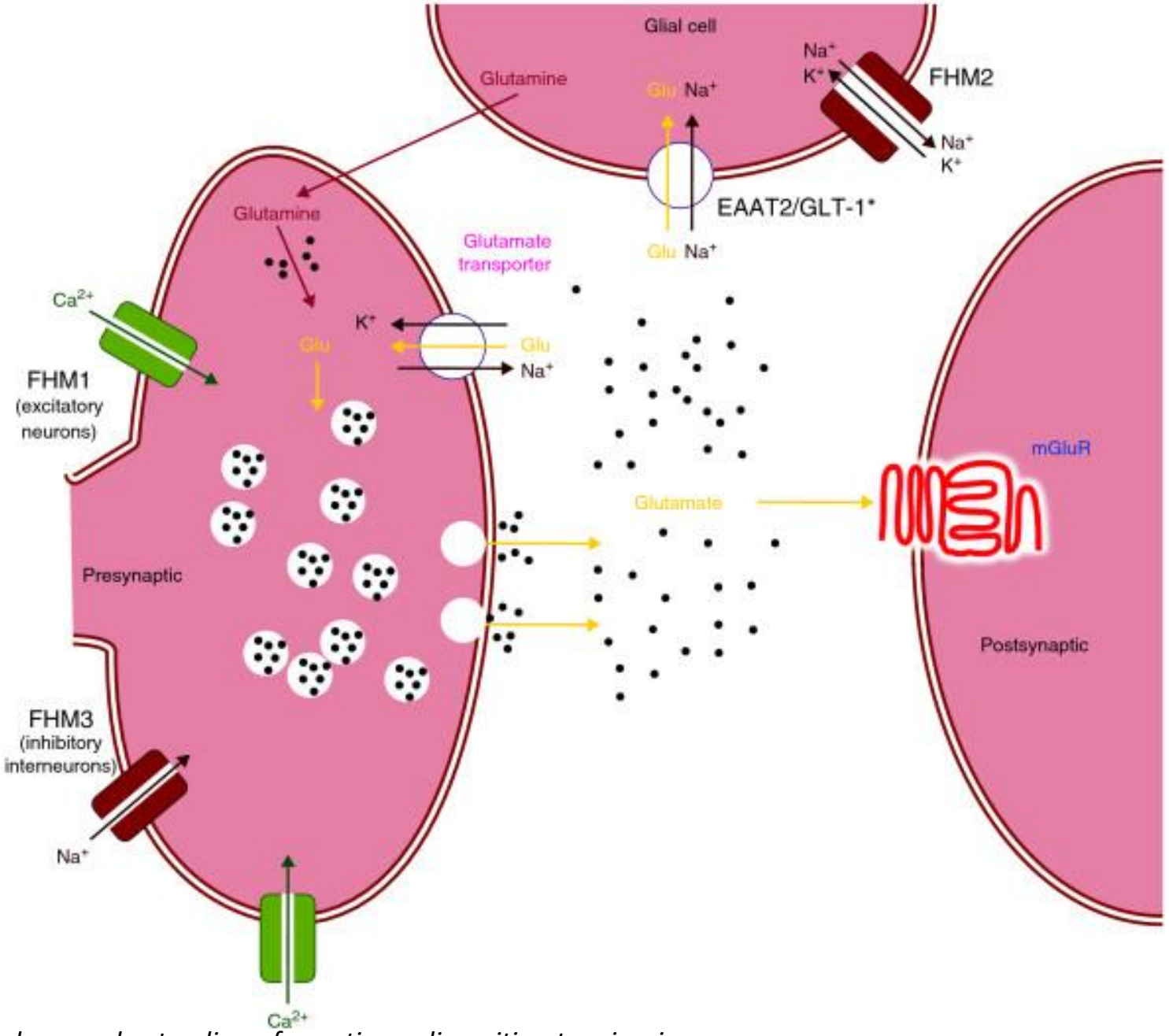
Effective Prophylactic Treatments of Migraine Lower Plasma Glutamate Levels. Cephalalgia, 29(4), 423–429. 2009

INFLAMAÇÃO E STRESS



Neuropsychiatr Dis Treat. 2011; 7: 431–439.

A biological pathway linking inflammation and depression: activation of indoleamine 2,3-dioxygenase



Towards an understanding of genetic predisposition to migraine

Genome Med. 2011; 3(3): 17.

ASPARTAME

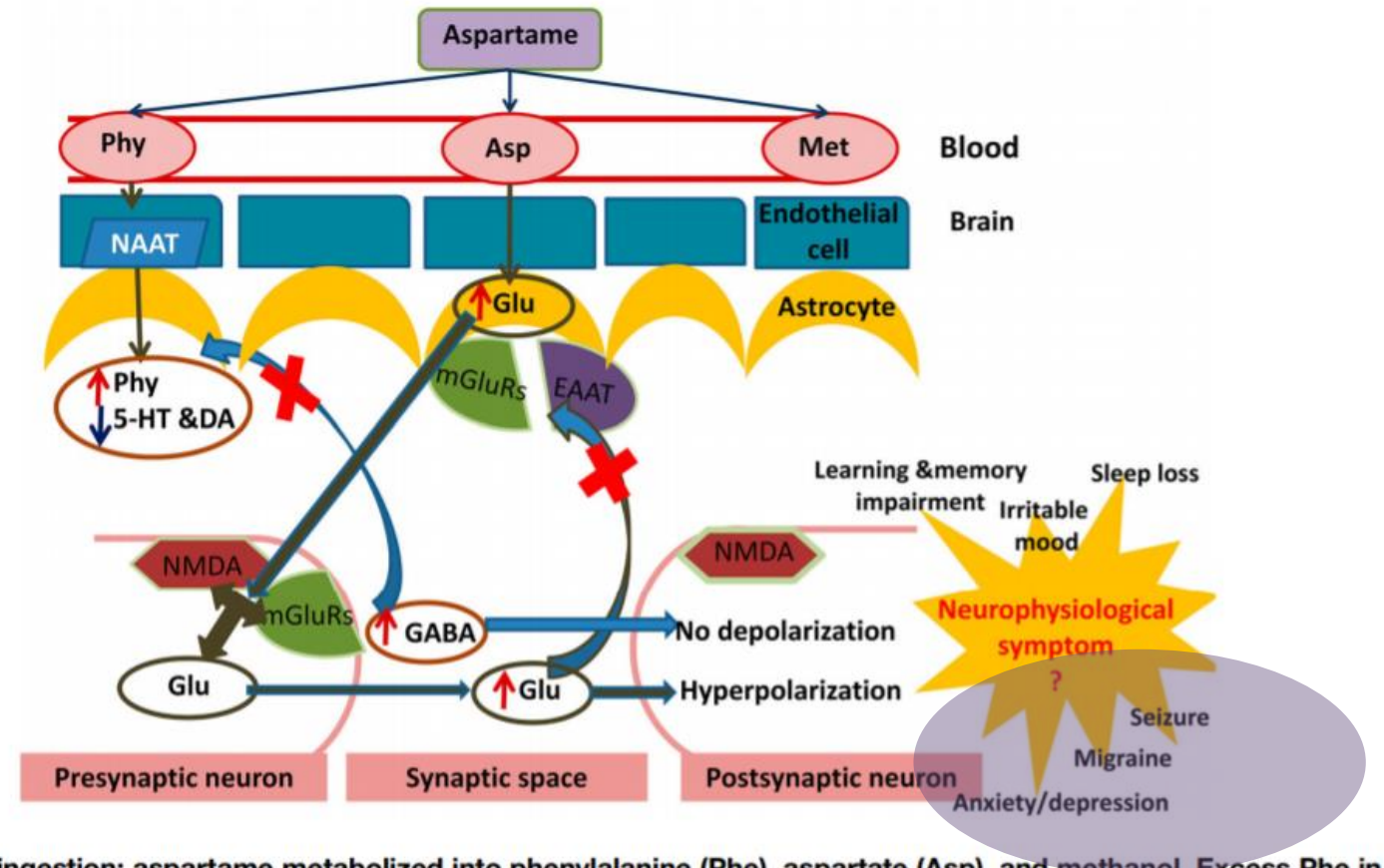
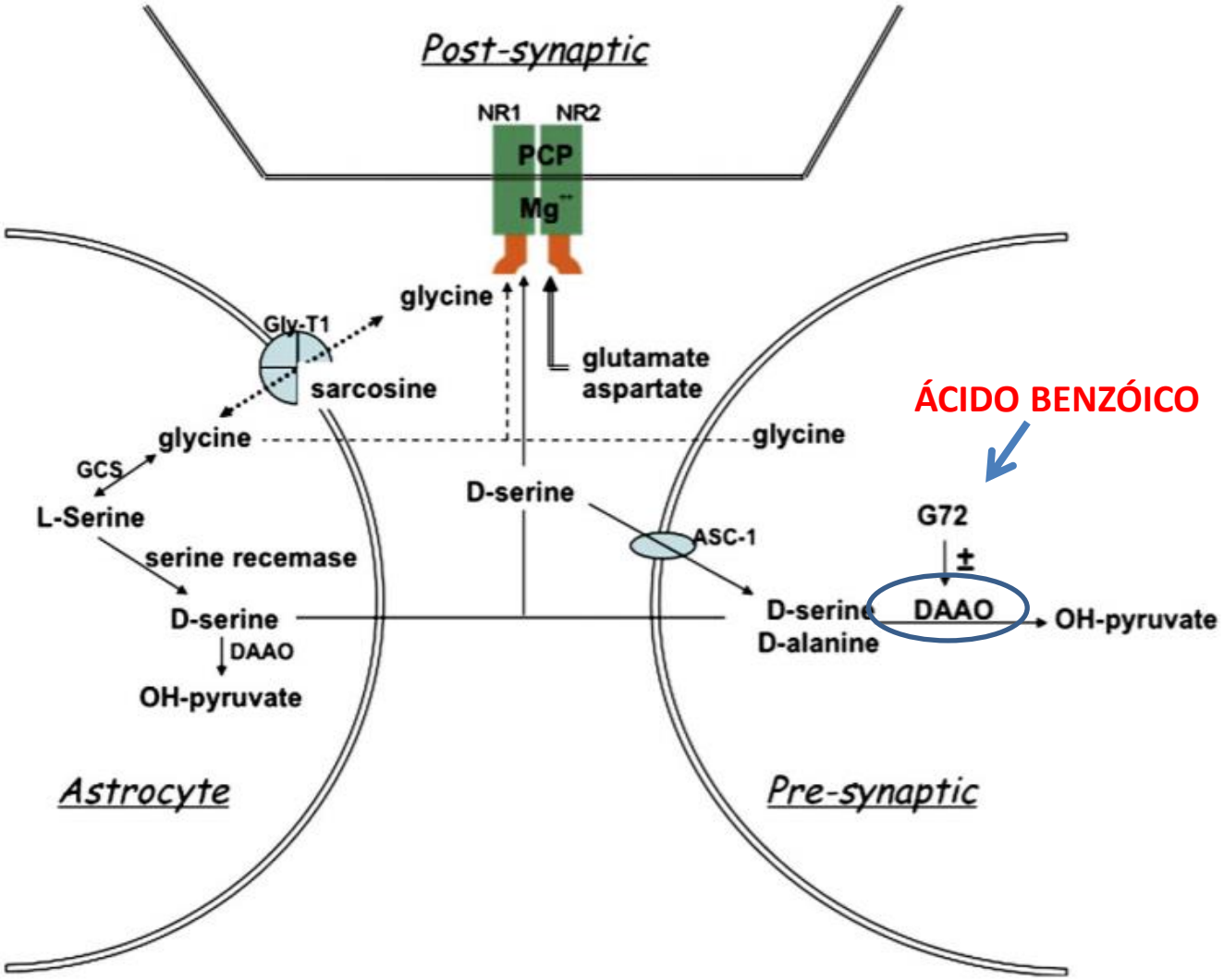


Figure 1 After ingestion; aspartame metabolized into phenylalanine (Phe), aspartate (Asp), and methanol. Excess Phe in the blood crosses the blood brain barrier (BBB) and subsequently decreases serotonin (5-HT) and dopamine (DA) levels by blocking NAAT transporters for precursor amino acids; tyrosine (Tyr) and tryptophan (Trp). Decreased 5-HT levels lead to inhibition of γ-amino butyric acid (GABA) transporters in astrocytes and impair the uptake of 5-HT resulting in inhibition of postsynaptic membrane depolarization. Excess of aspartate (Asp) is converted into glutamate (Glu) by astrocytes. Excess Glu accumulating in the synaptic space may act on presynaptic *N*-methyl-D-aspartate (NMDA) receptors and metabotropic glutamate receptors (mGluRs) by (i) inhibiting the uptake of Glu by excitatory amino acid transporters (EAAT) astrocytes (ii) exocytosis of Glu due to increased intracellular calcium levels caused by activating mGluRs in the astrocyte. Excess Glu is linked to the hyperexcitability of neurons.

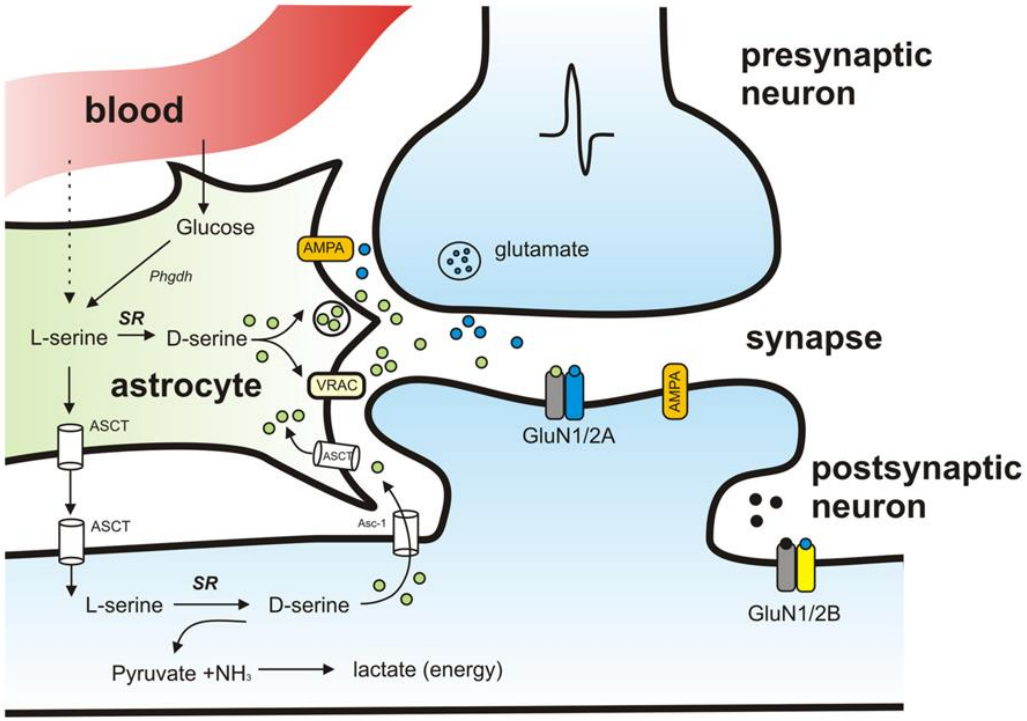
ÁCIDO BENZÓICO / BENZOATO



↑GLICOSE (SNC) ---------- LACTATO

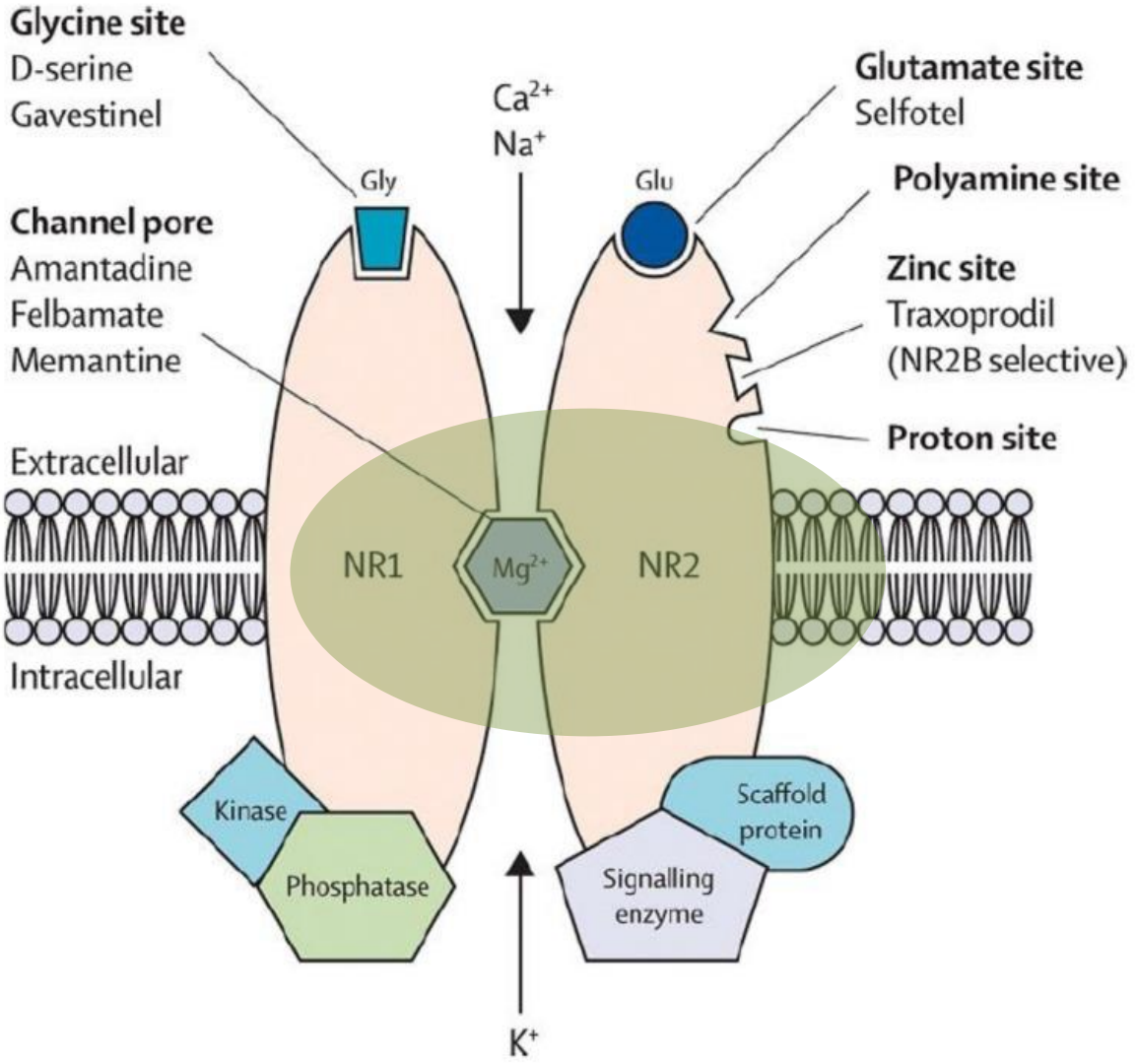
↓

↑ **LIBERAÇÃO DE GLUTAMATO NA FENDA SINÁPTICA**



It also functions in a protective role against excessive excitation that can lead to neuronal cell death (excitotoxicity)

MG ANTAGONIZA O GLUTAMATO NO RECEPTOR NMDA



Nutrients. 2018 Jun 6;10(6).
The Role of Magnesium in Neurological Disorders.

American Academy of Neurology and the American Headache Society

Magnesium was recommended for migraine prophylaxis (strong recommendation, low quality evidence)

Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the ***American Academy of Neurology and the American Headache Society***. Neurology [Internet]. 2012 Apr 24

Canadian Headache Society guideline

Prophylaxis recommends 24 mmol (600 mg) of elemental magnesium daily as magnesium citrate to be used for migraine prophylaxis

Canadian Headache Society guideline for migraine prophylaxis. Can J Neurol Sci 2012; 39: S1–S59.

Headache
© 2017 American Headache Society
ISSN 0017-8748
doi: 10.1111/head.13217
Published by Wiley Periodicals, Inc.

Review Article

Magnesium in Migraine Prophylaxis—Is There an Evidence-Based Rationale? A Systematic Review

Alexander von Luckner, Med. Pract.; Franz Riederer, MD

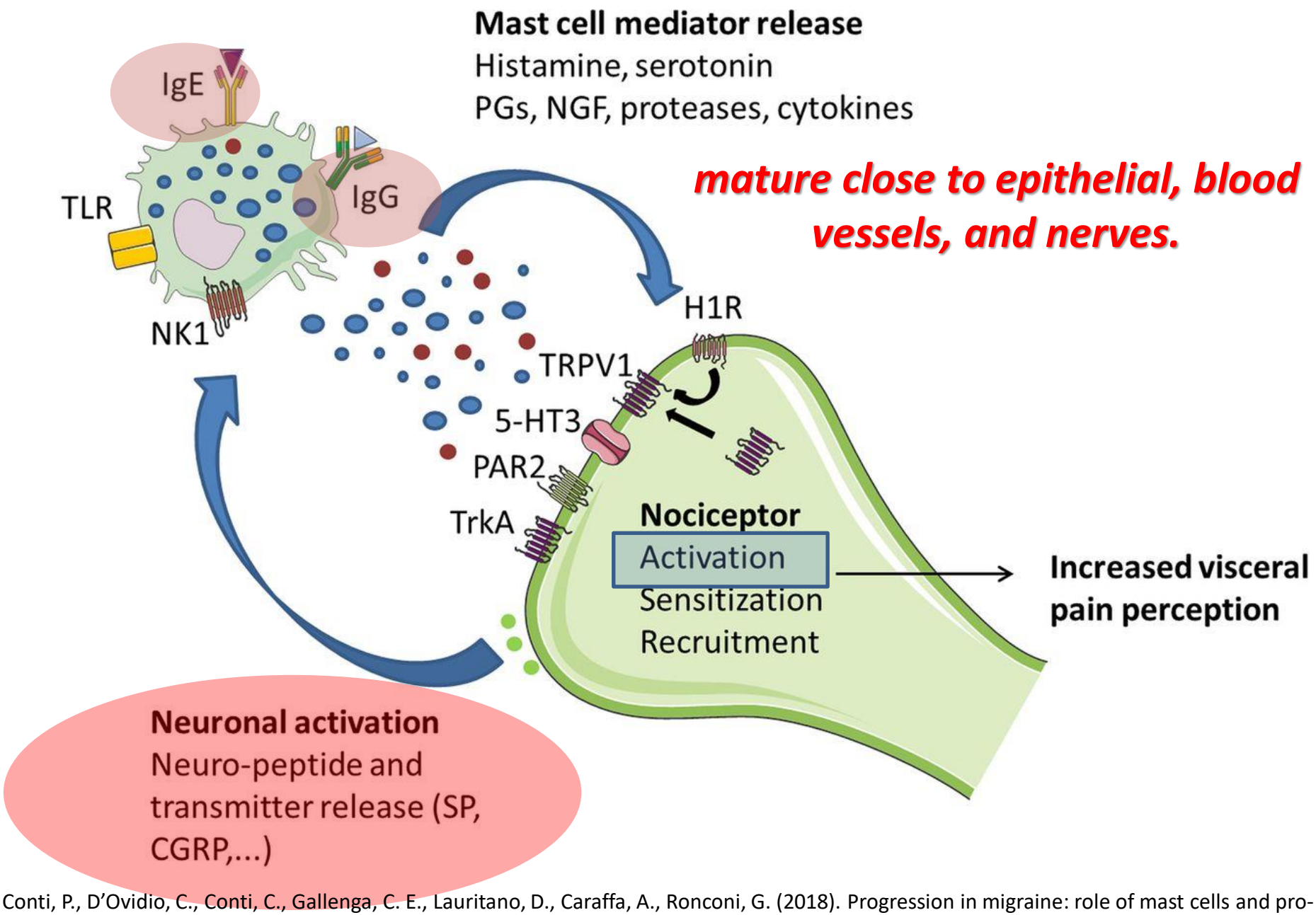
SUPLEMENTAÇÃO COM MAGNÉSIO : GRAU C DE EVIDÊNCIA (POSSIVELMENTE EFICAZ) NA PROFILAXIA DA ENXAQUECA
SEGURO
BAIXO CUSTO

MAGNÉSIO CITRATO – 600 mg/dia

	of menstrual cellular magnesium
	n prophylaxis in
	with oral a prospective, ntrolled and double-
	ylaxis of migraine - a double-blind placebo-controlled study
Taubert et al. (1994)	Magnesium in migraine. Results of a multicentre pilot study

Fig. 1.—Selection procedure.

2. ALERGIA ALIMENTAR E ENXAQUECA



Conti, P., D'Ovidio, C., Conti, C., Gallenga, C. E., Lauritano, D., Caraffa, A., Ronconi, G. (2018). Progression in migraine: role of mast cells and pro-inflammatory and anti-inflammatory cytokines. European Journal of Pharmacology.

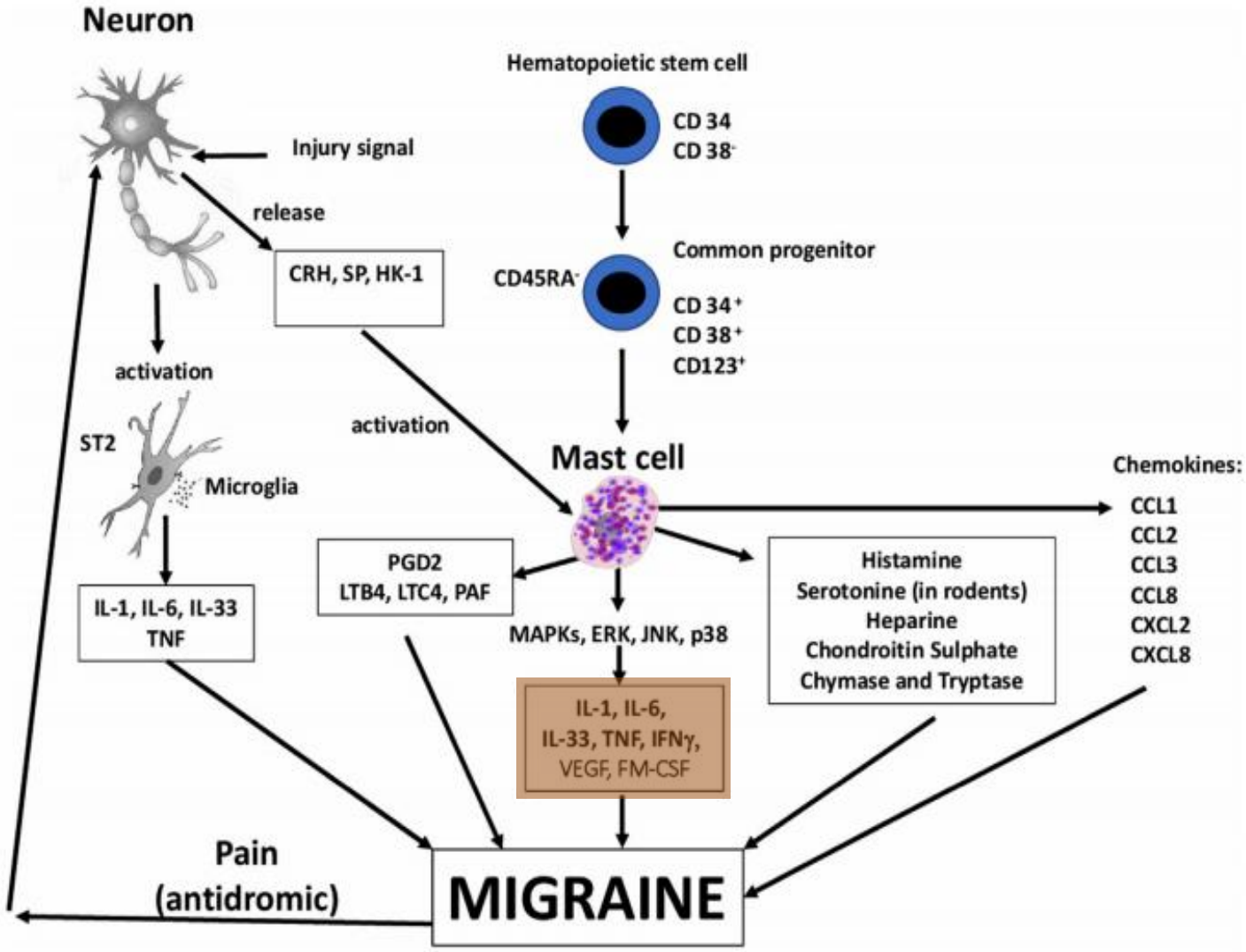
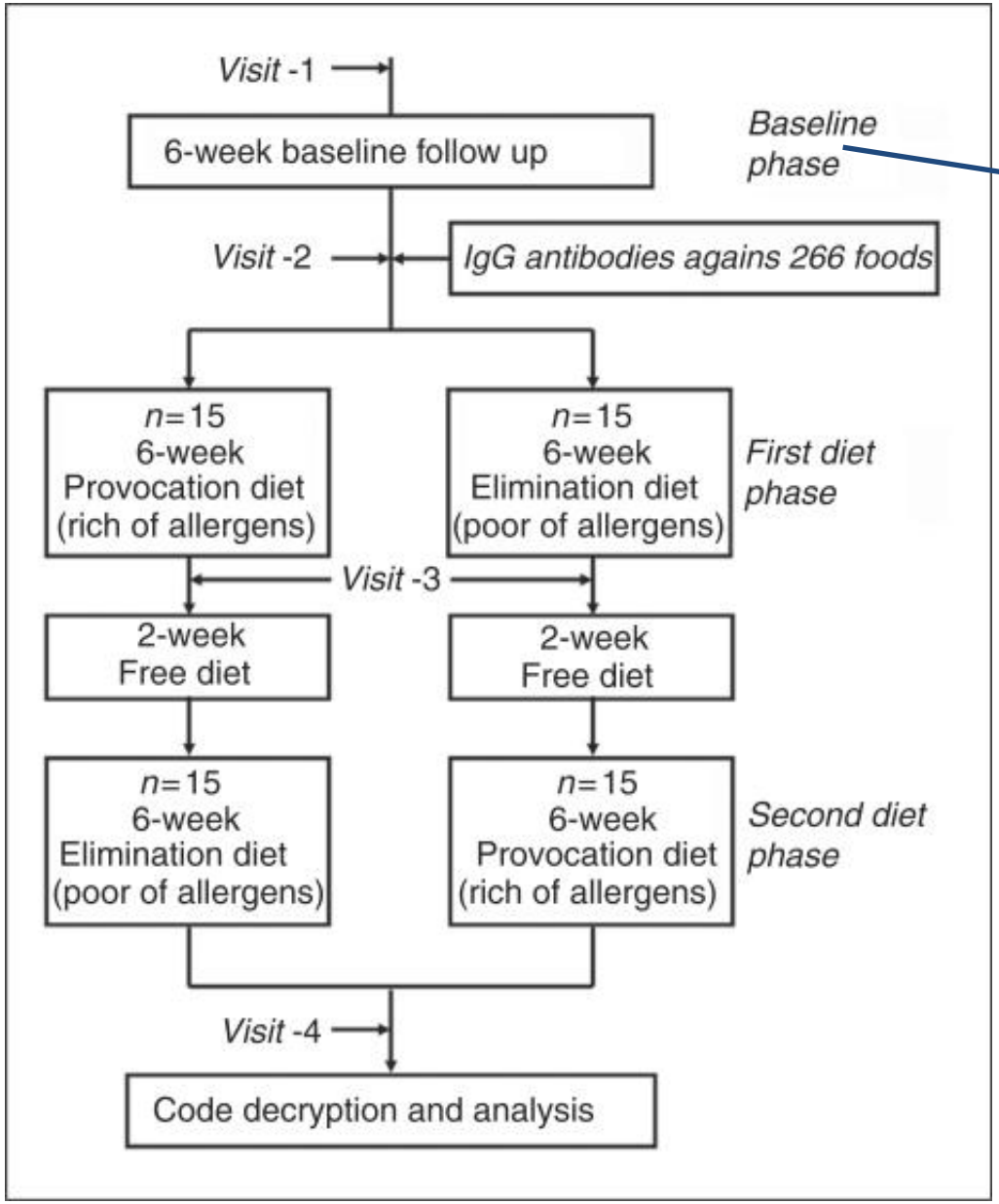


Fig. 2. Activated neuron injury signals release neurotransmitters which induce mast cell and microglia activation and release of proinflammatory cytokines/chemokines involved in migraine.

Conti, P., D'Ovidio, C., Conti, C., Gallenga, C. E., Lauritano, D., Caraffa, A., … Ronconi, G. (2018). Progression in migraine: role of mast cells and pro-inflammatory and anti-inflammatory cytokines. European Journal of Pharmacology.



Dieta usual + diário da Enxaqueca (freq, intens, duração)

Cephalalgia. 2010 Jul; 30(7): 829–837.
Diet restriction in migraine, based on IgG against foods: A clinical double-blind, randomised, cross-over trial

Table 2.

Headache and medication parameters during study phases

Parameters	Phases, each of 6 weeks ± SD (95% CI lower; upper limits)		
	Baseline	**Provocation diet**	**Elimination diet**
Attack count	8.97 ± 4.4 (7.32; 10.61)	8.13 ± 4.6 (6.43; 9.83)	*6.17 ± 3.8 (4.67; 7.58)
Number of headache days	10.53 ± 4.4 (8.90; 12.17)	10.20 ± 5.5 (8.15; 12.25)	*7.47 ± 3.7 (6.08; 8.85)
Number of attacks with acute medication	6.73 ± 2.9 (5.65; 7.81)	6.53 ± 4.0 (5.05; 8.01)	†4.90 ± 3.2 (3.69; 6.11)
Total medication intake (tablets)	11.37 ± 7.4 (8.61; 14.13)	10.57 ± 7.7 (7.69; 13.44)	‡7.77 ± 5.7 (5.65; 9.89)
Median attack severity (VAS)	6.02 ± 1.6 (5.42; 6.62)	6.07 ± 1.6 (5.47; 6.66)	6.07 ± 1.6 (5.60; 6.77)
Mean attack duration (hours)	11.39 ± 5.6 (9.30; 13.48)	12.53 ± 6.7 (10.04; 15.03)	12.53 ± 6.7 (9.57; 15.14)

*$P < 0.001/P < 0.001$; †$P < 0.001/P = 0.001$; ‡$P = 0.002/P = 0.001$ in Paired *t*-test/Wilcoxon signed test (with 95% confidence intervals) comparing elimination and baseline diet phases (differences are statistically significant).

NÖRO PSİKİYATRİ ARŞİVİ
ARCHIVES OF NEUROPSYCHIATRY

RESEARCH ARTICLE

Arch Neuropsychiatry 2018;55:233–237
https://doi.org/10.5152/npa.2016.15961

Efficacy of Diet Restriction on Migraines

Akçay Övünç ÖZÖN[1], Ömer KARADAŞ[2], Aynur ÖZGE[3]

[1]Department of Neurology, Private Liv Hospital, Ankara, Turkey
[2]Department of Neurology, Ankara Mevki Military Hospital, Ankara, Turkey
[3]Department of Neurology, Mersin University School of Medicine, Mersin, Turkey

Identificação dos "alimentos gatilho"
ANAMNESE

GRUPO 1

n=25
2 meses de Exclusão dos alimentos relatados como gatilhos

Após 2 meses, dieta sem restrições por mais 2 meses

GRUPO 2

n=25
2 meses de Exclusão dos alimentos relatados como gatilhos

Após 2 meses, restrições mantidas por mais 2 meses

VAS: attack frequency, duration, and severity

Table 3

The evaluation of the changes in clinical measurements before and after treatment in groups and between groups

	Group 1		Group 2		Group 1 vs. Group 2
	Mean±SD	p[a]	Mean±SD	p[b]	p[c]
VAS	13 (52%)	14 (56%)	0.8125		
Beginning	89.80±5.7		90.20±8.5		0.517
2 months later	72.80±20.9	0.003* α	72.20±19.9	0.003* α	0.868
4 months later	86.80±9.6	0.128 β	71.40±20.1	0.003* β	0.006*
Number of attacks	9 (36%)	7 (28%)	0.6257		
Beginning	6.08±1.7		5.96±1.7		0.759
2 months later	4.84±1.9	0.011* α	4.68±1.9	0.015* α	0.806
4 months later	5.96±1.7	0.426 β	4.64±1.8	0.007* β	0.013*
Pain duration	6 (24%)	6 (24%)	0.9920		
Beginning	29.44±21.8		30.56±22.3		0.953
2 months later	22. 2±15.2	0.041* α	23.52±18.1	0.037* α	0.829
4 months later	28.96±20.0	0.758 β	22.88±18.4	0.022* β	0.138

Noro Psikiyatr Ars. 2018 Sep; 55(3): 233–237.
Efficacy of Diet Restriction on Migraines

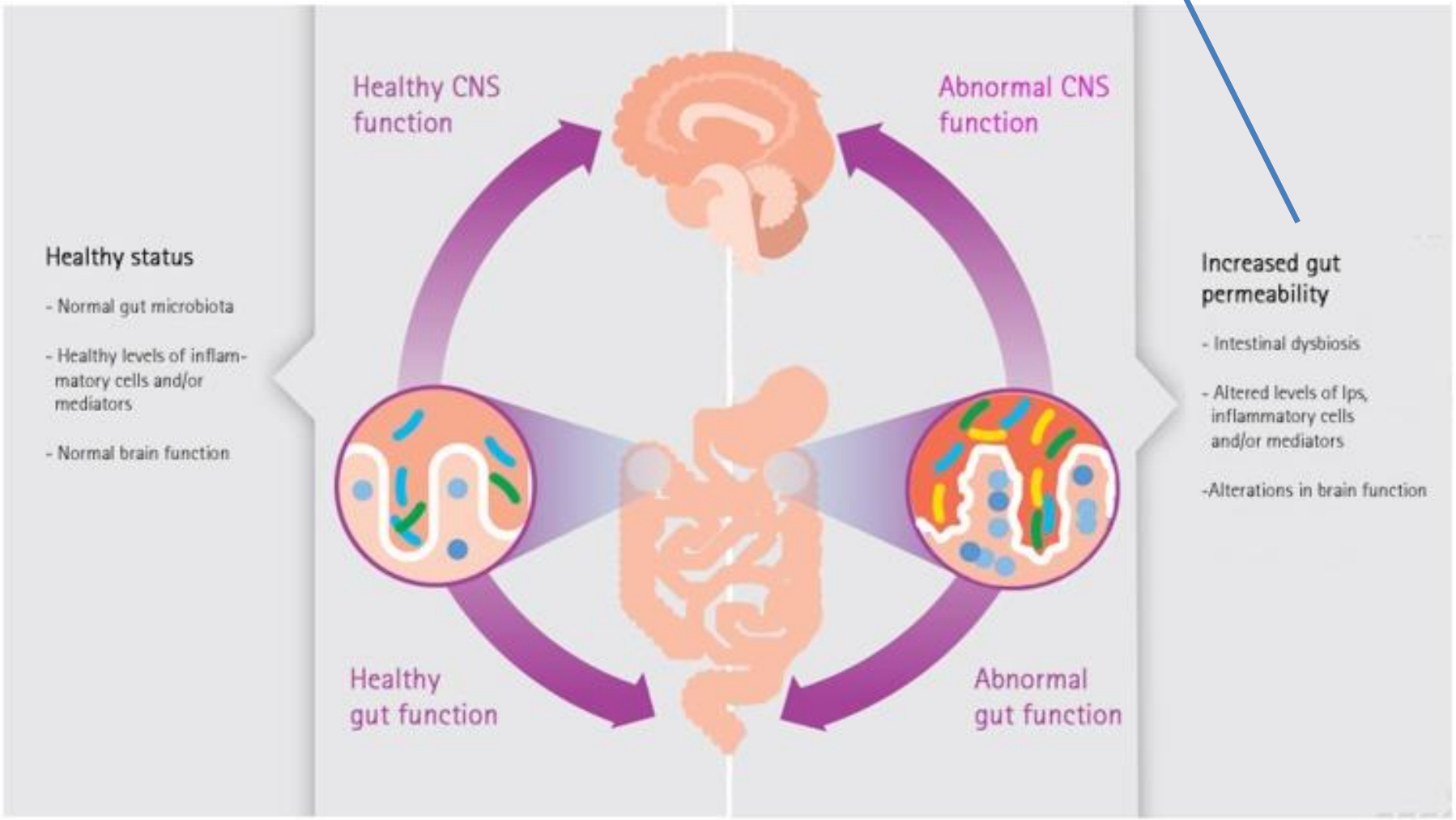
IDENTIFICAR E RETIRAR OS ALIMENTOS GATILHO É UMA ESTRATÉGIA QUE PODE TRAZER RESULTADOS POSITIVOS

INDIVIDUALIZAR/ ANAMNESE

NEM SEMPRE TEMOS EXAMES IgG/ IgE

Noro Psikiyatr Ars. 2018 Sep; 55(3): 233–237.
Efficacy of Diet Restriction on Migraines

MAIOR RISCO DE ALERGIAS ALIMENTARES



Front Neurol. 2014 Nov 21;5:241. **Migraine associated with gastrointestinal disorders: review of the literature and clinical**

3. DISFUNÇÃO MITOCONDRIAL E ENXAQUECA

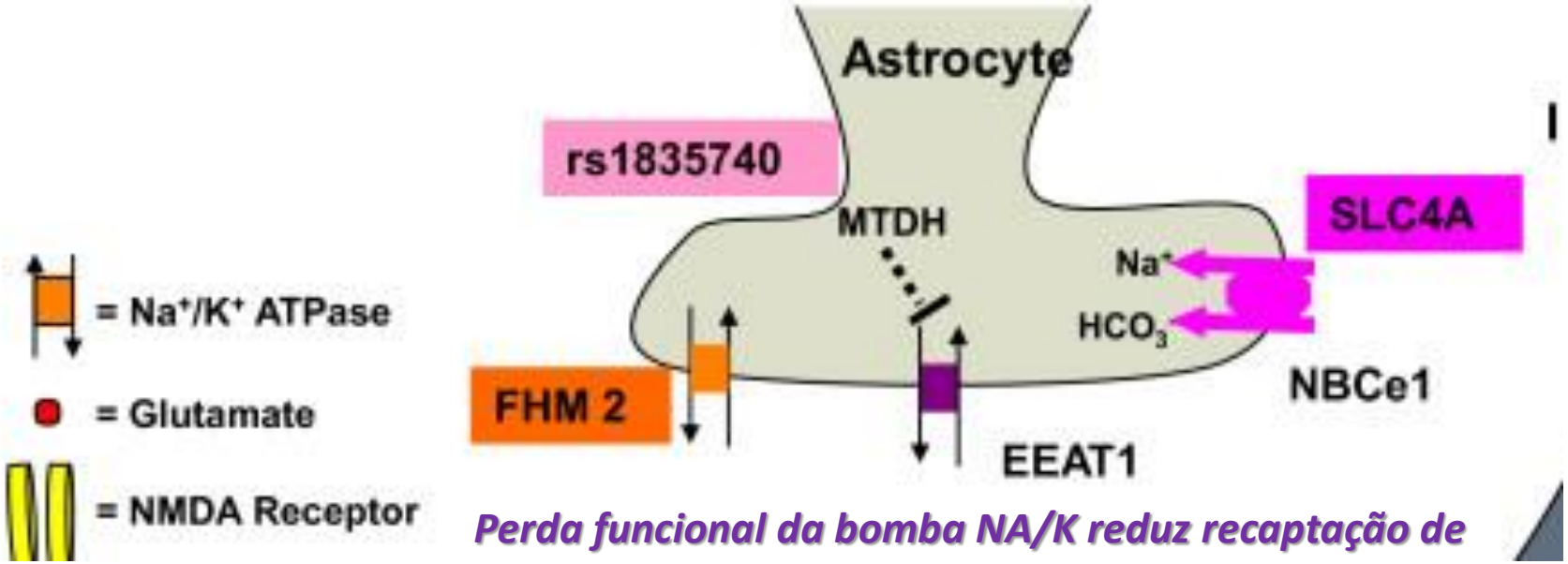
DISFUNÇÕES MITOCONDRIAIS AUMENTAM A EXCITABILIDADE NEURONAL, LEVANDO AO QUADRO DE ENXAQUECA

(2014). *Riboflavin and migraine: the bridge over troubled mitochondria. Neurological Sciences, 35(S1), 141–144.*

Table 2 The link between impaired mitochondrial activity and migraine

Mitochondrial dysfunction (abnormality of oxidative metabolism) → decreased ATP production and energy metabolism → imbalance in calcium ions → increase of neuronal excitability → disturbance of neuronal information processing → decreased migraine threshold → triggering of cortical spreading depression

(2014). *Riboflavin and migraine: the bridge over troubled mitochondria. Neurological Sciences, 35(S1), 141–144.*



Perda funcional da bomba NA/K reduz recaptação de glutamato no astrócito (baixo ATP)

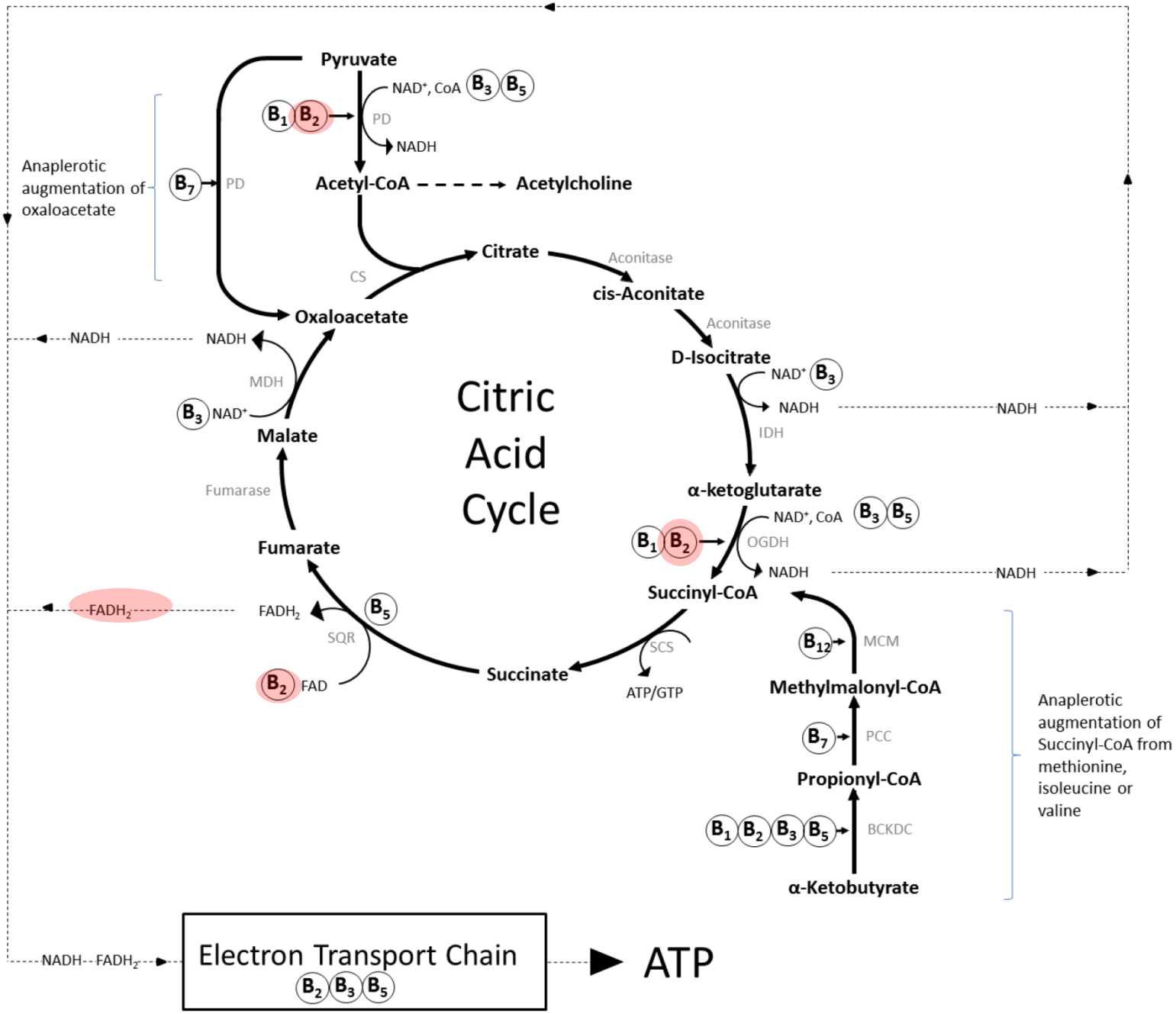
EXCESSO DE GLUTAMATO - Entrada excessiva de Cálcio - EXCITABILIDADE NEURONAL

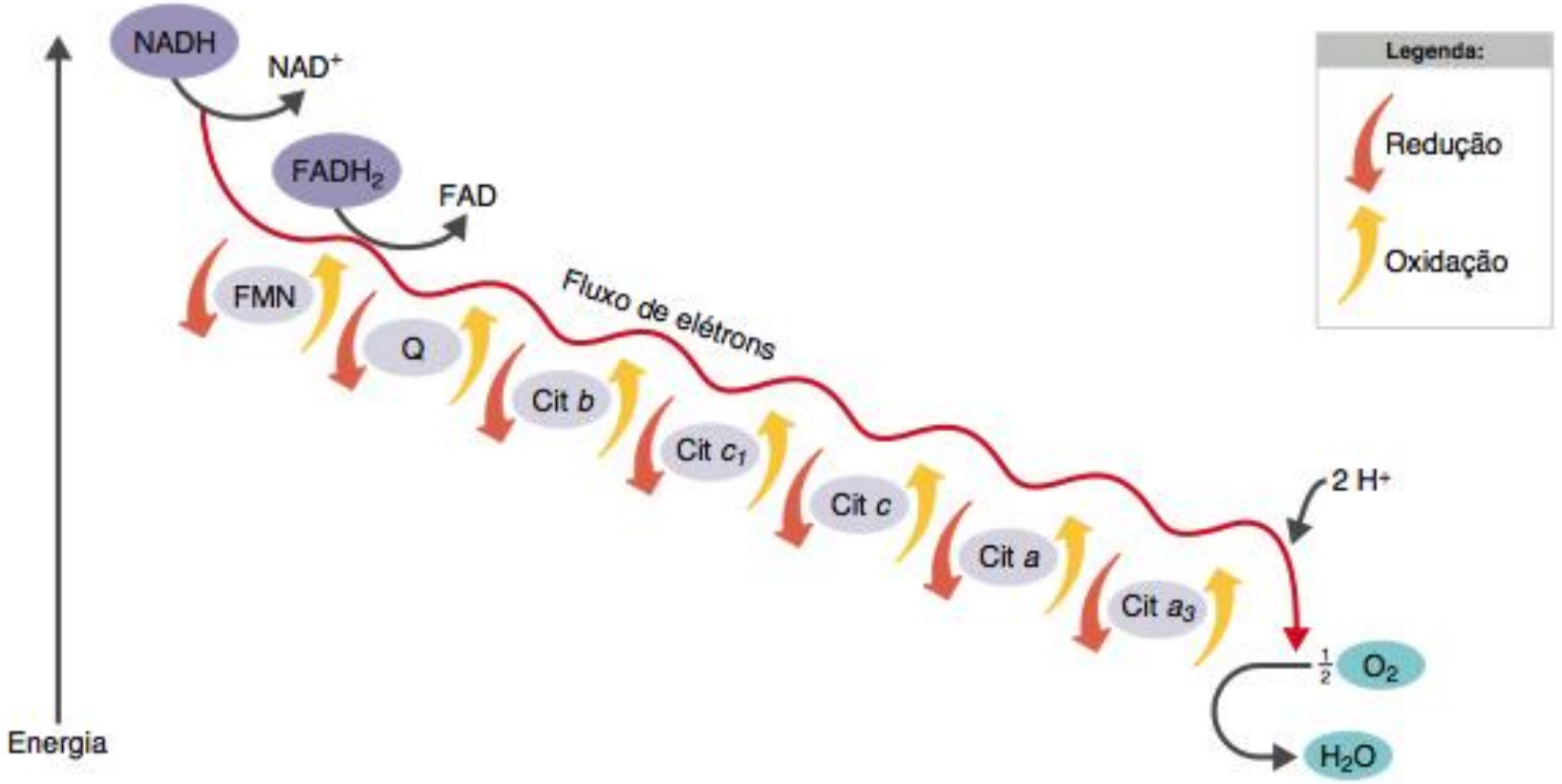
BMC Med. 2011; 9: 116. 10.1186/1741-7015-9-116
Published online 2011 Oct New directions in migraine

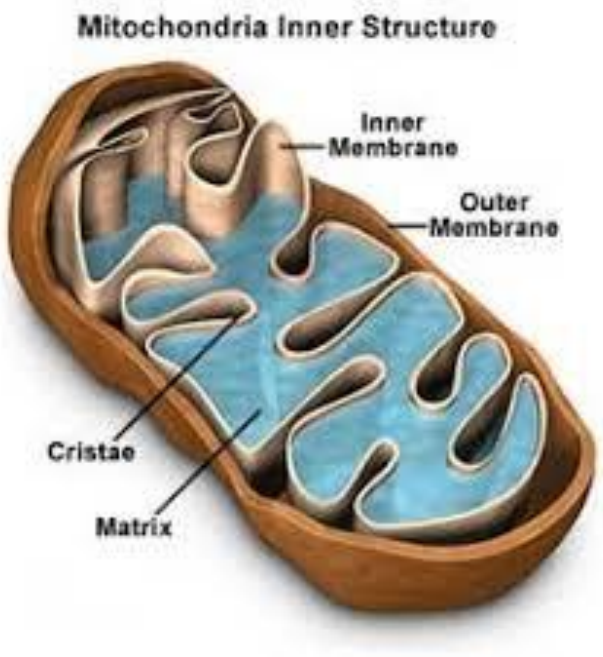
Therapeutic evidence: ***Several agents that have a positive effect on mt metabolism have shown to be effective in the treatment of migraines. The agents include riboflavin (B2), coenzyme Q10, magnesium, niacin, carnitine, topiramate, and lipoic acid***

Semin Pediatr Neurol. 2013 Sep;20(3):188-93. doi: 10.1016/j.spen.2013.09.002.
Mitochondrial dysfunction in migraine.

RIBOFLAVINA


Pyruvate
NAD+, CoA
B3 B5
B1 B2
PD
NADH
Acetyl-CoA
Acetylcholine
Anaplerotic augmentation of oxaloacetate
B7
PD
CS
Citrate
Aconitase
cis-Aconitate
Aconitase
D-Isocitrate
NAD+
B3
NADH
IDH
NADH
Oxaloacetate
NADH
NADH
MDH
B3 NAD+
Malate
Citric Acid Cycle
Fumarase
α-ketoglutarate
NAD+, CoA
B3 B5
B1 B2
OGDH
NADH
NADH
Fumarate
Succinyl-CoA
FADH2
FADH2
B5
SQR
SCS
B12
MCM
Methylmalonyl-CoA
B2 FAD
Succinate
ATP/GTP
B7
PCC
Propionyl-CoA
Anaplerotic augmentation of Succinyl-CoA from methionine, isoleucine or valine
B1 B2 B3 B5
BCKDC
α-Ketobutyrate
NADH FADH2
Electron Transport Chain
B2 B3 B5
ATP


NADH
NAD+
FADH2
FAD
FMN
Q
Cit b
Cit c1
Cit c
Cit a
Cit a3
Fluxo de elétrons
2 H+
½ O2
H2O
Energia
Legenda:
Redução
Oxidação



SOD ↓

NO ↑

LACTATO ↑

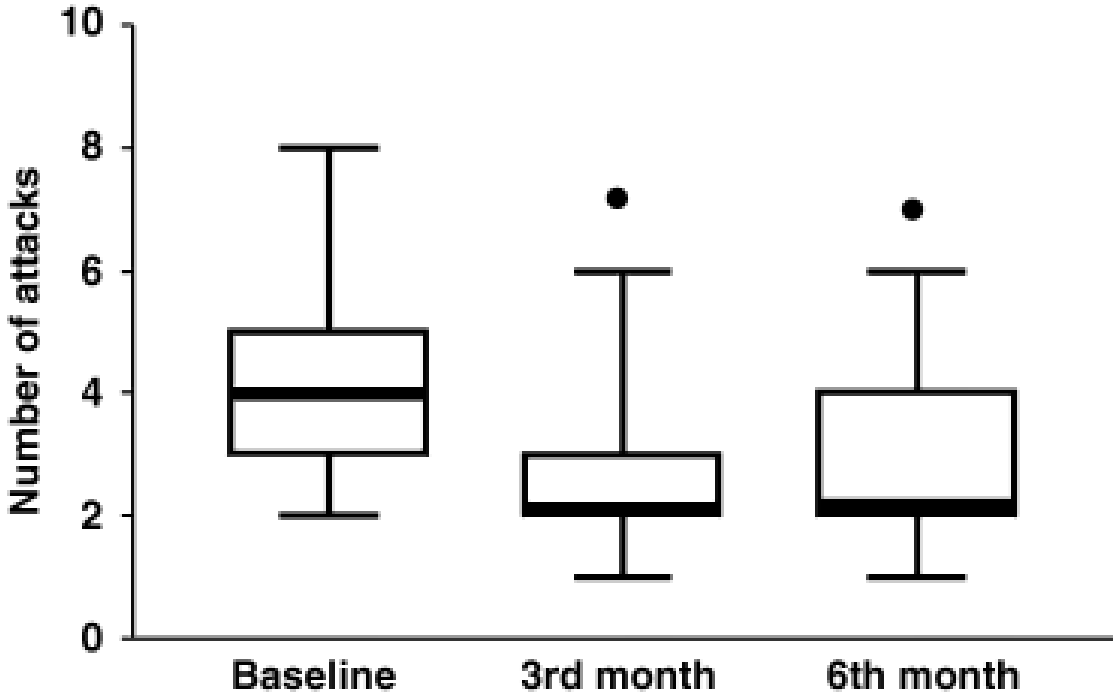
Cr-P ↓

Creatinina ↑

Ácido Urico ↑

european journal of neurology
the official journal of the european academy of neurology

400 mg Riboflavina / dia
N=23
frequency 2–8 attacks/month in the last 6 months prior to the study.
Sem grupo placebo
Intensidade das crises não apresentou mudanças



High-dose riboflavin treatment is efficacious in migraine prophylaxis: an open study in a tertiary care centre. 2008

Table 1. **Efficacy parameters (see text) (mean ± se) before and after treatment with 400 mg riboflavin (*n* = 25). The differences between pre- and post-treatment values are significant (**p* £ 0.01. Student's paired *t*-test).**

	Migraine days per month	Subjective score	Global severity score
Month before treatment	8.7 ± 1.5	8.9 ± 2.2	8.8 ± 1.9
Last month of treatment	2.9 ± 1.2*	2.7 ± 0.6*	2.8 ± 0.6*

High-dose (400 mg) riboflavin could thus be an effective, low-cost prophylactic treatment of migraine devoid of short-term side effects.

3 MESES

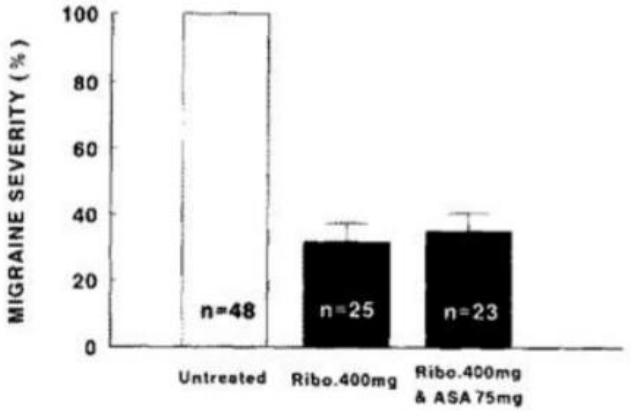


Fig. 1. Migraine severity score (see text) during the month before treatment and during the last month of treatment with either 400 mg riboflavin alone ($n = 25$) or an association of 400 mg riboflavin and 75 mg acetylsalicylic ($n = 23$).

patient who received riboflavin and aspirin withdrew from the study after 2 weeks because of gastric intolerance. No drug-related side effects were reported by the other patients.

Schoenen J, Lenaerts M, Bastings E. High-dose riboflavin as a prophylactic treatment of migraine: results of an open pilot study. Cephalalgia. 1994;14:328-329.

Duration of trial		Riboflavin adverse effects	Outcomes	Notes
3 mo	400 mg	One patient in the riboflavin group also receiving aspirin reported gastric intolerance	Migraine headache frequency reduced from a baseline of 8.7/month to 2.9/month ($P<.01$)	No difference between groups with and without aspirin
3 mo	400 mg	Diarrhoea (n=1) and polyuria (n=1)	Riboflavin group had a 59% reduction in migraine headache frequency vs placebo ($P<.0001$)	Used Intention-to-treat analysis
3 or 6 mo	400 mg	Three patients experienced diarrhoea, facial erythema or upper abdominal pain, described as mild	Migraine frequency reduced from a baseline of 4/month to 2/month ($P<.05$)	Five patients had previous treatment failures prior to this study
3 mo	200 mg	One child had a new onset of tension headache, four noted a change in urine colour	Migraine headache frequency was not reduced with riboflavin (4.4/month) vs placebo 4.2/month)	Used Intention-to-treat analysis
3 mo	400 mg Ou 200 mg	One patient dropped out because of vomiting; two others for unknown reasons	Migraine headache frequency reduced from a baseline of 21.7/month to 13.2/month ($P<.01$)	Twenty-one patients took 200 mg/d; 20 patients took 400 mg/d

J Clin Pharm Ther. 2017 Aug;42(4):394-403.

Prophylaxis of migraine headaches with riboflavin: A systematic review.

10 mo	50 mg	No adverse effects reported	Migraine headache frequency not statistically different between riboflavin and placebo	
3 mo	100 mg	Orange discoloration of the urine (n=10), vomiting (n=1), diarrhoea (n=1)	Both drugs decreased the frequency of headache from about 4 episodes/month to about 2.8 along with a reduction in duration and severity; however, no significant differences were found between groups.	Riboflavin side effects were significantly less than propranolol (*P*=.035)
3 mo	400 mg	Polyuria in 36% (n=18), diarrhoea (n=12), 24%)	Headache frequency was decreased from the 1st month (6.4 episodes/month) to the 2nd month (3.9) to the 3rd month (3.7 per month) and duration decreased (*P*=0.012 and *P*=.001, respectively) vs placebo. Disability, as measured by the PedMIDAS,[53] was also decreased (*P*=.001)	
3 mo	400 mg	Significantly fewer adverse effects were reported in the riboflavin group (*P*-.005)	Frequency of headaches was decreased from 9.2 to 2.4 for riboflavin and 6.5 to 2.1 per month for valproic acid. No statistical difference was found in the frequency, duration or severity of headache between riboflavin and sodium valproate.	

J Clin Pharm Ther. 2017 Aug;42(4):394-403.

Prophylaxis of migraine headaches with riboflavin: A systematic review.

TABLE 1 Riboflavin evidence quality as rated by three guidelines for prophylaxis of migraine headache

Guideline (y)	Rating
American Headache Society/American Academy of Neurology[6] (2012) Level A: established as effective (≥2 Class I trials Level B: probably effective (1 Class I trial or 2 Class II studies) Level C: possibly effective 1 Class II trials Level U: (Inadequate or conflicting data)	B
Canadian Headache Society[39] (2012) The overall recommendation is graded as strong or weak based on assessment of the balance of benefits and harm. Each drug is also assigned an evidence quality recommendation from high, moderate, low or very low	Strong recommendation, Low-quality evidence
European Federation of Neurological Societies[38] (2009) Level A: drugs of first choice Level B: drugs of second choice; evidence of efficacy but less effective or more side effects than Level A Level C: drugs of third choice; probably effective	C

J Clin Pharm Ther. 2017 Aug;42(4):394-403.

Prophylaxis of migraine headaches with riboflavin: A systematic review.

CRIANÇAS DE 5-13 anos com diagnóstico de Enxaqueca

Table 2

Mean (SD) frequency, duration and intensity of migraine attacks at baseline and end of riboflavin prophylaxis and mean decrease of them in each group[a]

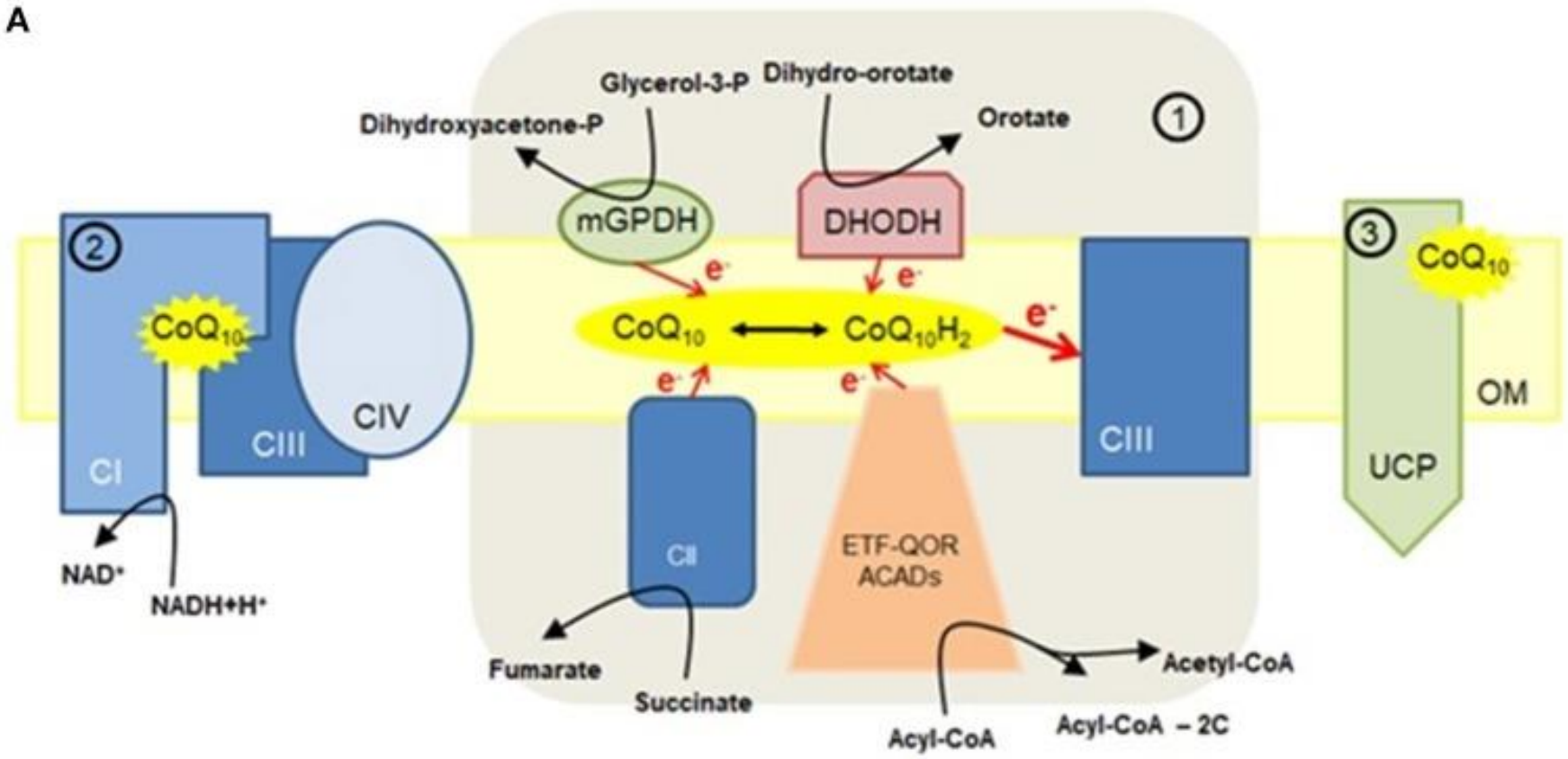
100 MG **200 MG**

Variables	Placebo group (n=30)			p-value	Low dose group (n=30)			p-value	High dose group (n=30)			p-value
	Wk0	Wk12	Decrease		Wk0	Wk12	Decrease		Wk0	Wk12	Decrease	
Frequency	8.20±3.25	8.17±3.97	0.03±2.24	0.94	7.8 3±3.83	7.23±4.17	0.60±4.07	0.43	9.27±3.03	2.87±1.66	6.40±3.98	0.000
Duration	7.87±2.92	7.57±2.91	0.30±1.12	0.15	6.97±2.62	6.80±2.55	0.17±1.49	0.54	7.90±3.03	3.90±2.62	4±3.49	0.000
Intensity	2.30±0.47	2.23±0.63	0.07±0.52	0.49	2.37±0.49	2.30±0.47	0.07±0.37	0.33	2.40±0.49	2.27±0.58	0.13±0.51	0.16

[a]SD, standard deviation; Wk. 0, week 0 (baseline); Wk. 12, week 12 (end); Frequency, frequency (number) of migraine attacks monthly; Duration, mean duration of migraine attacks in hours monthly; Intensity, mean intensity of migraine attacks in degree monthly; Decrease, decrease of headache items (baseline- end); p, p.value decrease of three items of headache in each group between two times (wk. 0 and wk. 12) with paired-samples t-test.

Electron Physician. 2018 Feb; 10(2): 6279–6285.
Prophylactic effect of riboflavin on pediatric migraine: a randomized, double-blind, placebo-controlled trial

COQ 10



Front Physiol. 2018; 9: 44.

400 mg COQ 10 / dia

Table 2 Within and between group comparisons of headache characteristics of patients with migraine before and after the intervention

Variables	CoQ10 (*n* = 23)	Placebo (*n* = 22)	*P*-value
Migraine frequency(per month)			
Baseline	8.47 (3.00–15.00)	6.36 (2.00–15.00)	0.062[a]
After	3.10 (1.00–12.00)	3.46 (1.00–14.00)	**0.018**[b]
GMD, *P*-value	−5.37, **<0.001**[c]	−2.9, **<0.001**[c]	
Migraine severity(VAS scale)			
Baseline	8.05 (6.00–10.00)	7.68 (5.00–10.00)	0.364[a]
After	4.19 (2.00–7.00)	5.34 (3.00–9.00)	**0.001**[b]
GMD, *P*-value	−3.86, **<0.001**[c]	−2.34, **<0.001**[c]	
Migraine duration(hour)			
Baseline	11.33 (4.00–24.00)	13.02 (1.00–24.00)	0.516[a]
After	4.16 (1.00–24.00)	7.63 (1.00–24.00)	**0.012**[b]
GMD, *P*-value	−7.17, **<0.001**[c]	−5.39, **0.002**[c]	

PACIENTES COM ENXAQUECA APRESENTAM NÍVEIS SÉRICOS DE COQ 10 DIMINUÍDOS

(2018). Oral coenzyme Q10 supplementation in patients with migraine: Effects on clinical features and inflammatory markers. Nutritional Neuroscience, 1–9. doi:10.1080/1028415x.2017.1421039

NUTRITIONAL NEUROSCIENCE
https://doi.org/10.1080/1028415X.2019.1572940

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Effect of coenzyme Q10 supplementation on clinical features of migraine: a systematic review and dose–response meta-analysis of randomized controlled trials

Mohammad Parohan[a,b], Payam Sarraf[c], Mohammad Hassan Javanbakht[a], Sakineh Ranji-Burachaloo[c] and Mahmoud Djalali[a]

[a]Department of Cellular and Molecular Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran; [b]Students' Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran; [c]Iranian Centre of Neurological Research, Department of Neurology, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran

The greatest impact of CoQ10 supplementation was on the frequency of attacks, indicating its potential use for migraine attacks which have frequent rather than in the case of long duration or severe attacks.

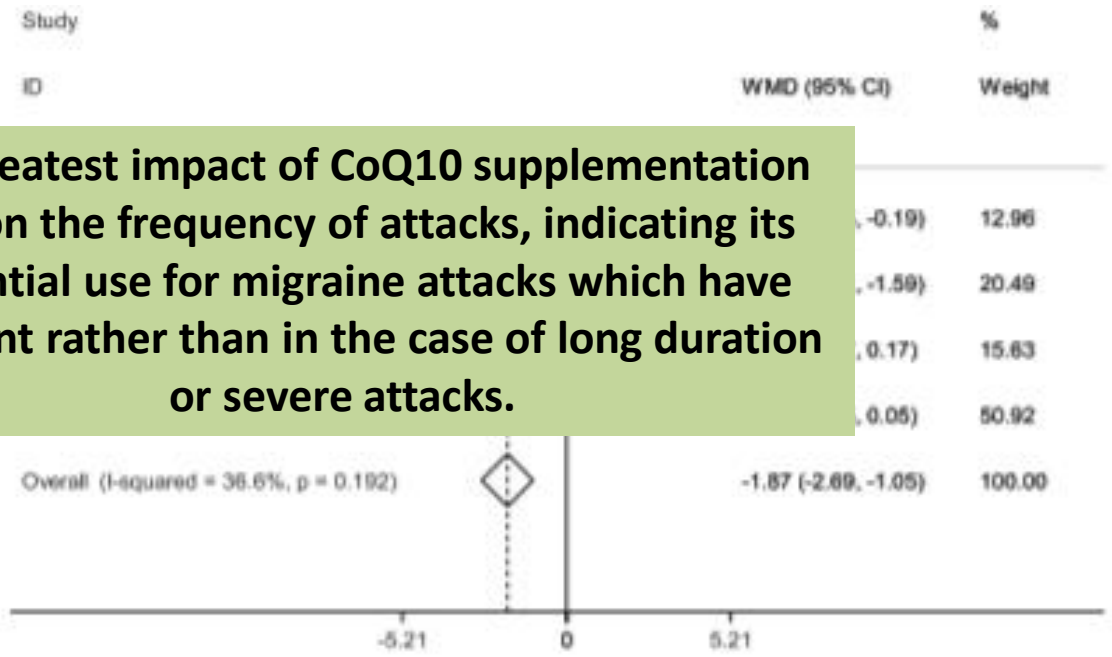
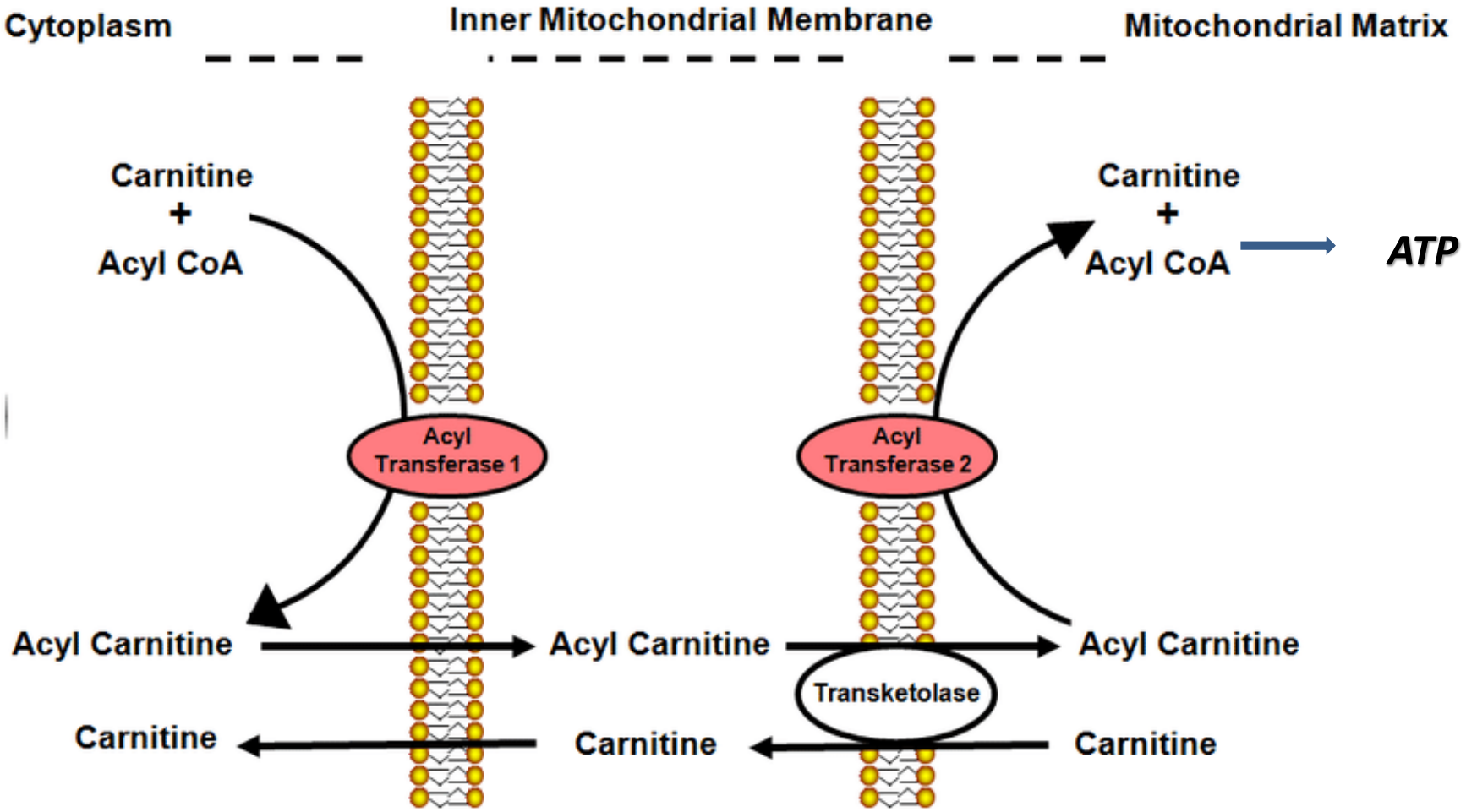


Figure 2. Forest plot of randomized controlled trials investigating the effects of CoQ10 on the frequency of migraine attacks.

(2019). Effect of coenzyme Q10 supplementation on clinical features of migraine: a systematic review and dose–response meta-analysis of randomized controlled trials. Nutritional Neuroscience, 1–8. doi:10.1080/1028415x.2019.1572940

L-CARNITINE


Cytoplasm
Inner Mitochondrial Membrane
Mitochondrial Matrix
Carnitine
+
Acyl CoA
Acyl Transferase 1
Acyl Carnitine
Carnitine
Acyl Carnitine
Carnitine
Acyl Transferase 2
Transketolase
Carnitine
+
Acyl CoA
ATP
Acyl Carnitine
Carnitine

L-carnitine

ANTIOXIDANTE
RESPIRAÇÃO CELULAR.

M.A. Kabbouche, S.W. Powers, A.L.B. Vockell, S.L. LeCates, A.D. Hershey, Carnitine palmityltransferase II (CPT2) deficiency and migraine headache: two case reports, Headache 43 (5) (2003) 490–495.

30 mg/day Coenzyme Q10 and 500 mg/day L-carnitine X placebo

Table 3. The effects of Coenzyme Q10 with L-carnitine supplementation on mitochondrial metabolic disorders marker and migraine symptoms[1].

	Intervention (n = 24)		Control (n = 26)				
	Baseline	8th week	Baseline	8th week	Difference change[2] (SE)	*p*-value	95% CI
Severity	7.50 ± 0.69	3.62 ± 1.28	7.39 ± 0.83	6.50 ± 1.20	−3.03 ± 0.31	<0.001	[−3.65, −2.40]
Frequency[3]	9.46 ± 5.59	3.41 ± 2.65	6.50 ± 4.63	5.30 ± 4.41	−5.42 ± 0.92	<0.001	[−7.31, −3.53]
Duration[4]	16.85 ± 13.05	8.48 ± 9.06	17.92 ± 16.17	15.11 ± 13.10	−7.67 ± 1.90	<0.001	[−11.47, −3.90]
HDR[5]	145.21 ± 111.88	28.39 ± 30.96	98.64 ± 90.32	60.88 ± 53.96	−103.03 ± 21.09	<0.001	[−145.76, −60.20]
Lactate (mg/dl)	13.78 ± 2.43	12.20 ± 2.57	11.71 ± 2.91	12.54 ± 2.97	−2.28 ± 0.69	0.002	[−3.65, −0.90]

[1]All data are means ± SD.
[2]Results of two independent sample t-tests.
[3]Frequency of attacks per month.
[4]Average duration of migraine attack.
[5]Headache dairy results: Duration of headache × frequency of headache.

(2019). *The effects of concurrent Coenzyme Q10, L-carnitine supplementation in migraine prophylaxis: A randomized, placebo-controlled, double-blind trial.*

500 mg **500 mg** **500 mg + 500 mg**

Table 3 Comparison of the changes in migraine indicators and serum levels of magnesium and L-carnitine between different study groups

	Magnesium	L-Carnitine	Mg–L-carnitine	Control	p^a
Reduction in the number of migraine attacks	4.44±0.77	3.04±0.64	3.45±0.55	0.12±1.38	0.008
Reduction in migraine days	4.59±0.91	4.63±0.98	6.61±1.62	2.54±1.91	0.217
Reduction in migraine severity	1.00±0.94	0.87±0.11	0.71±0.12	0.87±0.05	0.305
Reduction in migraine index	14.39±3.08	13.35±2.80	19.81±4.81	8.28±5.71	0.321
Increment in serum magnesium concentration	0.11±0.01 a	0.001±0.02 b	0.14±0.02 a	0.001±0.01 b	<0.001
Increment in serum L-carnitine concentration	−2.82±0.68 a	4.48±0.92 b	3.12±0.49 b	−3.05±0.42 a	<0.001

Values with the same letters in one row indicate insignificant differences according to the Tukey post-hoc results

[a] *p* value of one-way ANOVA test

Efeito sinérgico Mg + Carnitina

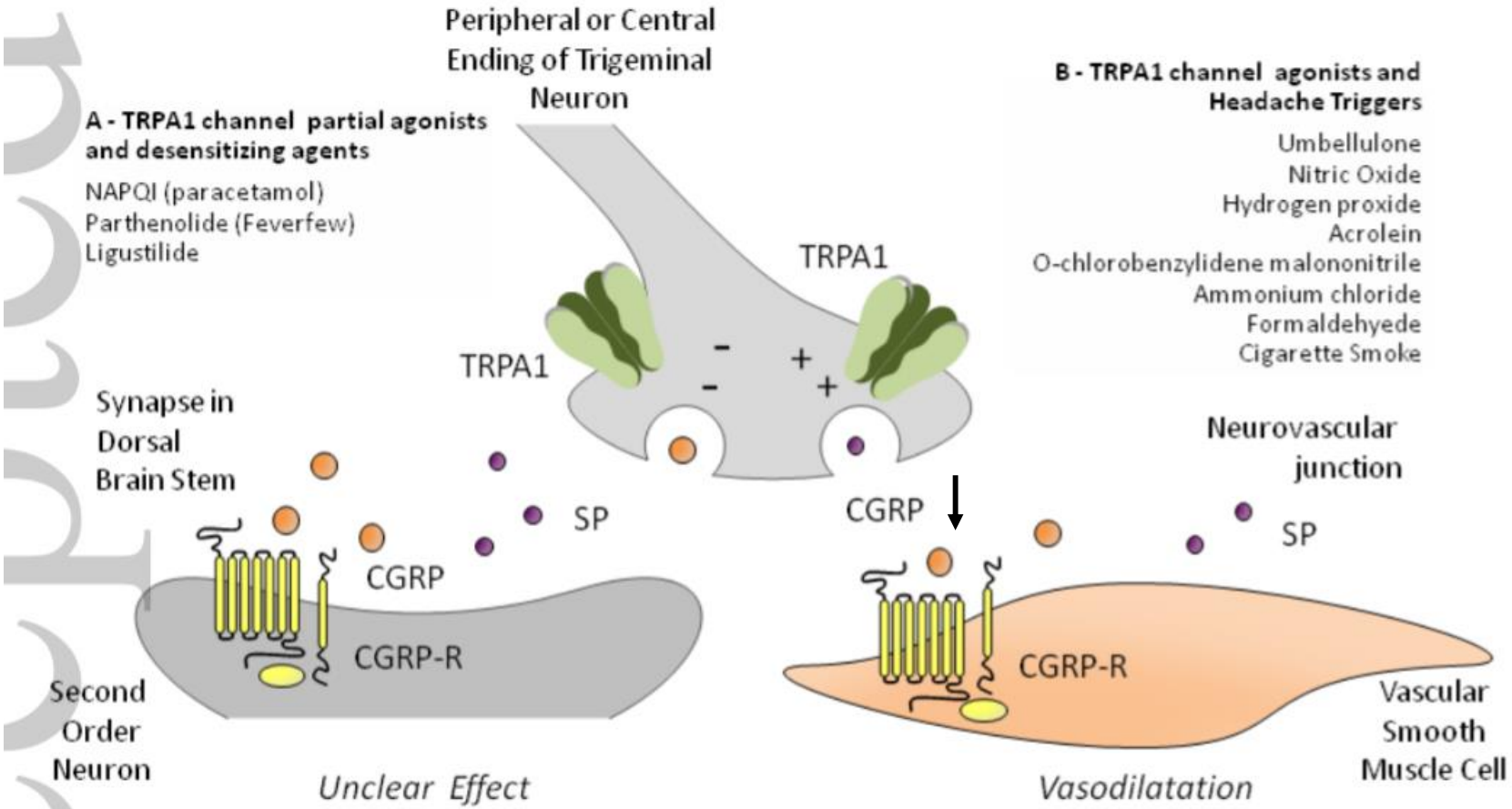
(2012). *The Effects of Magnesium, l-Carnitine, and Concurrent Magnesium–l-Carnitine Supplementation in Migraine Prophylaxis. Biological Trace Element Research, 150(1-3), 42–48.*

FITOTERÁPICOS NA ENXAQUECA

PETASITES HYBRIDUS

Fig. 2 Butterbur plant [102]

Putatively active chemical constituents of *Petasites* are the sesquiterpenes petasin and isopetasin as well as volatile oils, flavonoids and tannins



(2014). The TRPA1 channel in migraine mechanism and treatment. British Journal of Pharmacology, 171(10), 2552–2567. doi:10.1111/bph.12512

EFEITOS ANTIINFLAMATÓRIOS (REDUÇÃO DA ATIVIDADE DA LOX E DA COX-2)

Rajapakse, T., & Davenport, W. J. (2019). *Phytomedicines in the Treatment of Migraine. CNS Drugs.*doi:10.1007/s40263-018-0597-2

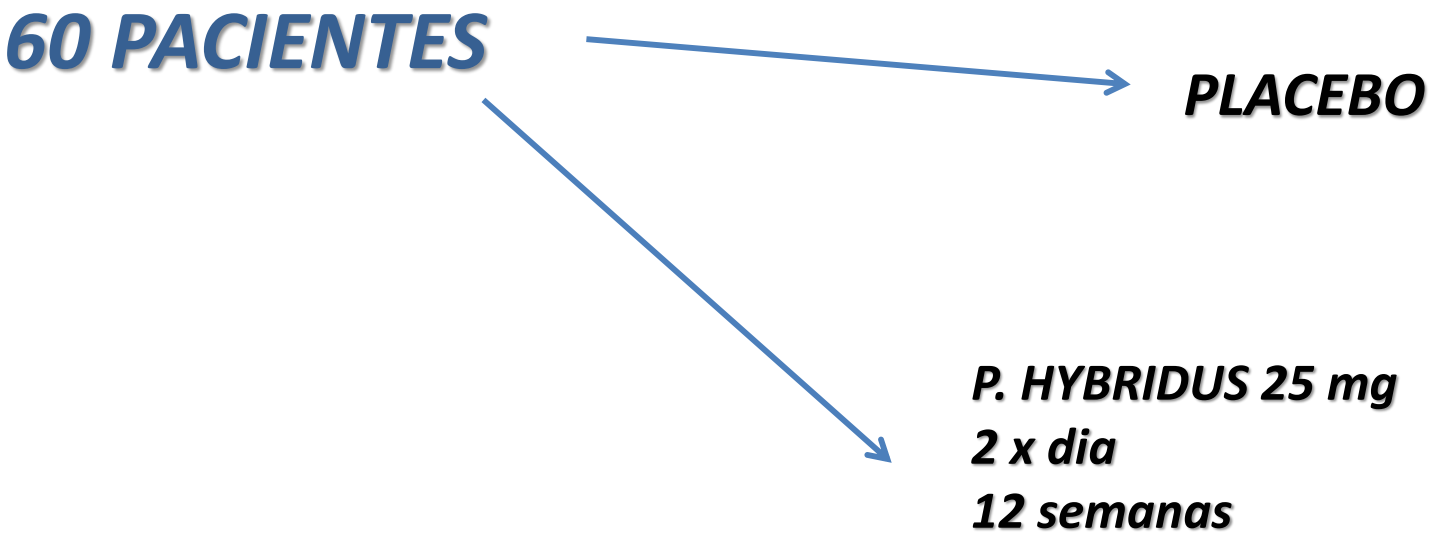
Table 1 Classification of migraine preventive therapies (available in the United States)

Level A: Medications with established efficacy (≥2 Class I trials)	Level B: Medications are probably effective (1 Class I or 2 Class II studies)	Level C: Medications are possibly effective (1 Class II study)	Level U: Inadequate or conflicting data to support or refute medication use	Other: Medications that are established as possibly or probably ineffective
Herbal preparations, vitamins, minerals, and other	NSAIDs	NSAIDs	NSAIDs	Probably not effective
Petasites	Fenoprofen[a]	Flurbiprofen[a]	Aspirin	Leukotriene receptor antagonist
	Ibuprofen[a]	Mefenamic acid[a]	Indomethacin[a]	Montelukast
	Ketoprofen[a]	Herbal preparations vitamins, minerals, and other	Herbal preparations vitamins, minerals, and other	
	Naproxen[a]	Co-Q10	Omega-3	
	Naproxen sodium[a]	Estrogen	Other	
	Herbal preparations, vitamins, minerals, and other	Antihistamine	Hyperbaric oxygen	
	Magnesium	Cyproheptadine		
	MIG-99 (feverfew)			
	Riboflavin			
	Histamines			
	Histamine SC			

Abbreviation: NSAID = nonsteroidal anti-inflammatory drug.
[a] Indicates classification based on original guideline and new evidence not found for this report.

Holland, S., Silberstein, S. D., Freitag, F., Dodick, D. W., Argoff, C., & Ashman, E. (2012). Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults. Neurology, 78(17), 1346–1353.

doi:10.1212/wnl.0b013e3182535d0c



Results: The frequency of migraine attacks decreased by a maximum of **60% compared** to the baseline

the results suggest that migraine patients can benefit from prophylactic treatment with this special extract.

Grossman W, Schmidramsl H. An extract of Petasites hybridus is effective in the prophylaxis of migraine. Altern Med Rev 2001;6:303–310.

Neurology®

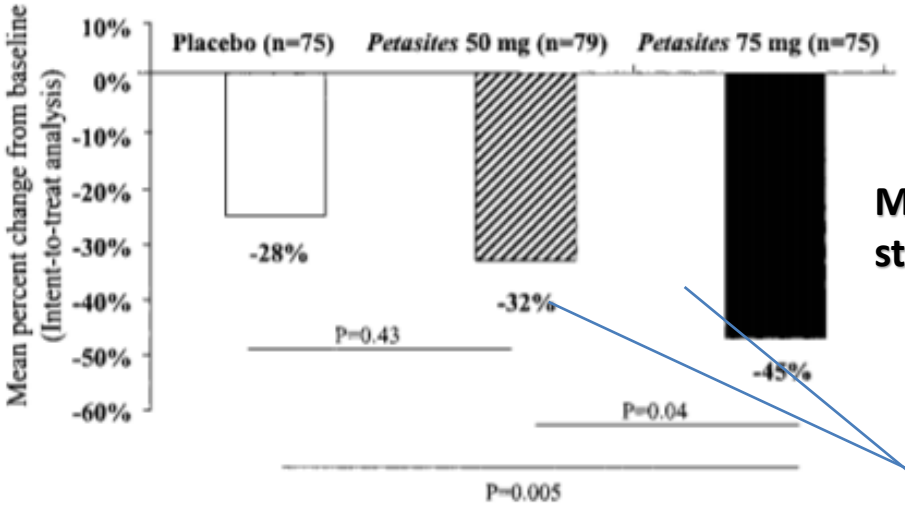
AMERICAN ACADEMY OF NEUROLOGY®

***Petasites hybridus* root (butterbur) is an effective preventive treatment for migraine**

R. B. Lipton, H. Göbel, K. M. Einhäupl, et al.

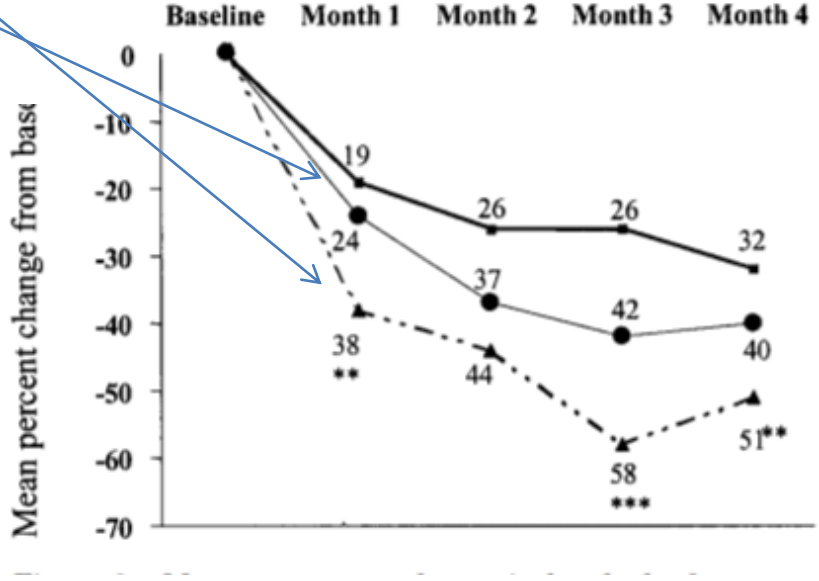
Neurology 2004;63;2240-2244
DOI 10.1212/01.WNL.0000147290.68260.11

This information is current as of December 28, 2004



Mean percentage change in headache frequency by study month

Reduction in headache frequency



Can J Neurol Sci. 2012 Mar;39(2 Suppl 2):S1-59.

Canadian Headache Society guideline for migraine prophylaxis.

Pringsheim T[1], Davenport W, Mackie G, Worthington I, Aubé M, Christie SN, Gladstone J, Becker WJ; Canadian Headache Society Prophylactic Guidelines Development Group.

Collaborators (23)

Author information

SUBSTÂNCIAS COM ÓTIVAS EVIDÊNCIAS DE INDICAÇÃO NA PROFILAXIA DA ENXAQUECA .

DENTRE ELAS :

Petasites Hybridus, riboflavin, coenzyme Q10, and magnesium citrate

Systematic Review and Meta-Analysis

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Therapeutic role of melatonin in migraine prophylaxis

A systematic review

Rujin Long, MD*, Yousheng Zhu, MD, Shusheng Zhou, MD

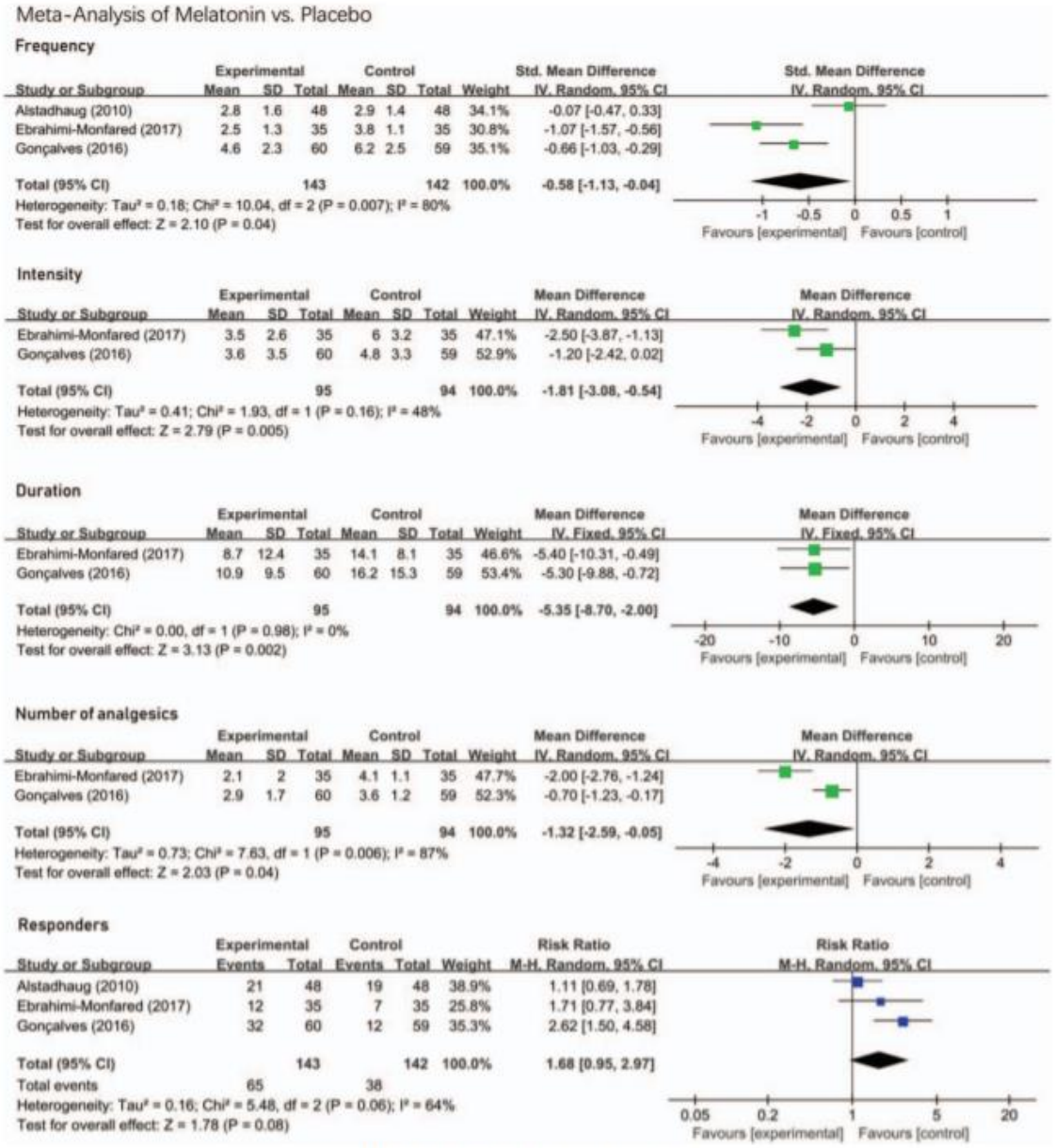

Figure 3. Meta-analysis of melatonin vs. placebo.

Medicine (Baltimore). 2019 Jan; 98(3): e14099.

Ann Transl Med. 2016 Mar;4(6):105. doi: 10.21037/atm.2016.03.13.

Migraine in the era of precision medicine.

Zhang LM[1], Dong Z[1], Yu SY[1].

Author information

Abstract

Migraine is a common neurovascular disorder in the neurologic clinics whose mechanisms have been explored for several years. The aura has been considered to be attributed to cortical spreading depression (CSD) and dysfunction of the trigeminovascular system is the key factor that has been considered in the pathogenesis of migraine pain. Moreover, three genes (CACNA1A, ATP1A2, and SCN1A) have come from studies performed in individuals with familial hemiplegic migraine (FHM), a monogenic form of migraine with aura. Therapies targeting on the neuropeptids and genes may be helpful in the precision medicine of migraineurs. 5-hydroxytryptamine (5-HT) receptor agonists and calcitonin gene-related peptide (CGRP) receptor antagonists have demonstrated efficacy in the acute specific treatment of migraine attacks. Therefore, ongoing and future efforts to find new vulnerabilities of migraine, unravel the complexity of drug therapy, and perform biomarker-driven clinical trials are necessary to improve outcomes for patients with migraine.

KEYWORDS: Migraine; genes; neuropeptides; precision medicine

PMID: 27127758 PMCID: PMC4828749 DOI: 10.21037/atm.2016.03.13

NA PRÁTICA CLÍNICA

- ***CONTROLE DA INFLAMAÇÃO***
  - ***CG DA DIETA***
  - ***W3 / W6 / GS***
  - ***DISBIOSE***
  - ***FITOQUÍMICOS***
- ***ANAMNESE DO PACIENTE / GATILHOS***
- ***CONTROLE DA HIPEREXCITABILIDADE NEURONAL (Mg / Zn), RETIRAR ASPARTAME***
- ***COENZIMAS MITOCONDRIAIS (B2, COQ 10, L-CARNITINA, B3) E HIDRATAÇÃO ADEQUADA E MELHORA DE PERFUSÃO SANGUÍNEA***
- ***PETASYDES HIBRIDUS (ANTIINFLAMATÓRIO / REDUÇÃO LIBERAÇÃO DE CGRP)***
- ***EXAMES COMPLEMENTARES (IgG / IgE)***

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