

Pain Management: Symptomatic Relief of Inflammation

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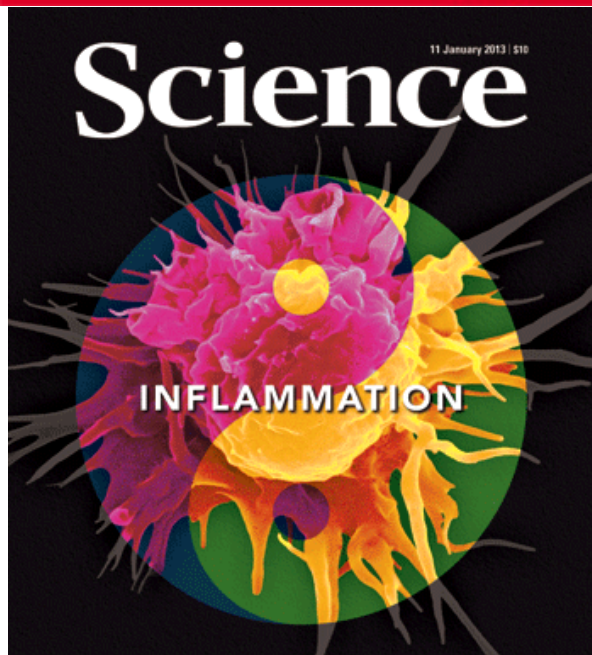
@DrB_Well



Too Much or Too Little Sleep Linked to Inflammation

Can Exercise Cause Inflammation in the Body?

Just 20 minutes of exercise enough to reduce inflammation, study finds



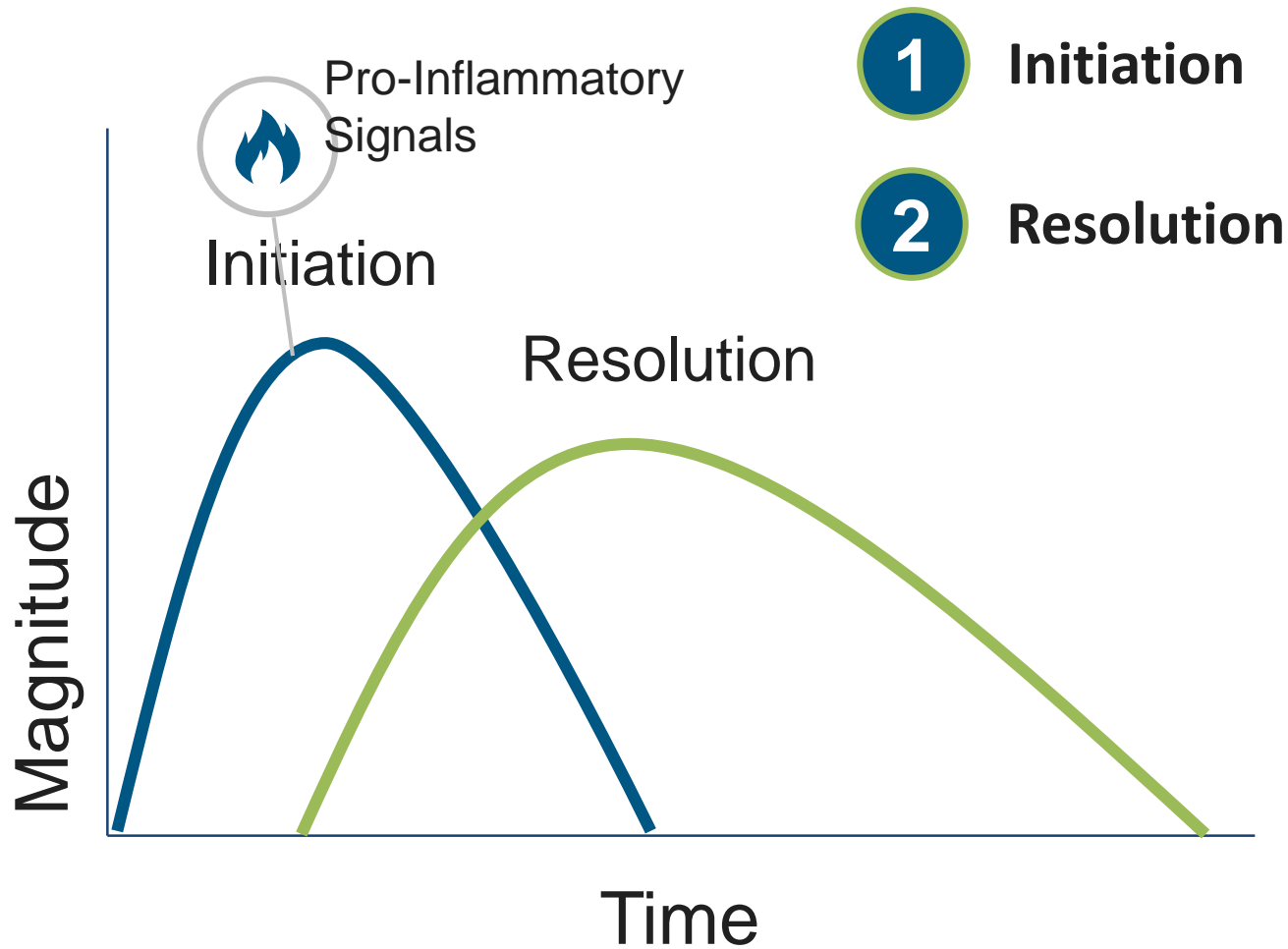
Irwin MR, et al. . Sleep disturbance, sleep duration, and inflammation: a systematic review and meta-analysis of cohort studies and experimental sleep deprivation. *Biological psychiatry*. 2016 Jul 1;80(1):40-52.

Dimitrov S et al. Inflammation and exercise: inhibition of monocytic TNF production by acute exercise via β 2-adrenergic activation. *Brain, Behavior, and Immunity*. 2016 Dec 21.

Overview: Understand

1. Inflammation: **timing & stages** matter
2. Inflammation manifests as key **causes** of pain (and disability)
3. Inflammation has many **sources** that travels down **key pathways**
4. New upstream approaches can **modify** these pathways and **resolve** ongoing inflammation

Inflammation Has Two Stages

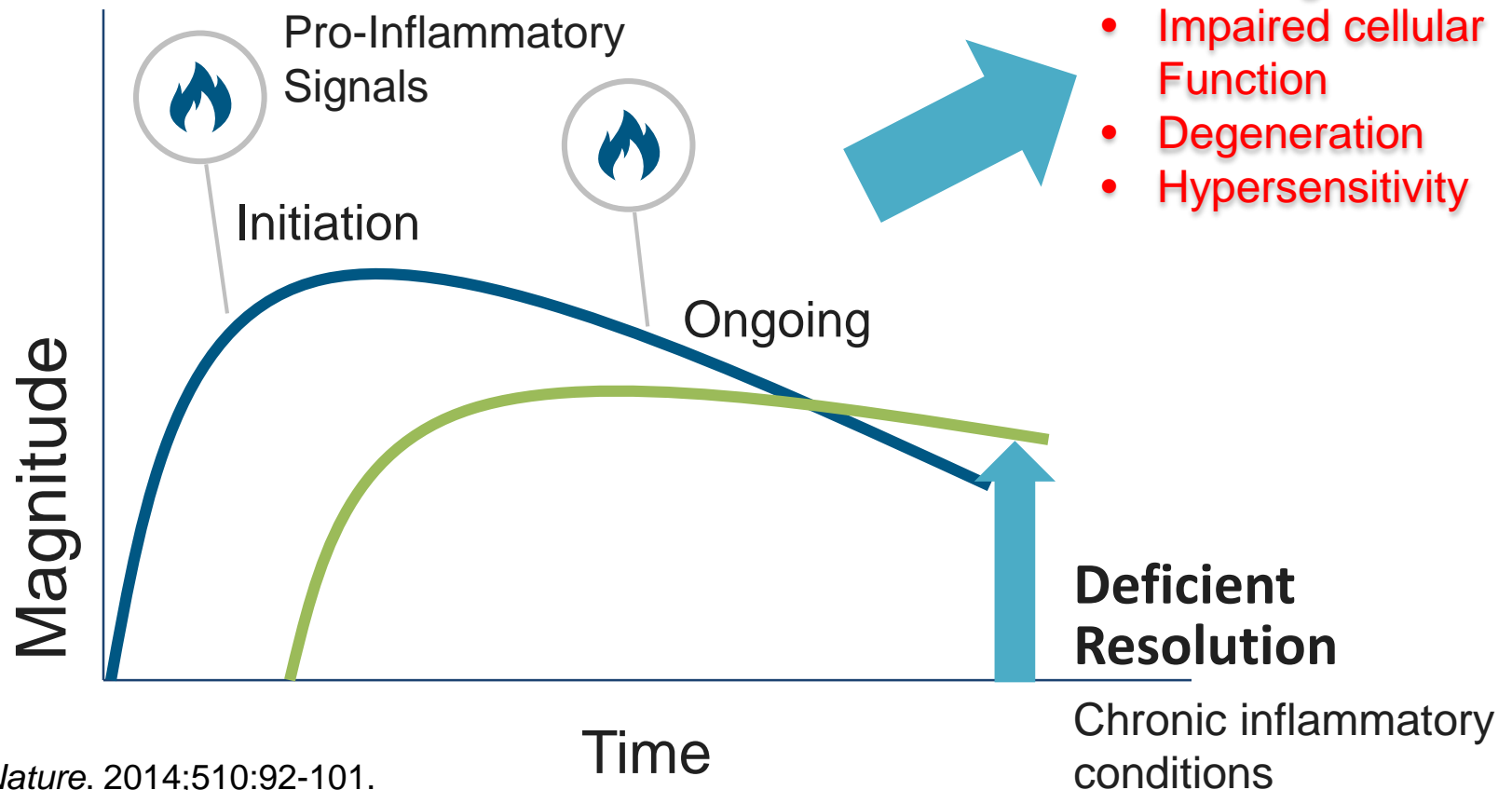


Serhan CN. *Nature*. 2014;510:92-101.

Spite et al. *Cell Metab*. 2014;19:21-36.

Without Resolution, Inflammation Can Become Persistent & Chronic

If the immune response is left unresolved, tissues can be **negatively impacted over time**.

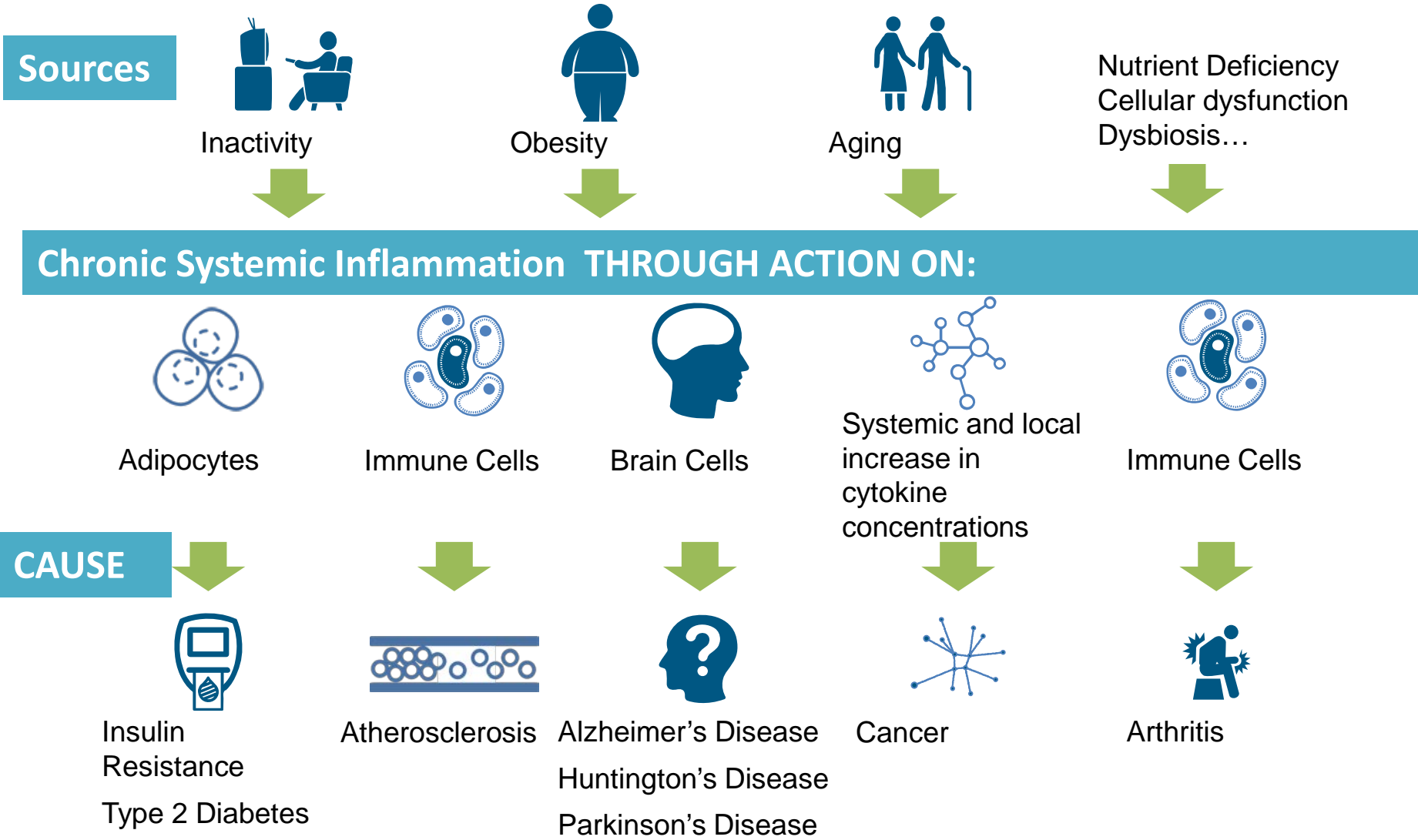


Serhan CN. *Nature*. 2014;510:92-101.

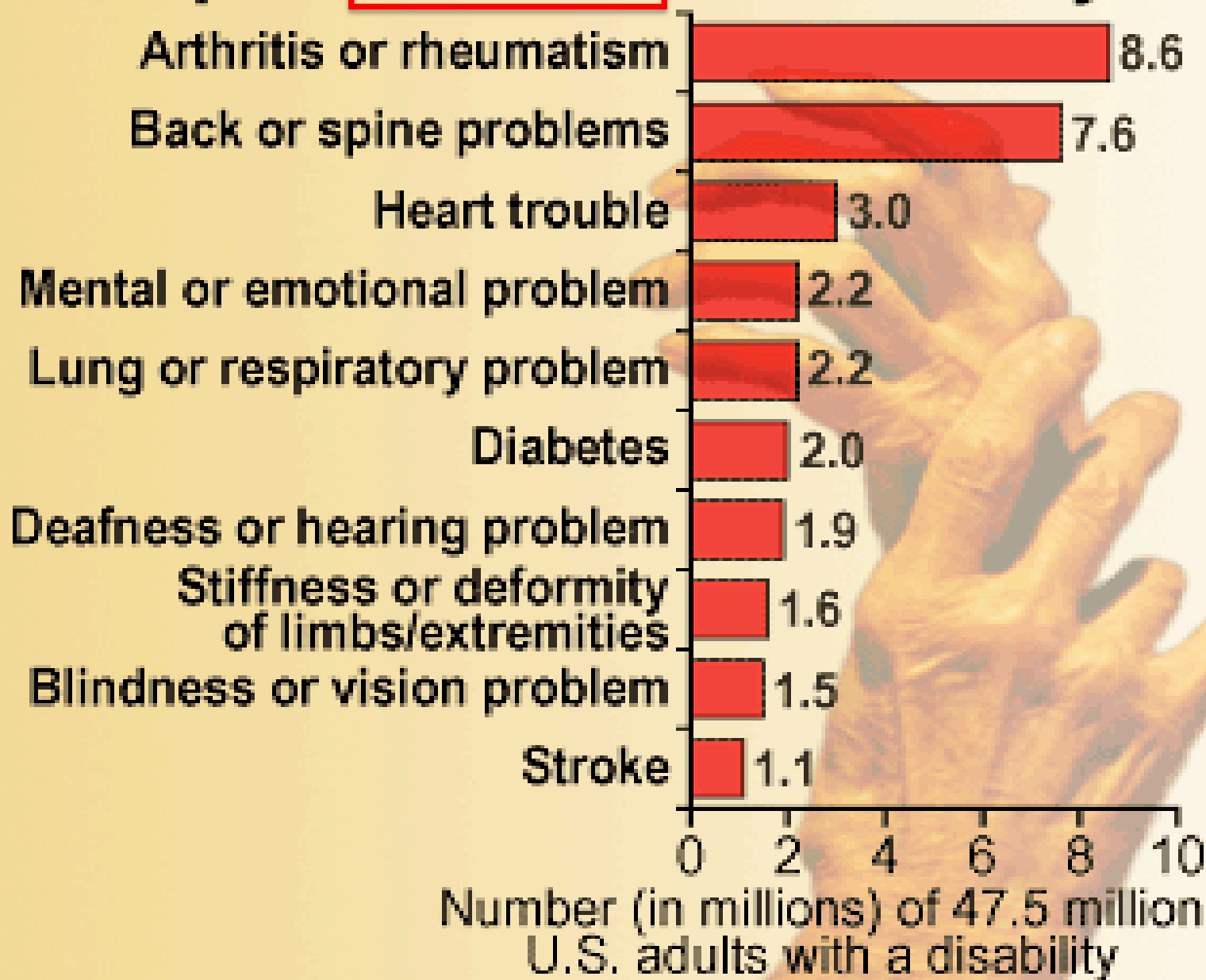
Spite et al. *Cell Metab*. 2014;19:21-36.

Sommer C et al. *Medicine Reports*. 2011;3-19. doi-10.3410_M3-19.

Chronic Inflammation Can Lead to Chronic Diseases



Top 10 Causes of Disability



[CDC. Prevalence and Most Common Causes of Disability --- Among Adults --- United States, 2005. MMWR 58\(16\): 421-426.](#)

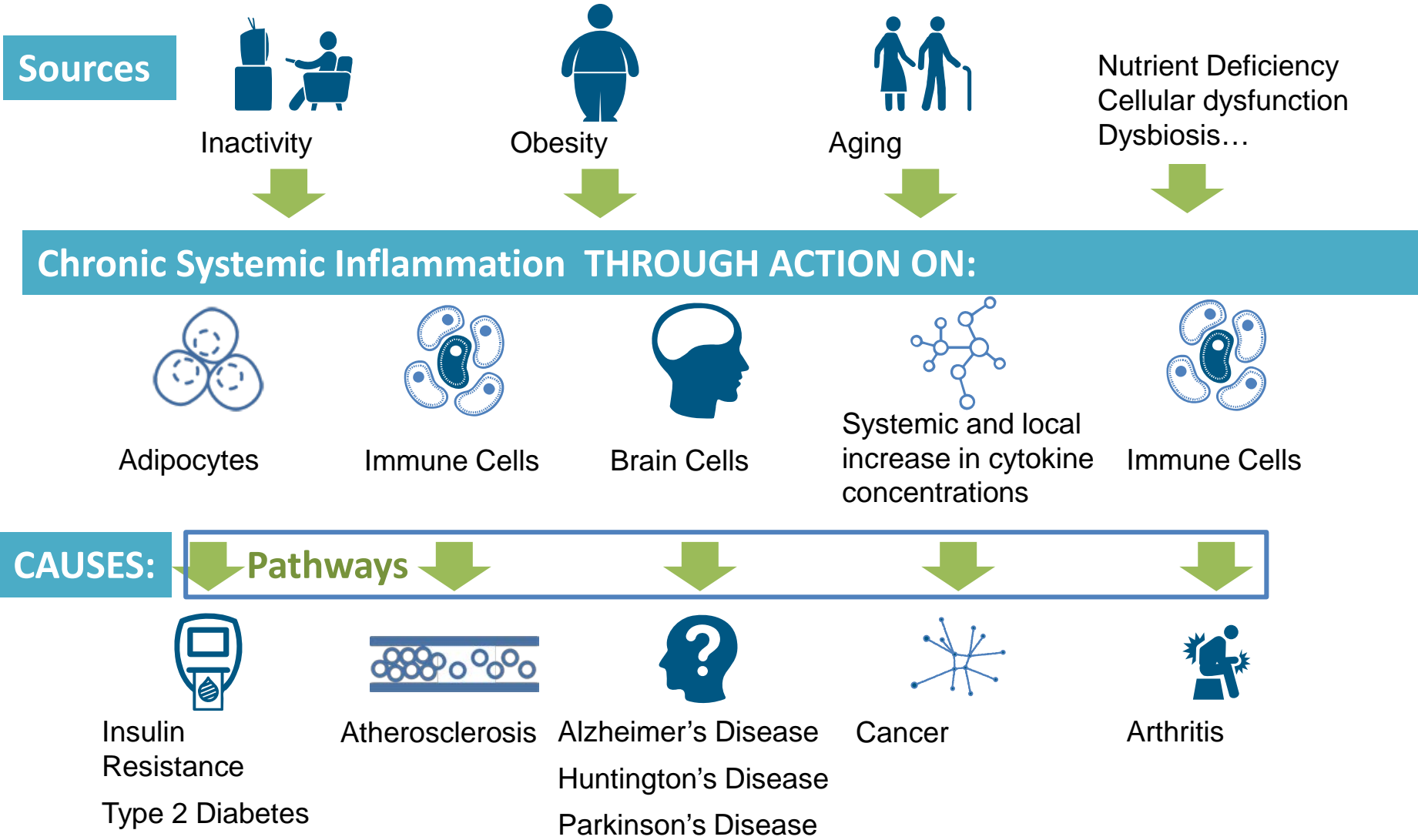
ORIGINAL ARTICLE

Relations of C-Reactive Protein and Obesity to the Prevalence and the Odds of Reporting Low Back Pain

- ..significant associations between... systemic inflammation (CRP) and LBP
- *Specifically, those with \uparrow CRP levels have nearly **twice** the odds of reporting LBP*



Chronic Inflammation Can Lead to Chronic Diseases



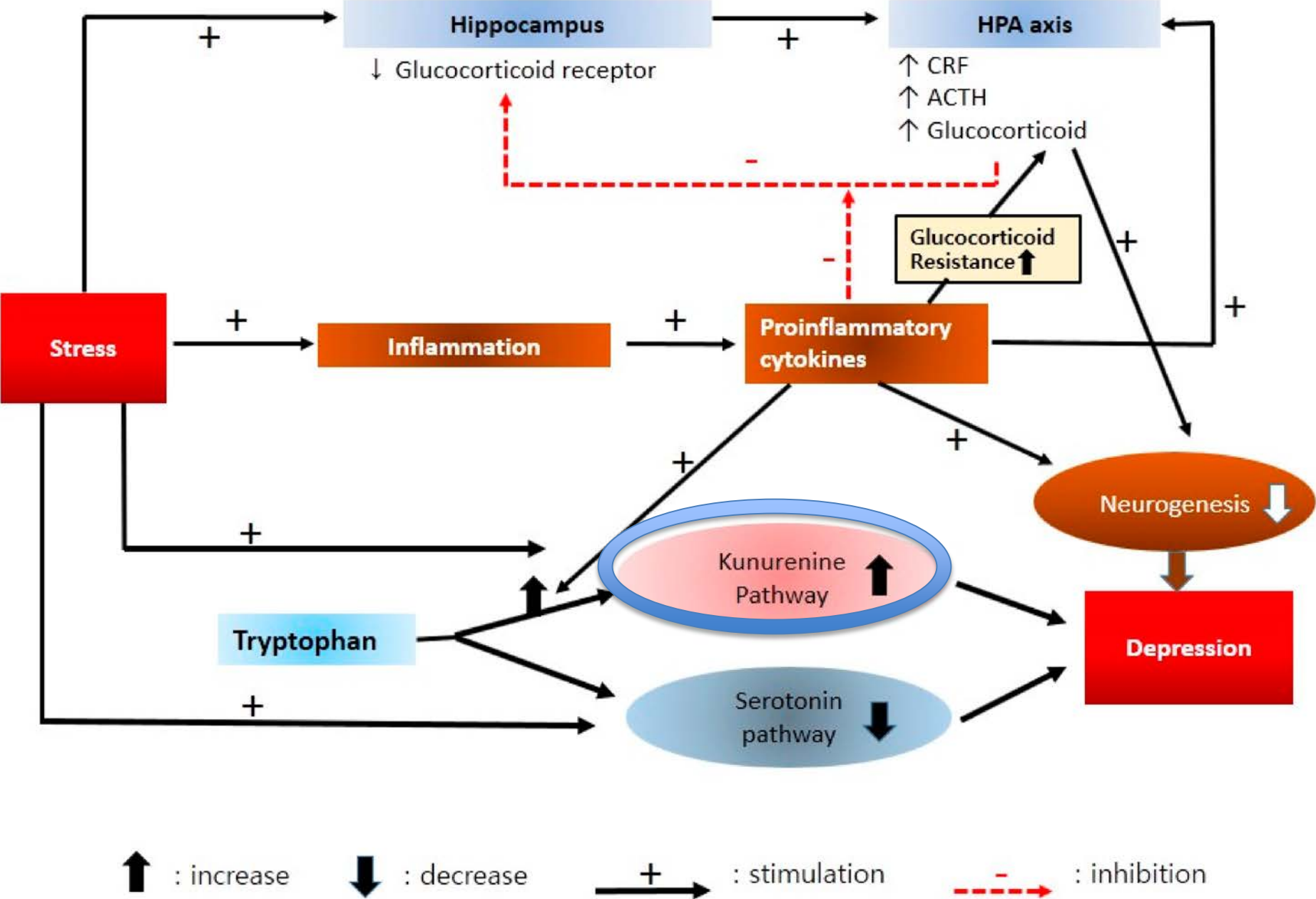
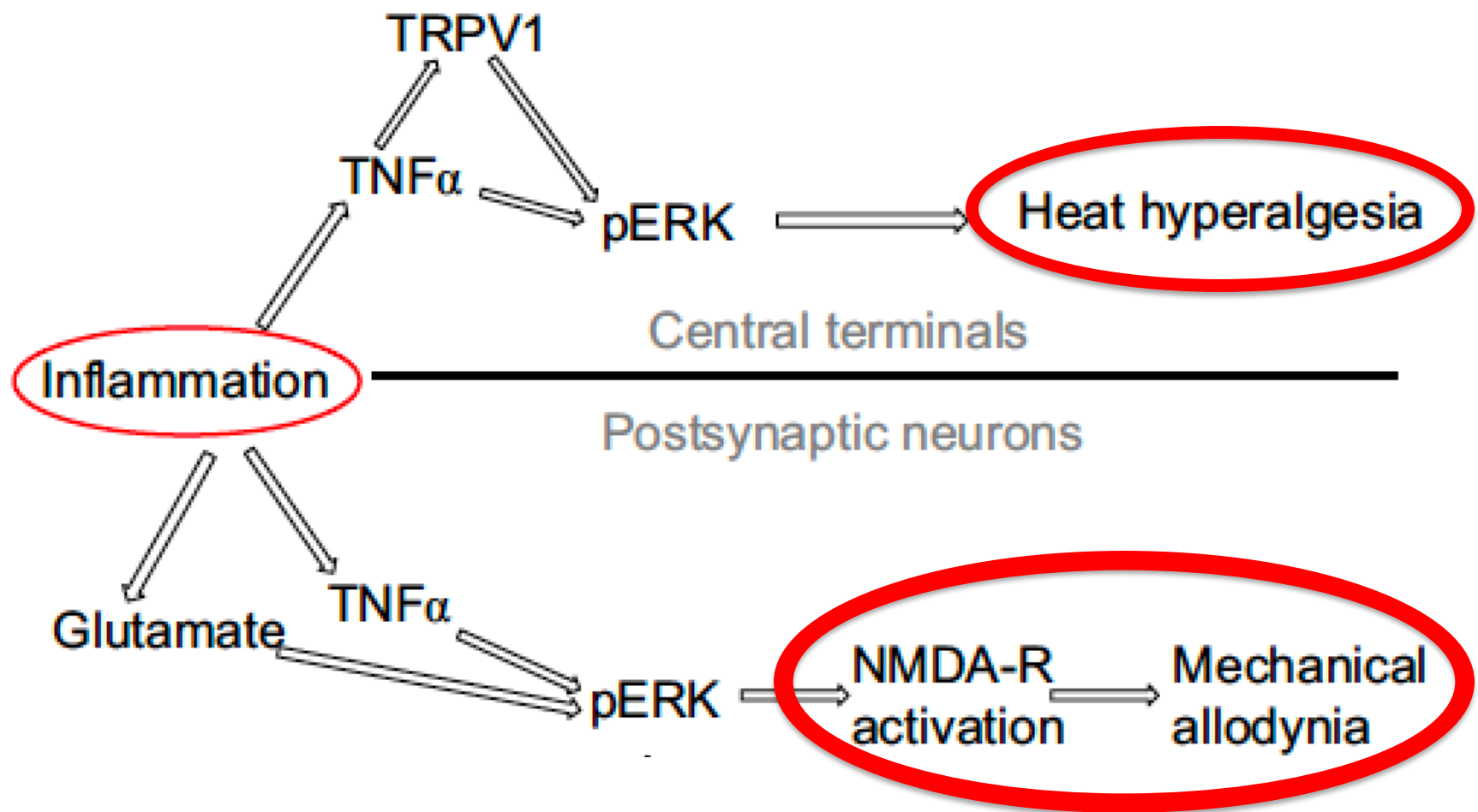


Figure 3. Assumed mode of action of RvEI in inflammatory pain



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Mind-body therapies and control of inflammatory biology: A descriptive review

- A number of lifestyle approaches can help:
 - Exercise: resistance, aerobic or combination
 - Deep breathing
 - Meditation / MBSR
 - Yoga / Tai Chi / Chi Gong
 - Sleep optimization
 - Social Support / Connection
 - Humor...

Our intake is one of the most
powerful anti-inflammatory
tools

Research shows typical American diet can worsen chronic pain

16 December 2015, by Katherine Shonesy

- *“resulted in altered acute nociceptive sensitivity, systemic inflammation, and persistent pain...”*



High fructose consumption combined with low dietary magnesium intake may increase the incidence of the metabolic syndrome by inducing inflammation*

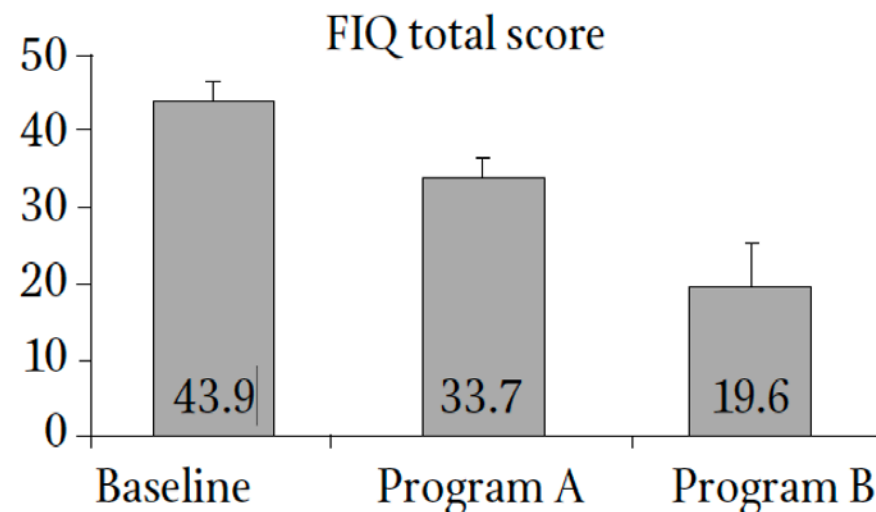
Dietary Strategies for Lowering Inflammation & Pain → R's

Description	Action
Low Allergenic	Remove Allergens, artificial colorings, sweeteners
Low Glycemic Load	Reduce High glycemic foods, processed simple carbs
Mindful portions/pace	Reduce Excess calories / pace
High polyphenol Medical foods	Repair GI Function Replace with phytonutrients
SPMs	Reverse inflammatory cycle
Nutrient Repletion	Replenish Mag Vitamin D CoQ10
Nutrient Support	Rebalance Probiotics Curcumin Ginger Hops

A Program Consisting of a Phytonutrient-rich Medical Food and an Elimination Diet Ameliorated Fibromyalgia Symptoms and Promoted Toxic-element Detoxification in a Pilot Trial

1. Eliminate Allergenic foods & 2.

- Refined and added simple sugars
- Artificial colorings, sweeteners;
- Caffeinated beverages;
- Gluten-containing grains;
- Eggs & dairy products
- Hi arachidonic acid foods



Mindful Portion & Rate

Cutting Calories Reduces Dangerous Inflammation

Non-obese people who ate 12% less showed benefits that might protect against chronic disease.

- Faster eating (<15 min to complete meal) associated with ↑ interleukin-1 β IL-6 even after accounting for caloric intake & BMI

Mochizuki K, Misaki Y, Miyauchi R, et al. A higher rate of eating is associated with higher circulating interleukin-1 β concentrations in Japanese men not being treated for metabolic diseases. *Nutrition* 2012;28:978–83

Eating rate is associated with cardiometabolic risk factors in Korean adults Lee, K.S. et al. *Nutrition, Metabolism and Cardiovascular Diseases*, Volume 23, Issue 7, 635 - 641

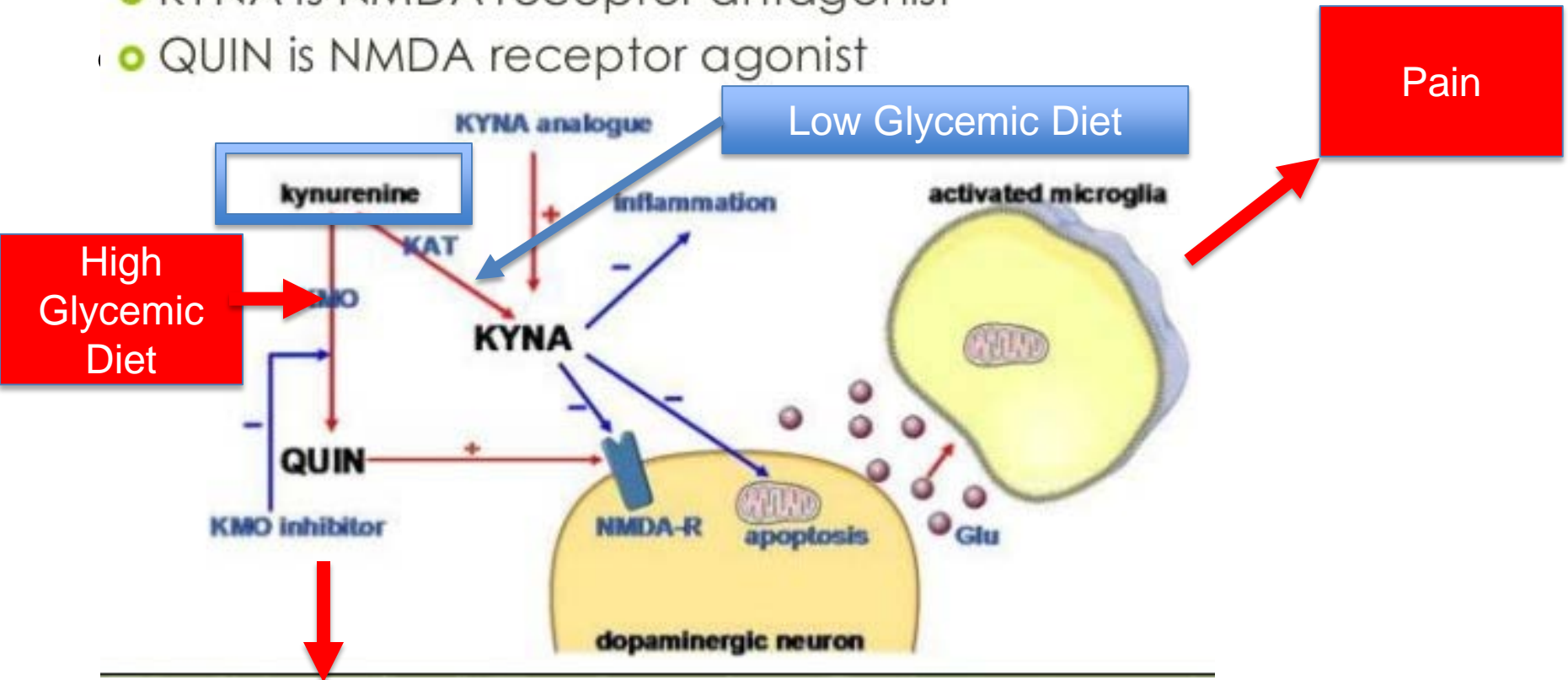
Meydani SN, Das S, Pieper CF, Lewis MR, Klein S, Dixit VD, Gupta A, Villareal DT, Bhapkar M, Huang M, Fuss PJ, Roberts SB et al. "Long-term calorie restriction inhibits inflammation without impairing cell-mediated immunity: A randomized controlled trial in non-obese humans." *Aging*, 8 (7). Published online July 13, 2016.

Targeted plasma metabolome response to variations in dietary glycemic load in a randomized, controlled, crossover feeding trial in healthy adults

- Low Glycemic load diet increased kynurenate by ~40%
 - compared with the HGL diet

Kynurenic and Quinolinic Acids Bind to NMDA Receptors

- KYNA is NMDA receptor antagonist
- QUIN is NMDA receptor agonist



MINIREVIEW

Quinolinic acid, the inescapable neurotoxin

Gilles J. Guillemin^{1,2}

Polyphenols

(Anti-oxidant / Anti-inflammatory)

Apples: Provide polyphenols



Blackberries: High levels of anthocyanins

Black tea: Theaflavins



Blueberries: High levels of anthocyanins

Broccoli: A range of health-giving polyphenols

Cereal bran: High in fibre and phenolic acids

Cherries: Contain antioxidant anthocyanins

Cherry tomatoes: High levels of quercetin

Coffee: Phenolic acids

Cranberries: Procyanadin, which can prevent infections

Dark chocolate: Cocoa contains epicatechin

Green tea: Polyphenols

Oranges: Contain hesperedin, which aids a healthy heart

Peaches: Contain epicatechin and phenolic acids



Plums: Similar role to peaches



Raspberries: Contain anthocyanins

Red grapes: Anthocyanins and phenolic acids

Red onions: High levels of cancer-fighting quercetin

Spinach: Polyphenols

Strawberries: Contain anthocyanins and ellagic acid

www.EWG.org

Polyphenols to the Rescue

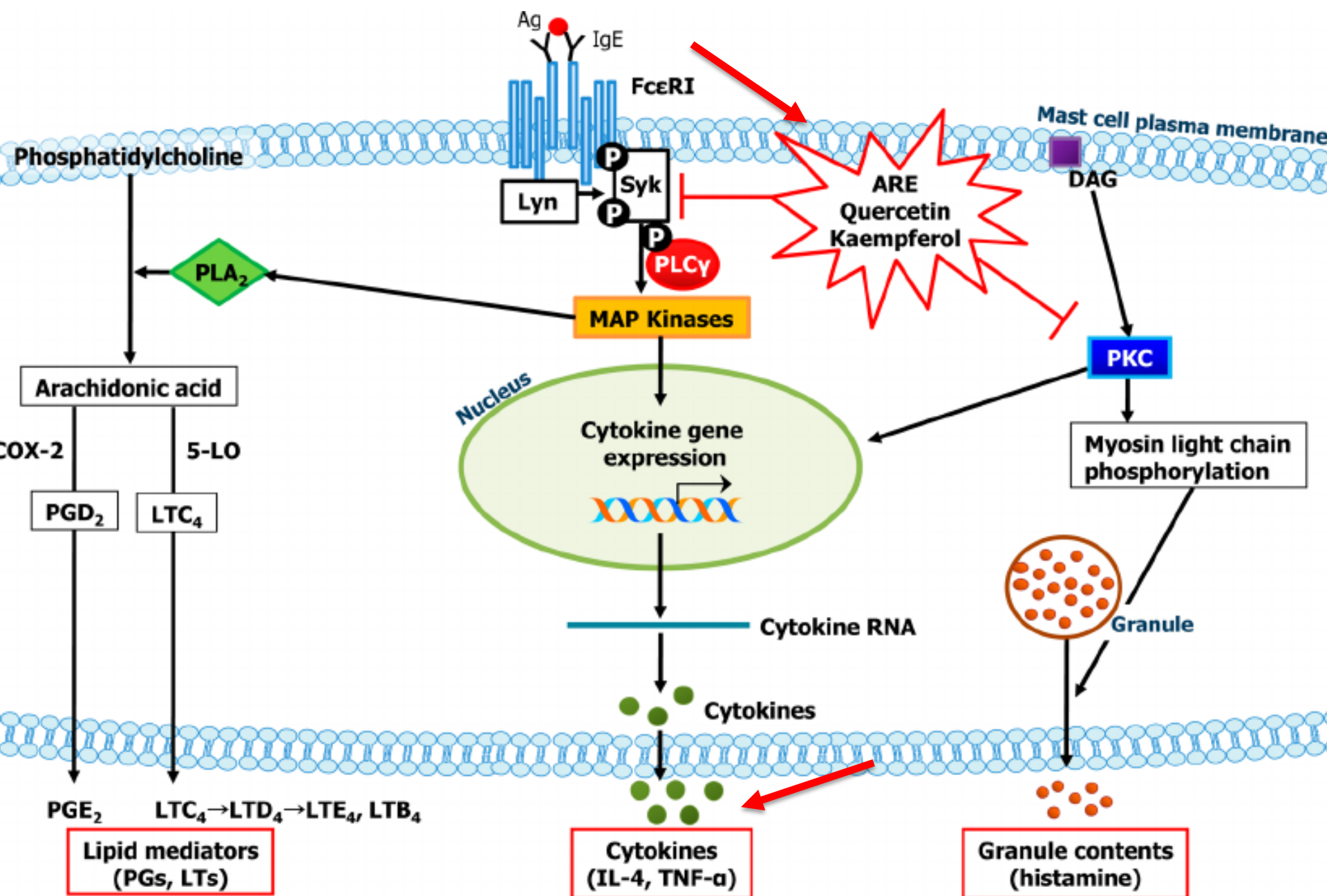
Kaempferol, a dietary flavonoid, ameliorates acute inflammatory and nociceptive symptoms in gastritis, pancreatitis, and abdominal pain

- *Kaempferol (KF) is the most abundant polyphenol in tea, fruits, vegetables, and beans*

https://www.researchgate.net/profile/Woo_Yang2/publication/275586979_Kaempferol_a_dietary_flavonoid_ameliorates_acute_inflammatory_and_nociceptive_symptoms_in_gastritis_pancreatitis_and_abdominal_pain/links/5594c5ff08ae99aa62c5ad1c.pdf

Kim SH, et al. Kaempferol, a dietary flavonoid, ameliorates acute inflammatory and nociceptive symptoms in gastritis, pancreatitis, and abdominal pain. *Molecular nutrition & food research*. 2015 Jul 1;59(7):1400-5.

Devi KP, Malar DS, Nabavi SF, Sureda A, Xiao J, Nabavi SM, Daglia M. Kaempferol and inflammation: From chemistry to medicine. *Pharmacological research*. 2015 Sep 30;99:1-0.



Kim M, Lim SJ, Kang SW, Um BH, Nho CW. Aceriphyllum rossii extract and its active compounds, quercetin and kaempferol inhibit IgE-mediated mast cell activation and passive cutaneous anaphylaxis. Journal of agricultural and food chemistry. 2014 Apr 17;62(17):3750-8.

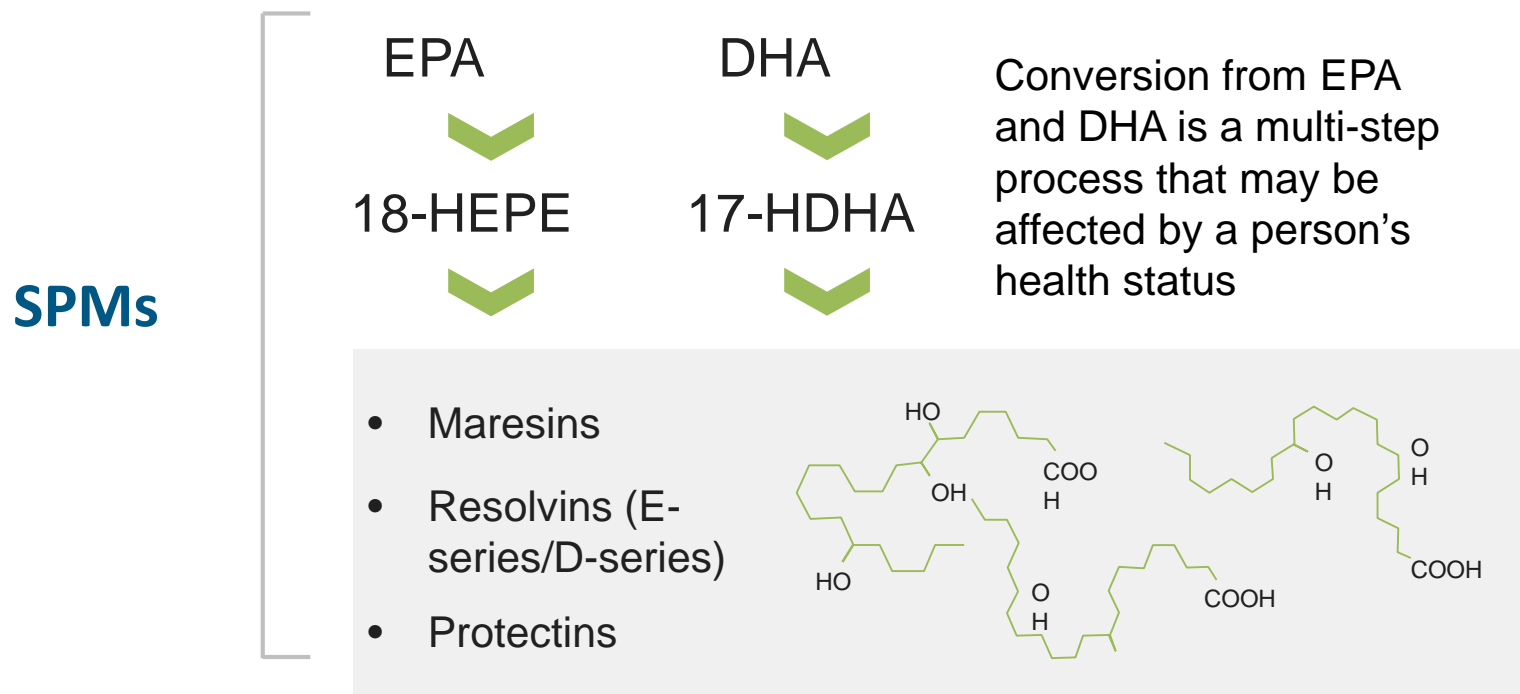
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Specialized Pro-Resolving Mediators

SPMs

- EPA and DHA are converted to SPMs that resolve inflammation
But the conversion is inefficient in the face of inflammation



Different SPMs work together to resolve the immune response and inflammation.

17-HDHA & 18-HEPE is reduced following fish oil supplementation in Metabolic Syndrome patients compared with healthy controls

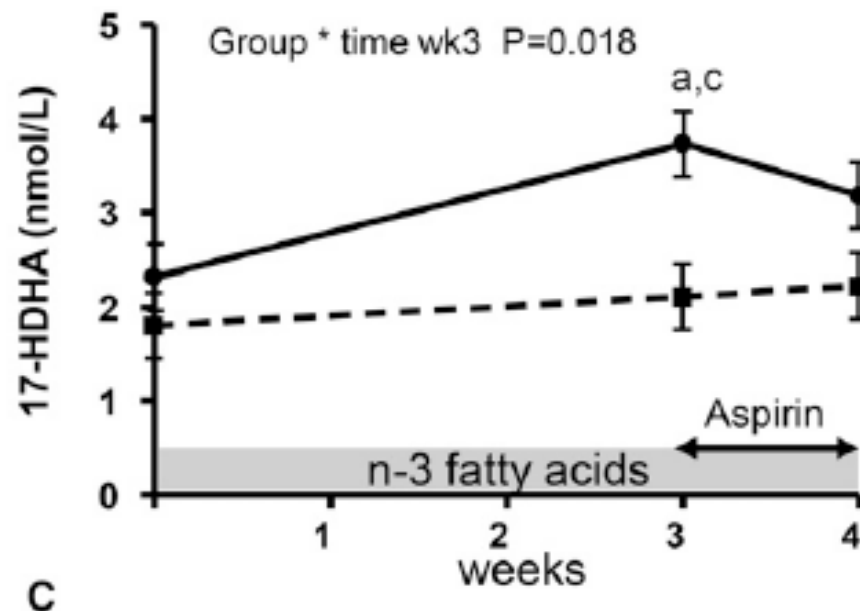
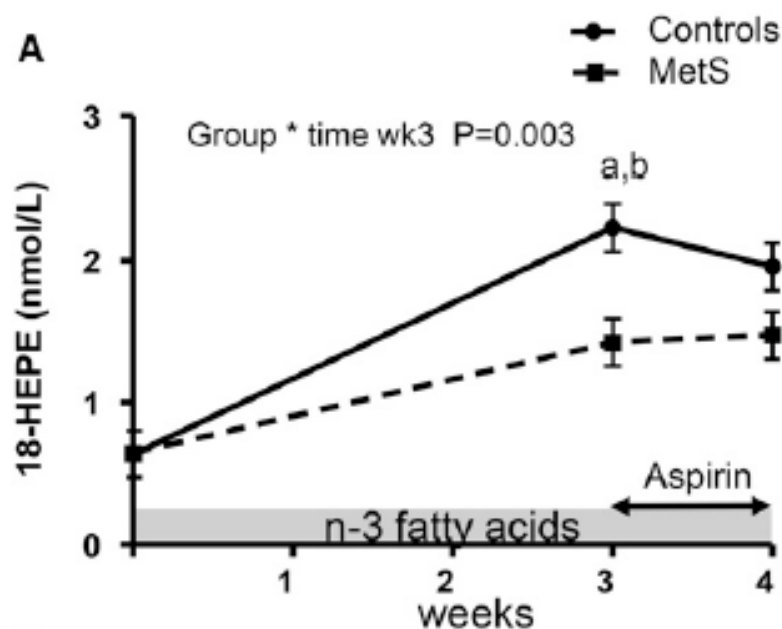
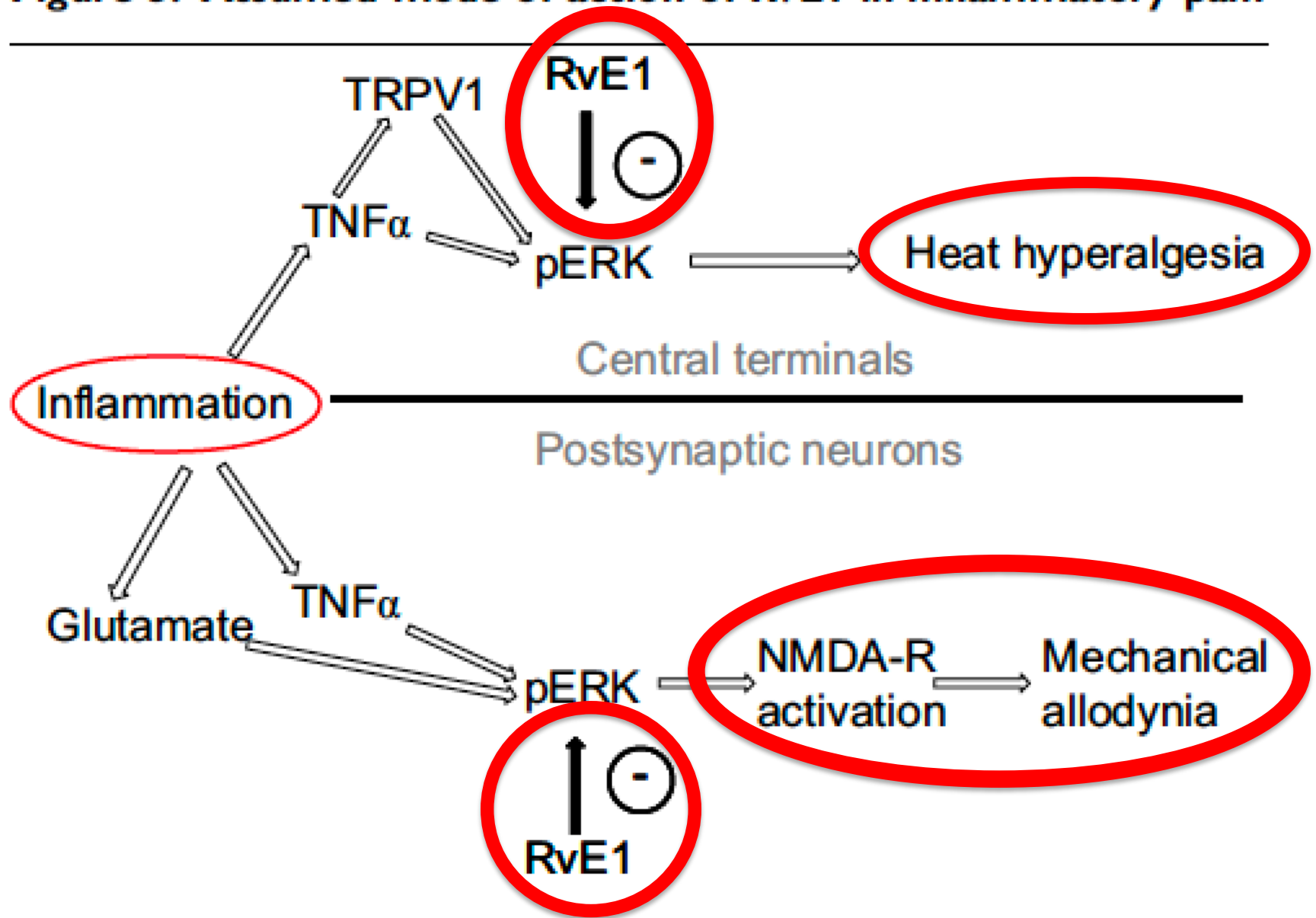


Figure 3. Assumed mode of action of RvE1 in inflammatory pain



IRB-approved multi-center open case series

Study Goals:

- ✓ Understand the role of SPMs in clinical management of chronic inflammatory conditions
- ✓ Assess the impact of 6 softgels per day for 4 weeks and potential for significant difference when dose was increased to 8 softgels per day. Doses chosen considering the chronic inflammatory nature of the patient types

Patients with inflammatory conditions/symptoms (n=34)

Inflammatory condition included:

- Chronic pain
- Fibromyalgia
- Increased inflammatory markers e.g. hsCRP

Week 1

Assessment of blood based biomarkers of inflammation, clinical assessment, subject assessment of pain, symptoms and quality of life.

Received 6 SPM softgels per day

Week 4

Assessment of blood based biomarkers of inflammation, clinical assessment, subject assessment of pain, symptoms and quality of life.

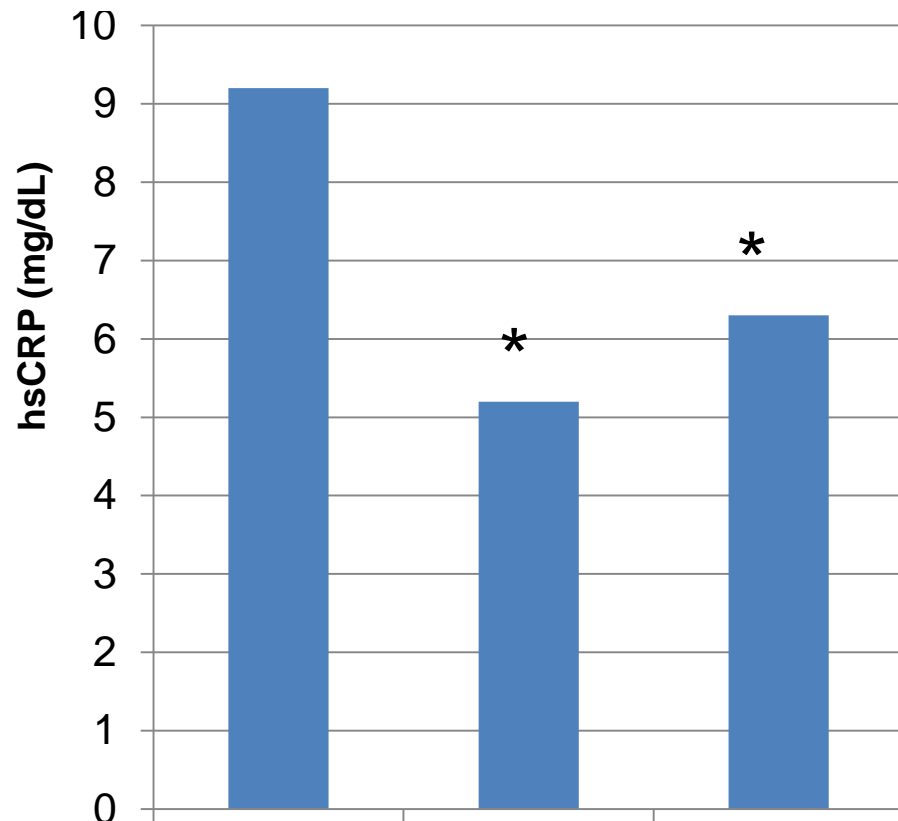
Received 8 SPM softgels per day

Week 8

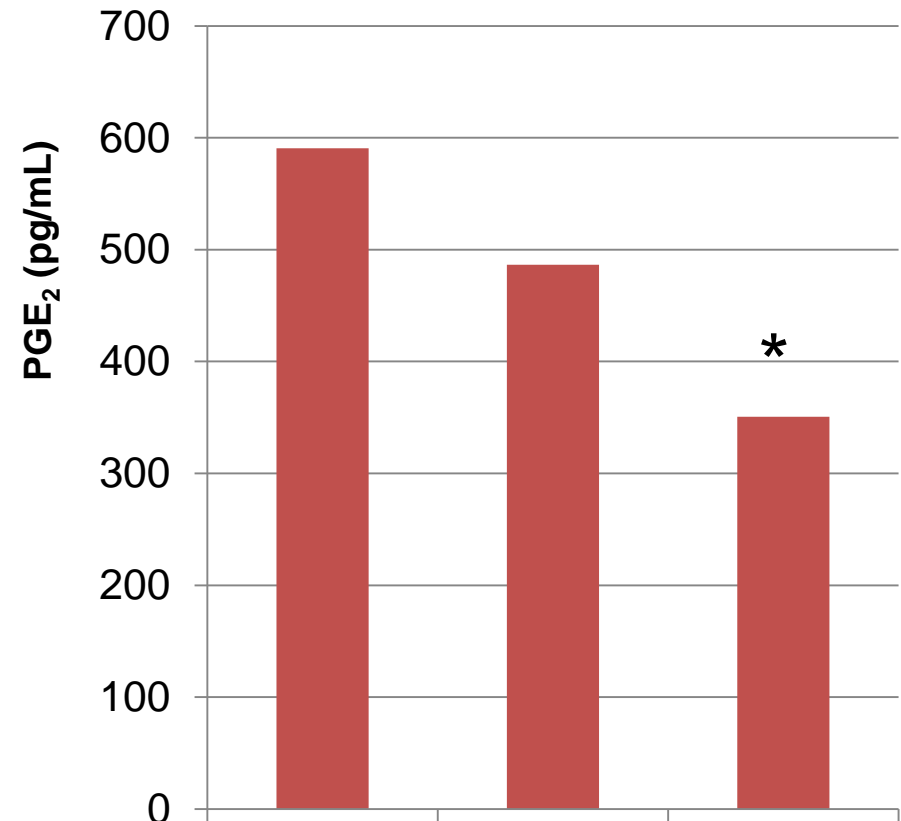
Assessment of blood based biomarkers of inflammation, clinical assessment, subject assessment of pain, symptoms and quality of life.

Key point: Inflammatory biomarkers significantly reduced – appropriate for tracking SPM response

hsCRP: 43% reduction from baseline within 4 weeks and remained significantly reduced

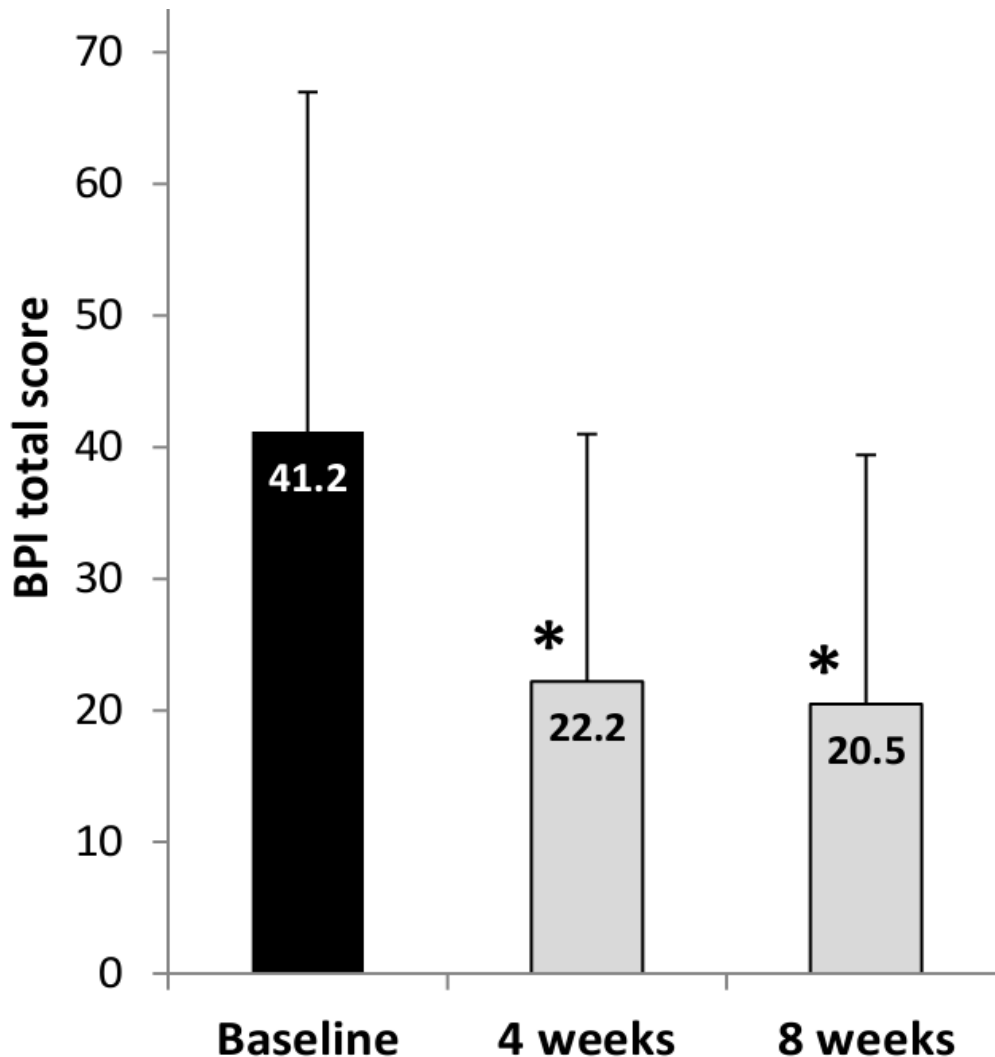


PGE₂ was reduced by 41% at 8 wks and was shown to normalize (200-400pg/mL) at 8 wks



SPMs and Pain:

Brief Pain Inventory (BPI) scores reduced significantly by 46% at 4 weeks and 50% at 8 weeks



At 4 and 8 weeks, there was a significant reduction in:

- ✓ Pain at its worst, least and average pain over last 24-hours

At 4 and 8 weeks, there was a significant reduction in interference of pain in

- ✓ General activity
- ✓ Mood
- ✓ Walking ability
- ✓ Normal work
- ✓ Relations with others
- ✓ Sleep
- ✓ Enjoyment of life

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Relations of Dietary Magnesium Intake to Biomarkers of Inflammation and Endothelial Dysfunction in an Ethnically Diverse Cohort of Postmenopausal Women

- An increase of 100 mg/day magnesium was associated with reductions in:
 - hs-CRP
 - IL-6
 - TNF--R2
 - sVCAM-1

Long term magnesium supplementation influences favourably the natural evolution of neuropathy in Mg-depleted type 1 diabetic patients (T1dm)

- RCT: 110 DM; Low Mag; (RBCMg < 2.3 mMol/l)
- Tx: to receive 300 mg Mg++ daily x 5 yrs
- EMG normalized only in early PNP
- HgA1c improved but not significant
- Longer DM and lower Mag predict worsen.

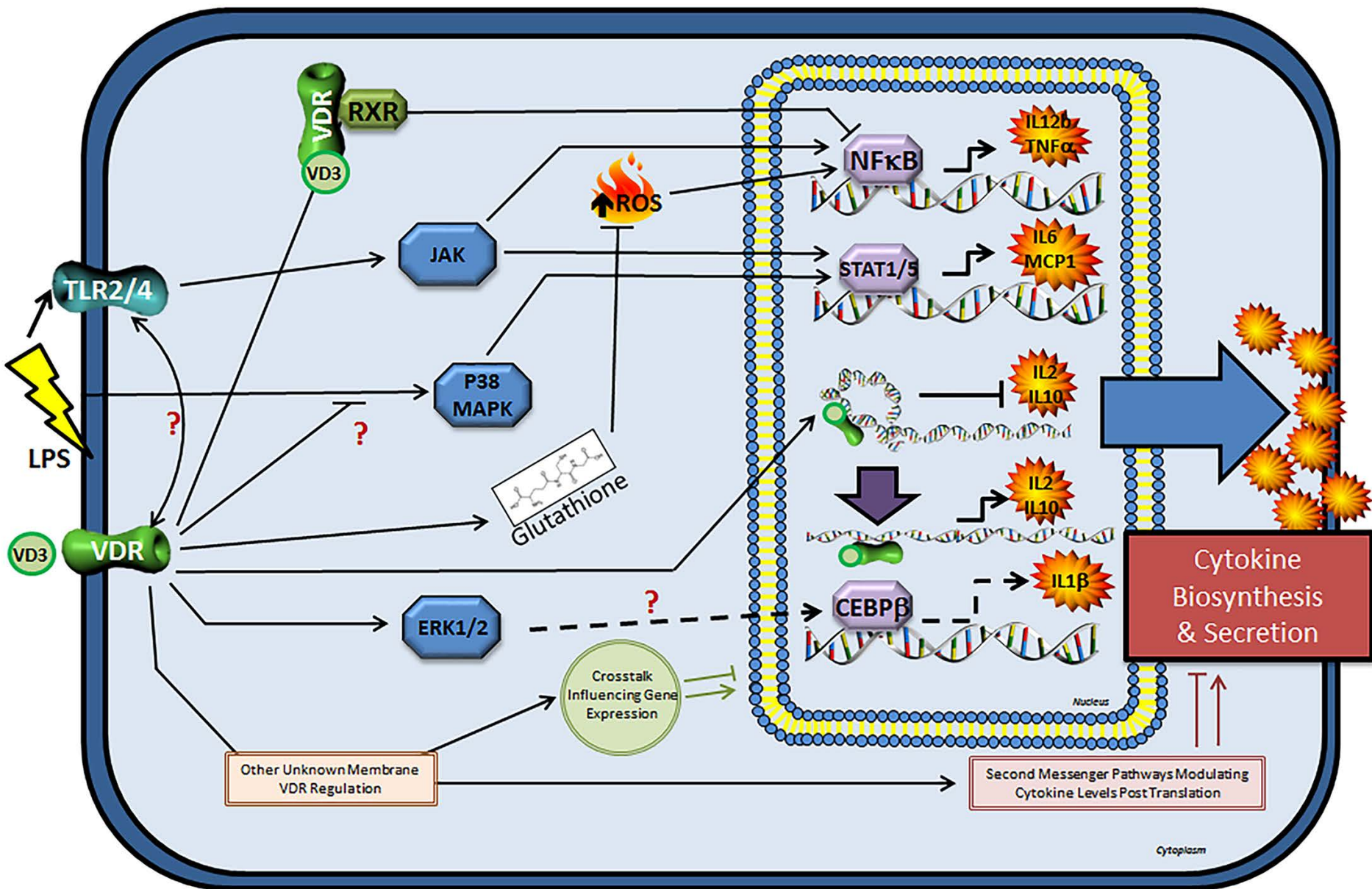
Neuropathy At 5 years	Decrease	No Change	Worsening
Magnesium	<u>39%</u>	49%	<u>12%</u>
Control	<u>8%</u>	31%	<u>61%</u>
			p < 0.0001

Vitamin D Repletion

Vitamin D Deficiency Promotes Skeletal Muscle Hypersensitivity and Sensory Hyperinnervation

Sarah E. Tague,^{1,4} Gwenaëlle L. Clarke,^{1,4} Michelle K. Winter,^{2,4} Kenneth E. McCarson,^{2,4} Douglas E. Wright,^{3,4} and Peter G. Smith^{1,4}

Departments of ¹Molecular and Integrative Physiology, ²Pharmacology, Toxicology and Therapeutics, and ³Anatomy and Cell Biology, and ⁴Kansas Intellectual and Developmental Disabilities Research Center, University of Kansas Medical Center, Kansas City, Kansas 66160

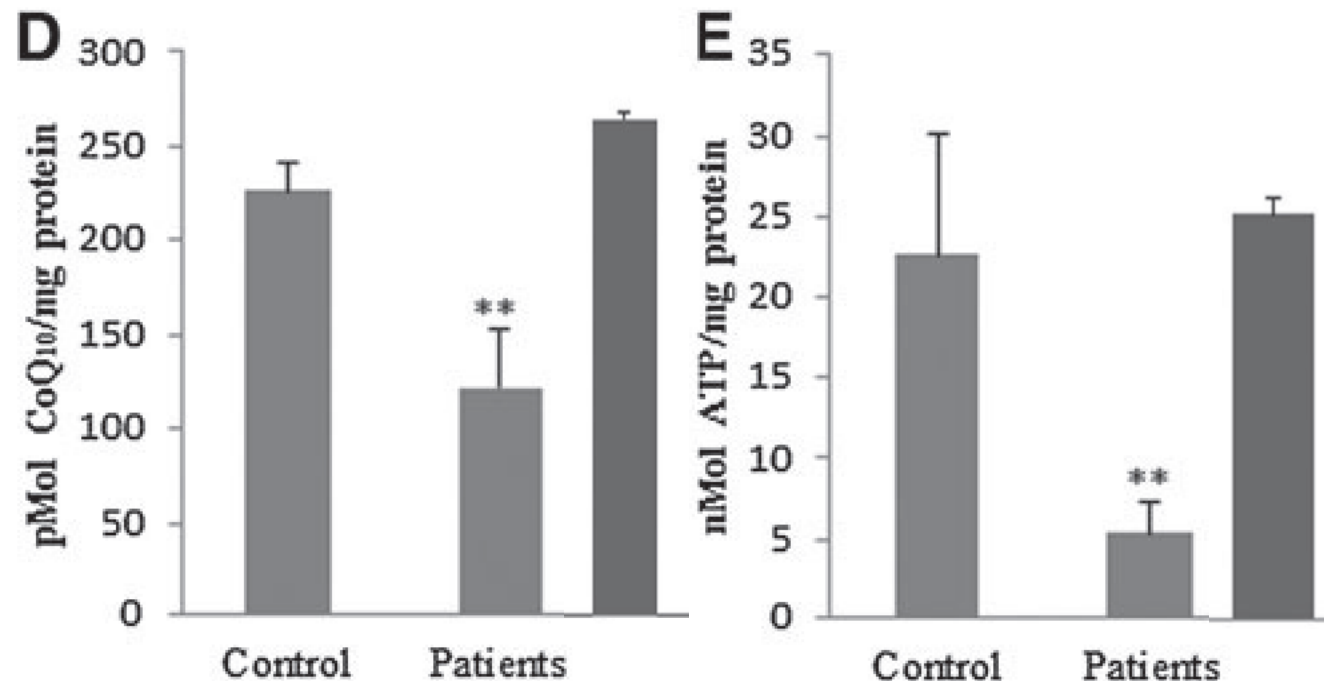


Vitamin D & Inflammatory Cytokines

- RDBPCT of 4,000 IU Vit D₃ to patients on analgesics for chronic pain
- Those on vitamin D versus placebo noted a significantly larger decline in pain scores & rescue medications at 3 months.

	TNF-a Decrease	PGE2 Decrease
Vit D	54.3%	39.2%
Placebo	16.1%	16%

Oxidative Stress Correlates with Headache Symptoms in Fibromyalgia: Coenzyme Q₁₀ Effect on Clinical Improvement



• **Coq10
300mg/day
able to
improve
energy
production
& reduce
pain by
>50%**

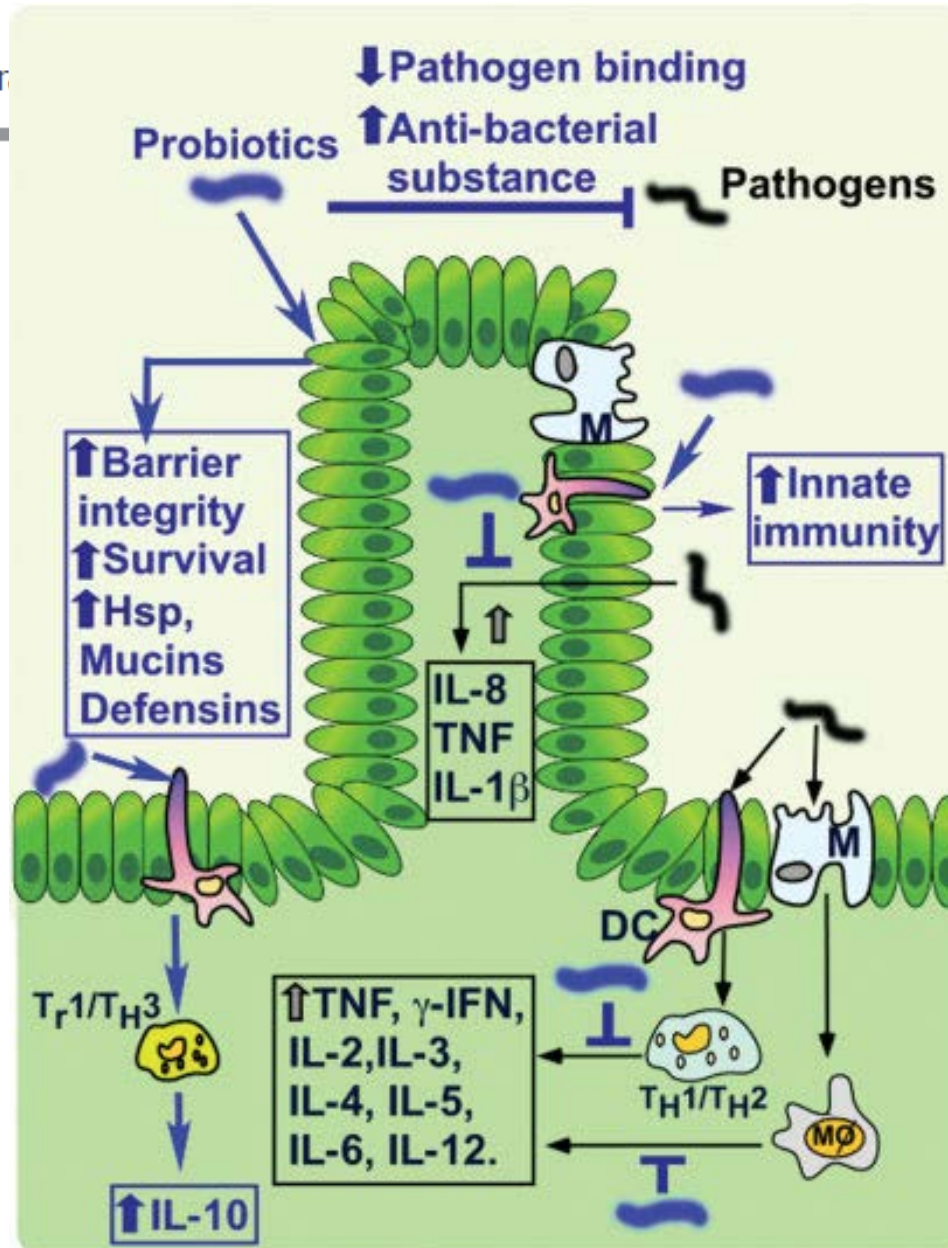
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Anti-inflammatory effects of bifidobacteria by inhibition of LPS-induced NF- κ B activation

Christian U Riedel, Fr

ins, Stephanie Blum



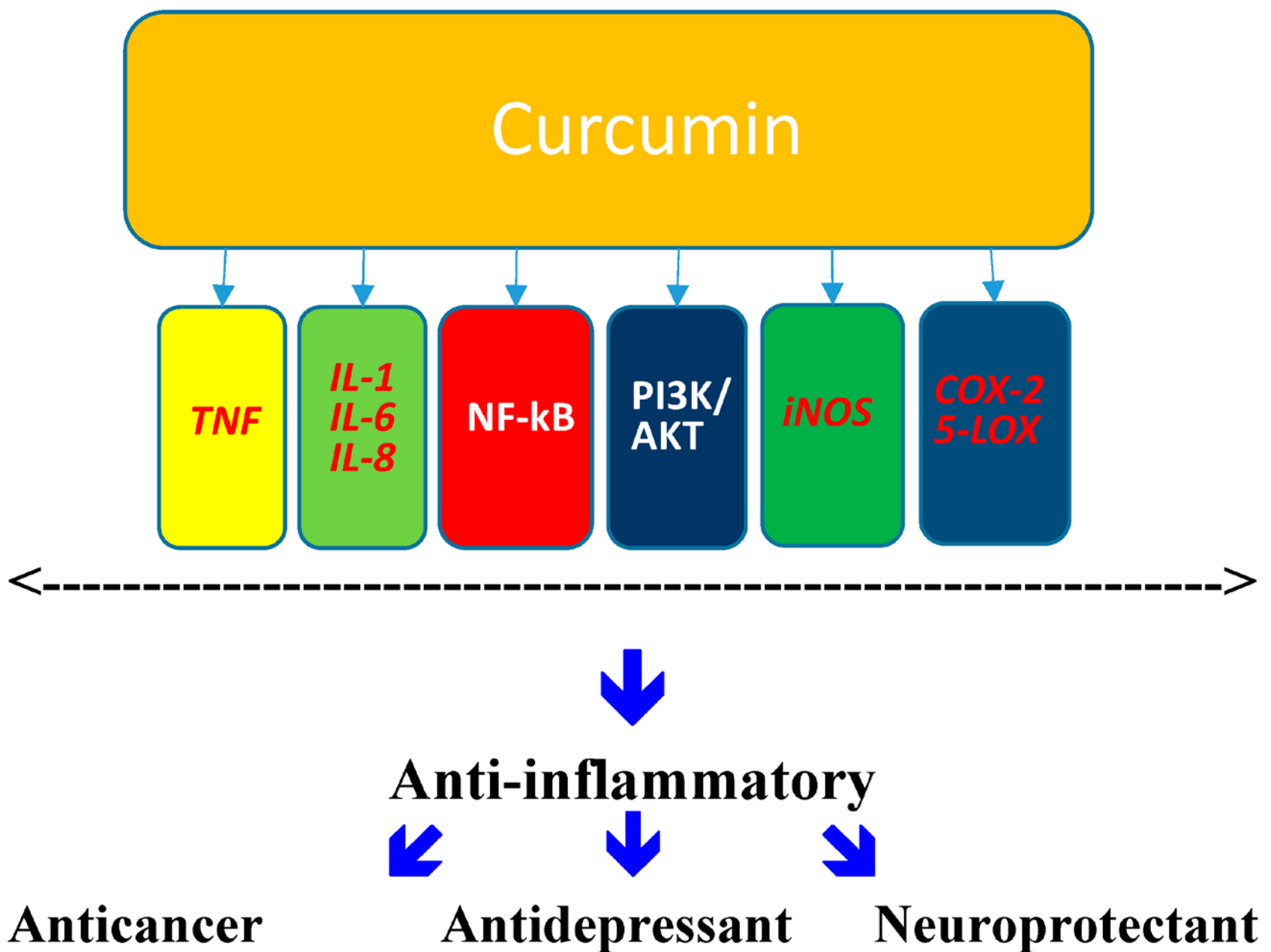
Inflamm Bowel
Dis • Volume 14,
Number 11,
November 2008

Hops & UC-II



Nutritional Approach for Relief of Joint Discomfort: A 12-week, Open-case Series and Illustrative Case Report

- Hops (THIAAs) 600 mg/d &
- Undenatured type 2 collagen (UC-II)
- MSQ decreased from 20.76 → 12.24 ± after 2 wk ($P < .001$).
- More than 2/3 of participants able to discontinue use of analgesics



Tizabi Y, Hurley LL, Qualls Z, Akinfiresoye L. Relevance of the anti-inflammatory properties of curcumin in neurodegenerative diseases and depression. *Molecules*. 2014 Dec 12;19(12):20864-79.

Efficacy of Turmeric Extracts and Curcumin for Alleviating the Symptoms of Joint Arthritis:

A Systematic Review and Meta-Analysis of Randomized Clinical Trials

- 8 RCTs
- *These RCTs provide scientific evidence that supports the efficacy of turmeric extract (about 1000 mg/day of curcumin) in the treatment of arthritis.*



The Use of Ginger (*Zingiber officinale*) for the Treatment of Pain: A Systematic Review of Clinical Trials

- *...the available data provide tentative support for the antiinflammatory role of Z. officinale constituents, which may reduce the subjective experience of pain in some conditions such as osteoarthritis.*

Combinations

- **Inflavonoid Intensive Care**
- **Ultrainflammex Powder***
 - Turmeric
 - Ginger
 - Quercetin
 - Bioflavanoids
 - Protein & Amino Acids*



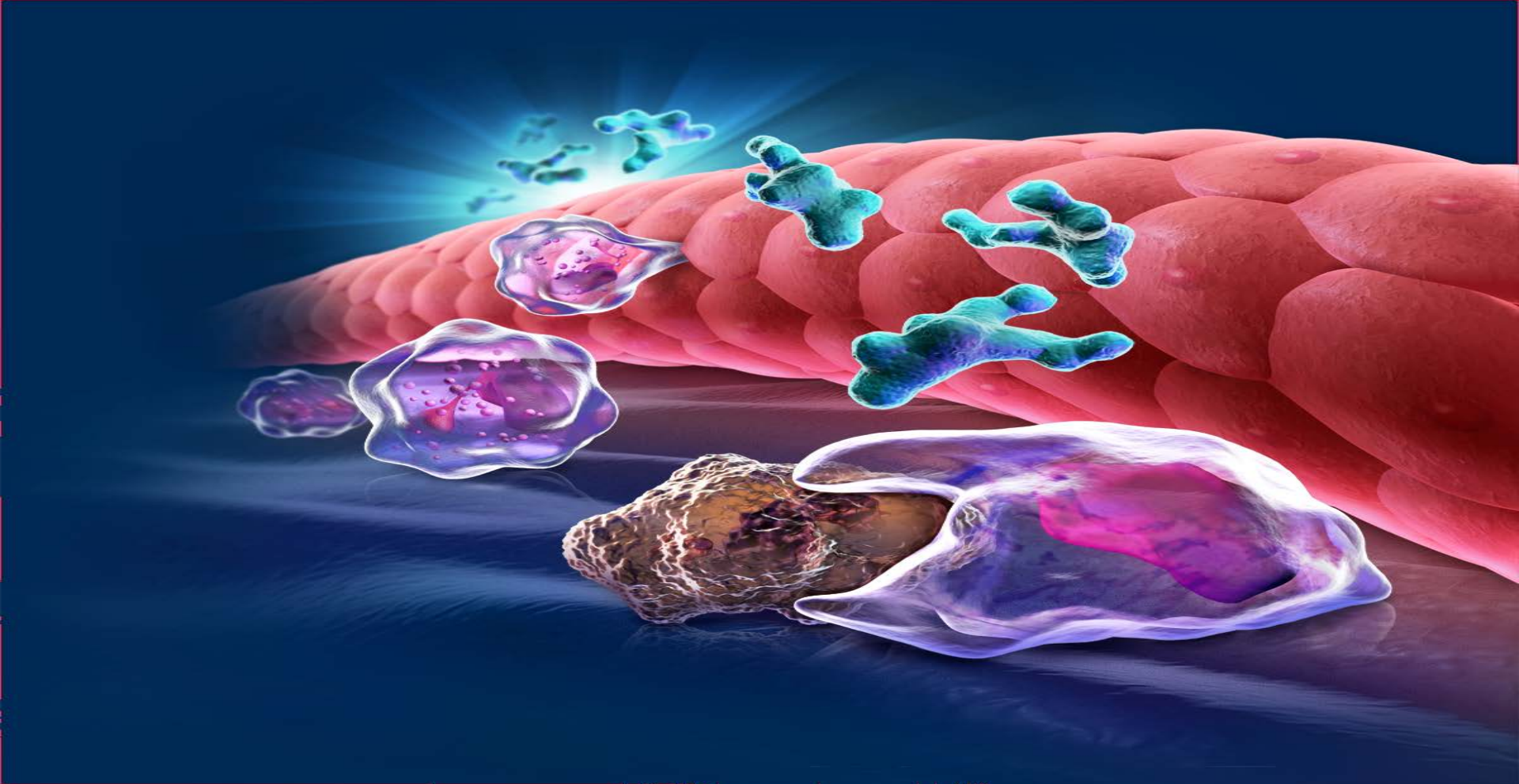
Next Steps: *Can we begin to use these approaches in our practice?*

A protein-enriched low glycemic index diet with omega-3 polyunsaturated fatty acid supplementation exerts beneficial effects on metabolic control in type 2 diabetes

- *This diet “in a real-life clinical setting improves glycemic control and also reduces waist circumference and silent inflammation...”*

Conclusions

- Chronic inflammation deserves special attention
- While there are many approaches to reducing inflammation and pain,
- **OPTIMIZING OUR INTAKE** is a foundationally important way to resolve chronic inflammation and pain
- An individualized approach which guides our patients towards a healing diet and evidence based supplementation is key.



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