Clinical Applications of Fish Oil Supplements

OPA ANNUAL CONFERENCE

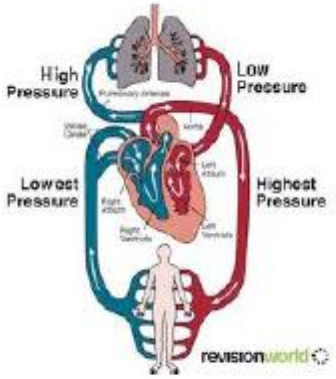
CHRISTOPHER OSWALD, DC, CNS

4/15/2016

EPA, DHA: Quintessential Functional Nutrients

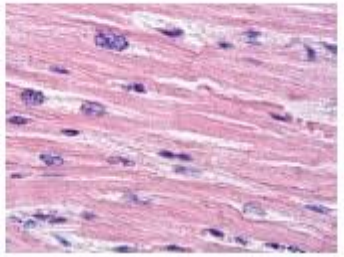
Quintessential: being the most typical representative

Body

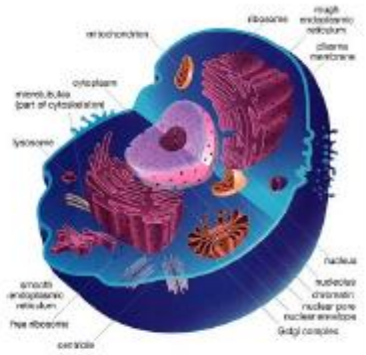


Organ Systems

Organs



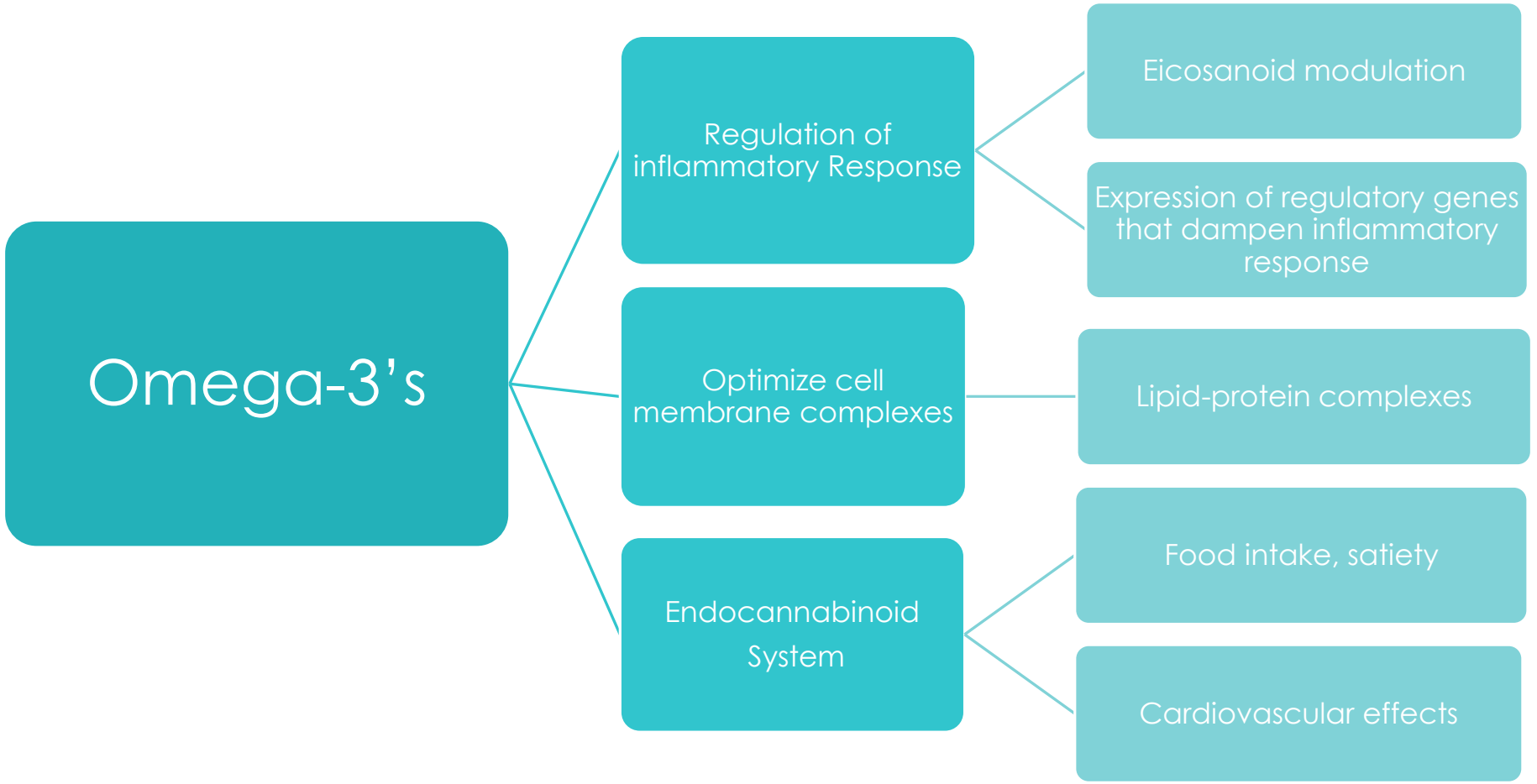
Tissues



Cellular elements

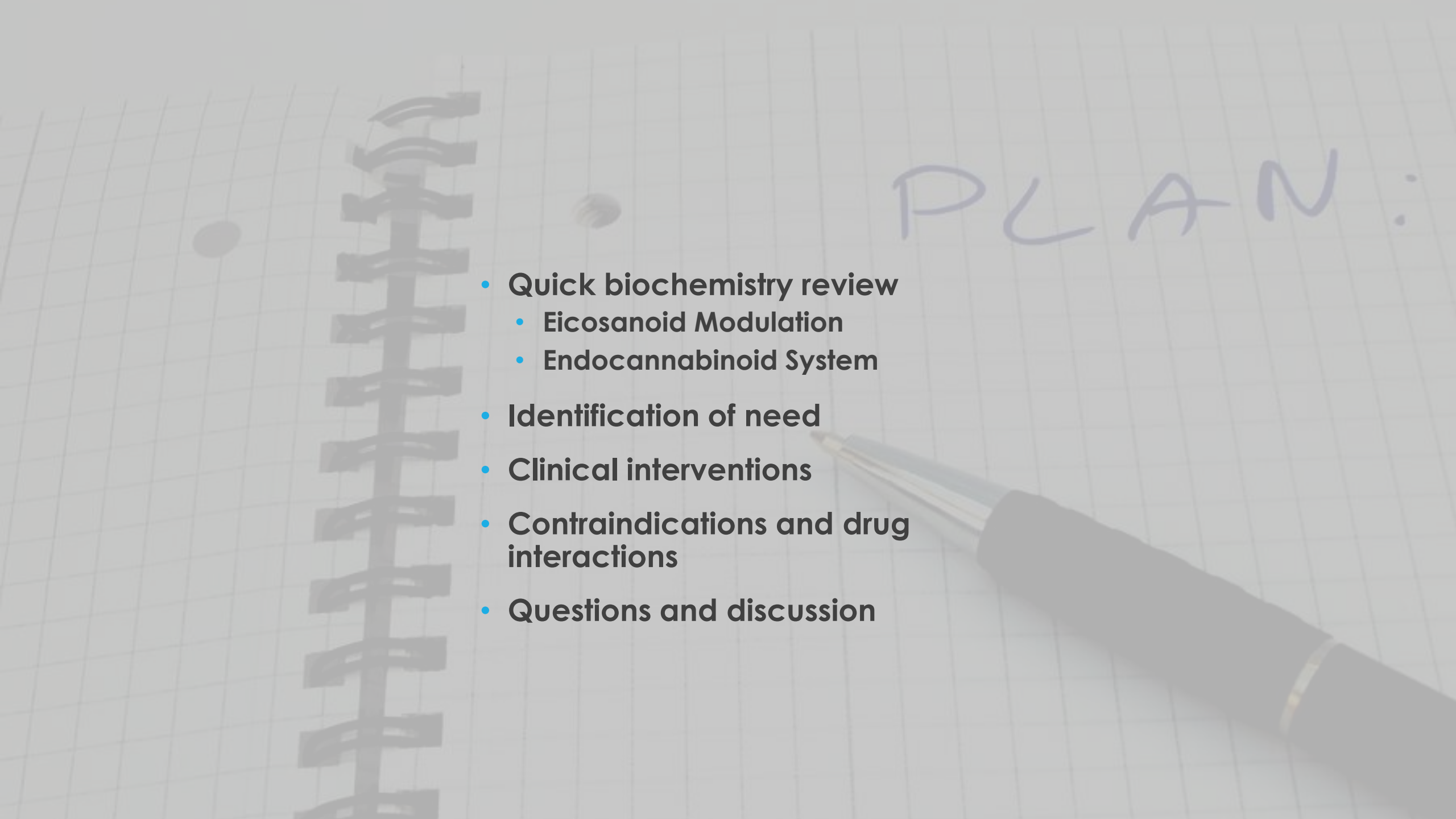
(membranes)

Pleiotropic Effects of EPA/DHA



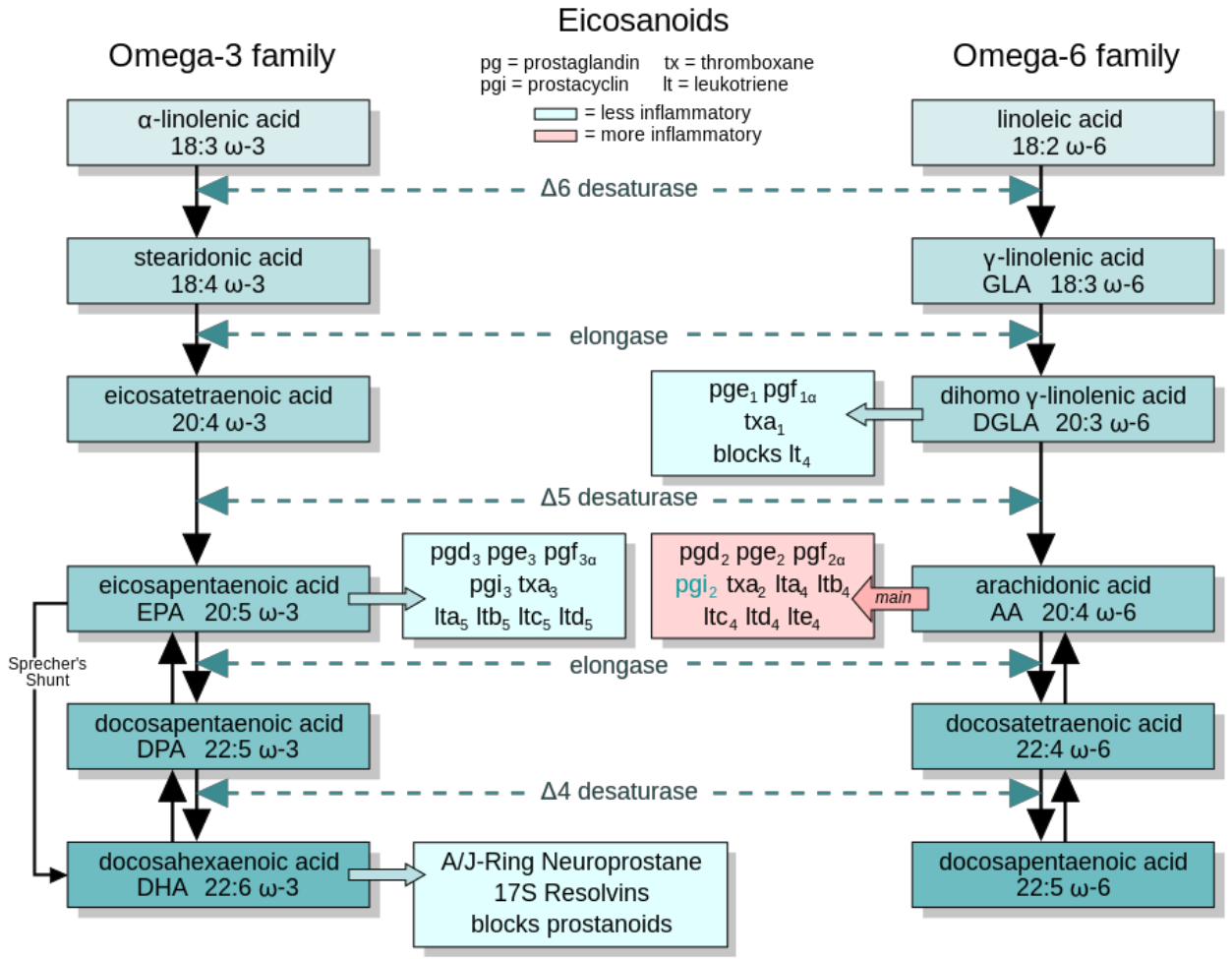
Many clinical uses

- "Swiss army knife" of supplements
- Due to the complex biochemistry associated
  - Eicosanoid modulation
  - Endocannabinoid system



- Quick biochemistry review
  - Eicosanoid Modulation
  - Endocannabinoid System
- Identification of need
- Clinical interventions
- Contraindications and drug interactions
- Questions and discussion

Eicosanoid Modulation



Eicosanoids modulate many important cell processes

Platelets

Endothelial cells

Mucosal endothelial cells

Neutrophils, Lymphocytes (T-cells, B-cells), Monocytes / Macrophages, Eosinophils, Basophils, Mast cells

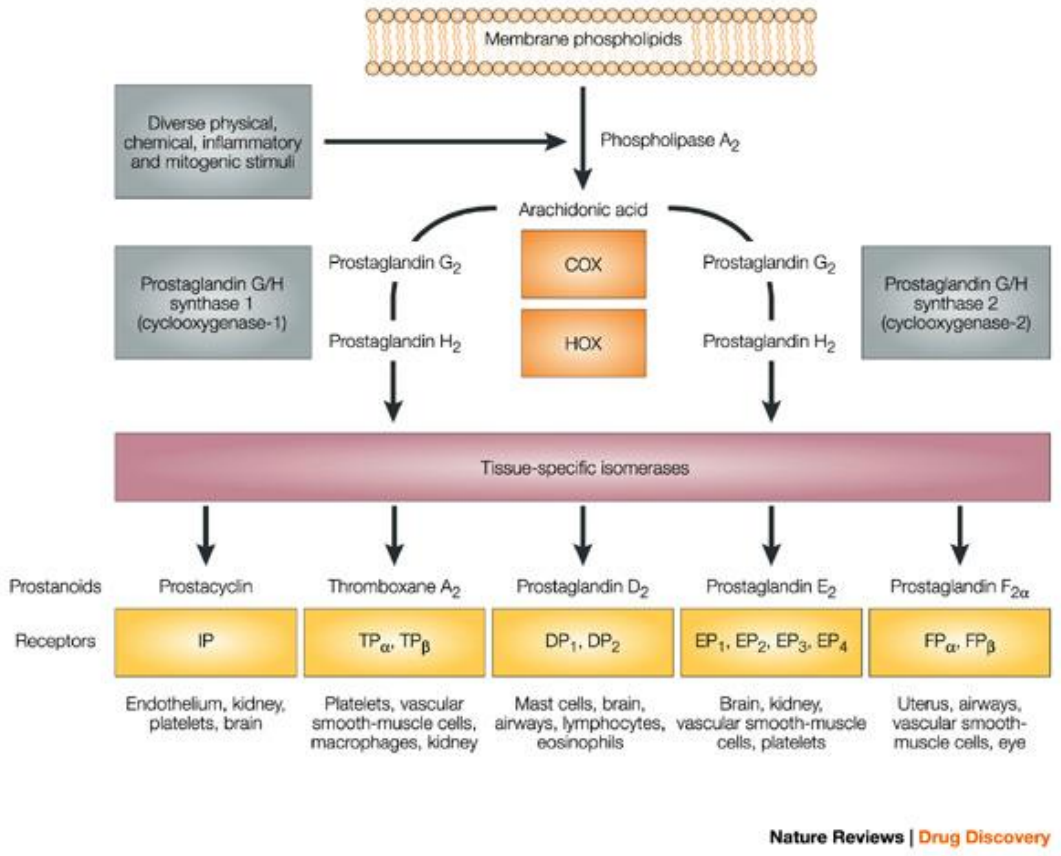
Smooth muscle (contraction, relaxation)

- Brain, Kidney, Spleen, Heart, Lungs

Prostaglandin

Functions

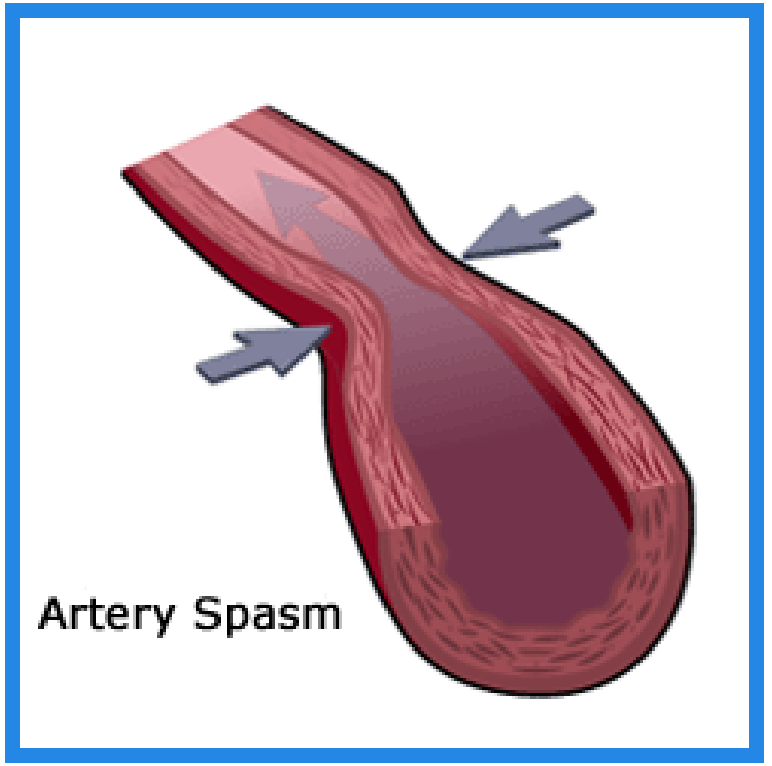
- Constriction of dilation of vascular smooth muscle
- Platelet aggregation/disaggregation
- Spinal neuron sensitivity to pain
- Labor induction
- Decreased intraocular pressure
- Regulation of inflammation
- Regulation of calcium movement
- Hormone regulation
- Cell growth control
- Action on hypothalamus to produce a fever
- GFR increase via action on the mesangial cells in the kidneys
- Inhibit stomach acid via action on parietal cells



Thromboxane

Functions

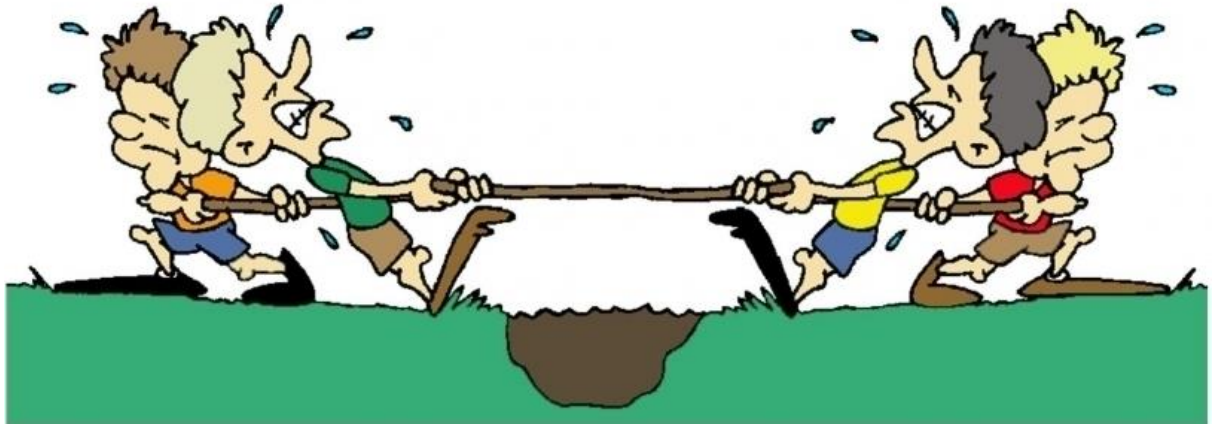
- Vasoconstrictor (hypertensive agent)
- Facilitation of platelet aggregation (clot production)
- Their function is believed to have a role in Prinzmetal's angina



Prostacyclin

Functions

- Inhibits platelet activation
- Prevents formation of platelet plug, thus inhibiting clog formation
- Increases Apoptosis
- Vasodilator
- Decreased pro-inflammatory cytokines
- Increased anti-inflammatory cytokines.
- The actions contrast that of thromboxane A_2



Leukotriene

Functions

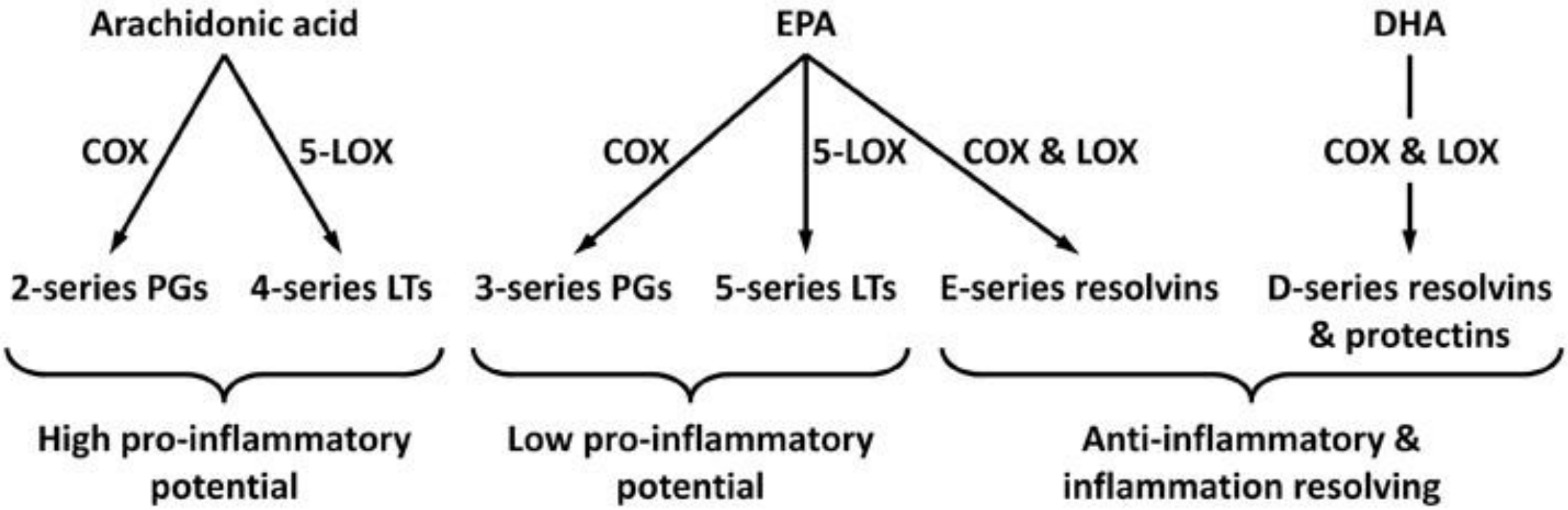
In leukocytes and other immune cells

Regulation of immune responses

Overproduction is a major cause of asthma and allergic rhinitis

- Airflow obstruction
- Increased mucus
- Bronchoconstriction
- Airway wall is infiltrated with inflammatory cells

A "Fork" in the Road



Specialized Pro-Resolving Mediators (SPM)

Lipoxin

Resolvin D series

Resolvin E series

Protectins (Neuroprotectins)

Maresins

Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. Nature 2014; 510:92-101

Semin Immunol. 2015 Apr 6. pii: S1044-5323(15)00012-3. doi: 10.1016/j.smim.2015.03.004. [Epub ahead of print]

The resolution code of acute inflammation: Novel pro-resolving lipid mediators in resolution.

Serhan CN[1], Chiang N[2], Dalli J[2].

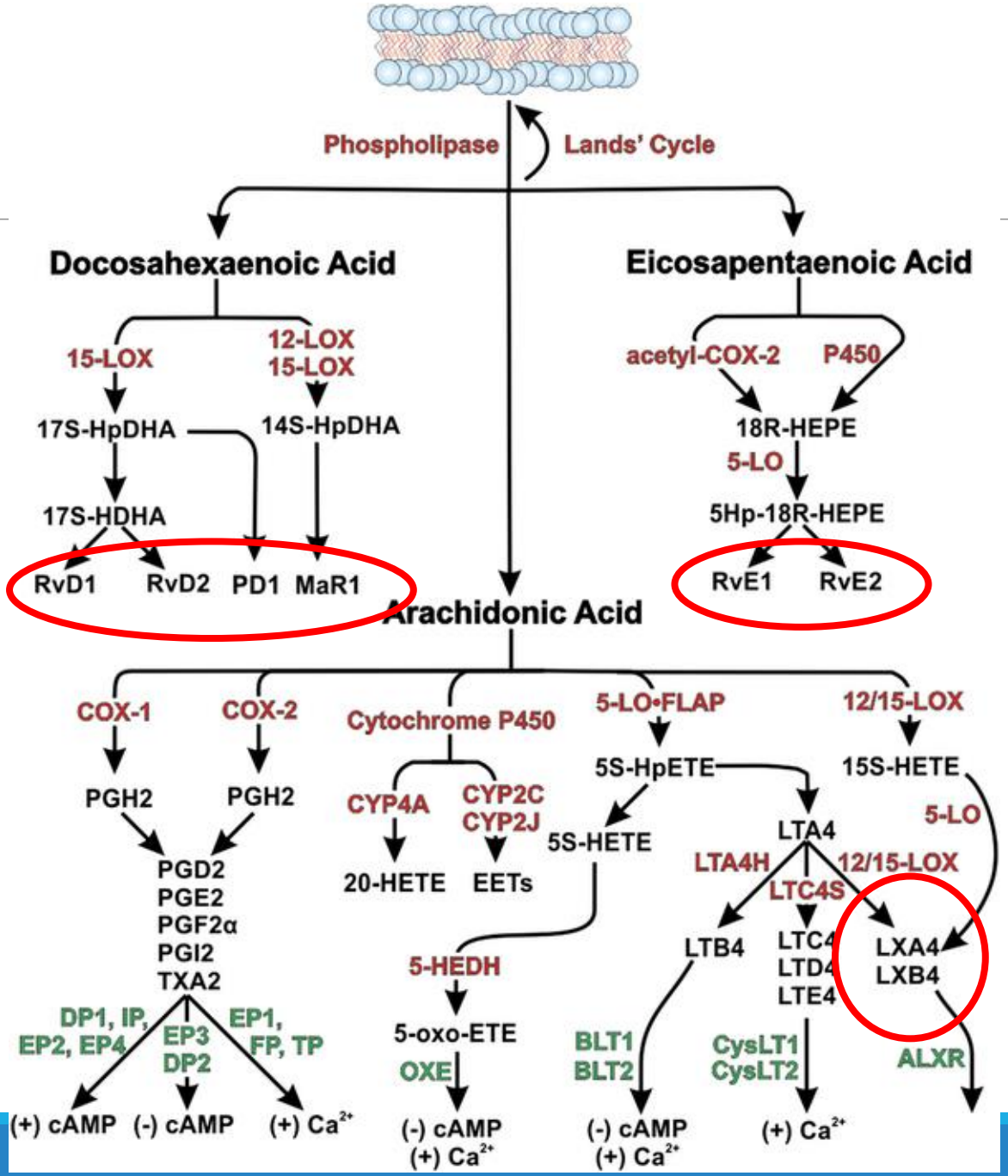
Author information

Abstract

Studies into the mechanisms in resolution of self-limited inflammation and acute reperfusion injury have uncovered a new genus of pro-resolving lipid mediators coined specialized pro-resolving mediators (SPM) including lipoxins, resolvins, protectins and maresins that are each temporally produced by resolving-exudates with distinct actions for return to homeostasis. SPM evoke potent anti-inflammatory and novel pro-resolving mechanisms as well as enhance microbial clearance. While born in inflammation-resolution, SPM are conserved structures with functions discovered in microbial defense, pain, organ protection and tissue regeneration, wound healing, cancer, reproduction, and neurobiology-cognition. This review covers these SPM mechanisms and other new omega-3 PUFA pathways that open their path for functions in resolution physiology.

Copyright © 2015 Elsevier Ltd. All rights reserved.

"functions discovered in microbial defense, pain, organ protection, tissue regeneration, wound healing, cancer, reproduction, and neurobiology – cognition."


Phospholipase
Lands' Cycle
Docosahexaenoic Acid
Eicosapentaenoic Acid
15-LOX
12-LOX
15-LOX
17S-HpDHA
14S-HpDHA
17S-HDHA
RvD1
RvD2
PD1
MaR1
acetyl-COX-2
P450
18R-HEPE
5-LO
5Hp-18R-HEPE
RvE1
RvE2
Arachidonic Acid
COX-1
COX-2
Cytochrome P450
5-LO•FLAP
12/15-LOX
PGH2
PGH2
CYP4A
CYP2C
CYP2J
5S-HpETE
15S-HETE
5-LO
20-HETE
EETs
5S-HETE
LTA4
LTA4H
12/15-LOX
LTC4S
PGD2
PGE2
PGF2α
PGI2
TXA2
LTB4
LTC4
LTD4
LTE4
LXA4
LXB4
5-HEDH
DP1, IP,
EP2, EP4
EP3
DP2
EP1,
FP, TP
5-oxo-ETE
OXE
BLT1
BLT2
CysLT1
CysLT2
ALXR
(+) cAMP
(-) cAMP
(+) Ca2+
(-) cAMP
(+) Ca2+
(-) cAMP
(+) Ca2+
(+) Ca2+

Lipoxin

Demetz E, Schroll A, Auer K, et al.. *Cell Metabolism*2014;20(5):787-798. doi:10.1016/j.cmet.2014.09.004.

- Potent anti-inflammatory lipid metabolite
- End result of the LOX pathway
- Part of the resolution of inflammation
- Derived from AA
- Blocks the action of LTB_4 PGE_2 and TXA_2
- Also helps to block the expression of IL-8, TNF-a
- There is also regulation of histamine, which can lead to a reduction in swelling due to edema
- Shown to regulate cholesterol metabolism

Cell Metab. 2014 Nov 4;20(5):787-98.

The arachidonic acid metabolome serves as a conserved regulator of cholesterol metabolism.

Demetz E[1], Schroll A, Auer K, Heim C, Patsch JR, Eller P, Theurl M, Theurl I, Theurl M, Seifert M, Lener D, Stanzl U, Haschka D, Asshoff M, Dichtl S, Nairz M, Huber E, Stadlinger M, Moschen AR, Li X, Pallweber P, Scharnagl H, Stojakovic T, März W, Kleber ME, Garlaschelli K, Uboldi P, Catapano AL, Stellaard F, Rudling M, Kuba K, Imai Y, Arita M, Schuetz JD, Pramstaller PP, Tietge UJ, Trauner M, Norata GD, Claudel T, Hicks AA, Weiss G, Tancevski I.

⊕ Author information

Abstract

Cholesterol metabolism is closely interrelated with cardiovascular disease in humans. Dietary supplementation with omega-6 polyunsaturated fatty acids including arachidonic acid (AA) was shown to favorably affect plasma LDL-C and HDL-C. However, the underlying mechanisms are poorly understood. By combining data from a GWAS screening in >100,000 individuals of European ancestry, mediator lipidomics, and functional validation studies in mice, we identify the AA metabolome as an important regulator of cholesterol homeostasis. Pharmacological modulation of AA metabolism by aspirin induced hepatic generation of leukotrienes (LTs) and lipoxins (LXs), thereby increasing hepatic expression of the bile salt export pump Abcb11. Induction of Abcb11 translated in enhanced reverse cholesterol transport, one key function of HDL. Further characterization of the bioactive AA-derivatives identified LX mimetics to lower plasma LDL-C. Our results define the AA metabolomeasconserved regulator of cholesterol metabolism, and identify AA derivatives as promising therapeutics to treat cardiovascular disease in humans.

"we definitively show that the AA metabolome plays a physiological role in whole body cholesterol homeostasis and HDL function in mammals"

Resolvins and Protectins

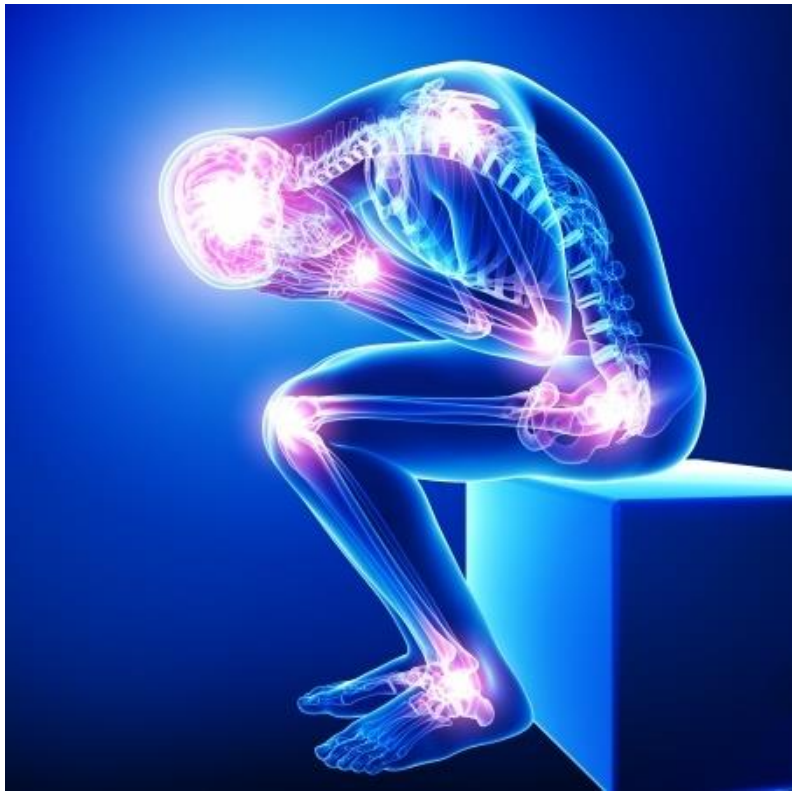
Anti-inflammatory actions that lead to resolution of the inflammatory cycle

Resolvin D and Protectin

- Anti-apoptotic, anti-inflammatory signaling and is neuroprotective
- Neuroprotective action during ischemia-reperfusion injury

Resolvin E1 and E2

- Action on monocytes, dendritic cells and neutrophils



Morita M, Kuba K, Ichikawa A, et al. Cell. 2013 Mar 5. pii: S0092-8674(13)00216-X.

Protectin D1

Derived from DHA

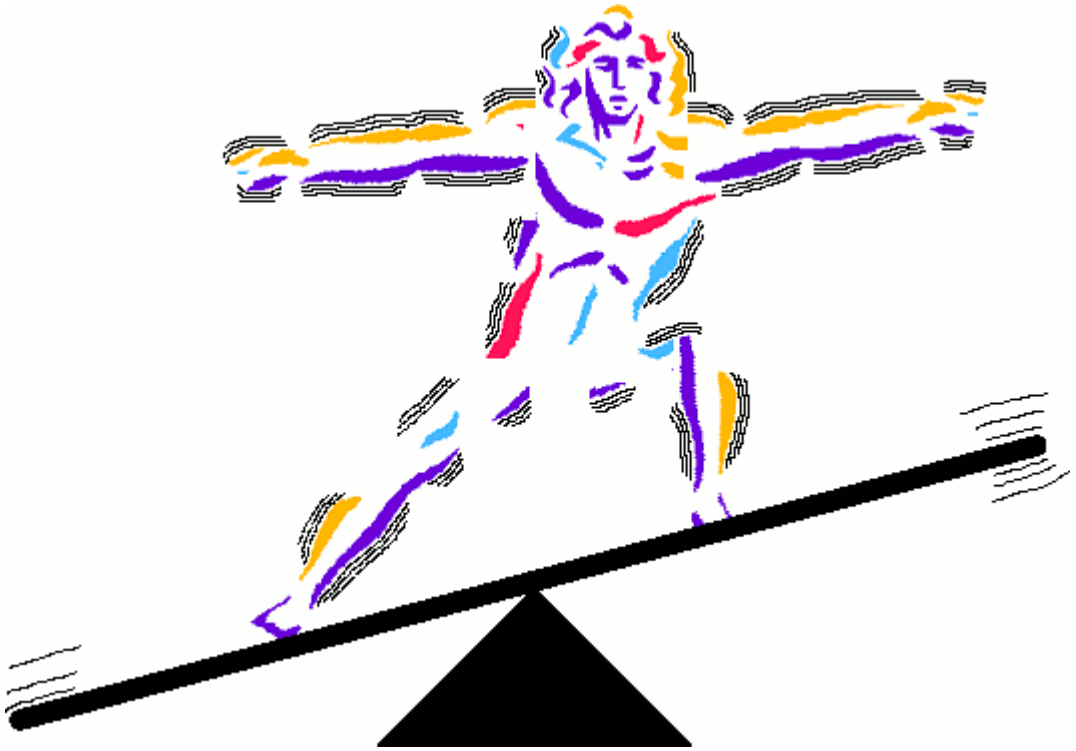
Human ALOX15 (15-LOX1) is key enzyme for the eventual formation of PD1

- Predominantly expressed in the epithelial cells of leukocytes in lungs

Inhibits the nuclear export of viral RNA

Could be a new innate suppressor of influenza virus replication

Maresins



Derived from DHA

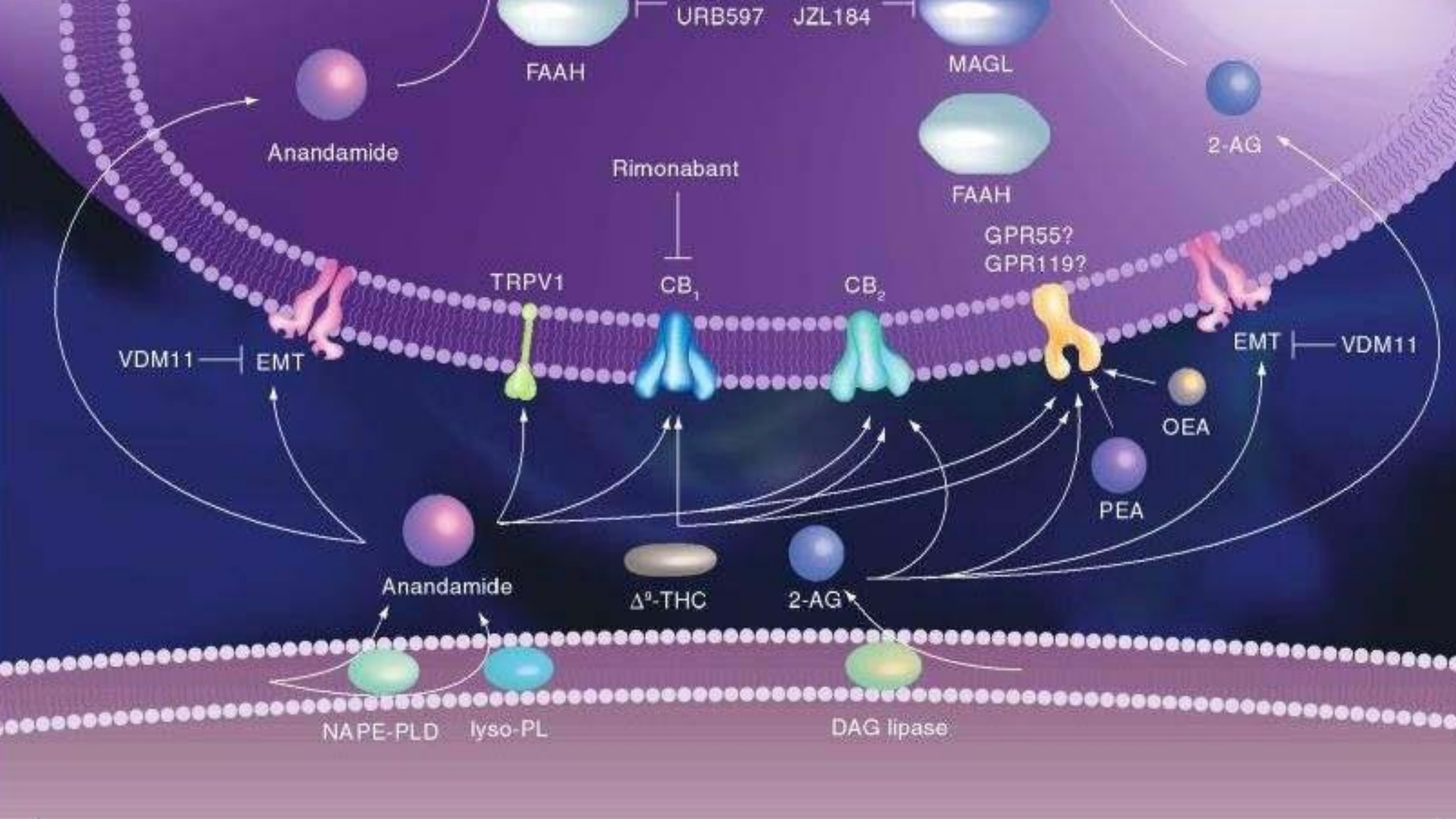
Inhibits LTA_4H

Believed to be involved in
- Tissue homeostasis
- Inflammation resolution
- Would healing
- Host defense

Macrophage mediator

Comes on very late in the resolution phase of inflammation

Serhan CN, Yang R, Martinod K, et al. *The Journal of Experimental Medicine* 2009;206(1):15-23. doi:10.1084/jem.20081880.
Dalli J, Zhu M, Vlasenko NA, et al. *The FASEB Journal*2013;27(7):2573-2583. doi:10.1096/fj.13-227728.


URB597
JZL184
FAAH
MAGL
Anandamide
2-AG
Rimonabant
FAAH
GPR55?
GPR119?
TRPV1
CB1
CB2
VDM11
EMT
EMT
VDM11
OEA
PEA
Anandamide
Δ9-THC
2-AG
NAPE-PLD
lyso-PL
DAG lipase

Endocannabinoid System

CB1 – Most abundant G-coupled protein receptor in the brain

- Substantia nigra
- Globus pallidus
- Hippocampus
- Cerebral cortex
- Putamen
- Caudate
- Cerebellum
- Amygdala
- Also found in MSK tissues, adipocytes, and hepatocytes

CB2

- Primarily associated with cells governing immune function

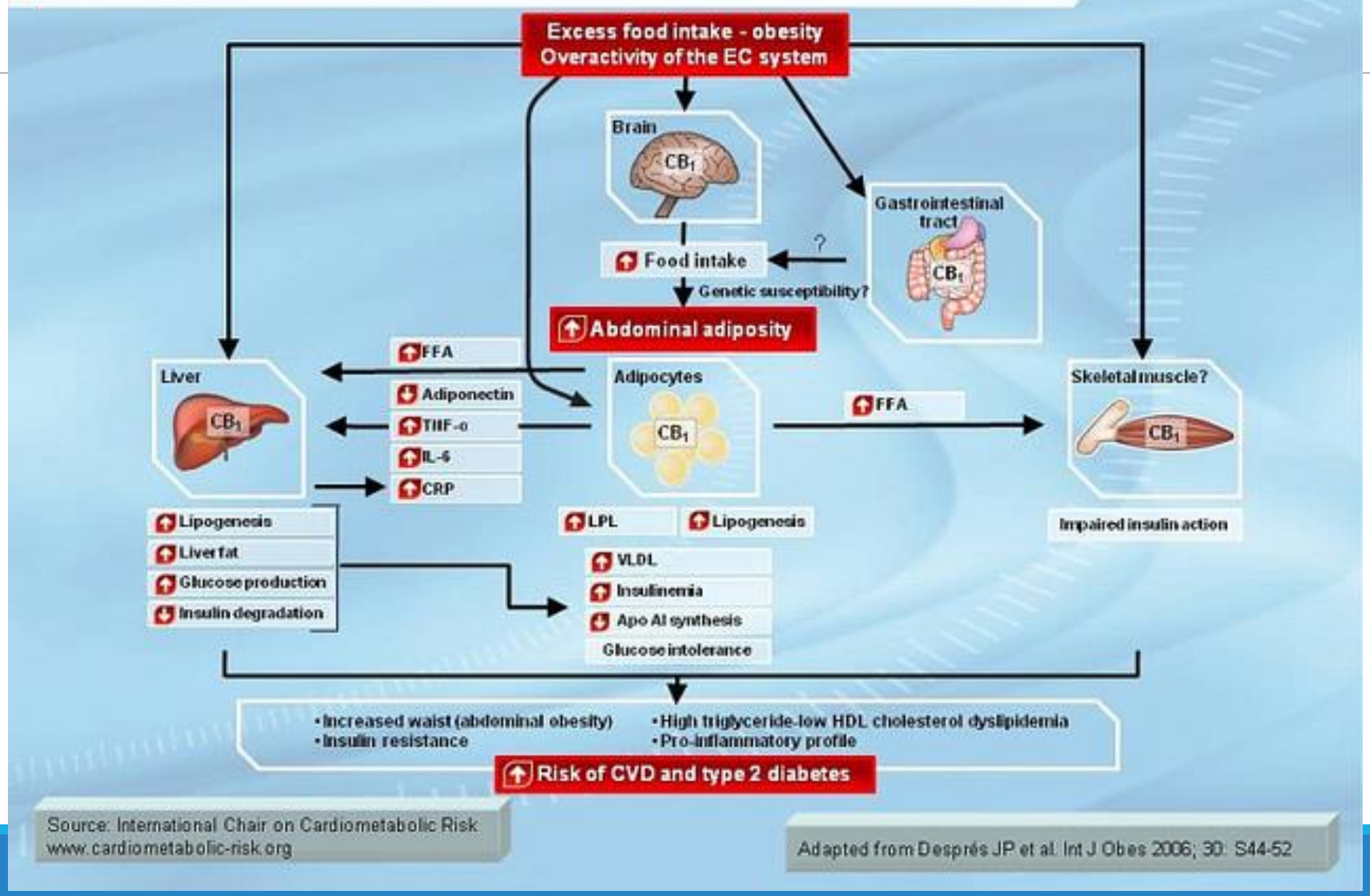
Role is summarized by "Relax, eat, sleep, forget, and protect"

Modulates

- Embryological development
- Neural plasticity
- Neuroprotection
- Immunity and inflammation
- Apoptosis and carcinogenesis
- Pain
- Emotional memory
- Hunger
- Feeding
- Metabolism

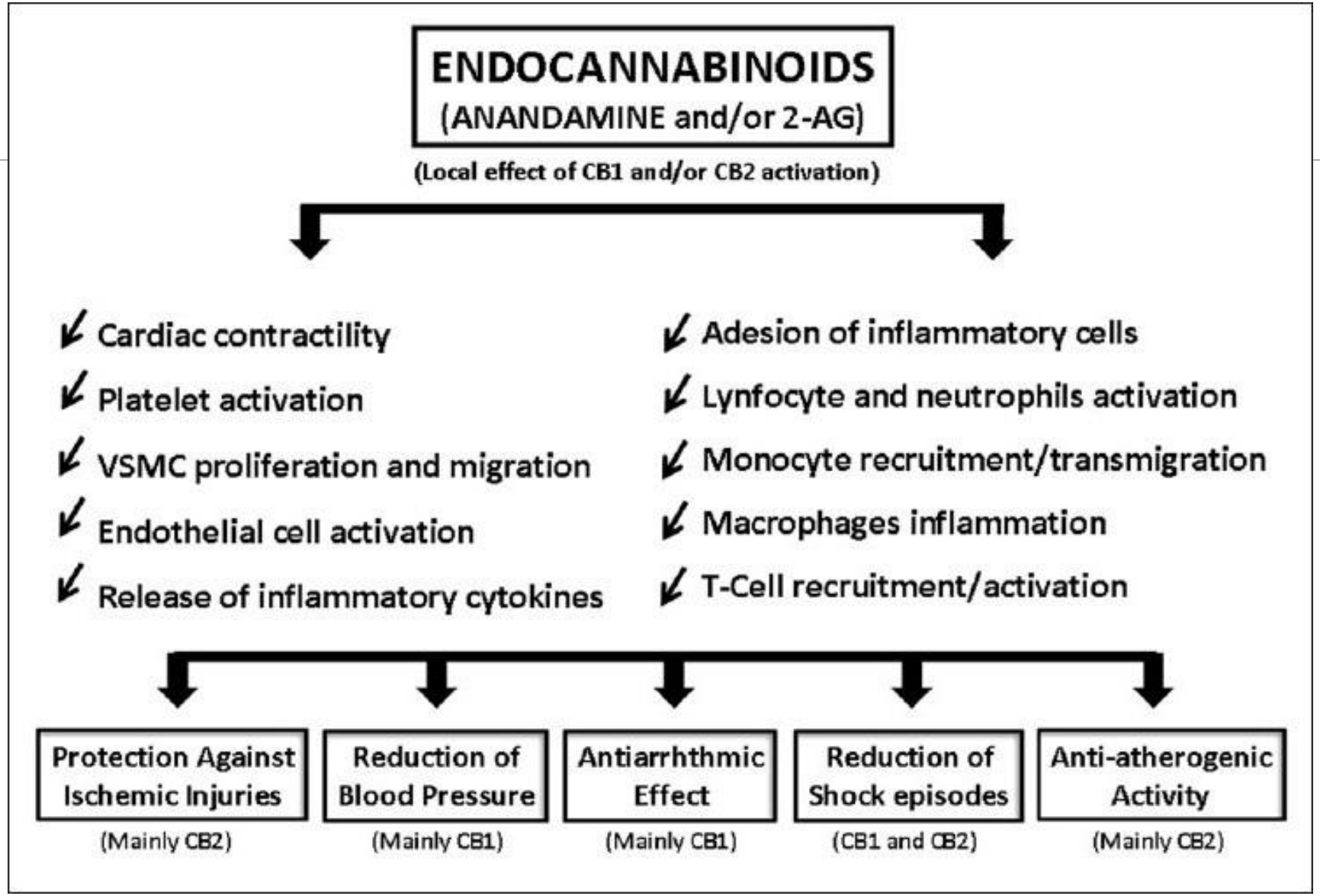
McPartland JM, Guy GW, Di Marzo V (2014) PLoS ONE 9(3): e89566. doi:10.1371/journal.pone.0089566

THE ENDOCANNABINOID SYSTEM AND CARDIOMETABOLIC RISK



Source: International Chair on Cardiometabolic Risk
www.cardiometabolic-risk.org

Adapted from Després JP et al. Int J Obes 2006; 30: S44-52



Cunha P, Romão AM, Mascarenhas-Melo F, Teixeira HM, Reis F. Endocannabinoid system in cardiovascular disorders - new pharmacotherapeutic opportunities. J Pharm Bioall Sci 2011;3:350-60

Endocannabinoid Production

Table 1

Effects of PUFA supplementation upon eCB levels.

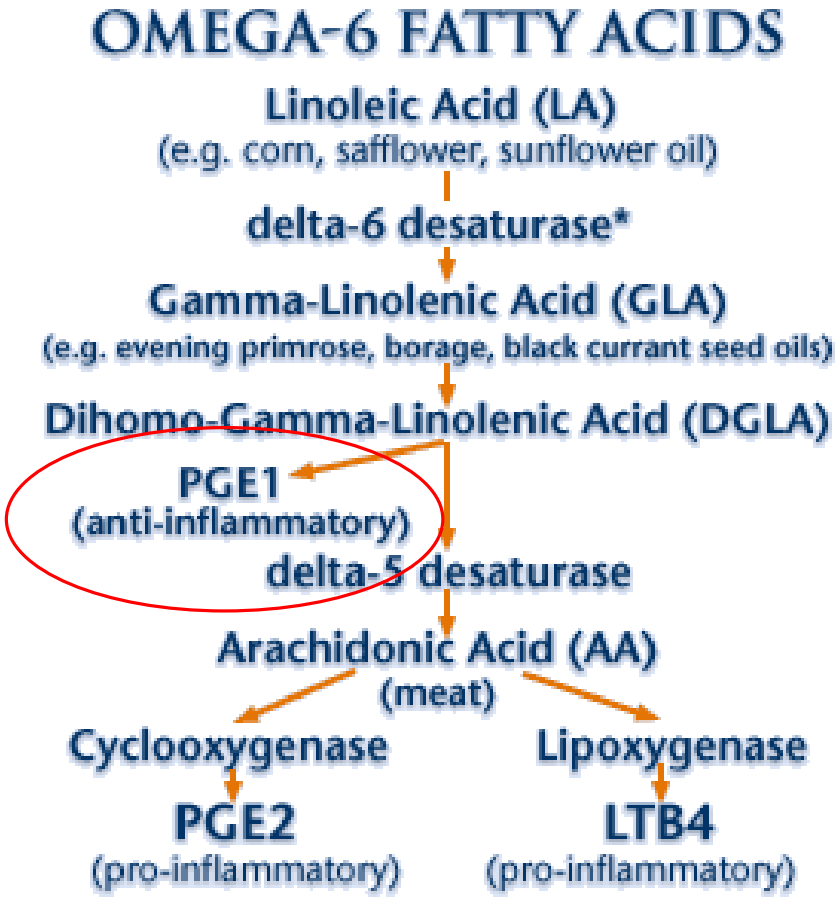
Supplemented PUFA	assay; result compared to unsupplemented controls[1]	reference
DHA+AA	*in vivo* piglets, whole brain homogenates; ↑AEA, ≈2-AG	[137]
AA	*in vivo* mice, whole brain homogenates; ↑AEA	[137]
DHA	*in vivo* mice, whole brain homogenates; ↓2-AG	[325]
AA	*in vivo* mice, whole brain homogenates; ↑2-AG	[325]
DHA	*in vitro* mouse 3T3-F442A adipocytes; ↓2-AG, ↓AEA	[326]
AA	*in vitro* mouse 3T3-F442A adipocytes; ↑2-AG	[326]
DHA+EPA	*in vivo* rats, whole brain homogenates; ≈AEA, ≈2-AG	[327]
or AA	*in vivo* rats, jejunum homogenates; ↑AEA, ↑2-AG	
DHA+EPA	*in vivo* Zucker rats, visceral adipose tissue; ↓↓2-AG, ↓AEA	[142]
DHA+EPA	*in vivo* Zucker rats, whole brain homogenates; ↓2-AG, ≈AEA	[143]
DHA+EPA	*in vivo* rats; serum: ↓↓AEA, ↓2-AG; brain: ↓AEA, ≈2-AG	[133]
DHA+EPA	*in vivo* obese humans; serum: ↓2-AG, ≈AEA	[144]
DHA+EPA	*in vivo* mice; liver: ↓AEA, ≈2-AG; brain: ↓AEA	[131]

[1]↑, increase; ↓, decrease; ≈, no change;

- Released on demand from cell membrane
- Produced from AA
  - AEA and 2-AG
  - Too much is a bad thing
- Omega-3 FA both balance AEA and 2-AG levels, but also compete for the enzymes involved in biosynthesis of ECBs
- Mice deficient in Omega-3 showed impairment in the CB1 signaling pathway
- Omega-3 seems to act as a homeostatic regulator of the system

McPartland JM, Guy GW, Di Marzo V (2014) PLoS ONE 9(3): e89566. doi:10.1371/journal.pone.0089566

Omega-6s aren't all bad



The western diet is just full of the stuff

Getting omega-6 from the proper sources can have some fairly impactful outcomes on inflammation driven disorders

Serves similar structural role as Omega-3

J Lipid Res. 2015 Feb;56(2):390-402. doi: 10.1194/jlr.M055590. Epub 2014 Dec 4.

Chronic dietary n-6 PUFA deprivation leads to conservation of arachidonic acid and more rapid loss of DHA in rat brain phospholipids.

Lin LE[1], Chen CT[1], Hildebrand KD[1], Liu Z[1], Hopperton KE[1], Bazinet RP[1].

⊕ Author information

Abstract

To determine how the level of dietary n-6 PUFA affects the rate of loss of arachidonic acid (ARA) and DHA in brain phospholipids, male rats were fed either a deprived or adequate n-6 PUFA diet for 15 weeks postweaning, and then subjected to an intracerebroventricular infusion of (3)H-ARA or (3)H-DHA. Brains were collected at fixed times over 128 days to determine half-lives and the rates of loss from brain phospholipids (Jout). Compared with the adequate n-6 PUFA rats, the deprived n-6-PUFA rats had a 15% lower concentration of ARA and an 18% higher concentration of DHA in their brain total phospholipids. Loss half-lives of ARA in brain total phospholipids and fractions (except phosphatidylserine) were longer in the deprived n-6 PUFA rats, whereas the Jout was decreased. In the deprived versus adequate n-6 PUFA rats, the Jout of DHA was higher. In conclusion, chronic n-6 PUFA deprivation decreases the rate of loss of ARA and increases the rate of loss of DHA in brain phospholipids. Thus, a low n-6 PUFA diet can be used to target brain ARA and DHA metabolism.

Copyright © 2015 by the America

"chronic n-6 PUFA deprivation decreases the rate of loss of ARA and increase the rate of loss of DHA"

ALA, EPA and DHA

Alpha linolenic acid – seed oils, green leaves

- Chia, flax, hemp, walnuts
- Most seeds are more rich in Linoleic acid (Omega-6)
- Very small amount is converted to EPA and even less to DHA

Eicosapentaenoic acid

- Oily fish, cod liver, cold water fish
  - Fish get it from the algae they consume

Docosahexaenoic acid

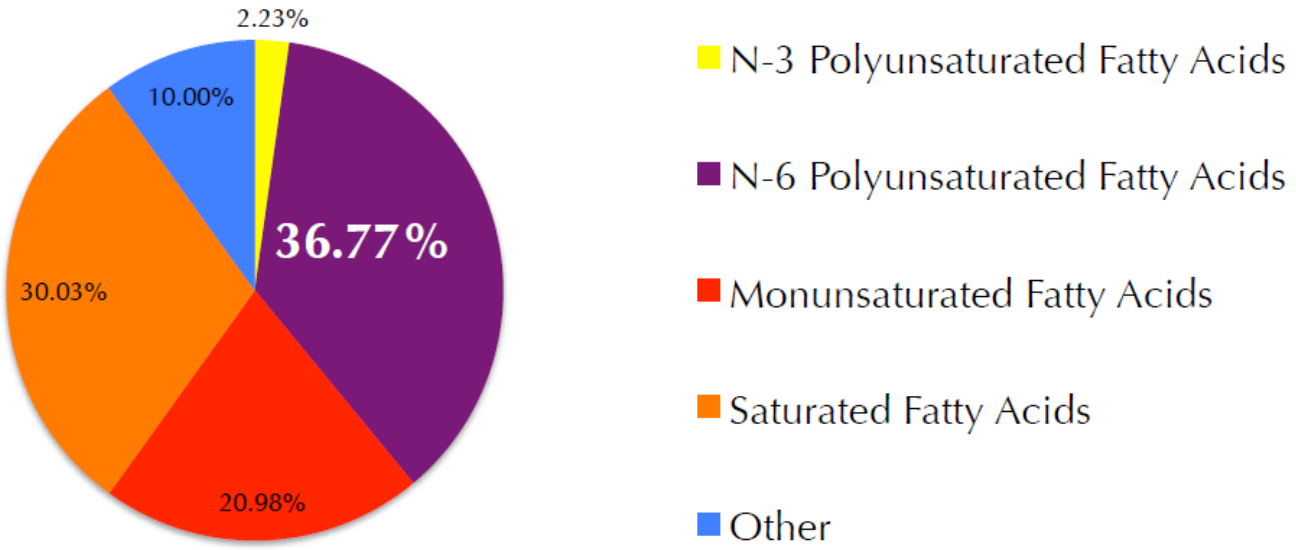
- Cold water ocean fish, algae

All are essential because humans don't possess the 12- and 15-desaturase enzymes

- This would synthesize PUFA from saturated fats

Nearly Everyone Needs More Omega-3

Percentage of Various Fatty Acids in the Typical American



National Center for Environmental Health
Division of Laboratory Sciences

CDC

Recognizing deficiency

Assume we all are!

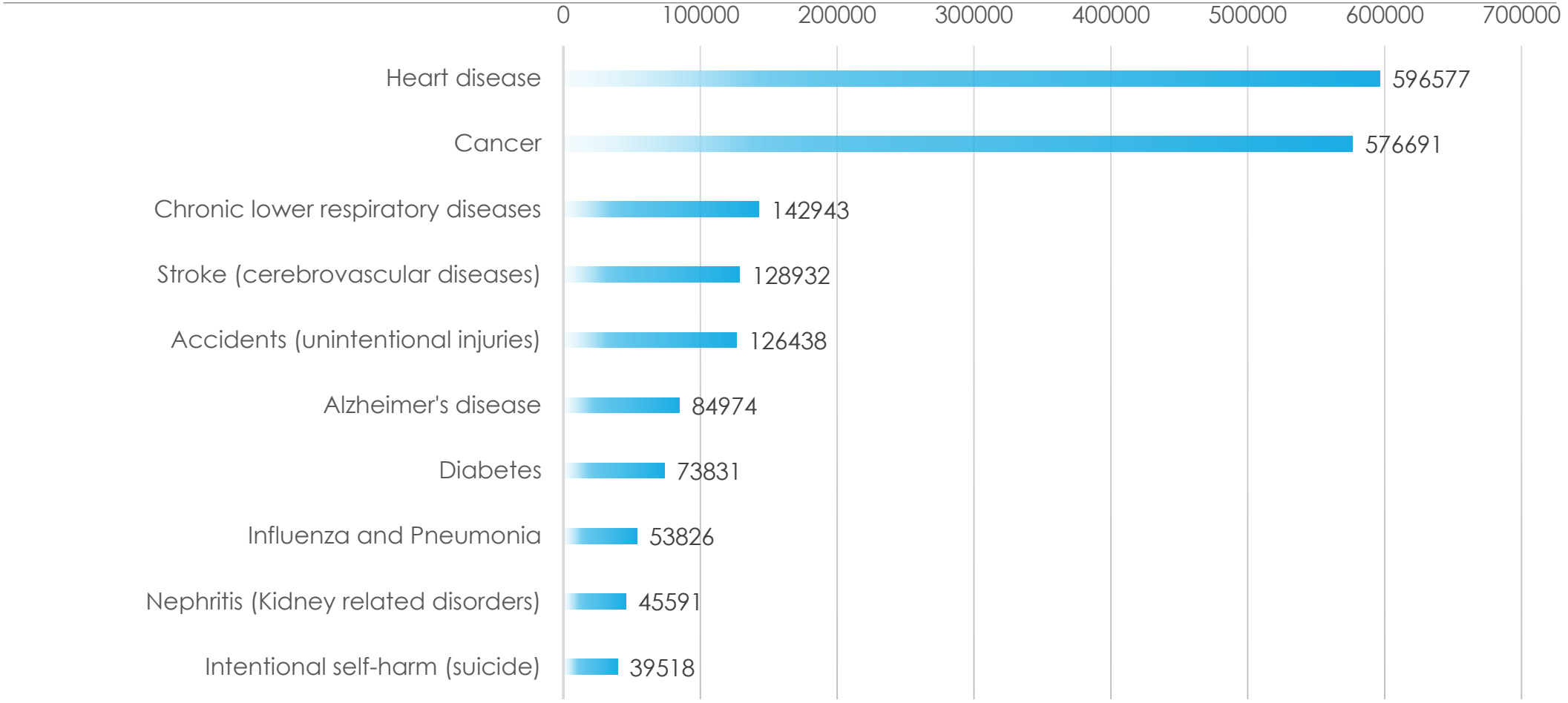
Signs/Symptoms
- Dry skin, eyes
- Small bumps on back of arm – Keratosis Pilaris
- Eczema
- Dandruff
- Concentration issues
- Mood problems
- Joint pain

Lab analysis
- FA analysis from RBC's
- Whole blood
- Blood spot

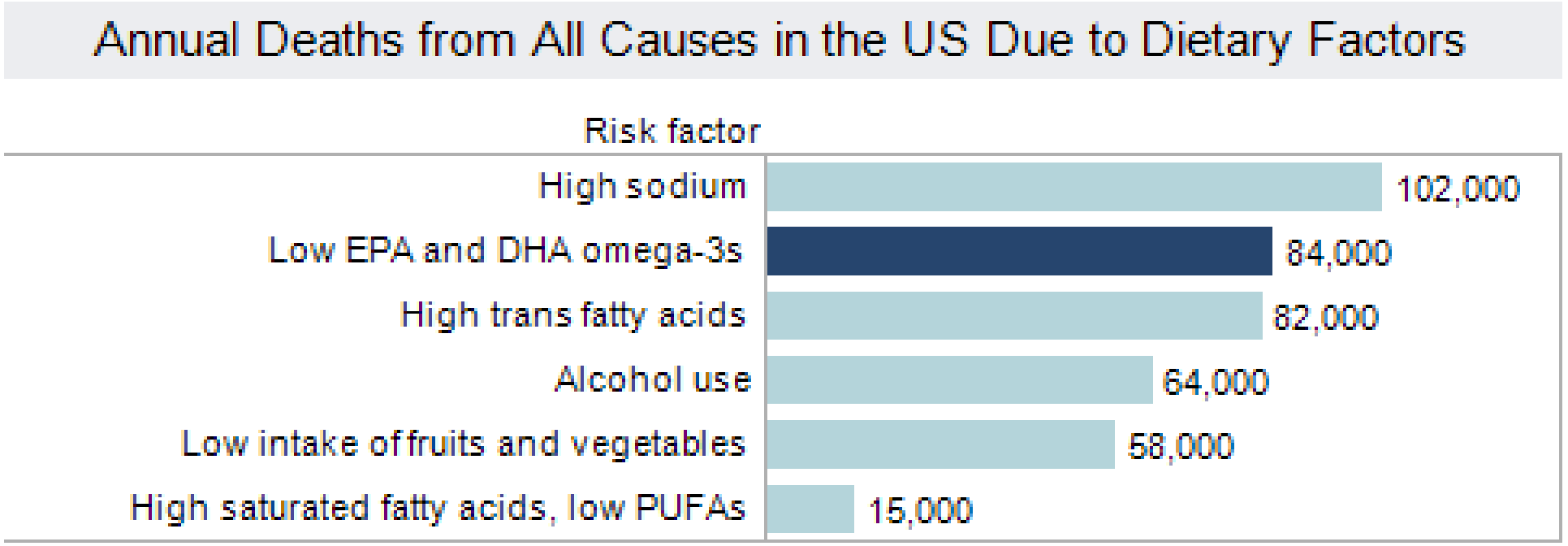
Chronic Inflammation is a component within many medical conditions

- Type I & II Diabetes mellitus
- Juvenile Rheumatoid Arthritis
- Juvenile Ankylosing Spondylitis
- Juvenile Dermatomyositis
- Rheumatic Fever
- Scleroderma
- Hemolytic anemia
- Idiopathic Thrombocytopenic Purpura
- Inflammatory Bowel Disease (IBD)
- Necrotizing Enterocolitis
- Vasculitis
- Kawasaki Disease
- Fibromyalgia
- Disseminated Intravascular Coagulation
- Immunodeficiency disorders
- Injuries
- Infections
- Irritants
- Autoimmune Disease
  - Rheumatoid arthritis; Osteoarthritis
  - Systemic Lupus Erythematosus (SLE)
  - Inflammatory Bowel Disease (IBD)
- Cardio-Cerebrovascular Disease
  - Stroke
  - Heart Disease
- Depression / Mental illness
- Spinal & Neurodegenerative Disease
  - Alzheimer's
  - Multiple Sclerosis
  - Neuropathy – from autoimmune, metabolic disorders
  - Herniated Disc; Compression injuries
  - Spinal Stenosis and Degenerative Disease
- Acute and Chronic MSK pain
- Sarcopenia
- Allergy / Atopy
- Cancer

2010 TOP CAUSES OF MORTALITY



Annual Deaths from All Causes in the US Due to Dietary Factors



Danaei G, Ding EL, Mozaffarian D, Taylor B, Rehm J, et al. (2009) The Preventable Causes of Death in the United States: Comparative Risk Assessment of Dietary, Lifestyle, and Metabolic Risk Factors. PLoS Med 6(4): e1000058.

Heart Disease – Omega-3, Triglycerides and Lipids

4:1 EPA/DHA ratio "had a *significant* effect on plasma triglyceride concentrations"

Omega-3 supplementation may provide clinical benefit to those with healthy blood lipid levels

This study was performed using 2640 mg fo per day for 28 days

*Henderson S, Lampel J, Hollenbeck C. J of Am Dietetic Assoc 2008 Sept; 108;9:A104**

Heart Disease: Omega-3 and Lipid Profiles in Athletes

Increase in **HDL**, 27% **decrease** in **LDL**, 17% decrease in vLDL, 8% decrease in triglycerides

Increase blood levels of DHA and EPA

Study was done with professional football players

2200mg was provided daily for 60 days

*Yates A, Norwig J, et. al. Sports Health 2009 Jan;1;1 21-30**

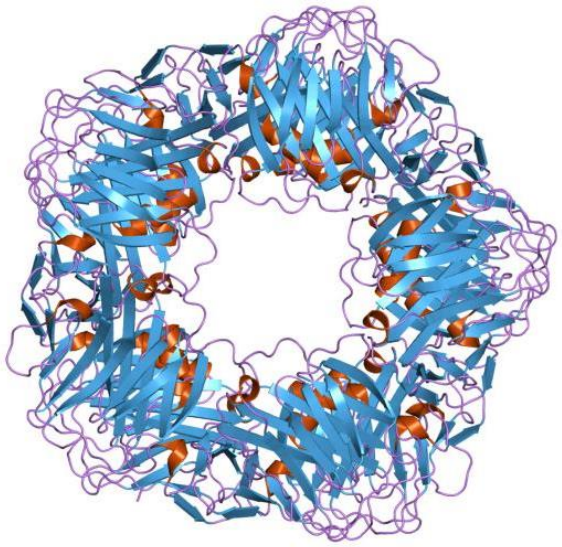
Heart Disease: Omega-3 and CRP

C-reactive protein is a marker of inflammation and strong predictor of future cardiovascular events

Patients with an elevated baseline CRP were selected for the study and were randomized into a PUFA group and a placebo group

PUFA group had 40.3% decrease while placebo group only had a 16.4% decrease

1575mg was used daily for 8 weeks in a 4:1 EPA:DHA ratio



*Muhammad K, Morledge T, Saachar R, et al. Clin Lipidol 2011. 6(6), 723-729 **

Heart Disease: Red Yeast Rice and Omega-3

Red Yeast Rice exhibited significant lowering effects of serum total cholesterol, triglycerides, and LDL-C with *no serious side effects reported*

"Lifestyle changes combined with red yeast rice and fish oil reduced LDL-C in proportions similar to standard therapy with simvastatin."

- 42.4% reduction in LDL-C (39.6% for simvastatin)
- 29% decrease in triglycerides

Clinical recommendation

- 1200mg RYR
- 1000mg Omega-3

PLoS One. 2014 Jun 4;9(6):e98611
Mayo Clin Proc. 2008 Jul;83(7):758-64.

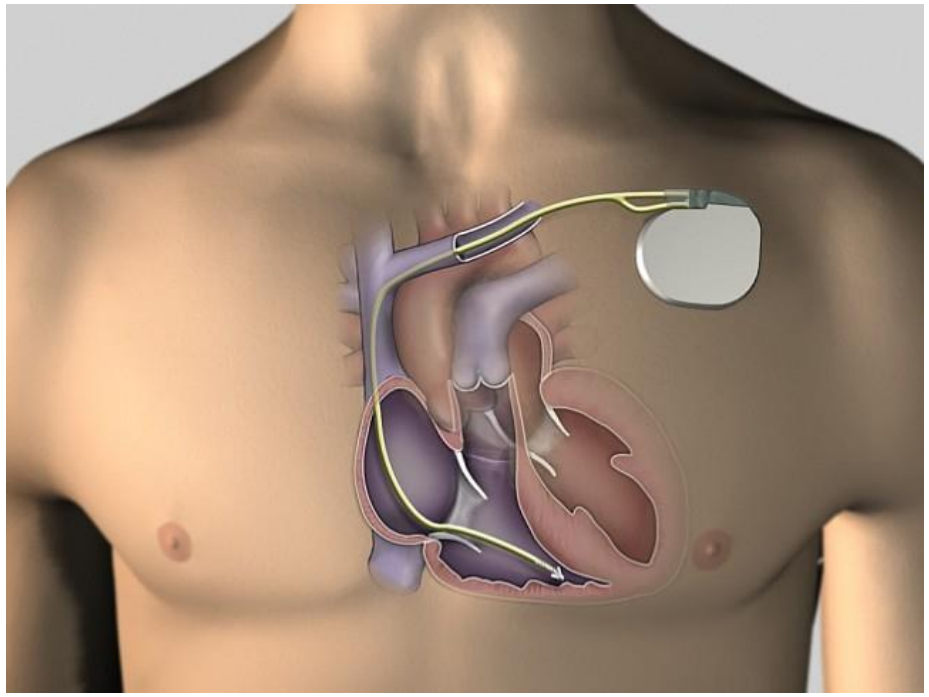
Heart Disease: Omega-3 and Implantable devices

No contraindications in literature

Combined use is safe

Studies are equivocal on anti-arrhythmic effects, but have shown a 20% decrease in pacing or shock.

Those with the highest n-3PUFA increase had a lower incidence of arrhythmic events



Finzi, A. A., Latini, R., Barlera, S., Rossi, M. G., Ruggeri, A., Mezzani, A., Marchioli, R. (2011). *American Heart Journal*, *161*(2), 338–343.e1. doi:10.1016/j.ahj.2010.10.032

Heart Disease: Clinical Considerations, Contraindications

Common medications seen in patients with CVD include:

- ACE inhibitors (Lisinopril)
- Aldosterone inhibitors (Spironolactone)
- Diuretics (Lasix, Hydrochlorothiazide)
- ARBs (Losartan)
- Beta-Blockers (Atenolol)
- Calcium channel blockers (Amlodipine)
- Statins (Atorvastatin)
- Digoxin
- Vasodilators (Clonidine)
- Warfarin (Coumadin)

Omega-3 and **-6 fatty acids** have been shown to be **safe** with most of the common medications prescribed in cardiovascular disease management

Warfarin (Coumadin) and Omega-3 fats might increase the chances of bruising or bleeding, but the risk is small under proper management, with older research has shown no risk at all, and more recent research unable to show increased risk

Omega-3 fats used in the presence of statin medication improves outcomes

- Recommended dose is 2640mg 4:1 EPA:DHA ratio

J. Chris Bradberry, PharmD and Daniel E. Hilleman, PharmD. P T. Nov 2013; 38(11): 681–691.

Omega-3 and Warfarin

No evidence to support increased bleeding risk

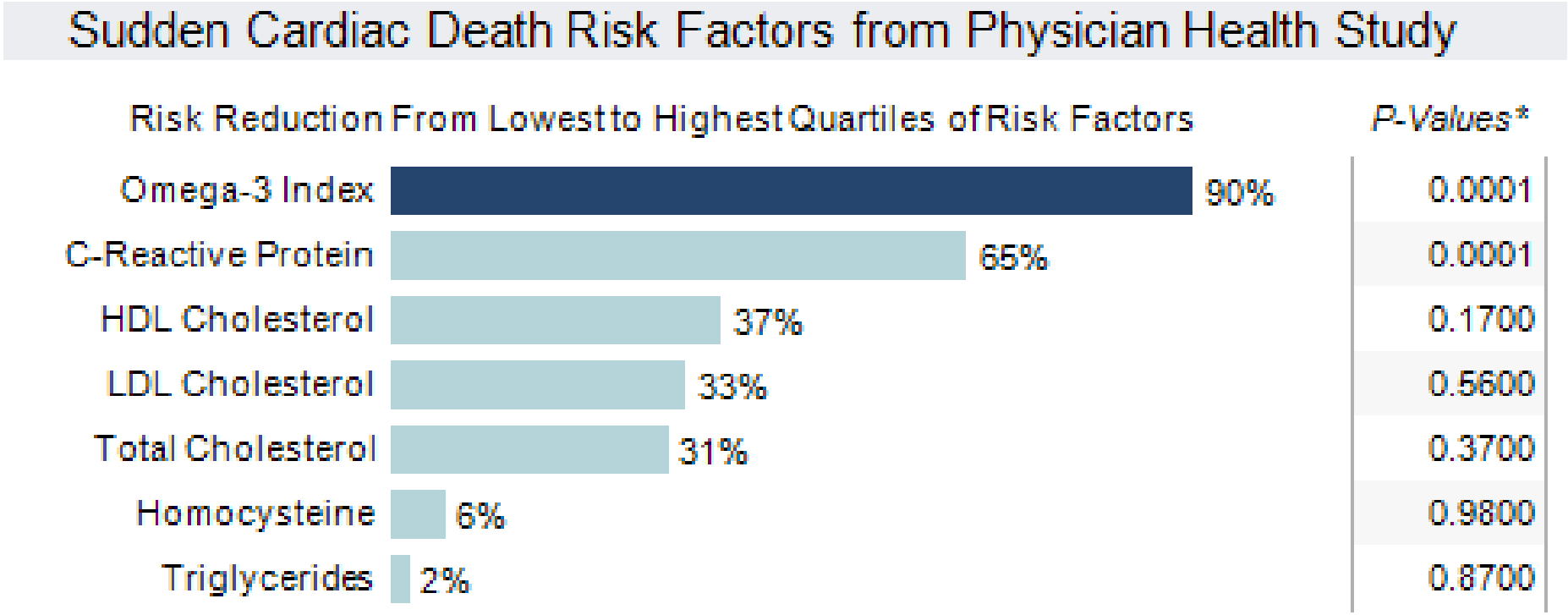
2-6g fish oil daily shown to not affect INR status

The lack of risk is likely due to the fact that omega-3 fats improve the signaling mechanisms associated with coagulation.

- Fish oils don't act as an anti-coagulant

Bender, N., Kraynak, M., Chiquette, E., Linn, W., Clark, G., & Bussey, H. (1998). *Journal of Thrombosis and Thrombolysis*, *5*(3), 257–261. doi:10.1023/A:1008852127668
Kanji, S., Seely, D., Yazdi, F., Tetzlaff, J., Singh, K., Tsertsvadze, A., Ansari, M. T. (2012). *Systematic Reviews*, *1*, 26. doi:10.1186/2046-4053-1-26

Sudden Cardiac Death Risk Factors



** P-values below 0.05 denote statistical significance.*

Albert CM et al. *Circulation* 2002;105:2595-2599.
Albert CM et al. *N Engl J Med* 2002;346:1113-1118.

Cancer

Increased Omega-3/Omega-6 ratio is inversely associated with breast cancer risk and has been shown to be causally linked to tumor prevention (in animal models)

The **Vitamins and Lifestyle study** looked at 70,495 people and found that **higher levels of EPA/DHA** intake **decreased cancer mortality**

- 23% decrease in all types of cancer
- 18% decrease from all causes of death
- 49% decrease in colorectal cancer (3+ years of 4+ days a week of supplement use) This was primarily in men

Improved CRP, CRP/albumin status, and potentially prevents weight loss during chemotherapy treatment

EPA's chemo protective potential in squamous cell carcinoma through amplification of the EGFR/ERK/p90RSK pathway – even in low doses

de Lorgeril M1, Salen P. BMC Med. 2014 Mar 27;12:54.
MacLennan MB, Clarke SE, Perez K, et al. J Nutr Biochem. 2013 Jan;24(1):388-95.
Bell GA, Kantor ED, Lampe JW, et al. Am J Epidemiol. 2014 Mar 15;179(6):710-20.
Yang B, Ren XL, Fu YQ, et al. BMC Cancer. 2014 Feb 18;14:105.
Kantor ED, Lampe JW, Peters U, et al. Nutr Cancer. 2013 Sep 20.
Mocellin MC, Pastore e Silva Jde A, et al. Lipids. 2013 Sep;48(9):879-88
Nikolakopoulou Z, Nteliopoulos G, Michael-Titus AT, et al. Carcinogenesis. 2013 Jul 26.

Cancer: Adjunct Care

Improved body weight and cachexia

Improving the **Omega-3/Omega-6 ratio** delays prostate cancer progression

Combination of gemcitabine and IV Omega-3 emulsion reduced levels of pro-inflammatory cytokines and growth factors in patients with advanced pancreatic cancer

- Up to 100g IV a week for 3 weeks immediately following chemo infusion (5:4:1 MCT:Soya:omega-3 FA triglycerides)

Prophylaxis against peripheral neuropathy associated with paclitaxel

- 2x at many developed PN in control vs those taking Omega-3 fatty acids (60% vs. 30%)
- 640mg EPA/DHA t.i.d. during chemo and for 1 month following

Improvement of inflammatory markers and antioxidant status in patients with advanced lung cancer

- Increase in body weight, decreased CRP and IL-6 levels
- 4 capsules with 850mg of EPA/DHA for 66 days

EPA may support the retention of lean body mass during chemotherapy

- Results point to earlier intervention having the best outcomes

Yeh KY, Wang HM, Chang JW, et al. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013 Apr 2. pii: S2212-4403(13)00042

Apte SA1, Cavazos DA, Whelan KA, et al. Nutr Cancer. 2013;65(4):556-62.

HPB (Oxford). 2013 Jun;15(6):428-32. doi: 10.1111/hpb.12002. Epub 2012 Nov 22.

Ghoreishi Z, Esfahani A, Djazayeri A, et al. BMC Cancer. 2012 Aug 15;12:355.

Finocchiaro C, Segre O, Fadda M, et al. Br J Nutr. 2012 Jul;108(2):327-33.

Murphy RA, Yeung E, Mazurak VC, et al. Br J Cancer. 2011 Nov 8;105(10):1469-73.

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbalip

Review

Lipid biology of breast cancer ☆

Jan Baumann [1], Christopher Sevinsky [1], Douglas S. Conklin *

Cancer Research Center, Department of Biomedical Sciences, University at Albany, State University of New York, Rensselaer, NY, USA

ARTICLE INFO

Article history:
Received 7 January 2013
Received in revised form 19 March 2013
Accepted 24 March 2013
Available online 2 April 2013

Keywords:
Breast cancer
HER2/neu
Signaling
Metabolism

ABSTRACT

Alterations in lipid metabolism have been reported in many types of cancer. Lipids have been implicated in the regulation of proliferation, differentiation, apoptosis, inflammation, autophagy, motility and membrane homeostasis. It is required that their biosynthesis is tightly regulated to ensure homeostasis and to prevent unnecessary energy expenditure. This review focuses on the emerging understanding of the role of lipids and lipogenic pathway regulation in breast cancer, including parallels drawn from the study of metabolic disease

"Our current understanding of breast cancer points to the importance of lipid synthesis and lipid related signaling alterations in the cells that cause this disease."

Prostate Cancer and Omega-3

J Natl Cancer Inst. 2013 Aug 7;105(15):1132-41. doi: 10.1093/jnci/djt174. Epub 2013 Jul 10.

Plasma phospholipid fatty acids and prostate cancer risk in the SELECT trial.

Brasky TM[1], Darke AK, Song X, Tangen CM, Goodman PJ, Thompson IM, Meyskens FL Jr, Goodman GE, Minasian LM, Parnes HL, Klein EA, Kristal AR.

⊕ **Author information**

Abstract

BACKGROUND: Studies of dietary ω-3 fatty acid intake and prostate cancer risk are inconsistent; however, recent large prospective studies have found increased risk of prostate cancer among men with high blood concentrations of long-chain ω-3 polyunsaturated fatty acids ([LCω-3PUFA] 20:5ω3; 22:5ω3; 22:6ω3]. This case-cohort study examines associations between plasma phospholipid fatty acids and prostate cancer risk among participants in the Selenium and Vitamin E Cancer Prevention Trial.

METHODS: Case subjects were 834 men diagnosed with prostate cancer, of which 156 had high-grade cancer. The subcohort consisted of 1393 men selected randomly at baseline and from within strata frequency matched to case subjects on age and race. Proportional hazards models estimated hazard ratios (HR) and 95% confidence intervals (CI) for associations between fatty acids and prostate cancer risk overall and by grade. All statistical tests we

RESULTS: Compared

CI = 1.08 to 1.93), hig

similar for individual lo

to 0.99) and total pros

CONCLUSIONS: This

The consistency of th

LCω-3PUFA intake should consider its potential risks.

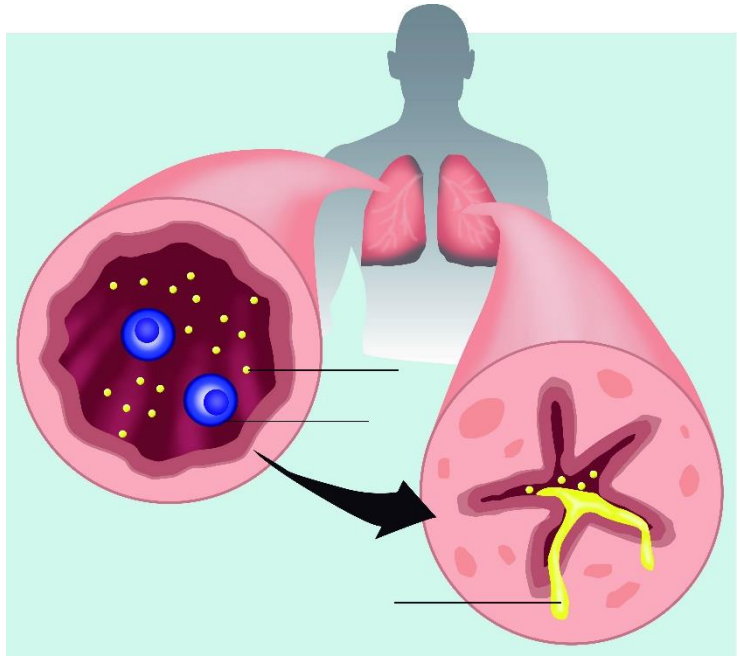
"It's important to note, however, that these results do not address the question of whether omega-3s play a detrimental role in prostate cancer prognosis," – T. Brasky (press release following publishing of study)

Chronic Lower Respiratory Disease
COPD, Emphysema, Chronic bronchitis

Airway inflammation is a very large component

What does the research say?

- "**Fish oil supplementation** should be considered as an alternative treatment for exercise-induced bronchoconstriction"*
  - Significant inhibition of hyperpnea-induced bronchoconstriction
- PUFA "intake was significantly inversely associated with incidence of asthma"
  - 1100mg to 2200mg EPA+DHA daily
- PUFA have vasodiliatory properties
- The Ω-3:Ω-6 ratio seems to be the important factor in positive outcomes



Tecklenburg-Lund, Mickleborough, et al. PLoS One. 2010 Oct 18;5(10):e134
Li J, Xun P, Zamora D, et al. Am J Clin Nutr. 2013 Jan;97(1):173-8
Omernik A. Pol Merkur Lekarski. 2012 Jan;32(187):55-8..

Stroke

In-vivo studies showed a 51% decrease in infarct volume when 0.1-0.375 g of DHA/kg was administered immediately after event (with-in 2 hours)

- In 150 pound human this would be 6.9 to 25.875 g

High EPA/AA ratio was associated with good outcome in ischemic stroke

DHA signaling has a potential in the development of treatments for those suffering the consequences of stroke

Williams JJ, Mayurasakorn K, Vannucci SJ, et al. PLoS ONE 2013 8(2): e56233.
Mishina M, Kim K, Kominami S, et al. Acta Neurol Scand. 2012 Jun 14.
Niemoller TD, Bazan NG. Prostaglandins Other Lipid Mediat. 2010 Apr;91(3-4):85-9.

Stroke

EPA levels prior seem to be more beneficial in positive outcomes

- **1-2g EPA+DHA daily** – 4:1 ratio would be appropriate depending on risk factors

DHA seems to be more beneficial in treatment of acute stroke consequences and those that remain after the event

- **1400mg**+ DHA focused formula

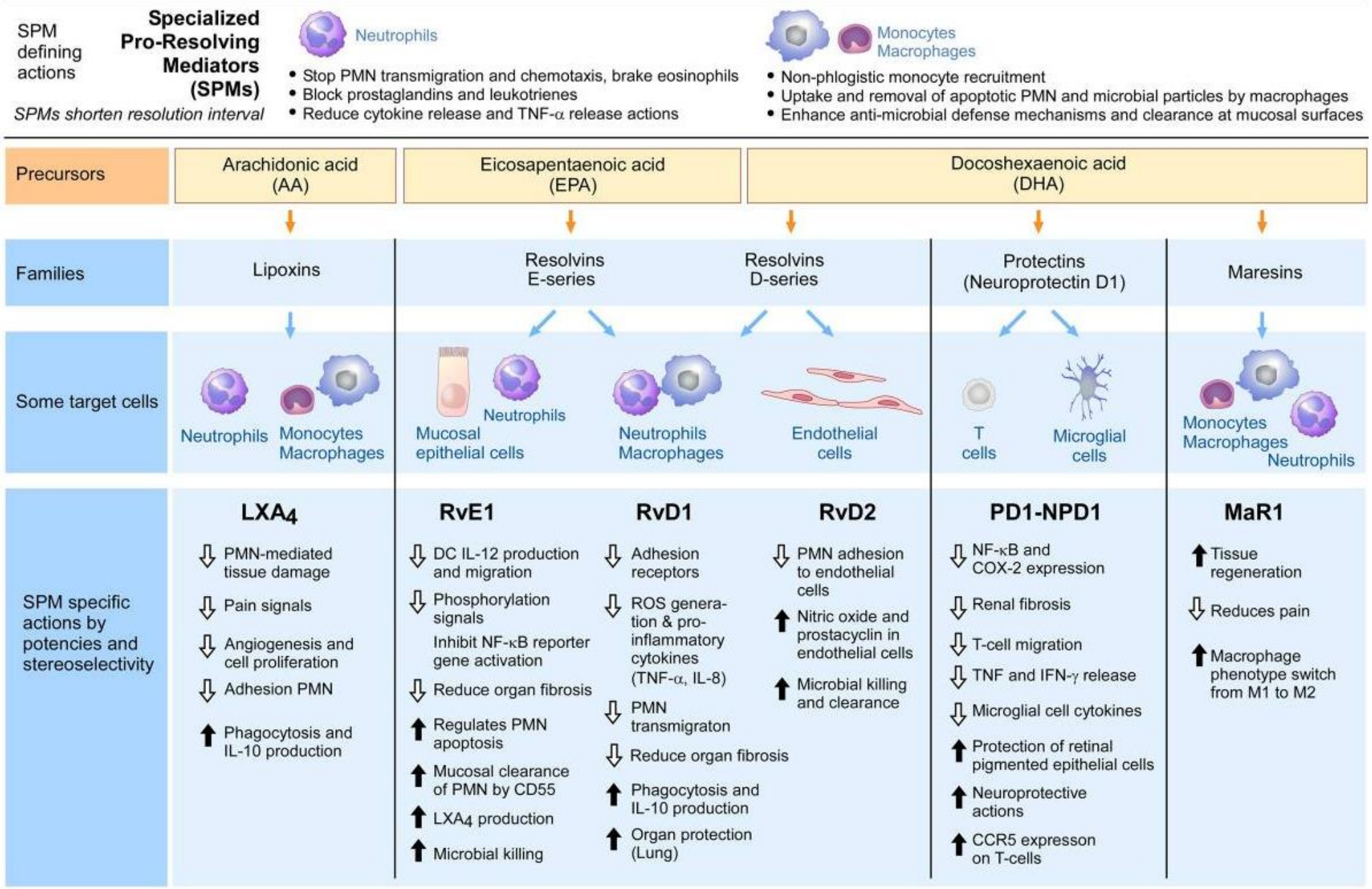
Pain

Everyday people have physical trauma occur to their bodies. This trauma, many times, results in pain.

Compared to ibuprofen, Omega-3 EFAs demonstrate an equivalent effect in reducing arthritic pain*.

Omega-3 fatty acids support musculoskeletal health through better signaling.

Maroon J, and Bost J. Surgical Neurology 2006 65:326-331
Watkins BA, Hutchins H, Li Y, et al. J Nutr Biochem. 2010 Dec;21(12):1141-52.



Buckley, C. D., Gilroy, D. W., & Serhan, C. N. (2014). Proresolving lipid mediators and mechanisms in the resolution of acute inflammation. *Immunity*, *40*(3), 315–27. doi:10.1016/j.immuni.2014.02.009

Arthritis/Pain

Alternative to ibuprofen*

- 4:1 EPA:DHA formula at a dose of 1050mg to 2100mg daily for 75 days

Musculoskeletal health through improved signaling

- 1000mg to 2000mg daily for 75 days

EPA has more anti-inflammatory effect than DHA, so higher doses of EPA generally work well with acute MSK injuries

Rheumatoid Arthritis

RCT trial shows patients with RA less than 12 months responded very well to high dose fish oil in conjunction with current medications.

- Triple DMARD therapy: methotrexate, sulphasalazine, and hydroxychloroquine
- 76% decrease in failure of triple DMARD therapy with FO group
- Remission was significantly greater in the FO group with patients 2.09 times more likely to experience remission

Long term intake of FO is associated with a 52% decreased risk of RA (>.21g/day)

EPA and DHA exert anti-inflammatory and pro-resolving properties via resolvins and are log-orders more potent than their precursors

The combination of GLA, EPA and DHA is useful in correcting dyslipidemia in patient with RA

- 8.4 mb/dL total cholesterol decrease
- 9.4 mg/dL LDL decrease
- 5.0 mg/dL HDL increase
- 24.4 mg/dL triglyceride decrease

Over the course of 12 months GLA treatment resulting in clinically significant reductions in RA signs and symptoms

Moderate evidence exists to support the use of GLA to RA symptom reduction

- 33% decrease in pain
- 15.75% decrease in disability

One of the main benefits is affect on the biochemical pathways associated with inflammation

Proudman SM, James MJ, Spargo LD, et al. Ann Rheum Dis. 2015 Jan;74(1):89-95
Di Giuseppe D, Wallin A, Bottai M, et al. Ann Rheum Dis. 2013 Aug 12
Norling LV, Perretti M. Curr Opin Pharmacol. 2013 Feb 2
Olendzki BC, Leung K, Van Buskirk S, et al. Evid Based Complement Alternat Med. 2011;2011:827286
Zurier RB, Rossetti RG, Jacobson EW, et al. Arthritis Rheum. 1996 Nov;39(11):1808-1
Cochrane Database Syst Rev. 2011 Feb 16;(2):CD002948

Rheumatoid Arthritis

EPA + DHA at a level of 5.5 g per day taken with DMARDs

Added GLA does show promise

- **4:1 EPA:DHA formula with GLA:** up to 2.8g daily

The primary clinical benefits are seen in CVD risk reduction and symptomatic improvements, likely due to biochemical interaction with inflammatory molecules

Alzheimer's

A combination of Omega-3 fatty acids and alpha lipoic acid over the course of 12 months showed less decline in MMSI and IADL vs. control and Omega-3 fatty acids alone*

Depleted levels of DHA in CSF are seen in those with Alzheimer's

Increased risk of Alzheimer's disease when in the lower quartile of Ω-3 fatty acids intake or blood levels

1550mg Omega 3 plus 600mg Alpha Lipoic Acid Daily

Shinto L, Quinn J, Montine T, et al. J Alzheimers Dis 2014 Jan 1;38(1):111-20.
Fonteh A, Cipolla M, Chiang J, et al. PLoS One. 2014 Jun 23;9(6):e100519.
Dacks PA, Shineman DW, Fillit HM. J Nutr Health Aging. 2013 Mar;17(3):240-51.

Diabetes

Fish oil has a potential benefit on glucose uptake and cell livability (in-vivo study)*

- The major concern in the total uptake concentration of omega-3 by the muscle cells

Daily omega-3 consumption decreases the risk of LADA

- .3 g daily of omega-3 PUFA resulted in a decrease of 40%
- .3 g daily of omega-3 fish oil resulted in a decrease of 53%

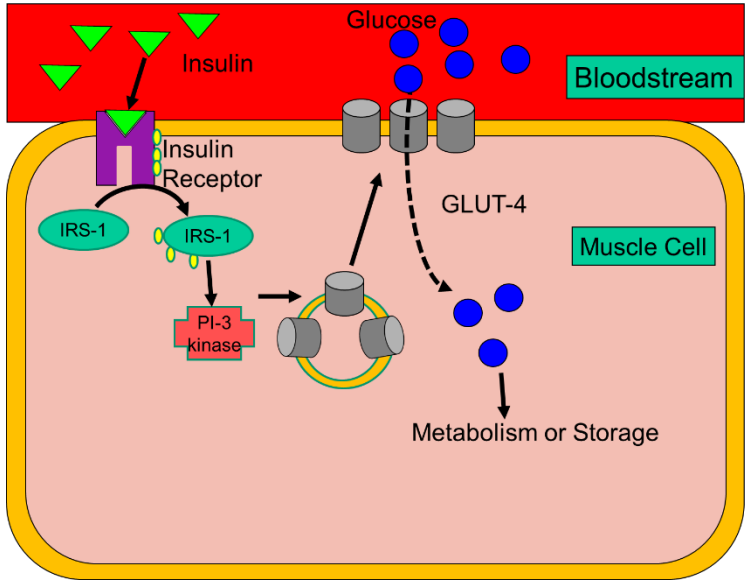
Higher serum omega-3 concentration is associated with decrease risk of type 2 diabetes

Promising early results in the prevention and treatment of obesity

- Affect the endocannabinoid and mesocorticolimbic pathways
- Hypothesized that EPA/DHA can reduce reward associated with food, thus reducing appetite and food intake

DHA can attenuate inflammation and improve insulin sensitivity (in vitro)

Fish oils may help to decrease obesity-induced insulin resistance



Deyhim F, Olivarez O. Diabetes 2006;55(1):A382. Texas A&M University, Kingsville, TX.
Löfvenborg JE, Andersson T, Carlsson PO, et al. Nutr Diabetes. 2014 Oct 20;4:e139.
Virtanen JK, Mursu J, Voutilainen S, et al. Diabetes Care. 2013 Sep 11.
Golub N, Geba D, Mousa SA, et al. Med Hypotheses. 2011 Dec;77(6):1114-20.
Oliver E, McGillicuddy FC, Harford KA, et al. J Nutr Biochem. 2011 Nov 30.
Oliver E, McGillicuddy F, et al. Proc Nutr Soc. 2010;69(2):232-43.

Eye Health

Increased DHA and reduced LA consumption beneficially effects age-related macular degeneration (AMD)

- Via reduction of MCP-1 expression via PPARγ and NF-κB

Red blood cell membrane EPA and DHA + EPA are highly associated with AMD

- Highest EPA levels had 75% decrease in risk
- Highest EPA + DHA levels had 48% decrease in risk

Lutein and Zeaxanthin both have favorable evidence supporting clinical use for AMD

- Have been shown to increase macular pigment optical density
- Lutein enhances retinal sensitivity

Fang, I.-M., Yang, C.-H., & Yang, C.-M. (2014). *Molecular Nutrition & Food Research*, *58*(10), 2053–65.
Merle, B. M. J., Benlian, P., Puche, N., Bassols, A., Delcourt, C., & Souied, E. H. (2014). *Investigative Ophthalmology & Visual Science*, *55*(3), 2010–9.
Schmidl, D., Garhöfer, G., & Schmetterer, L. (2015). *Acta Ophthalmologica*, *93*(2), 105–121.
Huang, Y.-M., Dou, H.-L., Huang, F.-F., Xu, X.-R., Zou, Z.-Y., Lu, X.-R., & Lin, X.-M. (2015). *The British Journal of Ophthalmology*, *99*(3), 371–5.

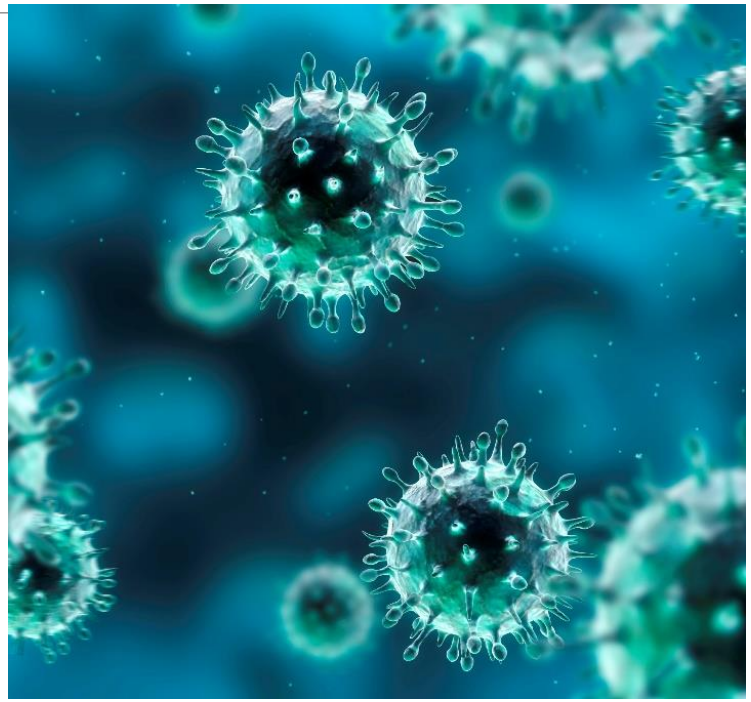
Influenza and Pneumonia

Protectin D1 (PD1) is derived from Omega-3 fatty acids
- PD1 suppresses influenza virus replication

Fish oil may support immune function through enhancement of B cell function (in vivo)

Fish oil protects against post exercise immune decrease
- Helps to reduce increased PBMC IL-2 production and NK cell cytotoxic activity post exercise

Potential for support of innate immunity development in infants, especially those who are not breast fed
- Asthma, Crohn's disease, rheumatoid arthritis
- Early intervention is necessary



Morita M, Kuba K, Ichikawa A, et al. Cell. 2013 Mar 5. pii: S0092-8674(13)00216-X.
Gurzell EA, Teague H, Harris M, et al. J Leukoc Biol April 2013 93:463-470.
Gray P, Gabriel B, Thies F, et al. Brain Behav Immun. 2012 Nov;26(8):1265-72.
Prentice AM, vander Merwe L. Matern Child Nutr 2011 Apr;7 Suppl 2:89-98

Depression and Mood Disorders

Combination therapy of **high dose EPA** and citalopram demonstrated a "significantly greater improvement in Hamilton Depression rating scores"*

Omega-3 PUFAs in clinical trial to be used as first line therapy in young people with MDD – 1.4g/day

The use of Omega-3 PUFAs in MDD and in those not diagnosed as MDD has significant clinical efficacy

High levels of AA were associated with suicide risk and major depressive episodes among pregnant Brazilian women

Gertsik L, Poland R, Bresee C, et al. Journal of Clinical Psychopharmacology February 2012 Volume 32, Issue 1, p 61-64.
Rice S, Hickie I, Yung A, et al. Early Interv Psychiatry. 2014 Aug 13.
Grosso G, Pajak A, Marventano S, et al. PLoS One. 2014 May 7;9(5):e96905.
Vaz JS1, Kac G, Nardi AE, et al. J Affect Disord. 2014 Jan;152-154:76-82.

Biochim Biophys Acta. 2015 May;1852(5):951-61. doi: 10.1016/j.bbadis.2014.12.005. Epub 2014 Dec 27.

Curcumin boosts DHA in the brain: Implications for the prevention of anxiety disorders.

Wu A[1], Noble EE[1], Tyagi E[1], Ying Z[1], Zhuang Y[1], Gomez-Pinilla F[2].

Author information

Abstract

Dietary deficiency of docosahexaenoic acid (C22:6 n-3; DHA) is linked to the neuropathology of several cognitive disorders, including anxiety. DHA, which is essential for brain development and protection, is primarily obtained through the diet or synthesized from dietary precursors, however the conversion efficiency is low. Curcumin (diferuloylmethane), which is a principal component of the spice turmeric, complements the action of DHA in the brain, and this study was performed to determine molecular mechanisms involved. We report that curcumin enhances the synthesis of DHA from its precursor, α-linolenic acid (C18:3 n-3; ALA) and elevates levels of enzymes involved in the synthesis of DHA such as FADS2 and elongase 2 in both liver and brain tissues. Furthermore, in vivo treatment with curcumin and ALA reduced anxiety-like behavior in rodents. Taken together, these data suggest that curcumin enhances DHA synthesis, resulting in elevated brain DHA content. These findings have important implications for human health and the prevention of cognitive disease, particularly for populations eating a plant-based diet or who do not consume fish, a primary source of DHA, since DHA is essential for brain function and its deficiency is implicated in many types of neurological disorders.

Copyright © 2015 Elsevier B.V. All rights reserved.

"These findings have important implications for human health and the prevention of cognitive disease, particularly for populations eating a plant-based diet"

Traumatic Brain Injury

DHA can mitigate mild TBI

DHA provides "nutritional armor" for common brain injuries

It may be a "prophylactic" against cerebral concussion

EPA and DHA increase serum levels and reduce the number of APP-positive axons at 30 days post-injury to levels similar to those in uninjured animals

Elevated DHA content in brain helps to normalize levels of BDNF (Study using ProDHA) and helped return to membrane homeostasis after trauma, potentially translating into preserved cognitive capacity*

Curcumin helps to enhance the effect of ProDHA in TBI*

Bailes JE, Patel V. Mil Med. 2014 Nov;179(11 Suppl):112-6.
Kim HY. 2014 Nov;179(11 Suppl):106-11.
Mills JD, Bailes JE, Sedney CL, Hutchins H, et al. J Neurosurg. 2011 Jan;114(1):77-84.
*Wu A, Ying Z, Gomez-Pinilla F. J Neurotrauma 2011 Oct;28(10):2113-22.**
*Wu A, Ying Z, Gomez-Pinilla F. Neurorehabil Neural Repair 2014 Jan;28(1):75-84**

Common Prescription Meds and Fish oils

Drug Interactions

Omega-3 and -6 fatty acids have been shown to be safe with most of the common medications prescribed in cardiovascular disease management

Warfarin (Coumadin) and Omega-3 fats can increase the chances of bruising or bleeding, but the risk is small under proper management – older research has shown no risk at all

Omega-3 fats used in the presence of statin medication improves outcomes

- Combo therapies have better results at attaining goal lipid level

Potential interaction when used in conjunction with glibizide, Metformin, or insulin due to action on insulin sensitivity

J. Chris Bradberry, PharmD and Daniel E. Hilleman, PharmD. P T. Nov 2013; 38(11): 681–691.
Bender NK, Kraynak MA, Chiquette E, et al. J Thromb Thrombolysis. 1998;5(3):257-261

Ulcerative colitis

Condition	Drugs	Product Recommendation	Supports, replaces, or contraindicated	Interactions?
• Ulcerative colitis	• budesonide	• ProOmega • 2-4 soft gels daily	• Support	• no

An estimated 30% of cases could be due to high levels of AA. Improve the Omega-3 : Omega-6 ratio.

Hart AR. Linoleic Acid, a Dietary N-6 Polyunsaturated Fatty Acid, and the Aetiology of Ulcerative Colitis - A European Prospective Cohort Study. Gut. 2009.

Pain

Condition	Drugs	Product Recommendation	Supports, replaces, or contraindicated	Interactions?
• Pain • Fibromyalgia	• Acetaminophen/ hydrocodone • NSAIDS • Lyrica	• ProOmega • 2-4 soft gels daily	• Support or replace	• no

Opioid effectiveness very similar to NSAIDs which happen to work about as well as EPA.
PUFAs play a vital role in pain regulation in regards to chronic pain syndromes such as fibromyalgia

Maroon J, and Bost J. Surgical Neurology 2006 65:326-331
Watkins BA, Hutchins H, Li Y, et al. J Nutr Biochem. 2010 Dec;21(12):1141-52

Lower Respiratory Disorders

Condition	Drugs	Product Recommendation	Supports, replaces, or contraindicated	Interactions?
• Asthma • Chronic bronchitis • COPD • Emphysema	• Albuterol • ProAir HFA • Ventolin HFA • Advair Diskus • Spiriva • Symbicort	• ProOmega • 2-4 soft gels daily	• Support or replace	• no

- Omega-3 FAs are a viable treatment modality and/or adjunct therapy in airway constriction/inflammation
- Increased ratio of omega-3 : omega-6 PUFA can help in reducing chronic inflammatory diseases
- PUFAs support pro-resolving mediators

http://www.ncbi.nlm.nih.gov/pubmed/15674003
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3335257
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3094721/pdf/nihms280746.pdf

Hypothyroidism

Condition	Drugs	Product Recommendation	Supports, replaces, or contraindicated	Interactions?
• Hypothyroidism	• Levothyroxine • Synthroid	• ProOmega • 2-4 soft gels daily	• Support	• no

Omega-3 FAs can have a neuro-protective effect against hypothyroid induced cognitive impairment

http://www.ncbi.nlm.nih.gov/pubmed/25183510

GERD

Condition	Drugs	Product Recommendation	Supports, replaces, or contraindicated	Interactions?
• GERD	• Nexium • esomeprazole	• ProOmega • 2-4 soft gels daily	• Support	• no

People with higher omega-3 intakes had a 54% decrease in Barrett's esophagus

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2765669/

Diabetes

Condition	Drugs	Product Recommendation	Supports, replaces, or contraindicated	Interactions?
• Type 1 Diabetes • Type 2 Diabetes	• Lantus • Levemir • NovoLog • HumaLog • Januvia	• ProOmega • 2-4 soft gels daily	• Support	• no

- Healthy omega-3 : omega-6 levels have been associated with decreased incidence
- There is potential the fish oils also improve glucose uptake
- EPA and DHA may improve kidney health in relation to diabetes
- Cod liver oil early

http://www.ncbi.nlm.nih.gov/pubmed/24026545
Deyhim F, Olivarez O. Diabetes 2006;55(1):A382. Texas A&M University, Kingsville, TX.
http://www.ncbi.nlm.nih.gov/pubmed/20357378
http://www.ajcn.org/content/78/6/1128.long

Mental health

Condition	Drugs	Product Recommendation	Supports, replaces, or contraindicated	Interactions?
• Depression • Anxiety • Bipolar • Schizophrenia • Chronic pain	• SSRI • Cymbalta • Abilify	• ProEPA • 4 soft gels daily	• Support or replace	• no

Combination therapies have significantly better outcomes and can be used as first line therapy in youth

Gertsik L, Poland R, Bresee C, et al. Journal of Clinical Psychopharmacology February 2012 Volume 32, Issue 1, p 61-64.
Rice S, Hickie I, Yung A, et al. Early Interv Psychiatry. 2014 Aug 13.

CVD

Condition	Drugs	Product Recommendation	Supports, replaces, or contraindicated	Interactions?

• High cholesterol
• High blood pressure
	• Statins
	• Crestor
	• Metoprolol
		• ProOmega
		  • 2-4 soft gels daily
		• ProOmega CoQ10
		  • 2-4 soft gels daily
		• Nordic CoQ10 Ubiquinol
		  • 1-4 soft gels daily
			• Support	• no

Combination therapies have better results at attaining goal lipid levels

J. Chris Bradberry, PharmD and Daniel E. Hilleman, PharmD. P T. Nov 2013; 38(11): 681–691.

Allergies

Condition	Drugs	Product Recommendation	Supports, replaces, or contraindicated	Interactions?
• Nasal allergy symptoms	• Nasonex	• ProOmega • 2-4 soft gels daily	• Support	• no

There is a lot of research on beneficial allergy outcomes when a pregnant women is exposed to PUFA or when the child is exposed early in childhood
There is early support for decreased airway inflammation after allergen exposures

http://www.ncbi.nlm.nih.gov/pubmed/20637584

Safety first!

Purity – Heavy metals, Dioxins, PCBs

- Know your source and ask them to proof it

DHA has been studied in rats at a level of 3290 mg/kg a day for 90 days and found to be completely safe

- That would be over 224 g of DHA daily for a 150 pound human!

DHA studies have been done at doses of 1.5g – 7.5g a day in adults with no safety concerns

3-6 g of fish oil daily is safe with warfarin (Coumadin)

No excess bleeding due to fish oil given in addition to aspirin or warfarin (4g fish oil daily)

There is some evidence of a rise in ALT and AST (liver enzymes), so in patients with severe liver disease, these levels should continue to be closely monitored

One of the biggest challenges people may have is GI related and due to difficulty with digesting the oils

Lien EL. Prostaglandins Leukot Essent Fatty Acids. 2009 Aug-Sep;81(2-3):125-32.
Bender NK, Kraynak MA, Chiquette E, et al. J Thromb Thrombolysis. 1998;5(3):257-261.
Eritsland J, Arnesen H, Seljeflot I, et al. Blood Coagul Fibrinolysis. 1995 Feb;6(1):17-22.

Excellent clinical utility

Many conditions respond favorably to improved levels of EPA and/or DHA

Positive health outcomes are associated with appropriate membrane levels of EFA

Most of us are deficient or imbalanced, so test everyone!

Omega-3 use is relatively safe with appropriate monitoring

Questions

Thank you!

If you want to reach me with additional questions

- facebook.com/drchristopheroswald
- droswald8@gmail.com