High-dose EPA and DHA: Are We Missing Something?

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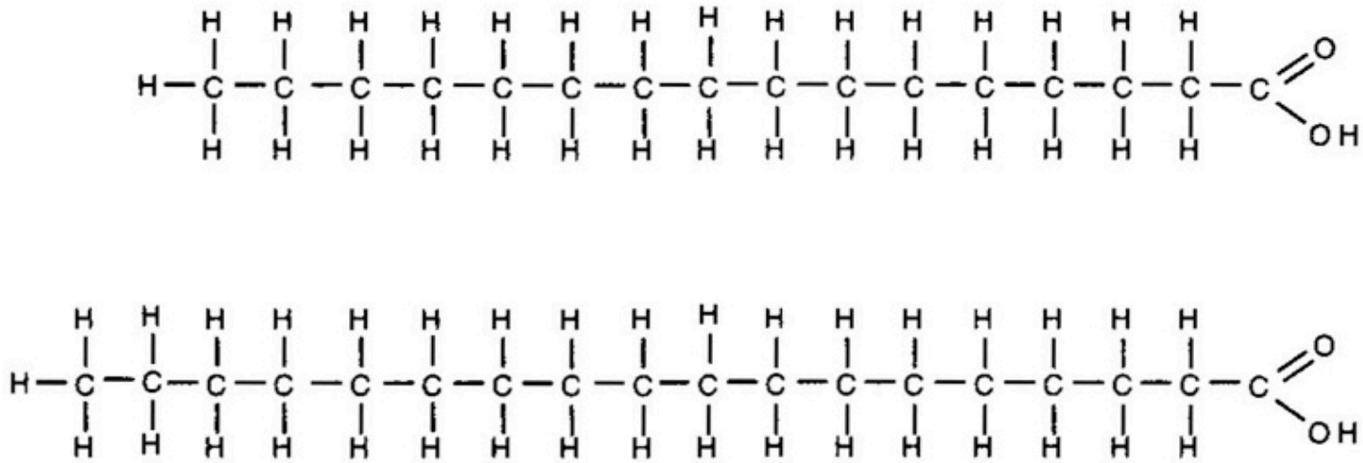
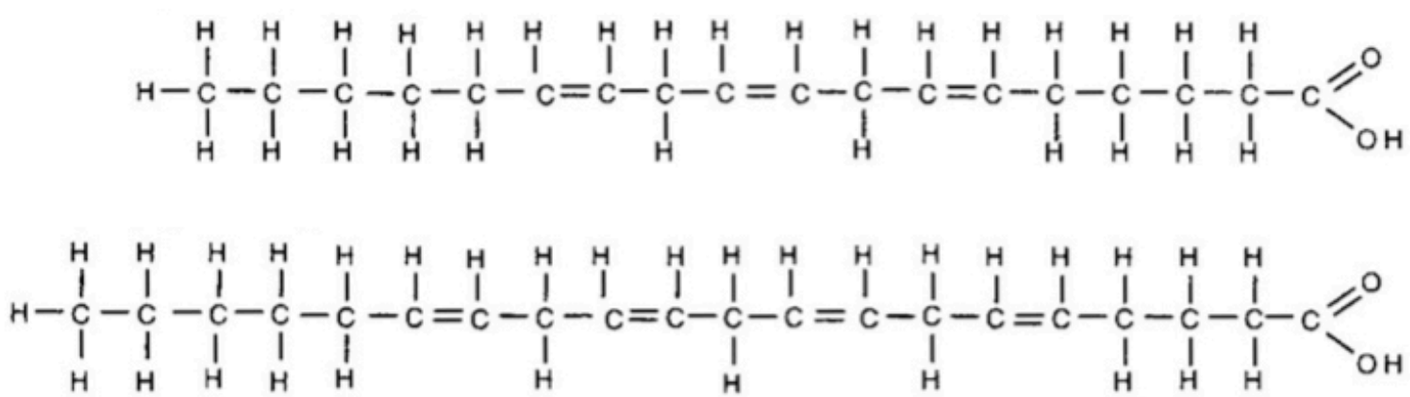
healthybyknowing.com

Lipid overview



Saturated fatty acid

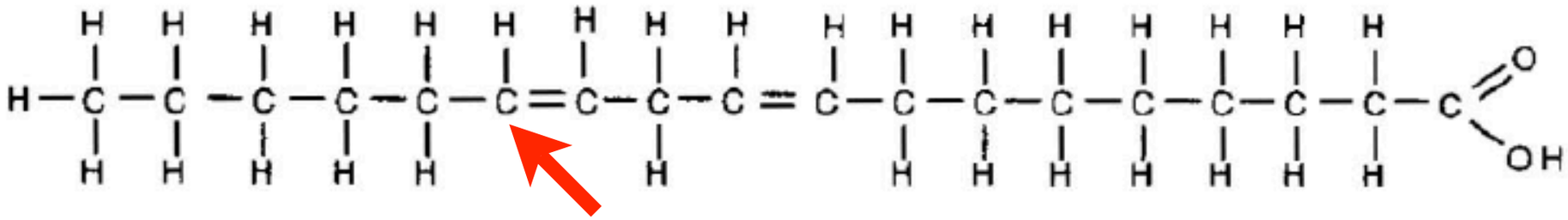


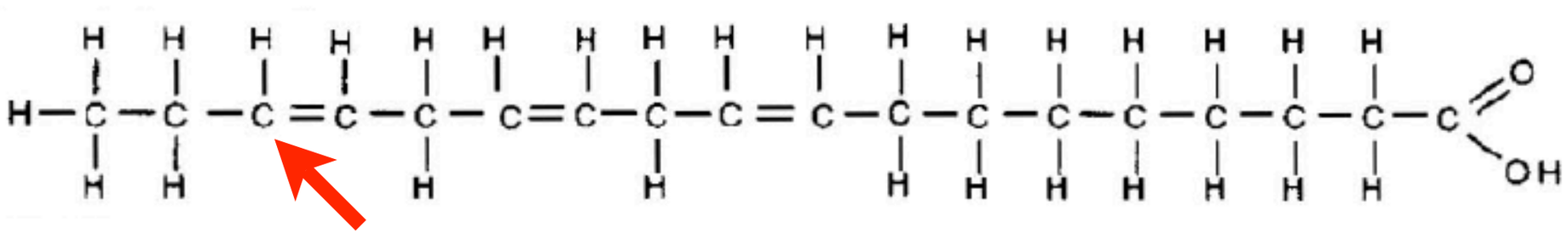
Unsaturated fatty acid

The Essential fatty acids

Omega 6

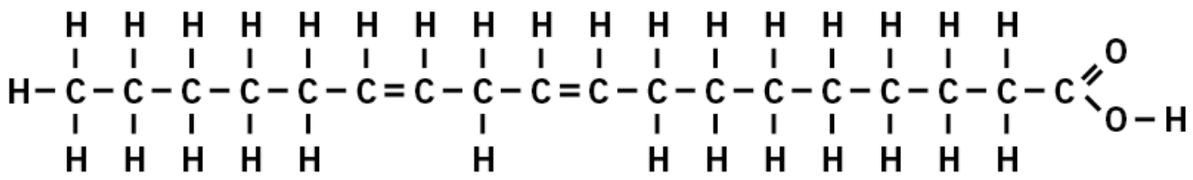
w6 Linoleic acid (LA)





Omega 3

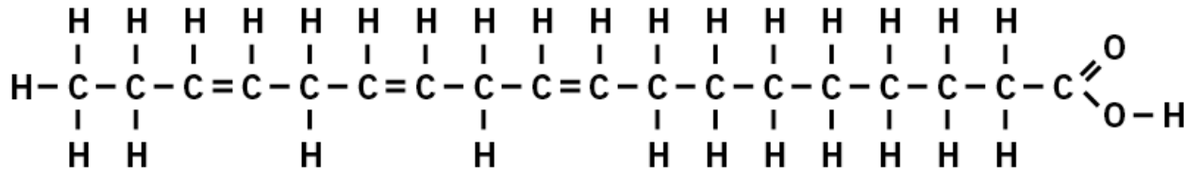
w3 Alpha linolenic acid



Omega 6

Linoleic acid – LA

18:2w6

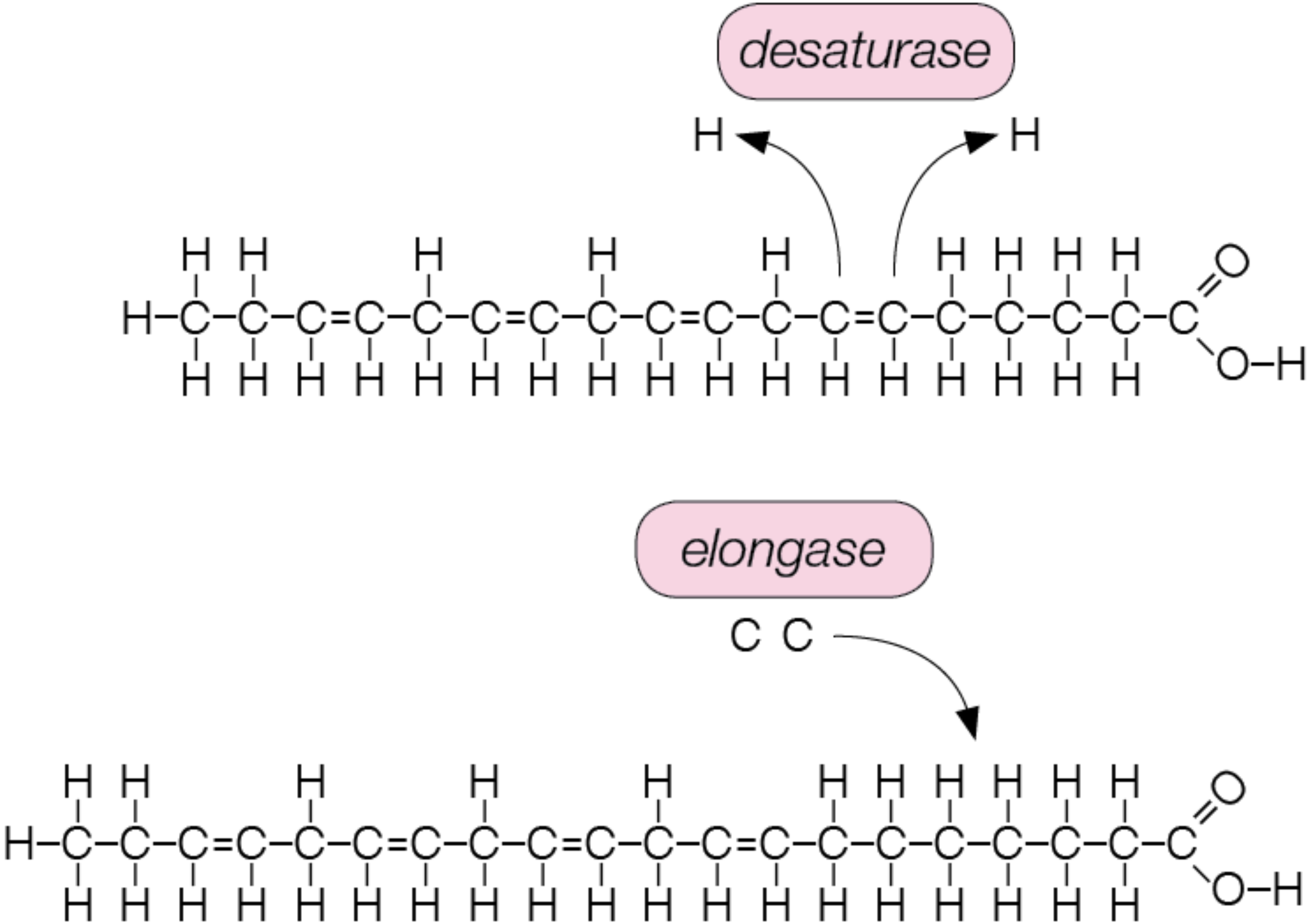


Omega 3

Alpha Linolenic acid – ALA

18:3w3

LA and ALA are “Parent” fatty acids


desaturase
elongase

1

w6 Linoleic acid — LA — ALA — w3 Alpha Linolenic acid

2

Delta 6 Desaturase — *D6D* — removes 2 hydrogens

Gamma Linolenic acid — GLA — SDA

3

Elongase — *EL* — adds 2 carbons + their hydrogens

Dihomo Gamma Linolenic acid — DGLA — ETA

4

Delta 5 Desaturase — *D5D* — removes 2 hydrogens

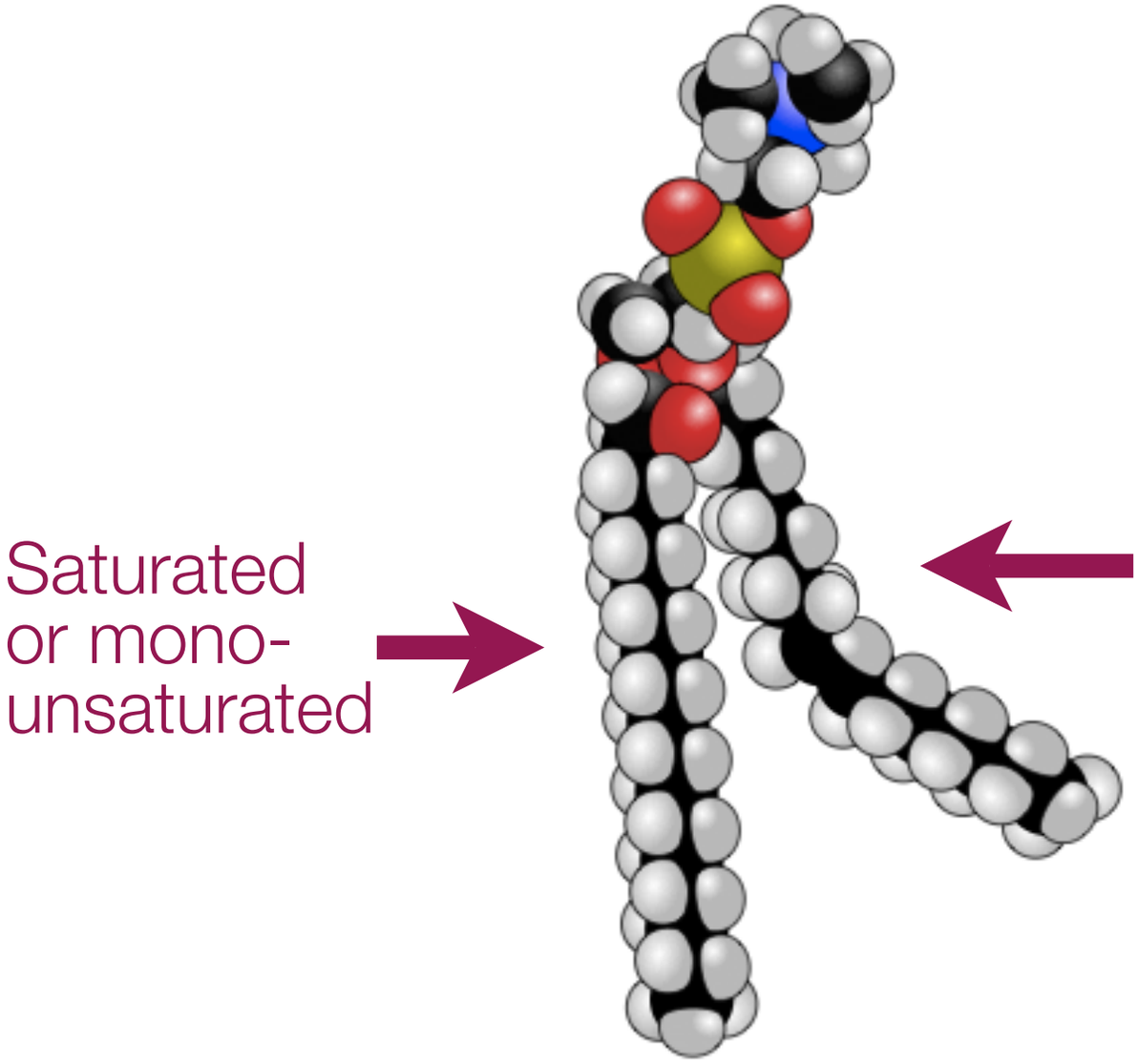
Arachidonic acid — AA — EPA — Eicosapentaenoic acid

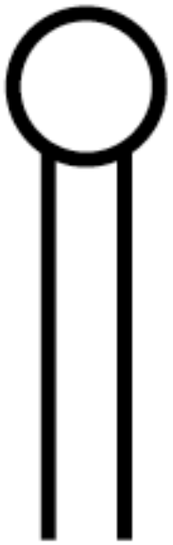
5

several steps...

DHA — Docosahexaenoic acid

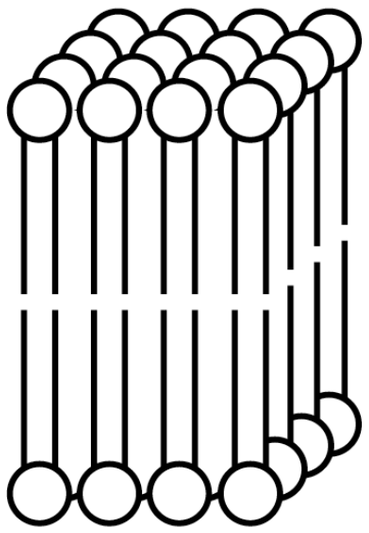
Omega 6 and 3 fatty acid metabolism

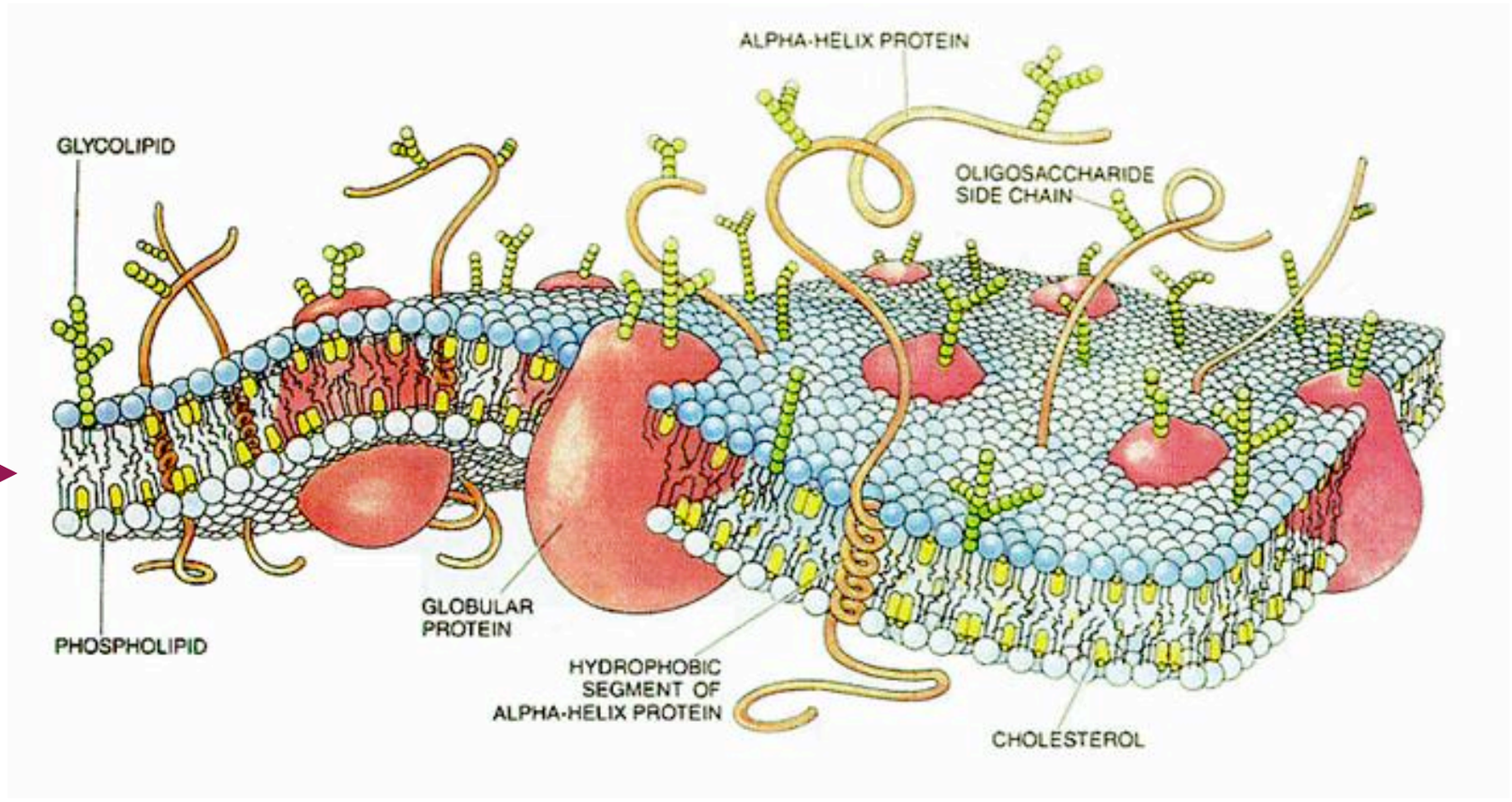




http://en.wikipedia.org/wiki/File:Cell_membrane_detailed_diagram_4.svg

Phospholipids





File:CellMembraneDrawing.jpg wikipedia
Drawing by Dana Burns, and can also be found in Scientific American, 1985, 253(4), pages 86-90, in the article
The molecules of the cell membrane by M.S. Bretscher.

Eicosanoids

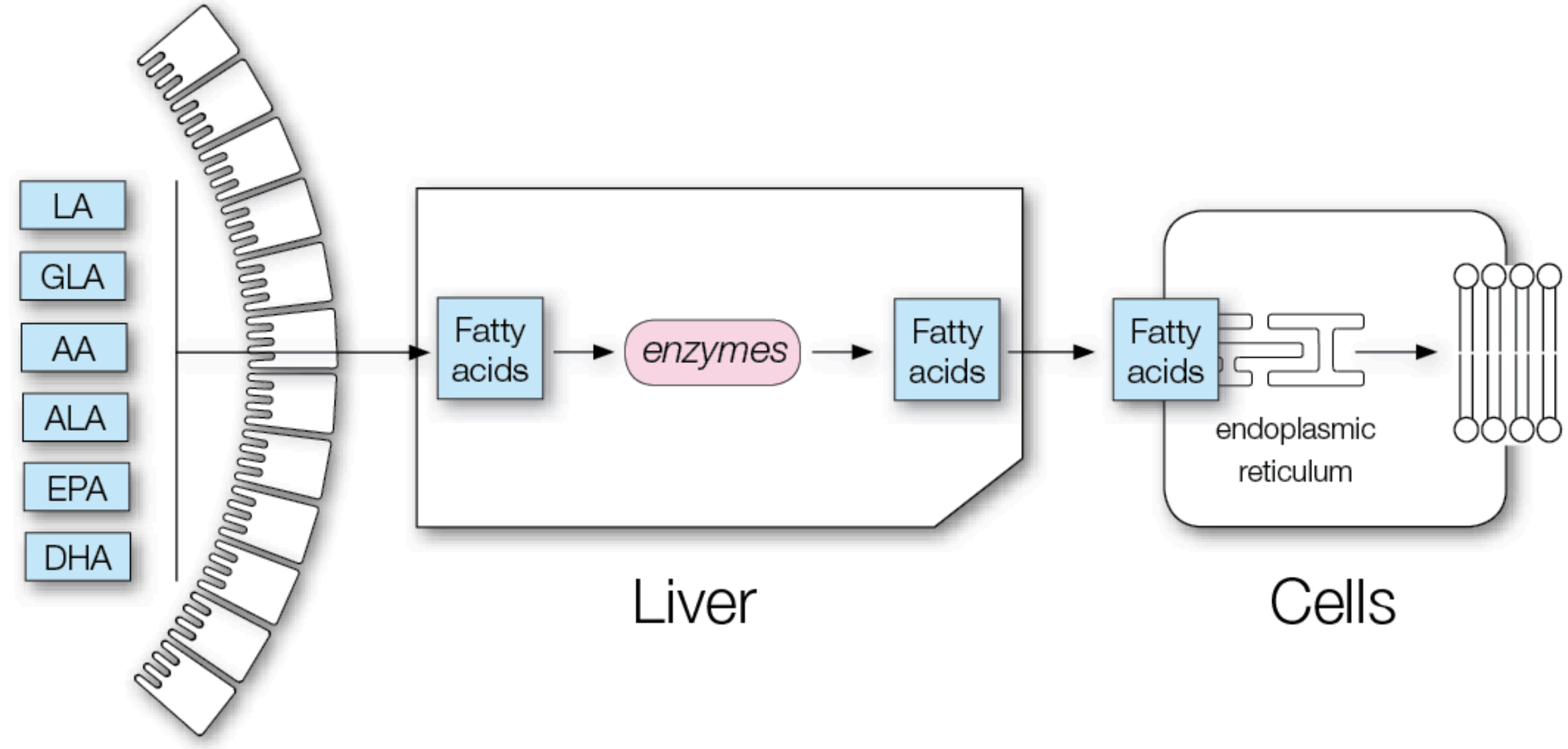
Signalling molecules made from 20-carbon fatty acids – DGLA, AA, EPA

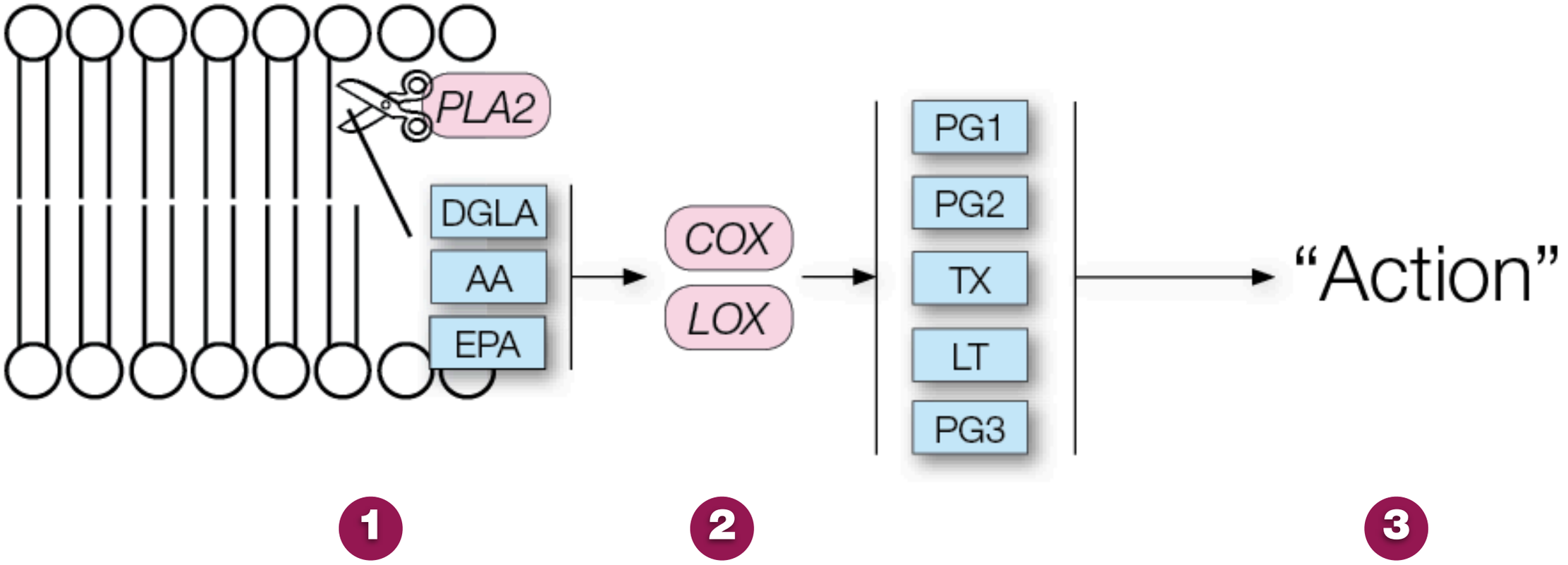
Key eicosanoids:

prostaglandins, tromboxanes, leukotrienes

Influence/control many body systems, especially:

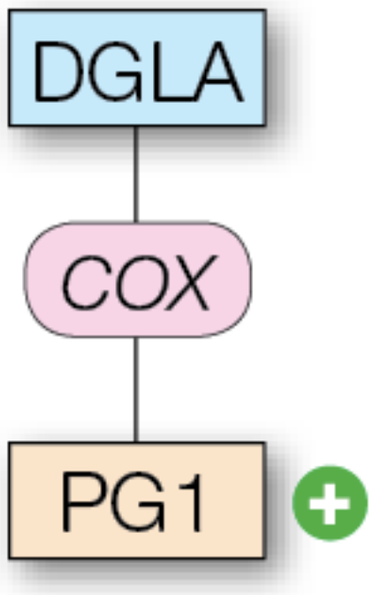
- **inflammation**
- **immune response**
- nervous system function


LA
GLA
AA
ALA
EPA
DHA
Intestines
Fatty acids
enzymes
Fatty acids
Liver
Fatty acids
endoplasmic reticulum
Cells
1
2
3



TX – Thromboxane
LT – Leukotriene

Key eicosanoids and their actions

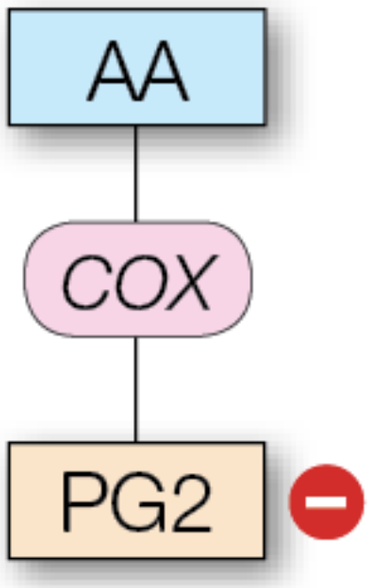


PG1 (Prostaglandin 1)

- increases **vasodilation**
- **inhibits platelet** aggregation
- **bronchodilation**
- mediates **inflammation**
- **inhibits** excess **T-cell** cytotoxicity

http://www.hmdb.ca/metabolites/HMDB01442

PG2 (Prostaglandin 2)



- mast cells
- macrophages
- platelets
- brain
- kidneys
- endothelium
- vascular smooth muscle
- airways

- stimulates **bone resorption**
- induces **fever**
- activates **platelet aggregation**
- pro-**inflammatory**
- **enhance** effects of bradykinin and **histamine**

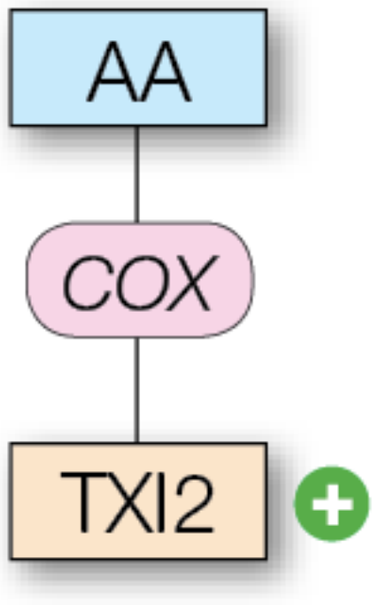
http://www.hmdb.ca/metabolites/hmdb01220

- exacerbates **allergies**
- **reduces apoptosis**
- increases **uterine contractions**

(Vasquez 2012)

- promotes **leukocyte chemotaxis** and adhesion

(Frits 2004)



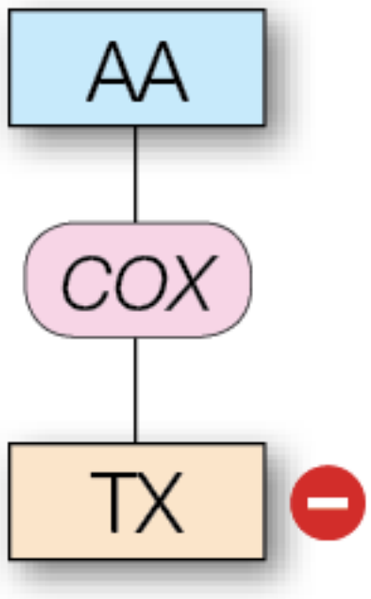
PGI2 (Prostacyclin)

- platelets
- brain
- kidneys
- endothelium
- vascular smooth muscle

- **vasodilation**
- **inhibits platelet** aggregation (primarily prevents formation of platelet plug)
- in circulatory system: in homeostatic **balance with thromboxane**

http://www.hmdb.ca/metabolites/hmdb01335

- **lowers** blood **pressure** (Vasquez 2012)



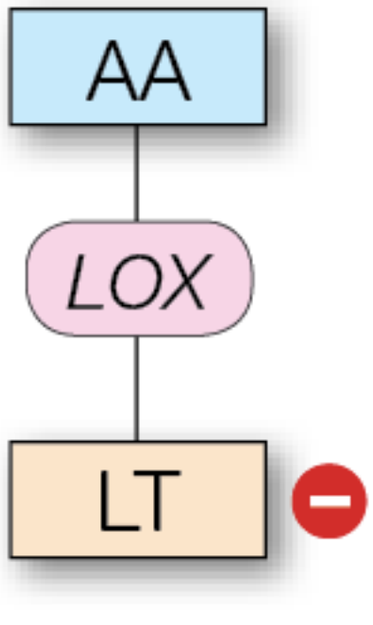
- platelets
- macrophages
- kidneys
- vascular smooth muscle

TX (Thromboxane)

- promotes **vasoconstriction**
- **hypertensive** agent
- facilitates **platelet** clumping
- in circulatory system: in homeostatic **balance with prostacyclin**

http://www.hmdb.ca/metabolites/HMDB03208

LT (Leukotrienes)



- mast cells
- eosinophils
- monocytes
- basophils

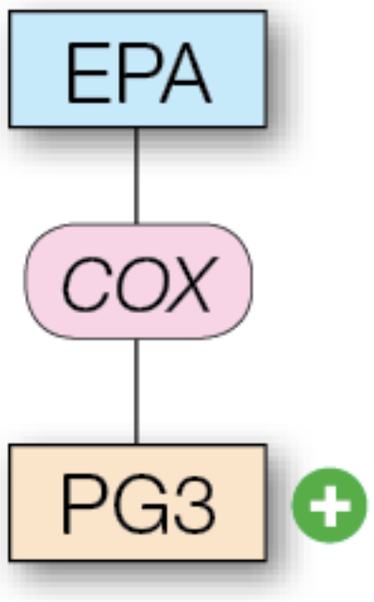
- participate in **host defense** reactions
- promote **immediate hypersensitivity**
- associated with **inflammation**

http://www.hmdb.ca/metabolites/HMDB01337

- decreases **immunity**
- **increases** edema, chemotaxis, reactive oxygen species, smooth muscle contraction, bronchoconstriction

(Vasquez 2012)

PG3 (Prostaglandin 3)



- competitively **bind PG2 receptors** with **weaker** affinity

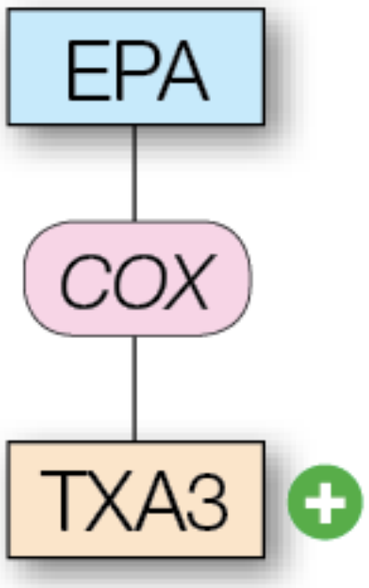
  (Hawcroft 2010)

- **inhibit tumour** formation

  REF 035 Yang

- **anti-inflammatory**, antipsychotic, cardioprotective

  (Vasquez 2012)



TXA3 (Thromboxane A3)

- **weaker aggregator** of platelets – net effect = anti-platelet

(Leukotrienes & Lipoxins)

- platelets
- macrophages
- kidneys
- vascular smooth muscle

The balanced eicosanoid response

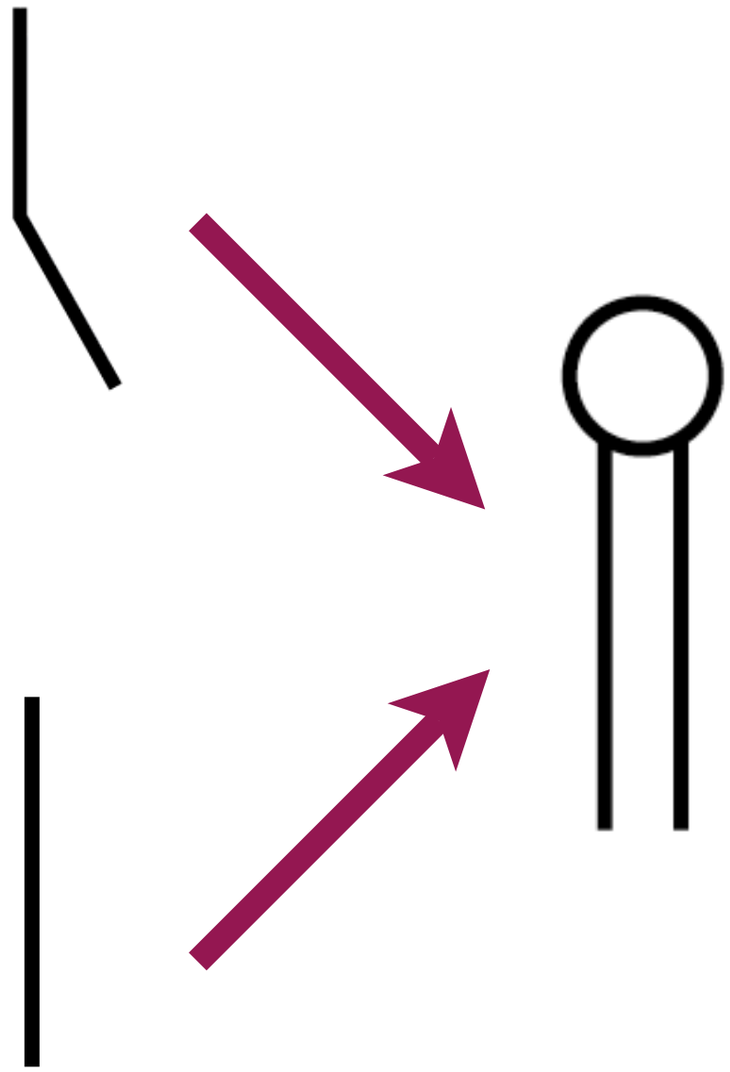
Balance of eicosanoid effects achieved by:

1 membrane loading

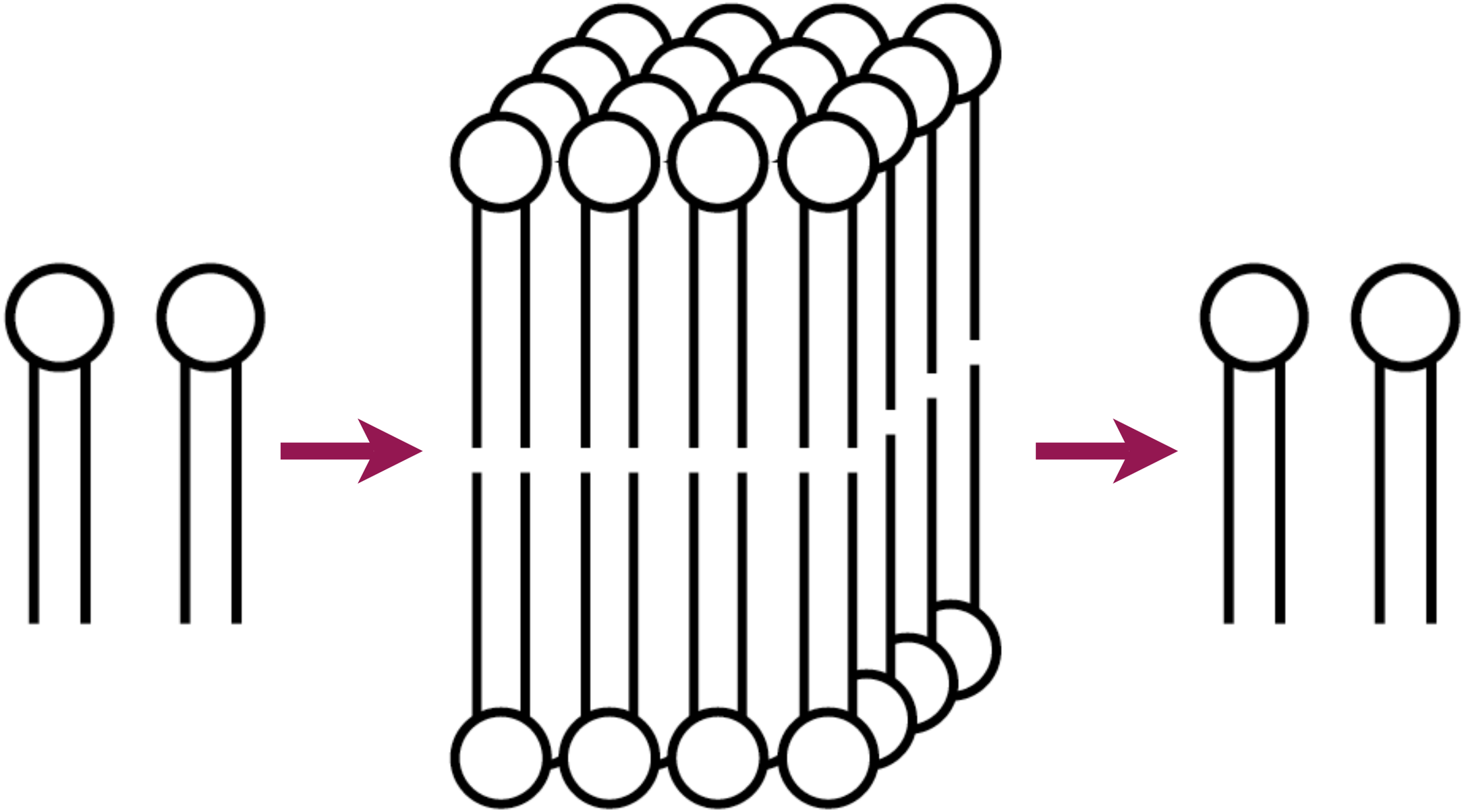
2 competition for enzymes

3 rate of activity of relevant enzymes

Membrane loading



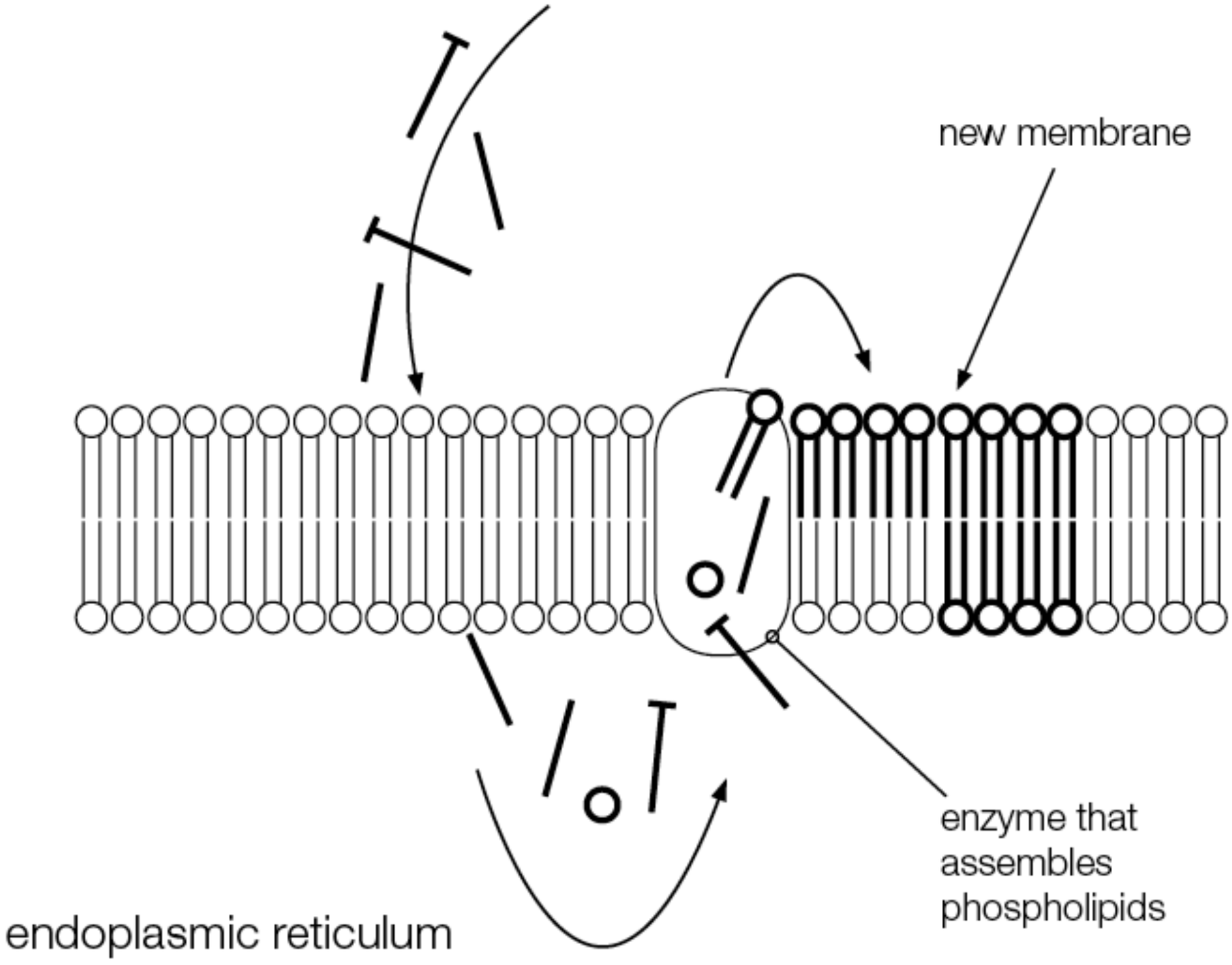
Competition for loading in phospholipids



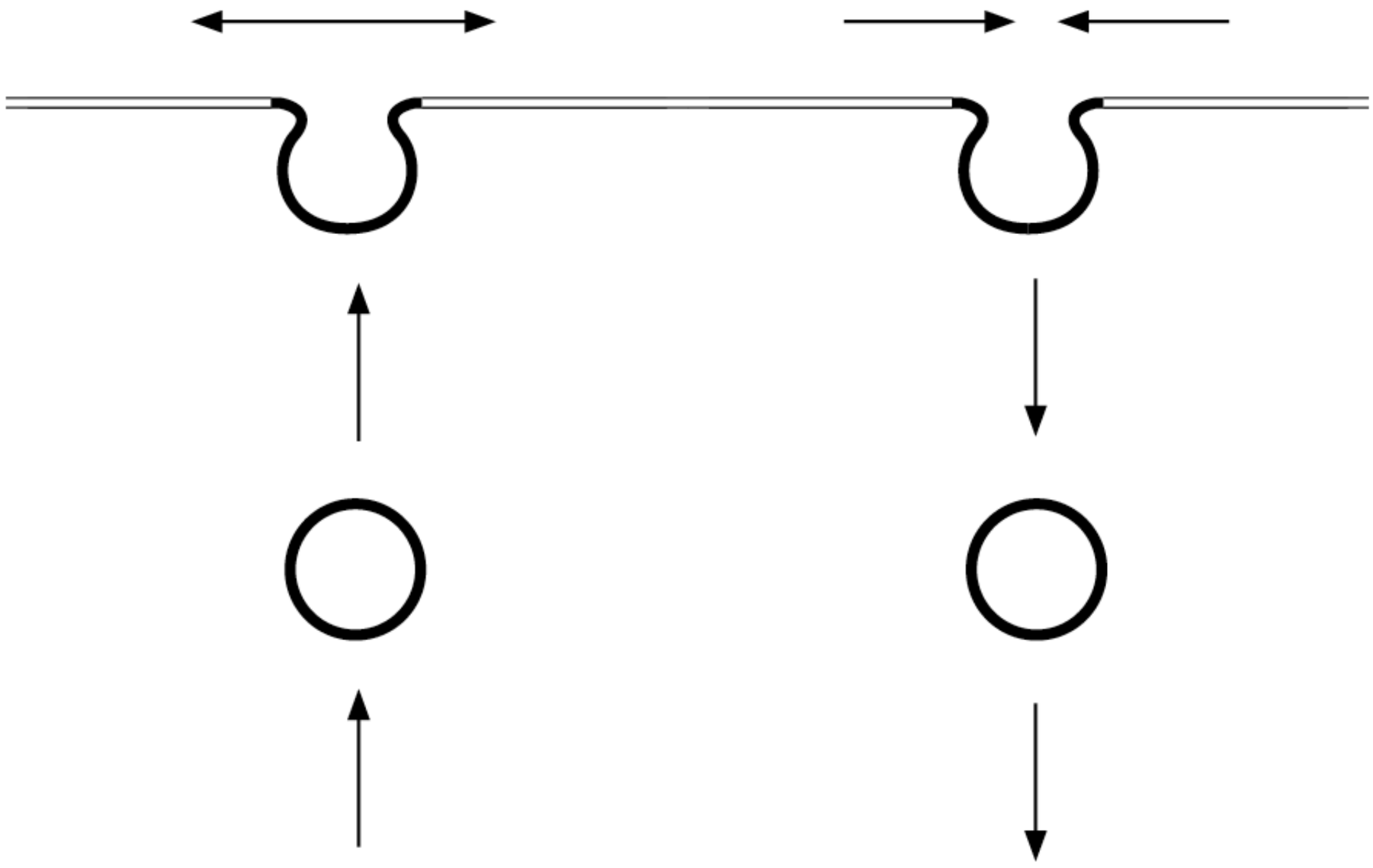
Competition for loading in cell membranes

Cell membrane fatty acid composition is not random.

i.e. not just a direct reflection of fatty acid intake



Cell membrane formation



Cell membrane formation

Indications of regulated membrane construction:

1. Cell membrane lipid composition differs between inner and outer layers

2. Different cells have different FA composition

The distribution of unsaturated fatty acids in the glycerophospholipids of the brain is tissue-specific, with the **white matter** higher in **monounsaturated** fatty acids and **grey matter** higher in **polyunsaturated** fatty acids. In the brain, DHA is the predominant omega-3 fatty acid and AA the predominant omega-6 fatty acid. In **grey matter**, there is **more DHA than AA**, but in **white matter** this is **reversed**.

(Rubin 1992)

Fatty acid composition differs between cell types

Muscle tissue

Table 7 Comparison of muscle tissue lipid concentrations (mg fatty acids/100 g sample) in elk (*Cervus elaphus*), deer (*Odocoileus hemionus*), antelope (*Antilicapra americana*), pasture and grain-fed cattle (*Bos taurus*). Data adapted from the present study; Marmer *et al* (1984); and Miller *et al* (1986)

Fatty acid	*Elk*	*Deer*	*Antelope*	*Pasture-fed steer*	*Grain-fed steer*
SAT[a]	610	989	895	910	1909
MUFA[b]	507	612	610	793	1856
PUFA[c]	625	746	754	262	341
n-3 PUFA	178	225	216	61	46
n-6 PUFA	448	524	536	138	243
18:2 n-6	286	352	336	86	155
18:3 n-3	58	99	87	24	11
Long chain PUFA	281	295	331	152	175

[a]SAT, total saturated fatty acids.
[b]MONO, monounsaturated fatty acids.
[c]PUFA, total polyunsaturated fatty acids.

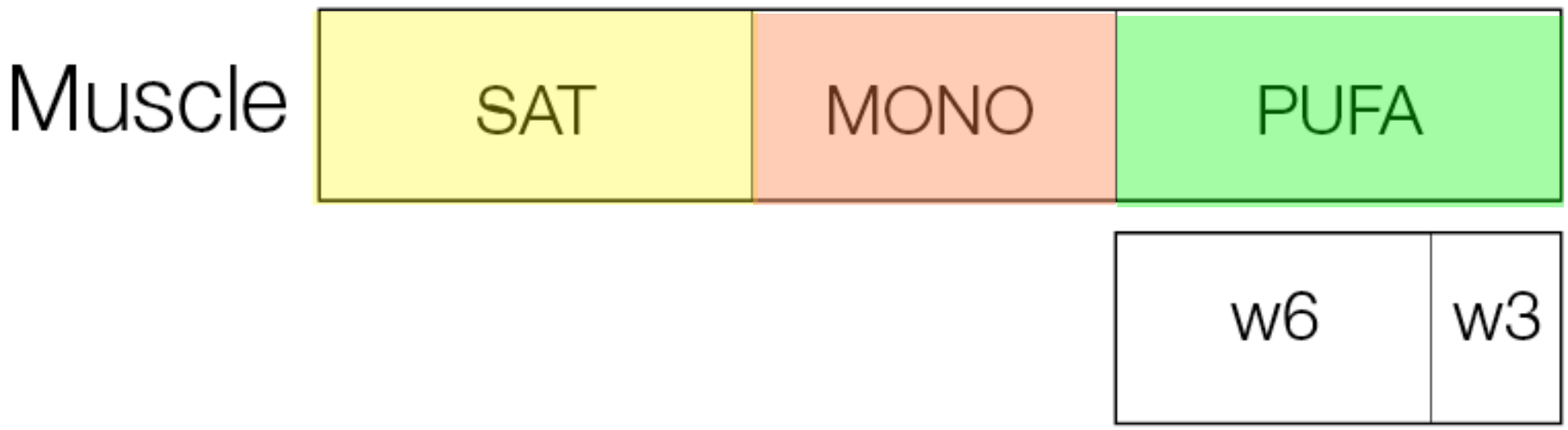
Samples from:
Elk, Deer, Antelope

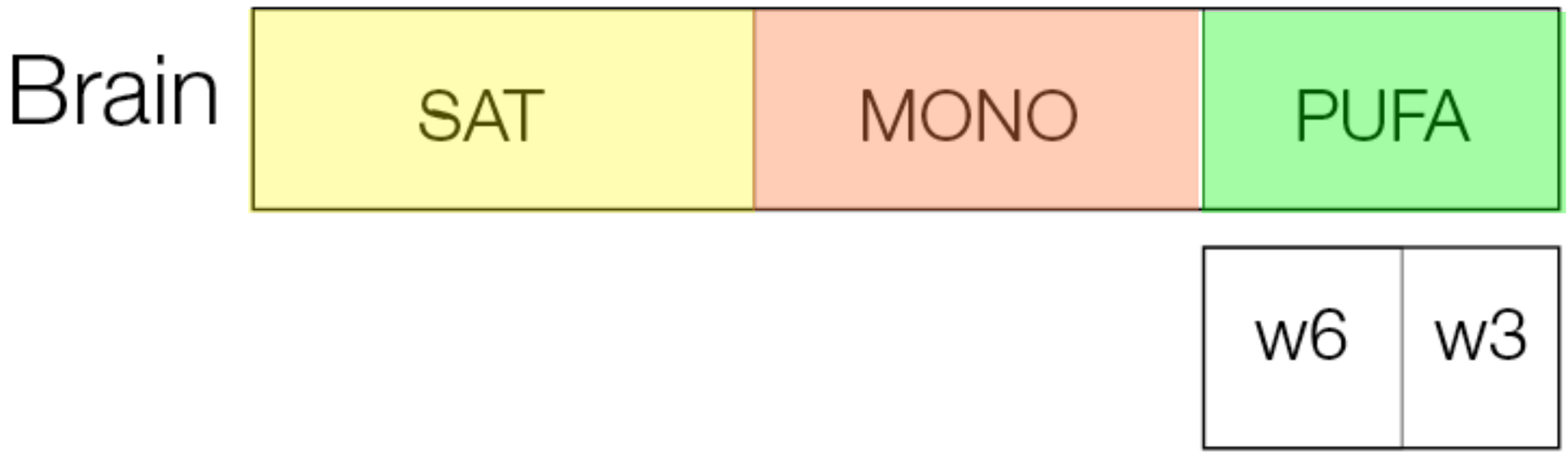
(Cordain 2002)

Brain tissue

Table 3 Fatty acid composition (wt %) of homogenized brain. Values are mean ± s.e.m.

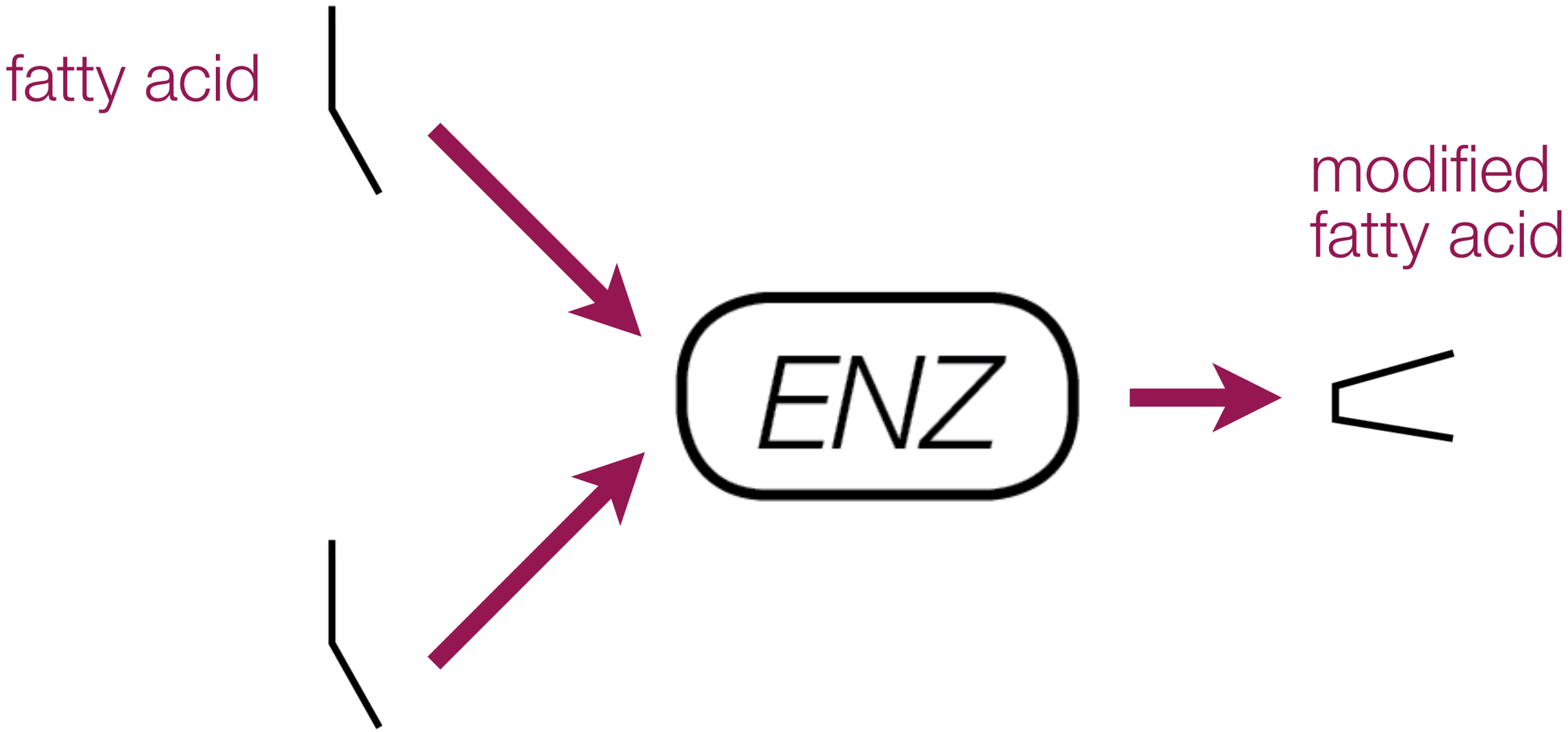
	Elk (n = 16)	*Deer (n = 15)*	*Antelope (n = 15)*
14:0	0.32† (0.04)	0.34† (0.02)	0.42* (0.02)
15:0	0.09* (0.01)	trace*,e	trace*
16:0	13.19* (0.56)	13.73* (0.55)	13.78†* (0.43)
16:1 n-7	0.61* (0.03)	0.53† (0.02)	0.48† (0.02)
17:0	0.28† (0.02)	0.30*† (0.01)	0.32* (0.01)
18:0	16.57* (0.58)	17.24* (0.43)	17.13* (0.30)
18:1 n-9	20.24†* (0.81)	22.14* (0.76)	19.92† (0.39)
18:1 n-7	4.04* (0.17)	3.37† (0.04)	3.58† (0.03)
t,t18:2	0.17* (0.03)	0.16* (0.03)	0.31* (0.06)
18:2 n-6	0.58†(0.05)	0.71*,† (0.04)	0.78* (0.05)
18:3 n-6	trace*	trace*	trace*
18:3 n-3	0.18* (0.03)	0.19* (0.03)	0.22* (0.03)
20:0	0.30* (0.03)	0.28* (0.02)	0.34* (0.02)
20:1 n-9	2.44* (0.37)	1.70† (0.21)	2.30†* (0.17)
20:2 n-6	0.65* (0.05)	0.59* (0.02)	0.47† (0.02)
20:3 n-6	0.45* (0.04)	0.57* (0.07)	0.47* (0.06)
20:4 n-6	5.58†,* (0.36)	5.24† (0.29)	6.39* (0.19)
20:5 n-3	0.10* (0.01)	trace*	trace*
22:0	0.33†,* (0.03)	0.29† (0.02)	0.38* (0.01)
22:1 n-9	0.65* (0.10)	0.49* (0.06)	0.62* (0.05)
22:4 n-6	4.11†,* (0.34)	4.47* (0.18)	3.57† (0.11)
22:5 n-6	0.36† (0.06)	0.50†,* (0.04)	0.54* (0.05)
22:5 n-3	0.61† (0.07)	0.76* (0.04)	0.53† (0.03)
22:6 n-3	8.90* (0.92)	9.62* (0.74)	9.25* (0.49)
18:2(9,11)	ND[f]	ND	ND
SAT	31.00* (0.60)	31.97* (0.94)	32.36* (0.56)
MONO[f]	27.98* (0.80)	28.10* (1.04)	26.82* (0.57)
PUFA	21.44* (0.82)	22.33* (1.02)	22.18* (0.57)
n-6/n-3 PUFA	1.29* (0.09)	1.20* (0.07)	1.29* (0.07)
PUFA/SAT	0.69* (0.02)	0.70* (0.02)	0.69* (0.02)





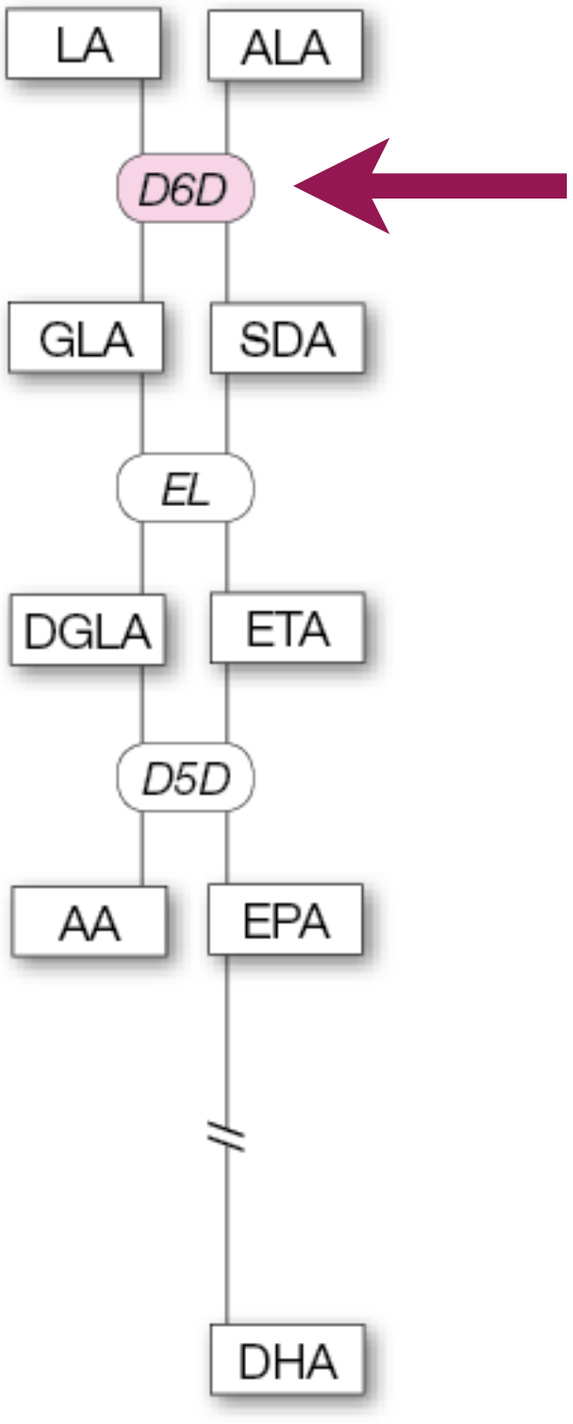
Samples from Elk

Competition for enzymes



Competition for enzymes

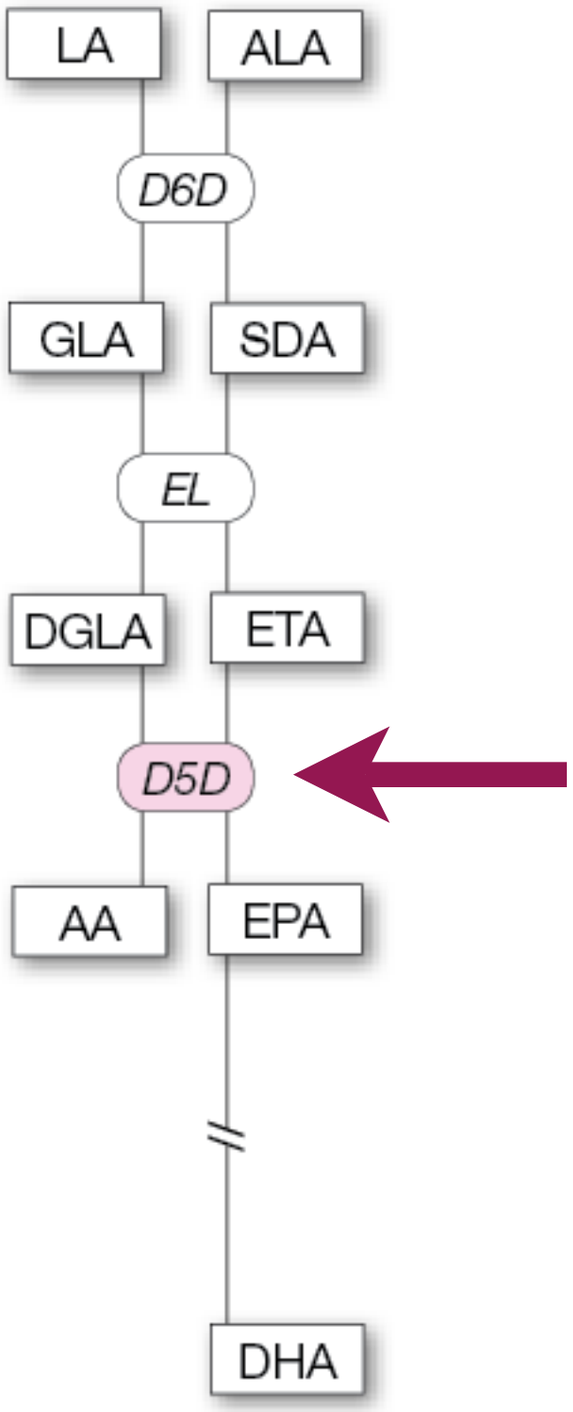
Rate of activity of enzymes



Delta-6-desaturase

Inhibited by:

- deficiencies of:
  vitamin A, B3, B5, B6, C,
  folic acid, biotin;
  calcium, zinc,
  magnesium, iron, copper
- sugar
- transfats
- adrenaline
- NSAIDS



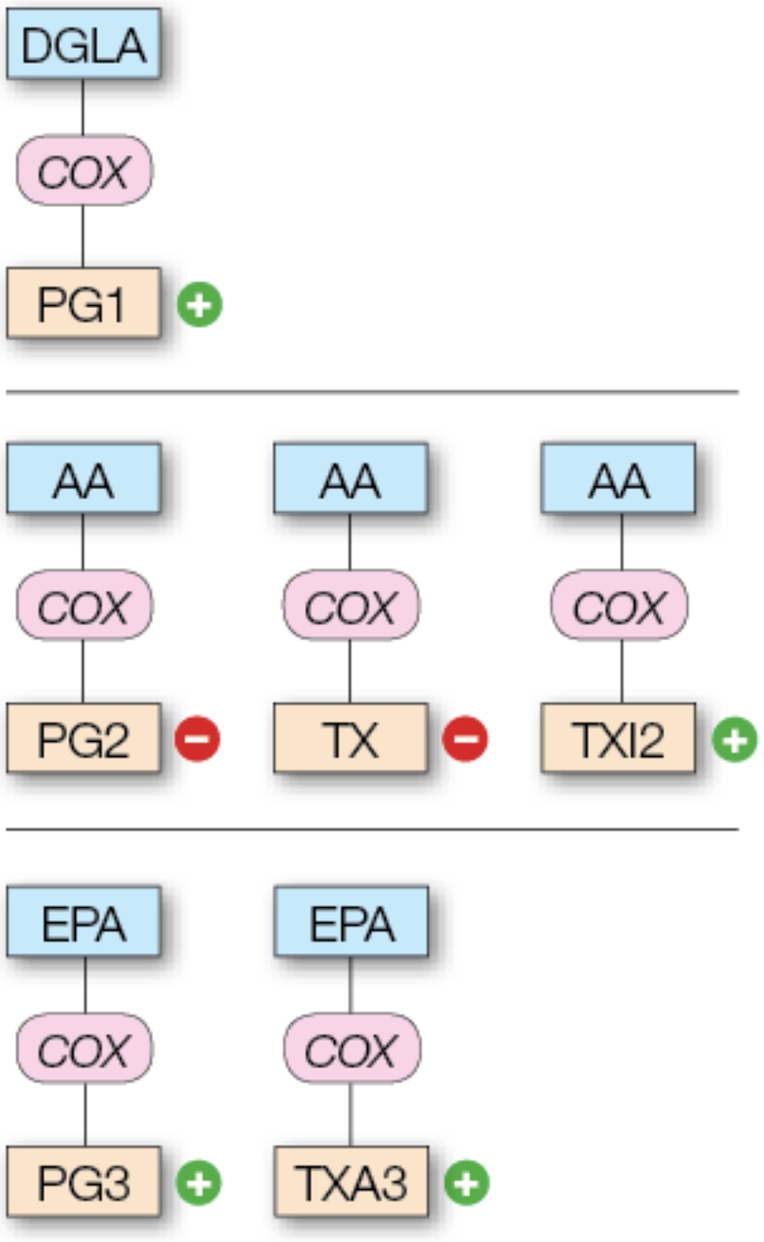
Delta-5-desaturase

Activated by:

- insulin

Inhibited by:

- sesamin, curcumin
- EPA
- alcohol
- glucagon

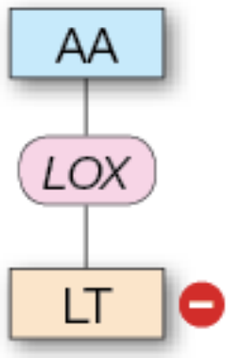


Cyclooxygenase

Inhibited by:

- bioflavanoids, ginger
- vitamin E
- zinc
- EPA
- NSAIDs

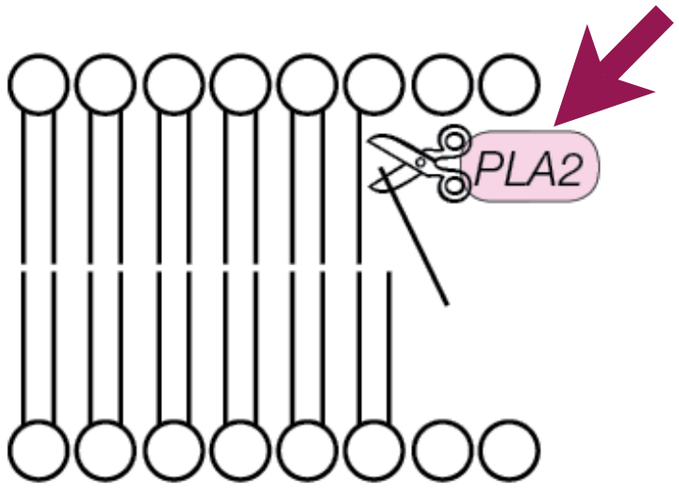
Lipooxygenase



Inhibited by:

- bioflavanoids, ginger
- vitamin E
- zinc, selenium
- EPA

Phospholipase A2



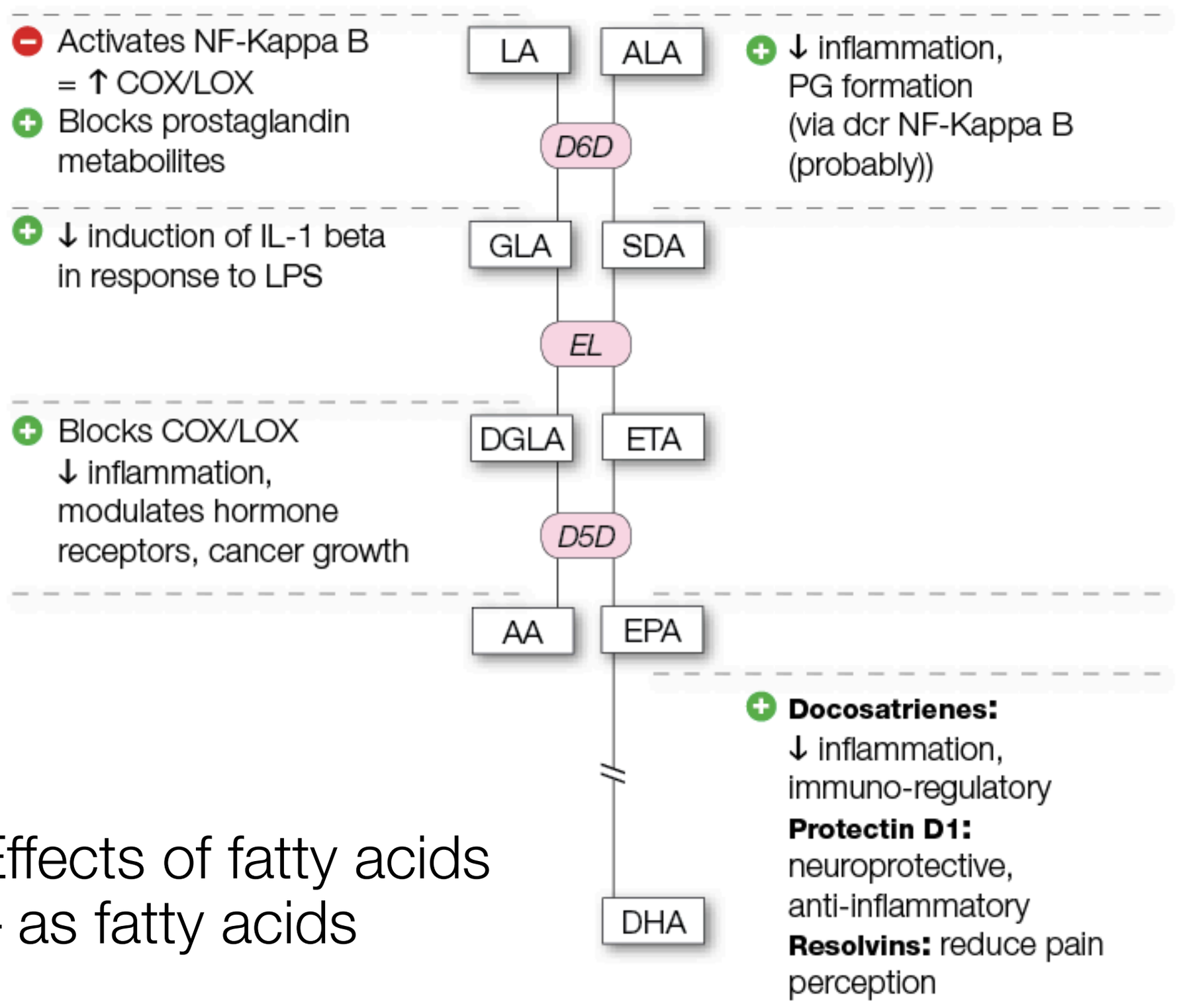
Activated by:

- IgE allergic reactions

Inhibited by:

- vitamin E
- GLA
- steroids

Overall balance



Effects of fatty acids – as fatty acids

Common questions about omega 6 and 3 fatty acids

w6 and w3

?

Omega 6 to 3 ratio

Evidence from studies on the **evolutionary aspects** of diet, **modern day hunter-gatherers**, and **traditional diets** indicate that human beings evolved on a diet in which the **ratio** of omega-6/omega-3 EFA was about **1**, whereas in the Western diets the ratio is **15/1** to **16.7/1**.

(Simopoulos 2000)

WHO: 5:1–10:1
Sweden: 5:1
Canada: 4:1–10:1
Japan: 4:1 to 2:1
NIH: 2:1–3:1

(Davis 2003)

Common SAD diet foods

	18:0	18:01	18:02	18:03	Ratio 6:3
Muffin	0.786	5.318	6.03	1.023	**6**
Potato chips	1.11	9.51	11.98	0.19	**63**
Fries	0.838	5.821	4.898	0.436	**11**
Bread Wht	0.218	0.569	1.418	0.166	**9**
Salad dressing	0.72	5.476	9.177	1.489	**6**
Cookies	2.179	4.845	0.681	0.256	**3**
Hamburger w/cheese	1.451	3.854	1.195	0.161	**7**
Pizza	0.858	2.388	1.463	0.177	**8**

http://ndb.nal.usda.gov/ndb/search/list

Common Mediterranean diet foods

	18:0	18:01	18:02	18:03	Ratio 6:3
Olive oil	1.953	71.27	9.762	0.761	**13**
Walnut oil	2	22.2	52.9	10.4	**5**
Almonds	0.658	30.61	12.055	0.006	**2009**
Cashew	3.223	23.52	7.782	0.062	**126**
Walnut	1.659	8.799	38.093	9.08	**4**
Pistachio	0.476	23.17	13.485	0.259	**52**
Sesame seeds	2.09	18.52	21.375	0.376	**57**
Feta cheese	1.488	3.975	0.326	0.265	**1**
Yogurt	0.317	0.743	0.065	0.027	**2**
Eggs	0.811	3.411	1.555	0.048	**32**
Goat	0.43	1.24	0.13	0.02	**7**
Pork	0.625	2.279	0.539	0.02	**27**
Chicken	0.77	4.4	2.57	0.11	**23**
Lamb	2.63	7.57	1.07	0.26	**4**
Cod	0.038	0.078	0.006	0.001	**6**
Shrimp	0.021	0.021	0.018	0.001	**18**
Sardines	0.343	2.145	3.543	0.498	**7**
Mullet	0.096	0.196	0.094	0.42	**0.2**

http://ndb.nal.usda.gov/ndb/search/list

Typical SAD diet:

- more LA-rich foods (meat, dairy)
- more LA in conventional meat and dairy
- more processed oils in prepared foods

Does LA only cause problems?

- **No evidence** LA increases **inflammatory** markers

Effect of dietary linoleic acid on markers of inflammation in healthy persons: a systematic review of randomized controlled trials.
(Johnson 2012)

- not only **alpha-linolenic** acid (n-3 PUFA) but also **linoleic acid** (n-6 PUFA) has a **beneficial** effect on systemic **inflammation** in men.
(Poudel-Tandukar 2009)

- **LA or ALA** reduced risk of CAD
(Djoussé 2001)

- margarine instead of saturated fat = increased risk
(Ramsden 2013)

Omega-6 fatty acids may be useful for the following health conditions:

Diabetic neuropathy
Rheumatoid arthritis
Allergies
Attention deficit/hyperactivity disorder (ADHD)
Breast cancer
Eczema
High blood pressure
Menopausal symptoms
Mastalgia
Multiple Sclerosis
Osteoporosis
Premenstrual syndrome

(Omega-6 fatty acids)

LA is **required** for the normal function of the stratum corneum ceramides – **prevents** trans-epidermal **water loss**.

Dietary **deficiency** is characterized by **severe scaly dermatosis** – that is reversible by LA but not ALA.

(Rubin 1992)

Compounds in processed /cooking oils

- transfats
- dimers
- polymeric compounds
- hydroperoxides
- carbonyls
- alcohols
- esters
- furans
- epoxy aldehydes
- ketones
- lactones
- aromatic compounds

Products resulting from hydrogenation:

LA = 18:2w6 cis, cis

LA transfats:
trans, cis
cis, trans,
trans, trans

LA with double-bonds shifts

(Erasmus 1993)

After prolonged heating, dimeric and polymeric **compounds are formed** and can accumulate up to a **concentration of 10-20%** without the functional properties of the oil becoming noticeably changed

It has been demonstrated that nonvolatile oxidized **products** such as monomers, dimers, and cyclic monomers are **absorbed into the body** and can be recovered from lymphatic and hepatic lipids.

(Kubow 1992)

More than half the margarine fats **contained less than 10% linoleic acid**

Trans fatty acids differed from their cis isomers and more closely **resembled saturated fatty acids** in acyl transferase reaction and incorporation into glycerolphospholipids

(Beare-Rogers 1979)

Chang and colleagues identified a total of **220 compounds** formed during deep-fat frying, many of which are potentially toxic

Damage caused by lipid oxidation

- destruction of essential **membrane** components
- disruption of cytosolic **enzyme** activities
- membrane **swelling** and lysis,
- mutagenic and **carcinogenic** activities.

(Kubow 1992)

Linoleic acid **hydroperoxides** can cause **irreversible damage** to porcine pulmonary **artery endothelial** cells, and injection of this compound into the bloodstream causes marked damage to aortic endothelial cells.

(Kubow 1992)

Early animal studies have shown that diets containing **polyunsaturated** oils **heated** for 20 min at 215°C were **more atherogenic** than diets containing unheated oils.

Results showed a **doubling of platelet thromboxane A2** production along with a **decrease** in vascular **prostacyclin** formation in rats fed the **oxidized oil** diet.

(Kubow 1992)

Does LA automatically turn into AA?

Prostaglandins Leukot Essent Fatty Acids. 2000 Sep;63(3):131-4.

Commentary on the workshop statement. Essentiality of and recommended dietary intakes for Omega-6 and Omega-3 fatty acids.

Crawford MA.

I have no problem with suggesting a reduction in the present level of LA in the USA but consider the expression 'adverse effects of arachidonic acid ...' to be misleading. Linking LA and AA in this way also implies a direct conversion of LA to AA, which is not the case. In fact, a very high dietary LA will reduce membrane AA.

High LA decreases membrane AA

J Nutr. 1998 Sep;128(9):1411-4.

Importance of dietary gamma-linolenic acid in human health and nutrition.

Fan YY, Chapkin RS.

Faculty of Nutrition, Molecular and Cell Biology Group, Texas A&M University, College Station, TX 77843-2471, USA.

Abstract

Considerable debate remains regarding the distinct biological activities of individual polyunsaturated fatty acids (PUFA). One of the most interesting yet controversial dietary approaches has been the possible prophylactic role of dietary gamma-linolenic acid (GLA) in treating various chronic disease states. This strategy is based on the ability of diet to modify cellular lipid composition and eicosanoid (cyclooxygenase and lipoxygenase) biosynthesis. Recent studies demonstrate that dietary GLA increases the content of its elongase product, dihomo-gamma-linolenic acid (DGLA), within cell membranes without concomitant changes in arachidonic acid (AA).

Erythrocyte membrane with EPO supplementation

Tab. 5. Erythrocyte membrane essential fatty acids before (D0) and after 30 (D30) and 90 (D90) days of treatment with evening primrose oil (Epogam). Results expressed in % of total fatty acids.

Fatty acid		D0	D30	D90
C 14:0	myristic	0.51±0.24	0.51±0.07	0.55±0.19
C 16:0	palmitic	27.50±7.8	27.80±3.6	29.00±8.00
C 16:1n-7	palmitoleic	1.13±0.55	1.16±0.37	1.06±0.14
C 18:0	stearic	15.90±2.0	16.10±2.6	16.40±3.2
C 18:1n-9	oleic	17.20±3.3	16.80±2.2	17.40±3.4
C 18:2n-6	linoleic	7.80±2.8	9.30±2.4	8.70±2.8
C 18:3n-3	α-linolenic	0.20±0.03	0.25±0.04	0.23±0.08
C 20:2n-6	eicosadienoic	0.32±0.08	0.32±0.04	0.36±0.09
C 20:3n-6	dihomo-τ-linolenic	1.27±0.81	1.42±0.20	1.48±0.91
C 20:4n-6	arachidonic	12.30±5.4	12.80±3.9	11.90±6.0
C 20:5n-3	eicosapentaenoic	0.79±0.19	0.60±0.28	0.78±0.23
C 22:4n-6	adrenic	2.97±0.98	2.92±0.95	2.57±0.91
C 22:5n-6	docosapentaenoic	1.54±0.52	1.47±0.44	1.18±0.31
C 22:5n-3	docosapentaenoic	2.15±0.44	1.51±0.58	2.22±0.42
C 22:6n-3	docosahexaenoic	4.53±2.71	4.27±1.55	3.94±2.67

% of total FAs

LA ~1 % higher
ALA ~.05% higher

AA ~.5% less
EPA ~same

DHA ~.5% less

GLA does not increase AA

(Cordain 2002)

With GLA supplementation:

- neutrophils – less leukotriene, platelet-activating factor, more DGLA, no change in GLA or AA
- DGLA – not AA accumulates after GLA supplementation

(Johnson 1997)

DGLA: the forgotten fatty acid

The increase in **DGLA** relative to AA is able to **attenuate** the biosynthesis of **AA metabolites**, i.e., 2-series prostaglandins, 4-series leukotrienes and platelet-activating factor (PAF), and exerts an anti-inflammatory effect **in human subjects.**

Although the increases in the tissue levels of PGE1 after DGLA supplementation are modest relative to PGE2, effects are noteworthy because select biological properties of **PGE1 are ~20 times stronger than PGE2.**

(Wang 2012)

Compared with the other fatty acids tested, **DGLA** exerted pronounced **modulatory effects** on cytokine production.

Tumour necrosis factor-α (TNF-α) and **interleukin** (IL)-10 levels were **reduced to 60%** of control levels, whereas IL-6 levels were not affected **by DGLA**.
(Frits 2004)

Both the **reduction of cytokine** levels and the **decrease in arachidonic acid** levels in these cells, induced by DGLA, were dose dependent...
(Dooper 2003)

DGLA is cyclooxygenated (by COX-1/2) to prostaglandins of the 1-series (PGE1) and/or metabolized by the 15- lipoxygenase into 15-(S)-hydroxy-8,11,13-eicosatrienoic acid (15-HETrE)

These two oxidative **metabolites of DGLA**, have been found to exert clinical efficacy in a variety of diseases, including **suppression** of chronic **inflammation**, **vasodilation** and lowering of **blood pressure**, **inhibition** of smooth **muscle cell proliferation** associated with atherosclerotic plaque development, **arresting of cancer** cell growth and the **differentiation** of tumor cells.

(Wang 2012)

In many cell types, **DGLA**, the elongase product of GLA, **but not AA**, **accumulates** after GLA supplementation.
(Wang 2012)

GLA

It was observed that **of all the fatty acids tested**, **GLA or DGLA** was the **most effective** in selectively killing the tumor cells.

GLA and DGLA were also found to be capable of **suppressing the expression of oncogenes** Her-2/neu and Bcl-2 and enhance p53 activity and thus, **induce apoptosis** of tumor cells.

(Wang 2012)

of all FAs GLA / DGLA most effective at killing tumours
suppress oncogenes

GLA supplementation with 3.0 and 6.0 g/d also resulted in an **enrichment of DGLA** in neutrophil phospholipids but **no change** in GLA or AA levels.

(Johnson 1997)

Neutrophils obtained from subjects after **3 wk of** supplementation with 3.0 g/d **GLA** synthesized **less leukotriene** B4 ($P < 0.05$) and **platelet-activating factor**.

(Johnson 1997)

Do we need to get ALA?

- institutionalized elderly patients
- fed entirely with gastric tubes a formula based on corn oil (61% LA, 1% ALA)
- **light, flakey skin dermatitis** together with **low blood** phospholipid levels of **EPA and DHA**
- **with ALA** inclusion – EPA and DHA **levels** were normalized in blood phospholipids, cutaneous symptoms were resolved within four weeks

(Rubin 1992)

- With **low dietary ALA trans-DHA** incorporation doubled – especially in eyes, myelin, and sciatic nerve.

  (rat study)

(Grandgirard 1994)

- In addition to identifying an **inverse correlation** between **breast adipose tissue ALA and breast cancer risk**, one of the studies noted a significant decrease in risk for women in the highest tertile of ALA intake.

(Anderson 2009)

Conversion rate of ALA to EPA

Estimates: – varies by population

~ 8% healthy young men

~ 21% healthy young women

Linus Pauling Institute: http://lpi.oregonstate.edu/infocenter/othernuts/omega3fa/#metabolism

Conversion of ALA to long-chain n-3 fatty acids appears to be **more efficient in women**: up to **21%** is converted to EPA and up to **9%** is converted to DHA between 0.3% and 8% in men.
(Arterburn 2006)

Insufficient energy or **protein** decreases the activity of conversion enzymes, as can **deficiencies of pyridoxine**, **biotin**, **calcium**, **copper**, **magnesium**, and **zinc**. Excessive intakes of **trans fatty acids** can also depress conversion enzymes. In addition, **alcohol** inhibits the activity of delta-5 and delta-6 desaturase and depletes tissues of long-chain n-3 fatty acids
(Davis 2003)

It appeared that the **early deficiency of ALA** had **irreversibly down-regulated** the converting enzyme delta-6 desaturase.
(Rubin 1992)

ALA-enriched supplements for 12 wk was sufficient to **elevate** erythrocyte **EPA and docosapentaenoic acid** content, which shows the effectiveness of ALA conversion and accretion into erythrocytes. The amounts of **ALA required** to obtain these effects are amounts that are **easily achieved** in the general population by **dietary modification**.
(Barcelo-Coblijn 2008)

Together, these findings **suggest** that humans can **convert meaningful quantities** of ALA to EPA and DHA, **particularly** in the presence of a **deficiency** or a background of **low n-6 fatty acids.**
(Arterburn 2006)

Studies generally agree that whole body **conversion of 18:3n-3 to 22:6n-3 is below 5%** in humans, and **depends on** the **concentration of n-6 fatty acids** and **long chain polyunsaturated** fatty acids in the diet
(Brenna 2002)

The majority of the ALA supplementation studies show a **limited conversion of ALA to** its **long-chain n-3** derivatives. These studies have been performed in healthy individuals consuming typical **Western diets generally high in n-6 fatty acids**.
(Arterburn 2006)

Eicosapentaenoic acid (**EPA**) **but not DHA** concentrations in plasma **increase** in response to dietary EPA.

Dietary DHA results in a dose-dependent, saturable **increase in plasma DHA** concentrations and modest **increases in EPA** concentrations

(Arterburn 2006)

Vegans who consume **ALA but not EPA and DHA** in their diets have **low but stable concentrations** of DHA in plasma

(Arterburn 2006)

Vegan plasma EPA levels were only **22%** of those of omnivores and **DHA** levels were **38%** of those of omnivores, although **AA levels were similar**.

(Simopoulos 2000)

Am J Clin Nutr. 2006 Jul;84(1):44-53.

Conversion of alpha-linolenic acid in humans is influenced by the absolute amounts of alpha-linolenic acid and linoleic acid in the diet and not by their ratio.

Goyens PL, Spilker ME, Zock PL, Katan MB, Mensink RP.

OBJECTIVE: We examined whether intakes of ALA or linoleic acid (LA; 18:2n-6) or their ratio influences ALA metabolism.

RESULTS: Compared with the control group, ALA incorporation into phospholipids increased by 3.6% in the low-LA group (P = 0.012) and decreased by 8.0% in the high-ALA group (P < 0.001). In absolute amounts, it increased by 34.3 mg (P = 0.020) in the low-LA group but hardly changed in the high-ALA group. Nearly all ALA from the plasma phospholipid pool was converted into eicosapentaenoic acid. Conversion of eicosapentaenoic acid into docosapentaenoic acid and docosahexaenoic acid hardly changed in the 3 groups and was <0.1% of dietary ALA. In absolute amounts, it was unchanged in the low-LA group, but increased from 0.7 to 1.9 mg (P = 0.001) in the high-ALA group. ALA oxidation was unchanged by the dietary interventions.

CONCLUSION: The amounts of ALA and LA in the diet, but not their ratio, determine ALA conversion.

http://www.ncbi.nlm.nih.gov/pubmed/16825680

Amounts – not ratio, determine conversion rate of ALA

Can only make vs only need to make

Two theories on D6D rate of conversion:

1. only makes small amount

2. only needs to make small amount

This paper reveals that the major metabolic route of ALA metabolism is beta-oxidation

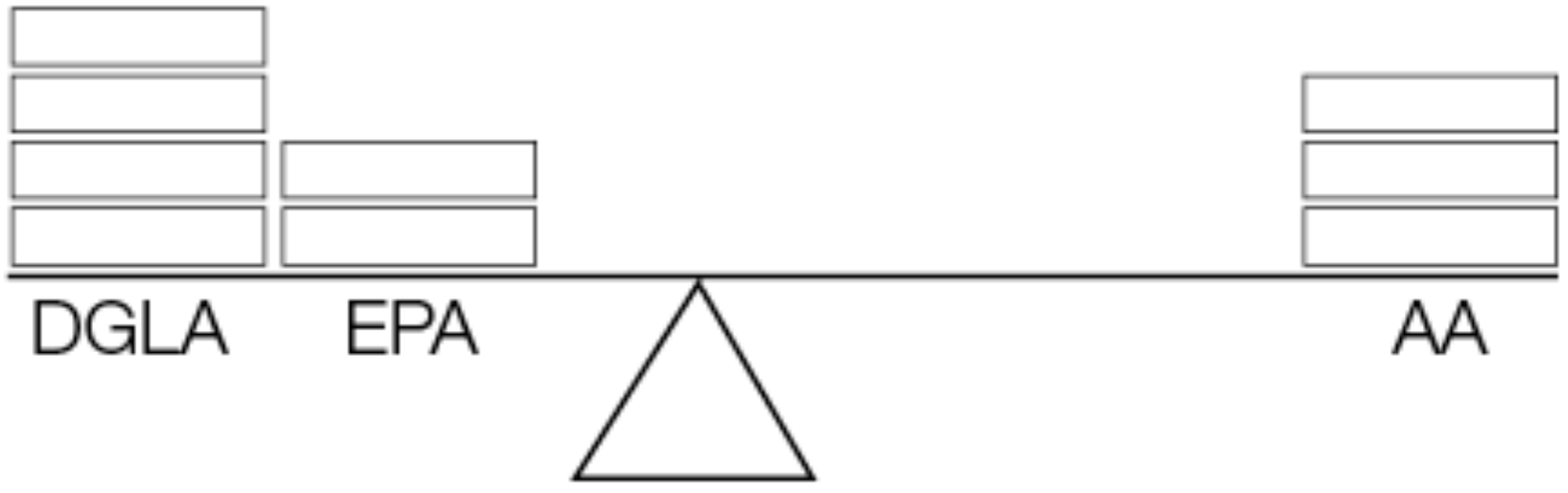
What is the role of alpha-linolenic acid for mammals?
(Sinclair 2002)

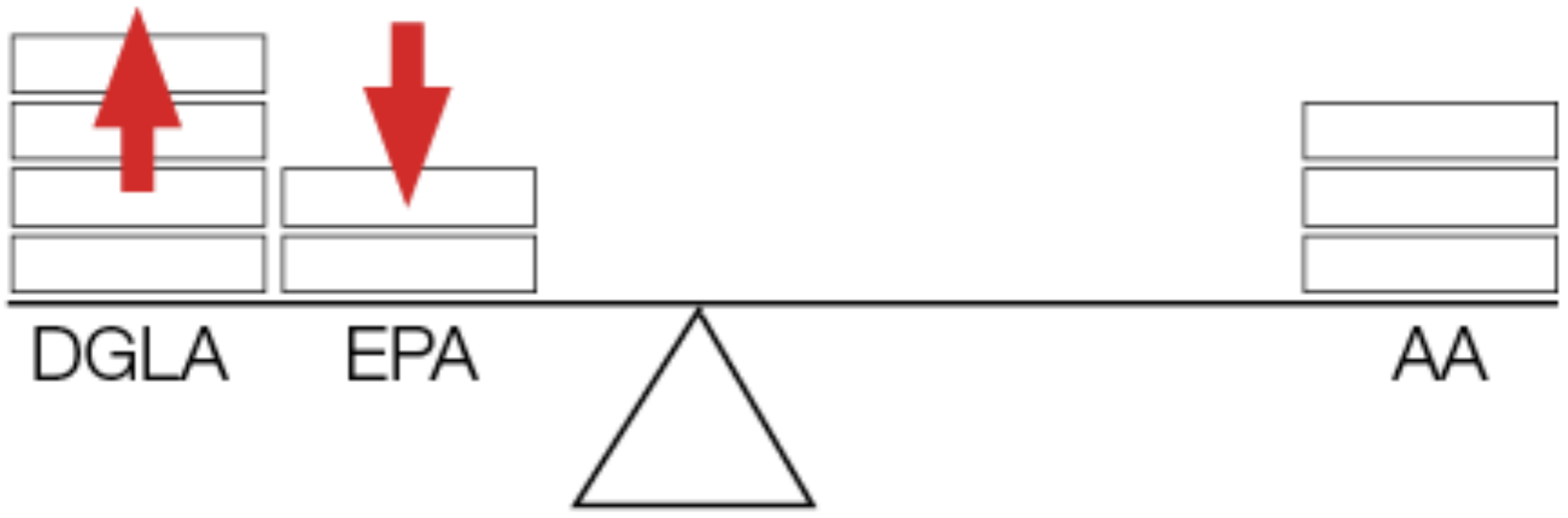
The proportions of **EPA and DHA in vegans** were only 29–36% and 49–52% those of non-vegetarian controls, respectively, while the **levels of AA were similar**, indicating no difficulty with the n-6 conversion

Increasing dietary ALA (3 wk intervention):

- increases EPA concentrations in plasma phospholipids
- DGLA concentrations were reduced
- AA concentrations were not altered

(Simopoulos 2000)


DGLA
EPA
AA

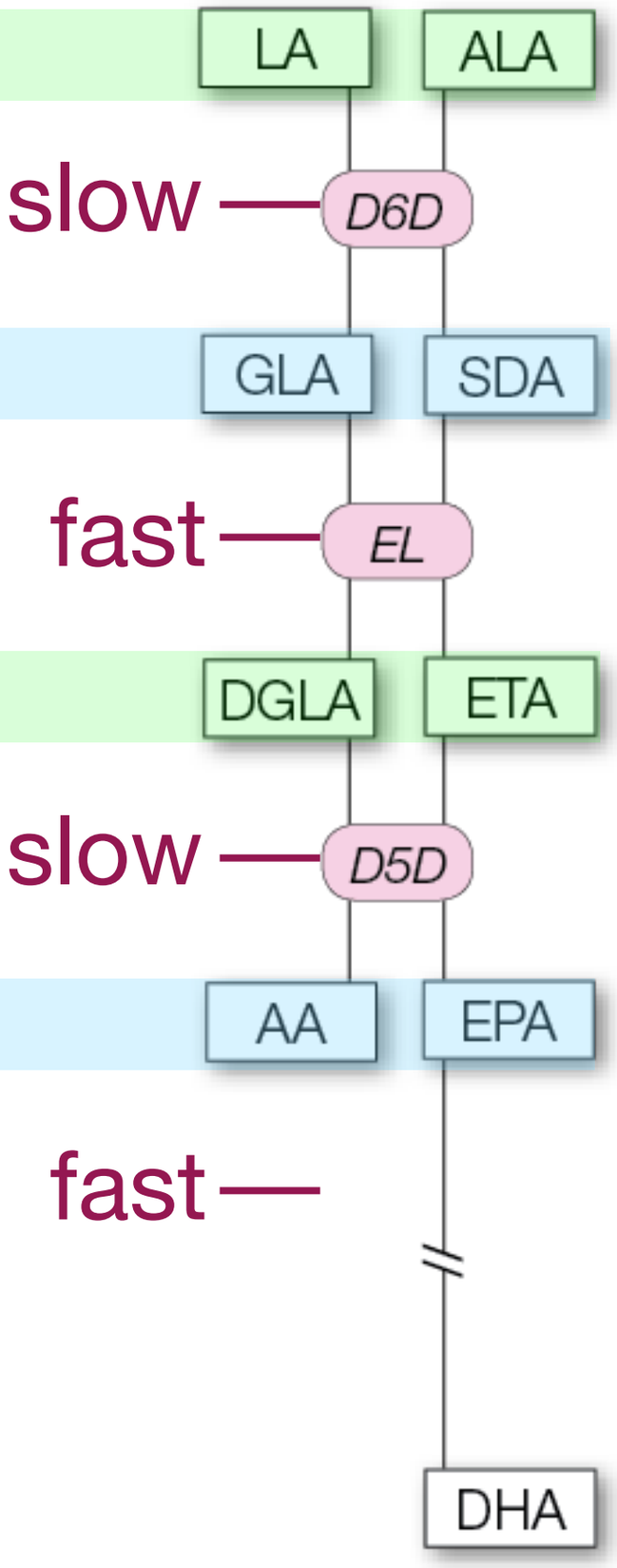

DGLA
EPA
AA

“want more” “more important”

“want less” “less important”

“want more” “more important”

“want less” “less important”



Desaturases – fast

Elongases – slow

DHA

Only minute quantities of ALA and EPA are generally present in tissues, and DHA generally exceeds EPA 5 to 30-fold in most organs.

(Arterburn 2006)

AA and DHA are among the most abundant fatty acids of brain phospholipids.

(Frits 2004)

DHA retained

- DHA is tenaciously retained at the expense of other fatty acids
  (Stillwell 2005)

- Neuronal membrane phospholipids preferentially retain DHA and do not release it readily
  (Rubin 1992)

- DHA and EPA washout after n-3 supplementation:
  - EPA ~ 4 weeks
  - DHA ~ 24 weeks

  (Arterburn 2006)

- 14 human volunteers – the global rate of DHA incorporation in the human brain was the equivalent of the consumption of 3.8 ± 1.7 mg/day DHA.

- Further, they used published estimates of the total amount of DHA in the human brain (5 g) and the daily incorporation rate of 0.076% per day, to determine that the **half-life of brain DHA was approximately 2.5 years** in humans

(Bradbury 2011)

The rate DHA synthesis is regulated

DHA synthesis machinery becomes somewhat **upregulated** in **conditions of high** DHA **demands**.
(Frits 2004)

The use of Delta 6 desaturase (**D6D**) **twice** in the conversion of alpha-linolenic acid (**ALA**; 18:3n-3) **to** docosahexaenoic acid (**DHA**; 22:6n-3) suggests that this enzyme may play a **key regulatory role** in the synthesis and accumulation of DHA from ALA.
(Portolesi 2007)

- **DHA** itself also serves as a **substrate** for metabolic **retro-conversion** to EPA and DPA through a beta-oxidation reaction

- **retro-conversion rate** of DHA to EPA in humans receiving normal dietary amounts of DHA to be **~1.4%**. Human clinical data have suggested rates **as high as 12%** with high **chronic DHA consumption**
(Arterburn 2006)

• the precursor/product ratio in vegans twice that of fish-eaters

• this finding suggests **basal conversions** from **ALA** to **DHA** may be **up-regulated** by the absence of, and **down-regulated** by the presence of, dietary preformed DHA.

REF 001 Rubin D

• **dietary DHA and EPA down-regulate** conversion of **DPA to DHA by 70%** (rate limiting step)

(Arterburn 2006)

DHA is highly susceptible to oxidation

- the **brain** is the **last** organ to **lose vitamin C**
- the brain has evolved robust mechanisms to **hoard ascorbate** even at the expense of other organs.
- the **highest levels of ascorbate** in the body occur in the brain.
- ascorbate has been shown to **recycle alpha-tocopherol in lipid bilayers**.

(Valentine 2012)

Why people may need fish oils:

- to turn decrease crisis inflammation and pain
- errors in membrane building = decreased EPA or DHA incorporation
- genetic issues with D6D or D5D enzyme
- mitochondrial, peroxisomal disorders
- increased breakdown of omega 3 FAs

Cellular incorporation of EPA and DHA occurred mainly at the expense of arachidonic acid.

EPA and DHA bump AA out of cells

Concomitantly, thromboxane B (TXB)2 and leukotriene B (LTB)4 in supernatants decreased, while levels of TXB3 and LTB5 increased

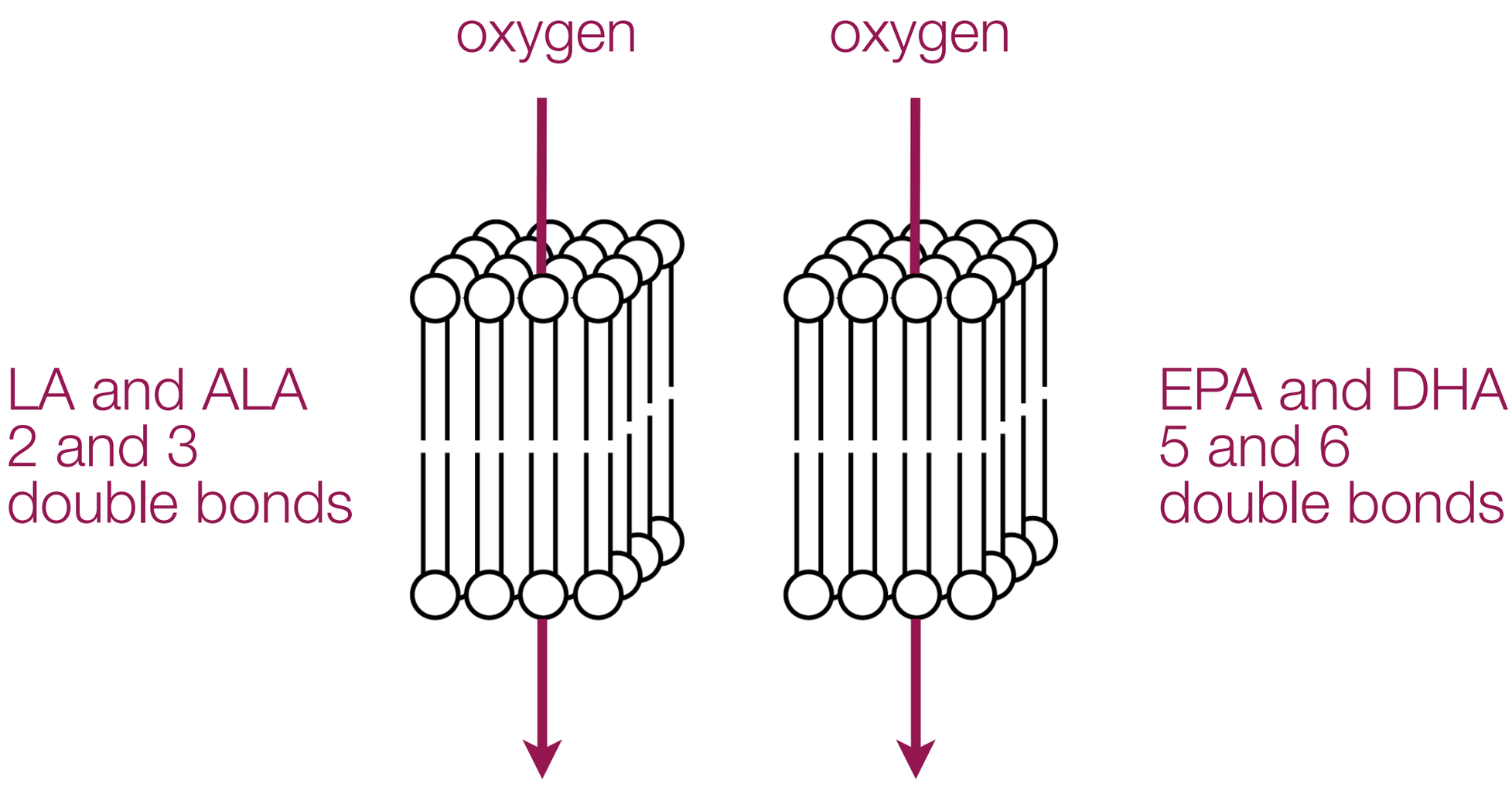
(Jaudszus 2013)

EPA:
decreased w6 TX / LT
increased w3 TX / LT

Moreover, **EPA and DHA** gave rise to a variety of mono- and tri-hydroxy **derivatives** of highly **anti-inflammatory** potential, such as **resolvins** and their precursors

Our results suggest that **EPA and DHA** do **not** generally affect immune cell functions in an **inhibitory manner** but rather **promote pro-resolving** responses (Jaudszus 2013)

Issues with fish oils



Double bonds are protected by antioxidants

- ingestion of **fish oil by rabbits** has been shown to enhance **cholesterol-induced atherosclerosis** and elevate **serum lipid peroxides.**

(Kubow 1992)

- despite their beneficial anti-inflammatory properties, eicosapentaenoic acid (**EPA**) and docosahexaenoic acid (**DHA**) may **increase the infection risk at high doses**, likely by generating an immune-depressed state

(Jaudszus 2013)

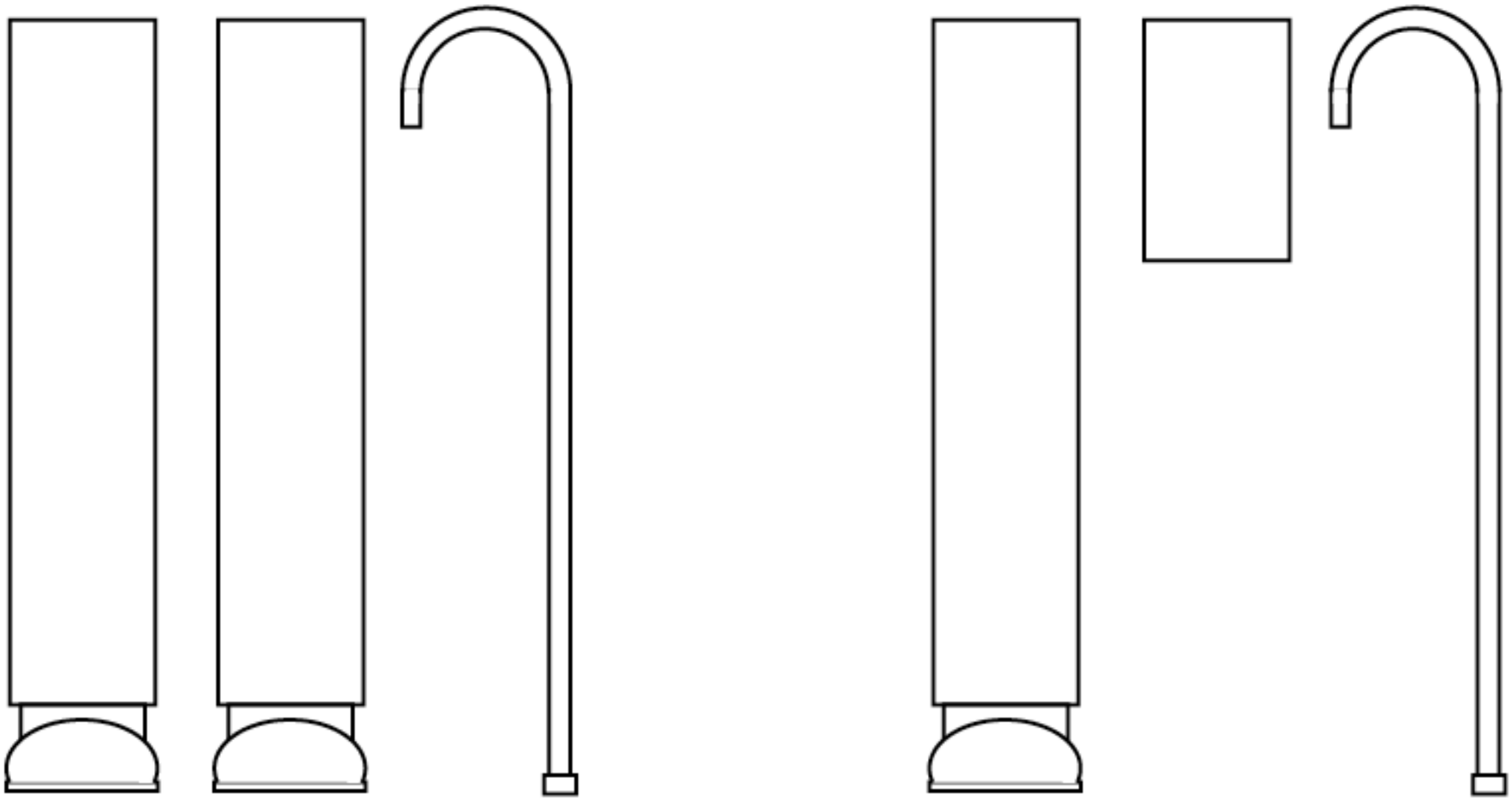
• **omega 3** fats do **not** have a **clear effect** on total **mortality**, combined **cardiovascular events**, or **cancer**.

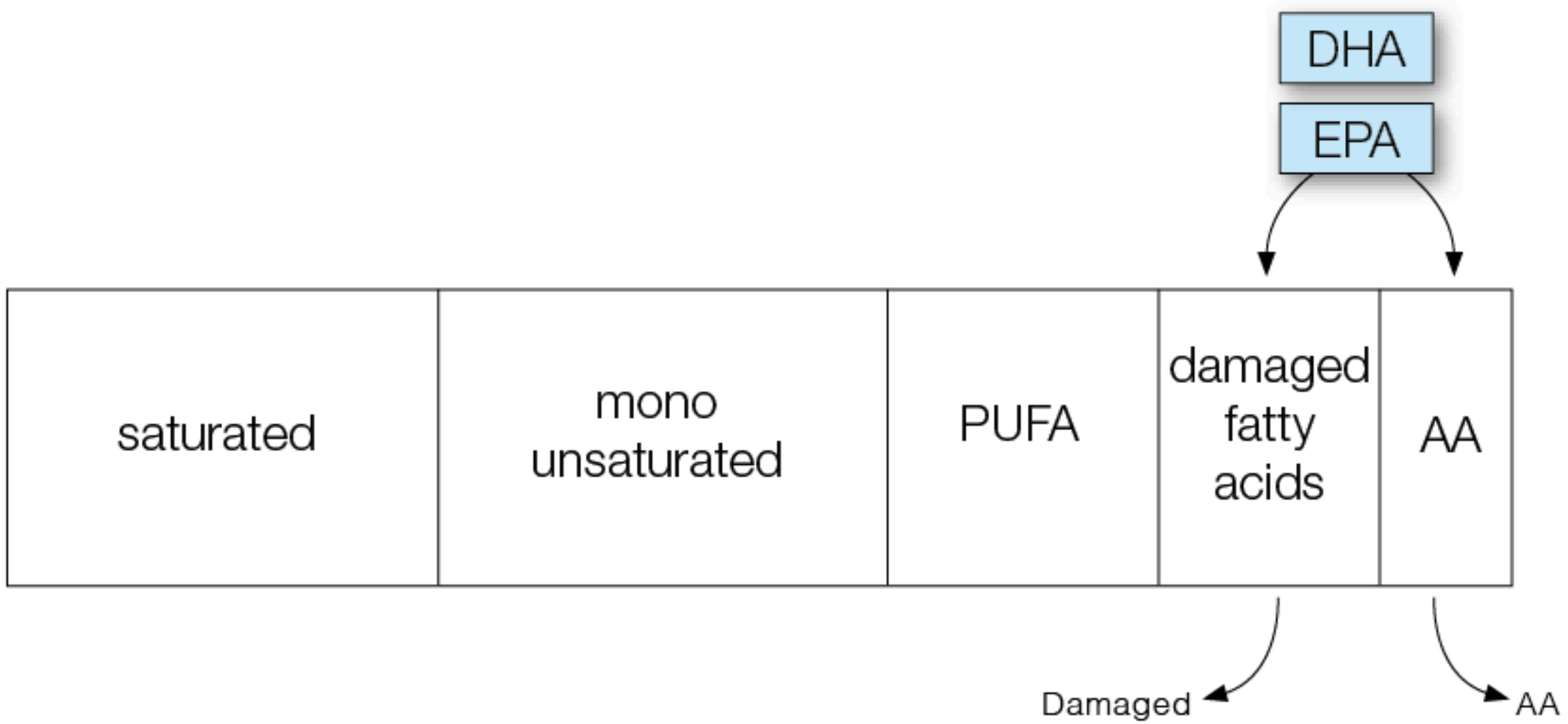
Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review.
(Hooper 2006)

We conclude that substitution of commercially available **omega-3 for omega-6 fatty acids** improves hypertriglyceridemia but **may worsen** other **lipoproteins indices** and may **increase insulin** requirements in diabetic hypertriglyceridemic subjects.
(Stacpoole 1989)

Why fish oils look good in studies

- EPA mediate eicosanoid negative effects
- EPA/DHA vs placebo
- EPA/DHA vs nothing
- EPA/DHA vs damaged oils
- EPA vs olive oil
- EPA vs cholesterol scores
- EPA vs triglyceride scores
- tests done outside the body





Fish oils are very beneficial in a poorly loaded membrane

using fatty acids

Plant-based fatty acids

The **primary fat** in the diet should come from foods and oils rich in **monounsaturated** fat.

When **monounsaturated** fats predominate, **saturated** fats, **trans** fatty acids, and **n-6 fatty acids** are kept in check and the **ratio** of n-6 to n-3 fatty acids **improves.**

Monounsaturated fats are high in nuts (except for walnuts and butternuts), peanuts (a legume), olive oil, olives, avocados, canola oil, high-oleic sunflower oil, and high-oleic safflower oil

(Davis 2003)

Parent fatty acids promote:

Decreased:

- gum bleeding
- skin inflammation
- psoriasis
- tinnitus
- cravings
- hunger recurrence
- lactic acid burn

Increased:

- smooth skin
- energy

Omega-6:3 ratios in body tissues[1-4]

Brain/nervous system	1:1
Skin	1000:1
Organs and other tissues	4:1
Adipose tissue	22:1
Muscles	6.5:1

(Peskin 2009)

1. Spector AA. Plasma free fatty acid and lipoproteins as sources of polyunsaturated fatty acid for the brain. J Mol Neurosci. 2001;16:159-65; discussion 215-221.
2. Andersson A, Sjödin A, Hedman A, Olsson R, Vessby B. Fatty acid profile of skeletal muscle phospholipids in trained and untrained young men. Am J Physiol Endocrinol Metab. 2000;279:E744-E751.
3. Chapkin RS, Ziboh VA, Marcelo CL, Voorhees JJ. Metabolism of essential fatty acids by human epidermal enzyme preparations: evidence of chain elongation. J Lipid Res. 1986;27:945-954.
4. Garaulet M, Pérez-Llamas F, Pérez-Ayala M, et al. Site-specific differences in the fatty acid composition of abdominal adipose tissue in an obese population from a Mediterranean area: relation with dietary fatty acids, plasma lipid profile, serum insulin, and central obesity. Am J Clin Nutr. 2001;74:585-591.

N-6-rich whole foods such as sunflower seeds, pumpkin seeds, sesame seeds, walnuts, wheat germ, and soy foods **need not be avoided**, as they tend to be relatively minor contributors to overall n-6 intake

Eggs provide a reasonable amount of **DHA** (< 50 mg/ egg) but **very little EPA**.
(Davis 2003)

The average **diet provides sufficient omega-6** fatty acids, so supplementation is usually not necessary **unless you're treating a specific condition**, such as eczema or psoriasis, arthritis, diabetes, or breast tenderness (mastalgia).
(Omega-6 fatty acids)

To reduce LA intakes, oils rich in n-6 fatty acids should **not be used as primary cooking oils**.

Cooking oils with the greatest n-6 fatty acid content:

- safflower oil (75% n-6)
- grapeseed oil (70% n-6)
- sunflower oil (65% n-6)
- corn oil (57% n-6)
- cottonseed oil (52% n-6)
- soybean oil (51% n-6)

(Davis 2003)

Marine-based fatty acids

Combined neuroimaging (positron-emission tomography, or PET) with radioactive labelling of intravenously administered DHA and AA to quantify the rate of incorporation into human brain phospholipids.

The whole adult human brain was estimated to consume the equivalent of:

- 4.6 mg/day of DHA
- 17.8 mg/day of AA.

(Rubin 1992)

Hibbeln et al. estimated that **900 mg per day of EPA + DHA from seafood** during pregnancy would be **adequate** to provide for the **neurodevelopment** requirements of the **fetus** and the **prevention** of maternal **depression** in the mother.
(Rubin 1992)

Red blood cell took **4–6 mo** after the start of **DHA supplementation** to reach new steady state concentrations, which is consistent with the slower turnover of these cells
(Arterburn 2006)

Dosing information

GLA – no side effects at 2.8g for 12 months
EPO – avoid with seizures
Flax oil – anaphylaxis reported

EPA, DHA – no adverse effects reported
Less than 3g day not cause excessively long bleeding times
may suppress immune at high doses

Linus Pauling Institute: http://lpi.oregonstate.edu/infocenter/othernuts/omega3fa/#metabolism

Dosing information

European Commission
- omega-6 – 4-8% of energy
- 2 g/day of ALA
- 200 mg/day of long-chain omega-3 fatty acids (EPA and DHA)

World Health Organization
- omega-6 – 5–8% energy
- omega-3 – 1–2% energy

American Heart Association
- EPA, DHA 1g/day
- EPA, DHA 2–4g/day to lower serum triglycerides

Linus Pauling Institute: http://lpi.oregonstate.edu/infocenter/othernuts/omega3fa/#metabolism

Dosing information

Omega 6
need enough to supply
2–3% of energy

2000 kcal diet – 4.4–6.7 g

sunflower	2 tsp
evening primrose oil	2 tsp
borage	2 tbsp
flax	2 tbsp
canola	2 tbsp
olive	5 tbsp

Omega 3
need enough to supply
1–1.5% of energy

2000 kcal diet – 2.2–2.3 g

flax	1.5 tsp
canola	1 tbsp
walnut	2 tbsp
soybean	3 tbsp

(Enig 2000)

Dosing information

Anorexia: 1g/day OMT 2009_14
Cancer: 2–6g/day Dr Michael Schachter OMT 2009
ADHD: DHA 6–12 yrs 100 mg, 12 + yrs 300 mg

Encyclopedia of Natural Medicine, Murray + Pizzorno
1–3 g for most conditions

Dosing information

Depression:	1–6g fish oils
Autism:	1.5 mg/lb EPA/DHA to start
MS:	DHA 400–600 mg, GLA 240–320 mg
Hypertension:	1g EPA/DHA
CAD:	1g EPA/DHA, 1–4g EPA/DHA to lower triglycerides
Insulin resistance:	1g EPA/DHA
Rheumatoid arthritis:	EPA 30 mg/kg, DHA 50 mg/kg, GLA 1.4–2.8 mg

Integrative Medicine, David Rakel

Various approaches for using fatty acids

Brian Peskin:

- support balance of all fatty acids
- use Parent oils + GLA – 6g oils per day
- avoid fish oils

Paul Beatty:

- assume D6D not adequate counter by using GLA
- evening primrose oil + cod liver oil 3:1 ratio

Orthomolecular:

- provide correct ratio of all fatty acids
- strategically use oils to correct fatty acid ratios
- address causes of imbalances

Paul Demeda:

1:1:1 ratio –> 1–2 tbsp per day

- flax oil
- sesame oil
- evening primrose oil

- Low EPA, high DHA fish oil for maintenance

- High-dose fish oils to address crisis inflammation

1 tbsp / 13.6g

	Sat/ 18:0	w9	w6	w3	GLA
Flax oil	1.2	2.5	1.9	7.2	
Sesame oil	1.9	5	6		
EPO	1.1	0.81	9.5	0.27	1.2
	4.2	8.31	17.4	7.47	1.2

Note:

- Hemp oil also has a favourable fatty acid profile

Also:

- ensure digestion – enzymes as needed
- lecithin – for emulsification of fats
- consider curcumin to inhibit D5D

Considerations

Membrane loading:

- balanced sat, mono, poly
- LA – too much, too little
- ALA – too little
- ratio 6:3 ideal

- DGLA – enough
- AA – too much, too little
- EPA, DHA – too much, too little, lost for some reason?
- trans, toxic metabolites

Enzymes:

- D6D – inhibited
- D5D – stimulated, inhibited
- COX, LOX – appropriately inhibited

Also:

- AO protection for long-chain fatty acids
- overall system balance – parent + derivative fatty acids

Considerations when working with fatty acids

Considerations when working with fatty acids

Supplementing / Using fatty acids:

- correct for context – maintenance vs therapeutic
- EPA countered with GLA
- enough dietary or supplemental DHA and EPA
- enough monounsaturated fatty acids

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