Dietary n-6 and n-3 fatty acids: health and disease

Professor Asim K. Duttaroy
Department of Nutrition

Room No. 2199

Tel: 22 85 15 47
Email: a.k.duttaroy@medisin.uio.no

Type of Dietary Fatty Acids

Saturated fatty acids

(Palmitic acid, 16:0, Stearic acid, 18:0)

Monounsaturated fatty acids

(Palmiteloic acid, 16:1,n-7, Oleic acid, 18:1n-9)

Polyunsaturated fatty acids

(Linoleic acid, 18:2,n-6, Alpha linolenic acid, 18:3n-3)
Essential Fatty acids (EFA)

Long chain polyunsaturated fatty acids

Arachidonic acid, 20:4n-6, Eicosapentaenoic acid, 20:5n-3, Docosahexaenoic acid, 22:6n-3

Biologically Important Long chain fatty acids

Fatty acid	Functions
Myristic (14:0)	Acylation of proteins
Palmitic (16:0)	Energy storage, Oxidative substrate Acylation of proteins
Stearic (18:0)	Phospholipid structure
Oleic (18:1n-9)	Regulation of bulk membrane fluidity
Linoleic (18:2n-6)	Arachidonic acid (AA) precursor
Arachidonic (20:4n-6)	Eicosanoid synthesis,second messenger
Eicosapentaenoic(20:5n-3)	Competitor of AA metabolism & AA -derived eicosanoids
Docosahexaenoic (22:6n-3)	Membrane structure

Dietary Fat

Fatty Acids in Cell Membranes

Biological Functions of Fatty Acids

Murphy, 1991; Clandinin, 1991; Lai, 1993;
Salvati, 1993; Weisinger, 1995

Biological Actions of Fatty acids are Mediated Via

A. Membrane phospholipid fatty acid composition

B. Eiocsanoid production

Via

Cyclooxygenases
Lipoxygenases
P450 mediated
omega hydroxylation

→ House keeping activity (phsyiological)

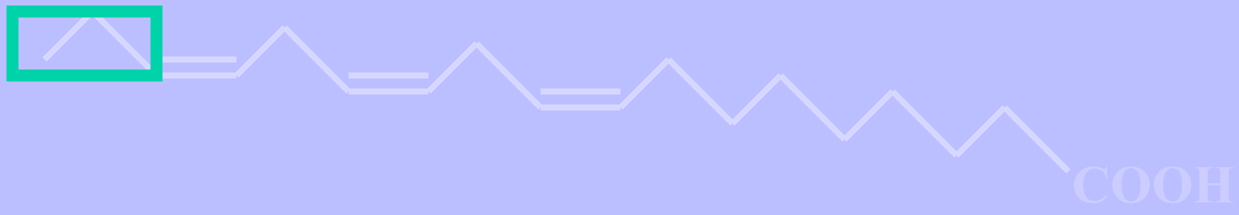
→ Explosive production (pathophsyiological)

C. Regulation of gene expression, cell growth, apoptosis mediated by proliferator activated receptors

Essential Fatty acids

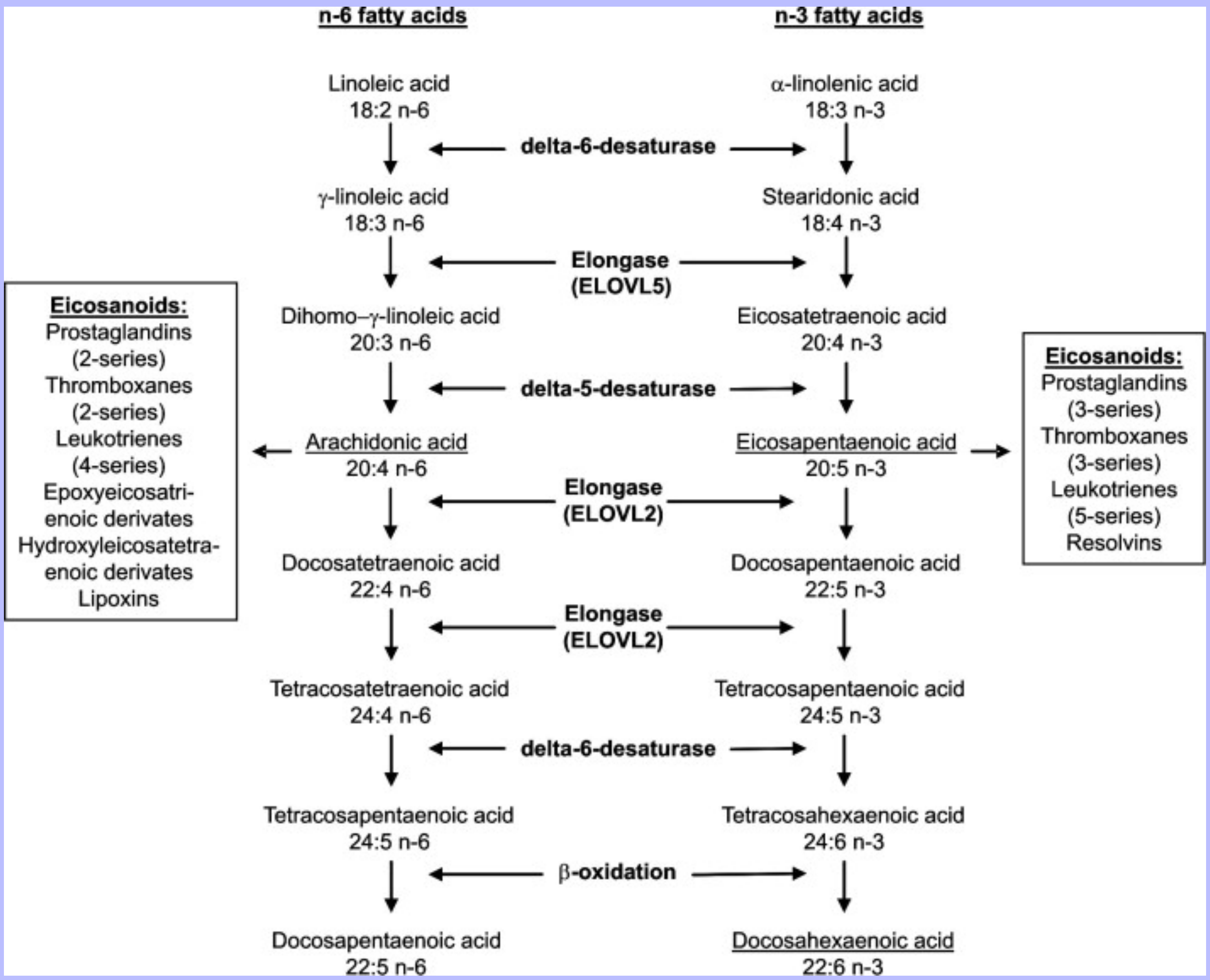
Linoleic acid, 18:2n-6

Alpha linolenic acid, 18:3n-3



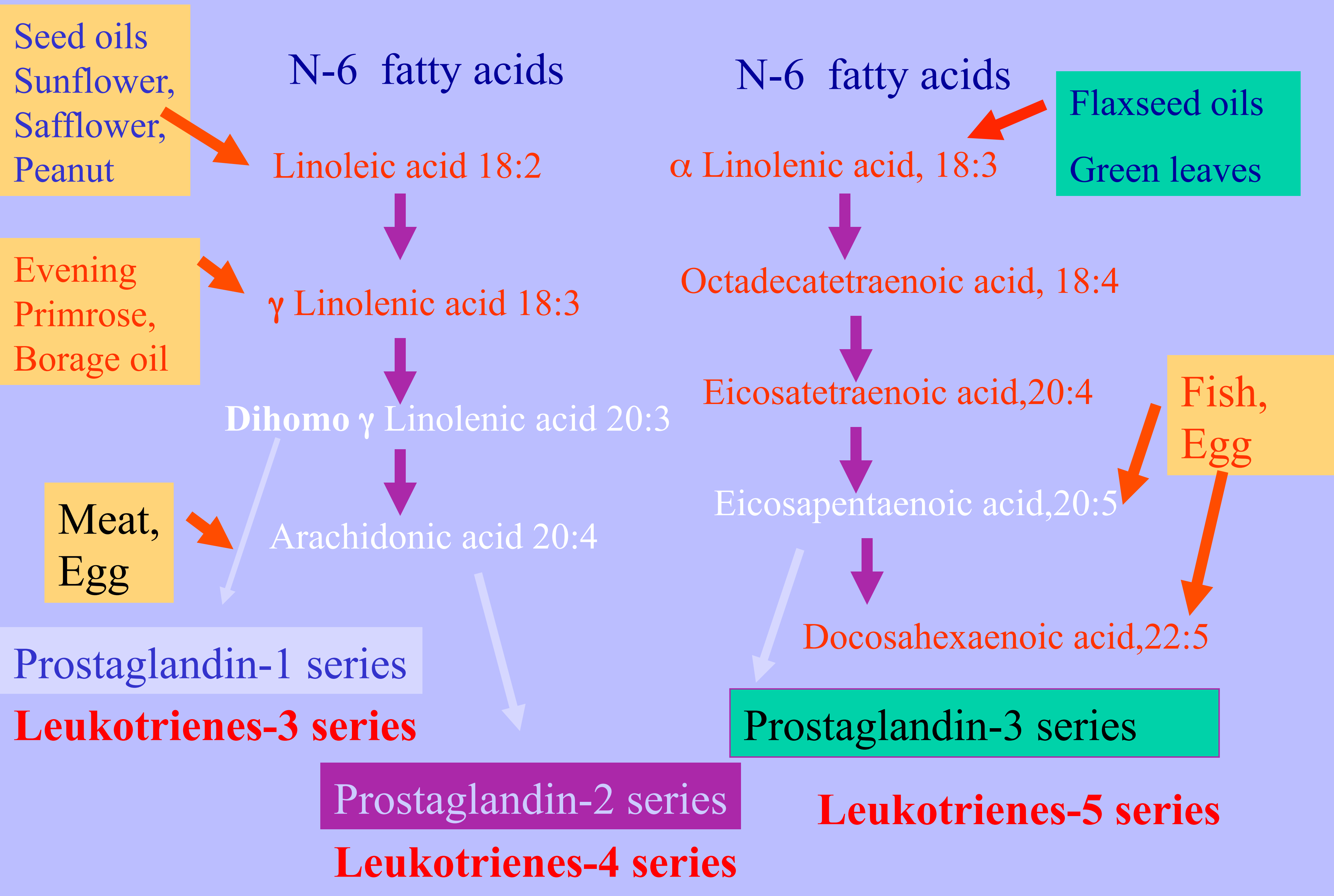
Metabolic Conversions of Essential Fatty Acids in Mammals

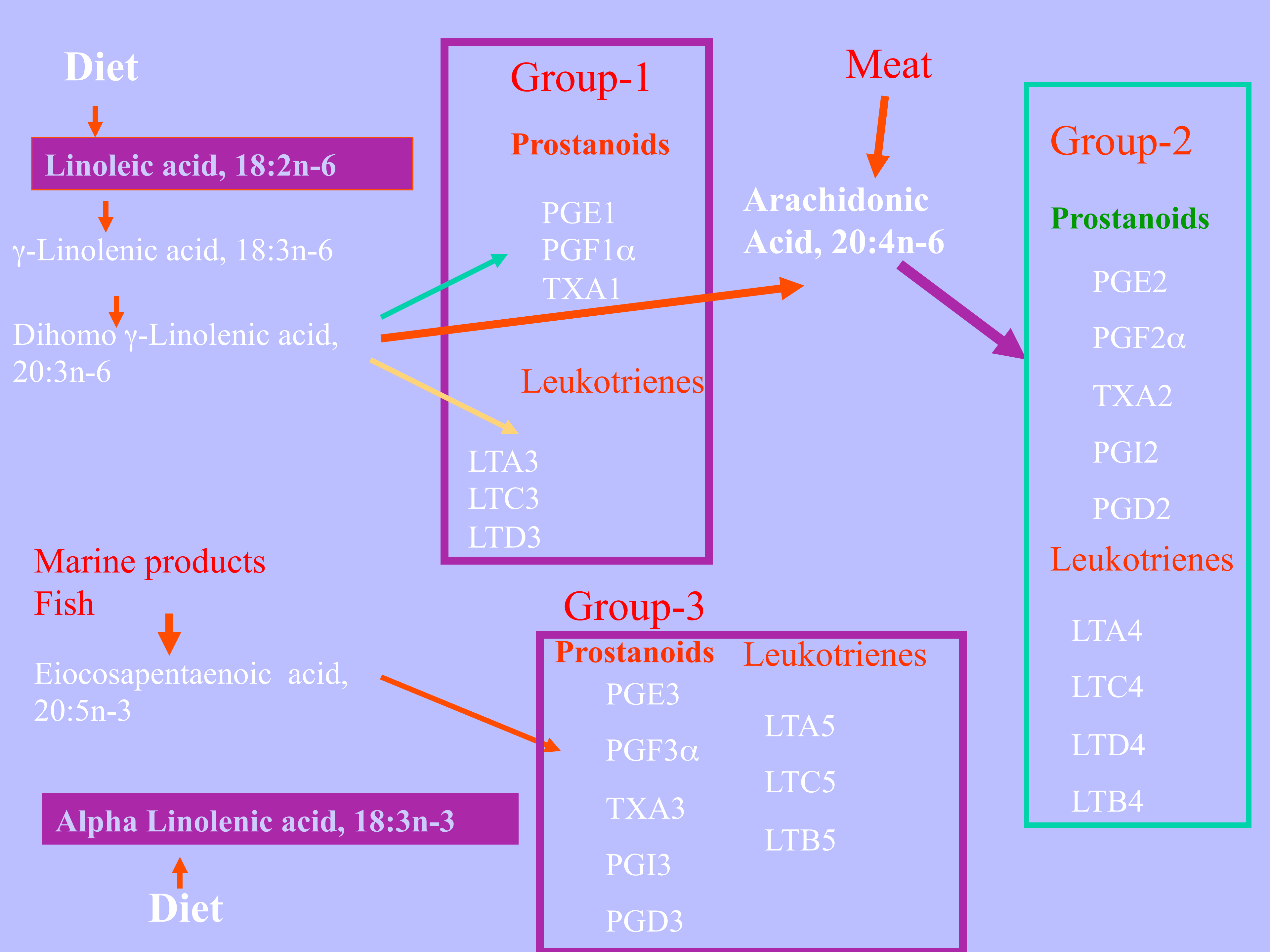
N6-Series	Enzyme	N3-Series
Linoleic (18:2)		**α-linolenic (18:3)**
↓	*Δ⁶-desaturase*	↓
γ-linolenic (18:3)		Octadecatetraenoic (18:4)
↓	*Elongase*	↓
Dihomo–γ–linolenic (20:3)		Eicosatetraenoic (20:4)
↓	*Δ⁵-desaturase*	↓
Arachidonic (20:4)		**Eicosapentaenoic (20:5)**
↓	*Elongase*	↓
Adrenic (22:4)		Docosapentaenoic (22:5)
↓	*Elongase*	↓
Tetracosatetraenoic (24:4)		Tetracosapentaenoic (24:5)
↓	*Δ⁶-desaturase*	↓
Tetracosapentaenoic (24:5)		Tetracosahexaenoic (24:6)
↓	*β-oxidation (Peroxisome)*	↓
Docosapentaenoic (22:5)		**Docosahexaenoic (22:6)**



n-6 fatty acids
n-3 fatty acids
Linoleic acid
18:2 n-6
α-linolenic acid
18:3 n-3
delta-6-desaturase
γ-linoleic acid
18:3 n-6
Stearidonic acid
18:4 n-3
Elongase
(ELOVL5)
Eicosanoids:
Prostaglandins
(2-series)
Thromboxanes
(2-series)
Leukotrienes
(4-series)
Epoxyeicosatri-
enoic derivates
Hydroxyleicosatetra-
enoic derivates
Lipoxins
Dihomo–γ-linoleic acid
20:3 n-6
Eicosatetraenoic acid
20:4 n-3
Eicosanoids:
Prostaglandins
(3-series)
Thromboxanes
(3-series)
Leukotrienes
(5-series)
Resolvins
delta-5-desaturase
Arachidonic acid
20:4 n-6
Eicosapentaenoic acid
20:5 n-3
Elongase
(ELOVL2)
Docosatetraenoic acid
22:4 n-6
Docosapentaenoic acid
22:5 n-3
Elongase
(ELOVL2)
Tetracosatetraenoic acid
24:4 n-6
Tetracosapentaenoic acid
24:5 n-3
delta-6-desaturase
Tetracosapentaenoic acid
24:5 n-6
Tetracosahexaenoic acid
24:6 n-3
β-oxidation
Docosapentaenoic acid
22:5 n-6
Docosahexaenoic acid
22:6 n-3

Contributions of dietary fats to PUFA Metabolism




Diet
Linoleic acid, 18:2n-6
γ-Linolenic acid, 18:3n-6
Dihomo γ-Linolenic acid, 20:3n-6
Group-1
Prostanoids
PGE1
PGF1α
TXA1
Leukotrienes
LTA3
LTC3
LTD3
Meat
Arachidonic Acid, 20:4n-6
Group-2
Prostanoids
PGE2
PGF2α
TXA2
PGI2
PGD2
Leukotrienes
LTA4
LTC4
LTD4
LTB4
Marine products
Fish
Eiocosapentaenoic acid, 20:5n-3
Group-3
Prostanoids
PGE3
PGF3α
TXA3
PGI3
PGD3
Leukotrienes
LTA5
LTC5
LTB5
Alpha Linolenic acid, 18:3n-3
Diet

Physiological Effects of n-6 fatty acids (Linoleic acid, and Arachidonic acid)

Cell growth and development

Homeostasis

Haemostasis

Cell – cell interactions

Skin structure

N-6 fatty acid derived eicosanoids

Responsible for numerous functions

Arachidonic Acid

- Must be ingested or synthesized from the essential fatty acid, linoleic acid
- Esterified in *sn*-2 position of glycerophospholipids

Arachidonic Acid Metabolism

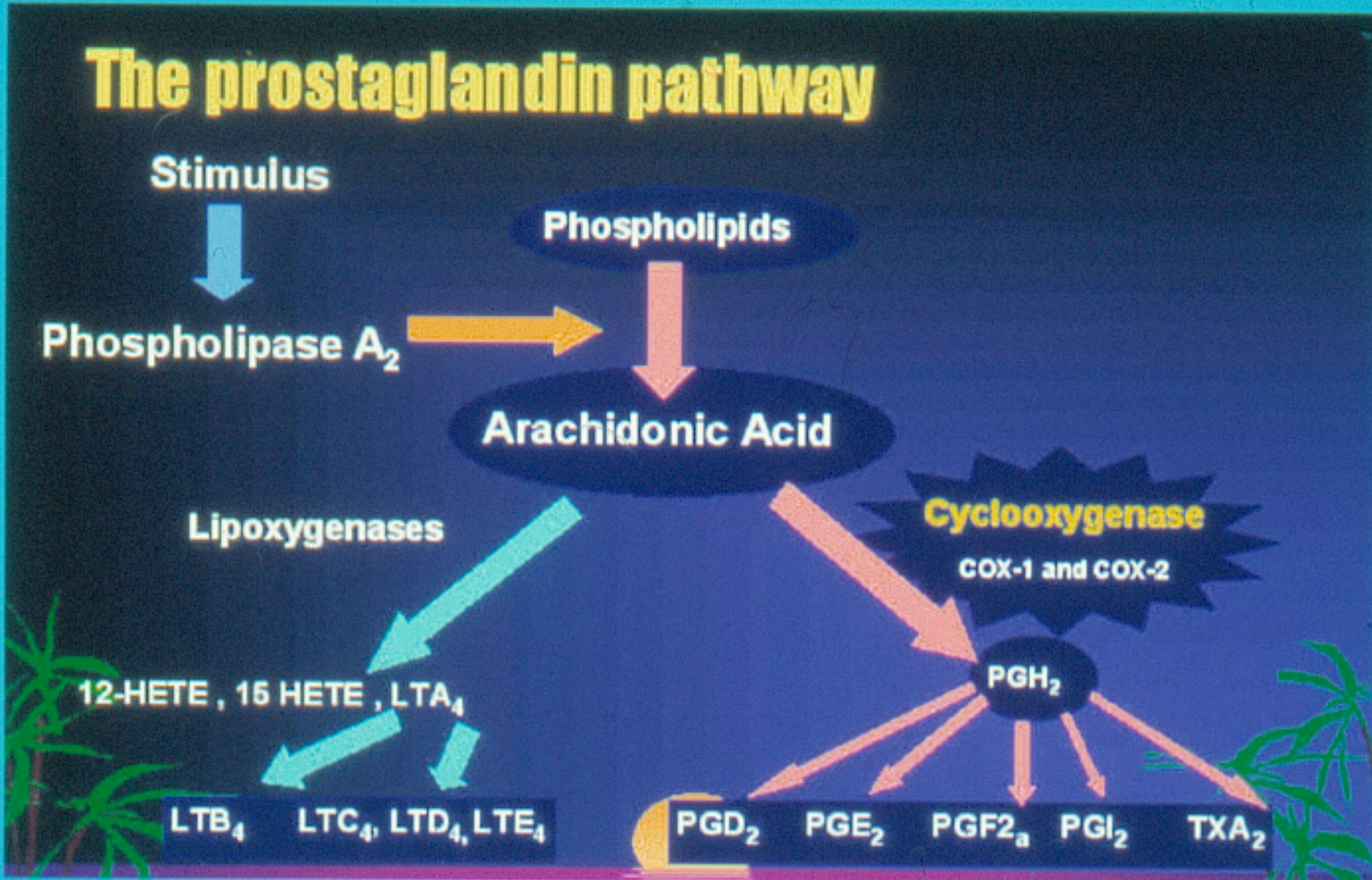
Biosynthesis of Prostaglandins and other Eicosanoids

Metabolism of Prostaglandins

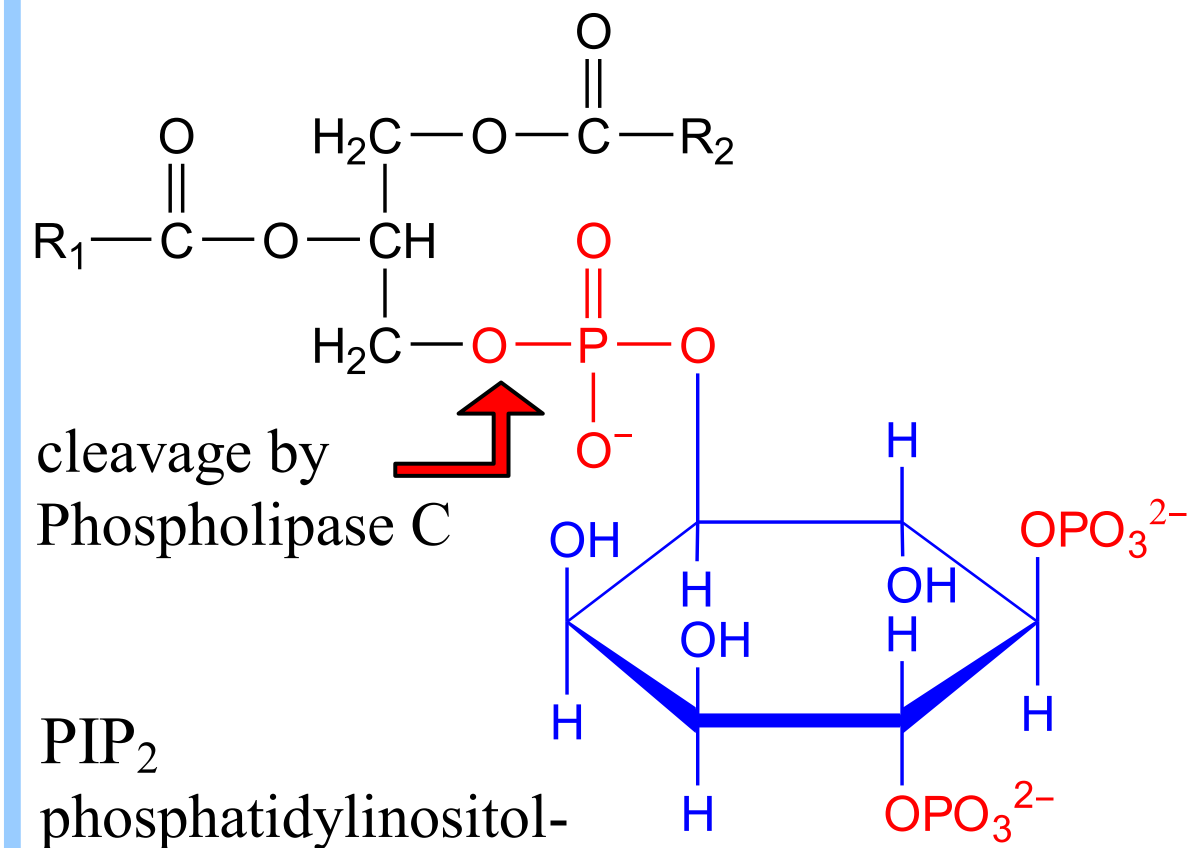
Actions of Eicosanoids

Prostaglandins

Prostaglandins and related compounds are "**local hormones**." They have specific effects on target cells. They are rapidly degraded, so they act only close to their site of formation.
Examples include: **prostaglandins, prostacyclins, thromboxanes, & leukotrienes**.
They have **roles** in inflammation, fever, regulation of blood pressure, blood clotting, control of reproductive processes and tissue growth, and regulation of the sleep/wake cycle.

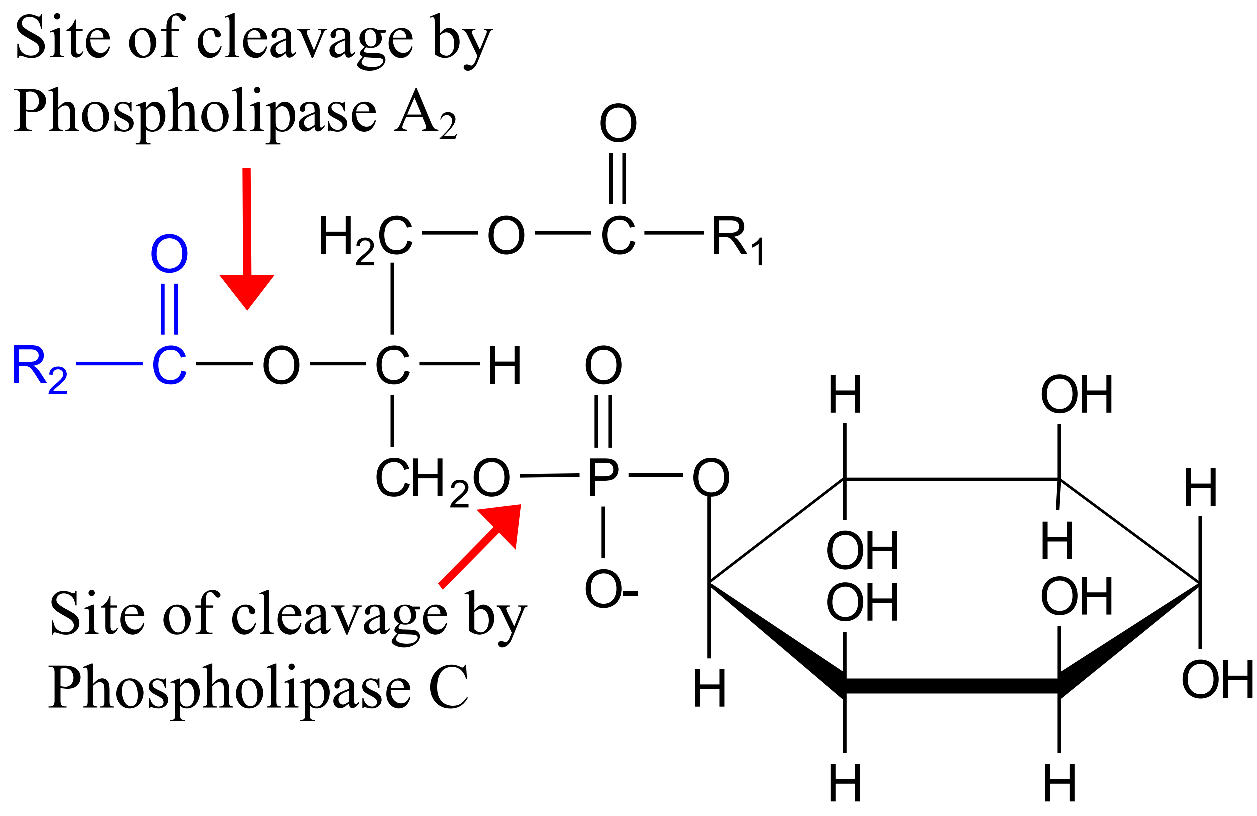

The prostaglandin pathway
Stimulus
Phospholipids
Phospholipase A_2
Arachidonic Acid
Lipoxygenases
Cyclooxygenase
COX-1 and COX-2
12-HETE , 15 HETE , LTA_4
PGH_2
LTB_4
LTC_4, LTD_4, LTE_4
PGD_2
PGE_2
$PGF2_a$
PGI_2
TXA_2

Phosphatidyl inositol signal cascades may lead to release of arachidonate.



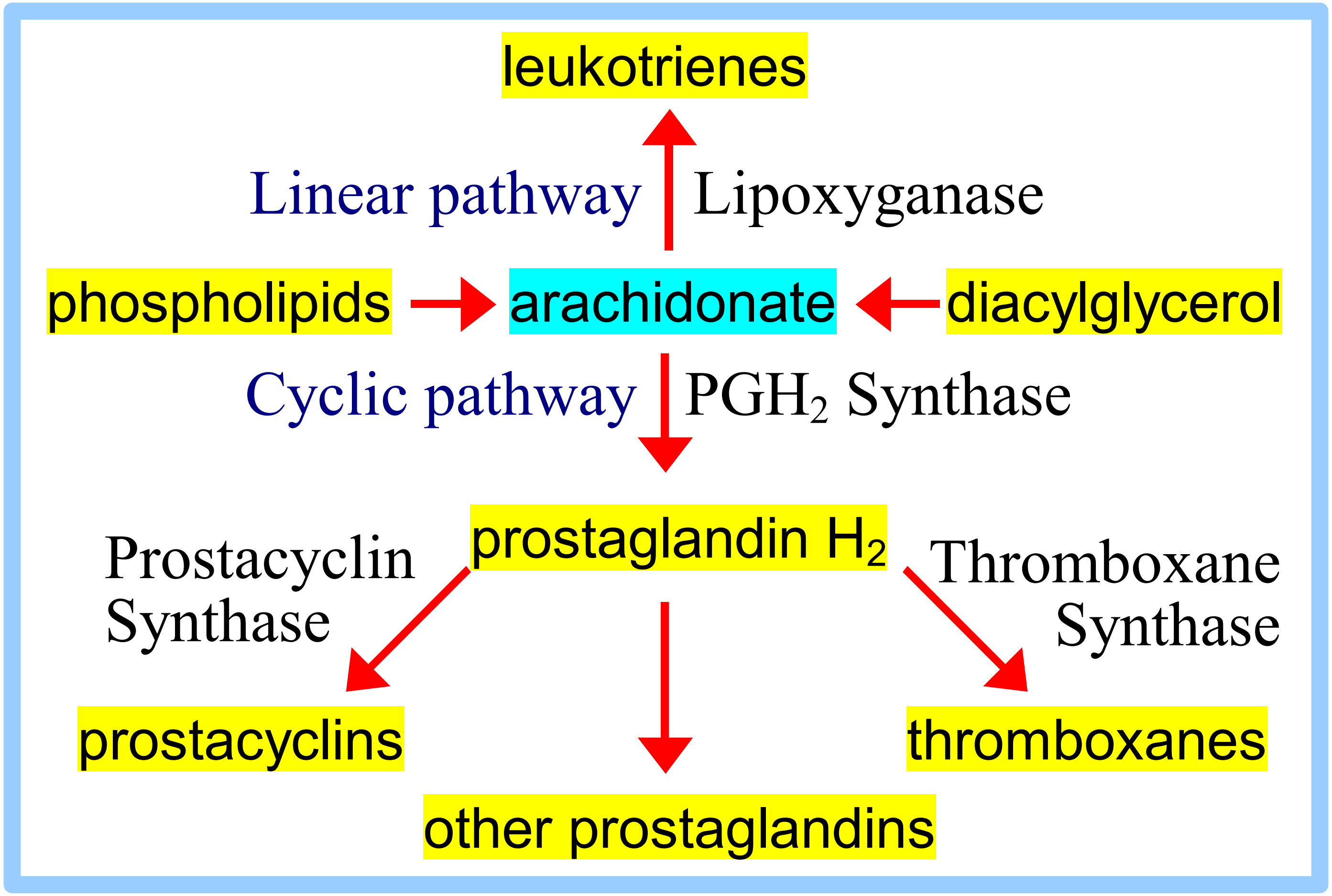
After phosphatidyl inositol is phosphorylated to **PIP_2**, cleavage via **Phospholipase C** yields **diacylglycerol** (& IP_3). Arachidonate release from diacylglycerol is then catalyzed by **Diacylglycerol Lipase**.

Sites of hydrolytic cleavage by **Phospholipases A_2 & C** are shown.



Phosphatidyl inositol

The fatty acid **arachidonate** is frequently esterified at OH on C-2 of glycerophospholipids, especially phosphatidyl inositol (arachidonate in blue). Arachidonate is released from phospholipids by hydrolysis.

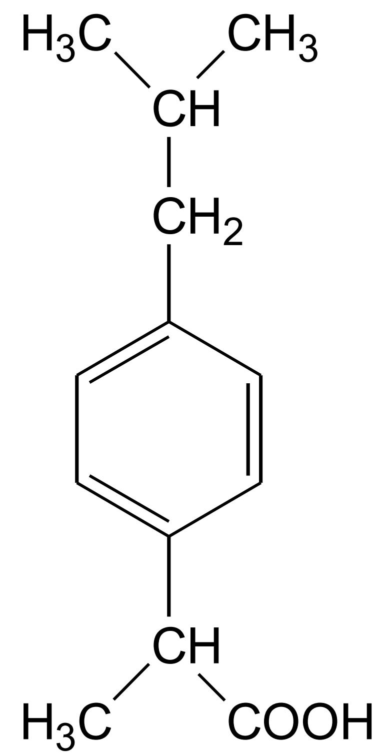


Prostaglandin H_2 Synthase catalyzes the **committed step** in the "**Cyclic Pathway**" leading to production of prostaglandins, prostacyclins, & thromboxanes.

PGH_2 Synthase is a heme-containing **dioxygenase** of ER membranes (dioxygenase incorporates **O_2** into a substrate).

Non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin and derivatives of ibuprofen, inhibit cyclooxygenase activity of PGH_2 Synthase.

They inhibit formation of prostaglandins involved in fever, pain, & inflammation. They inhibit blood clotting by blocking thromboxane formation in blood platelets.

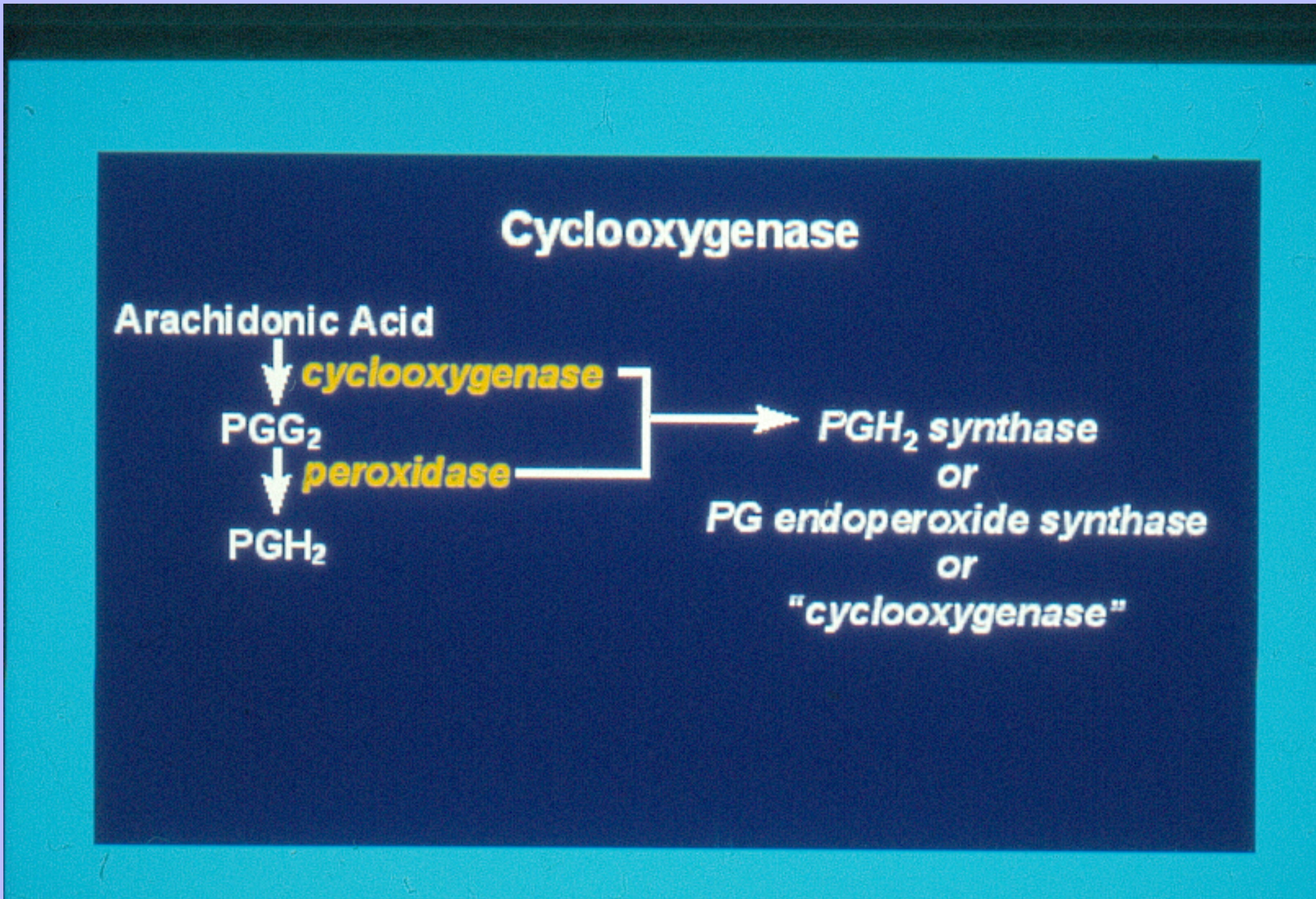


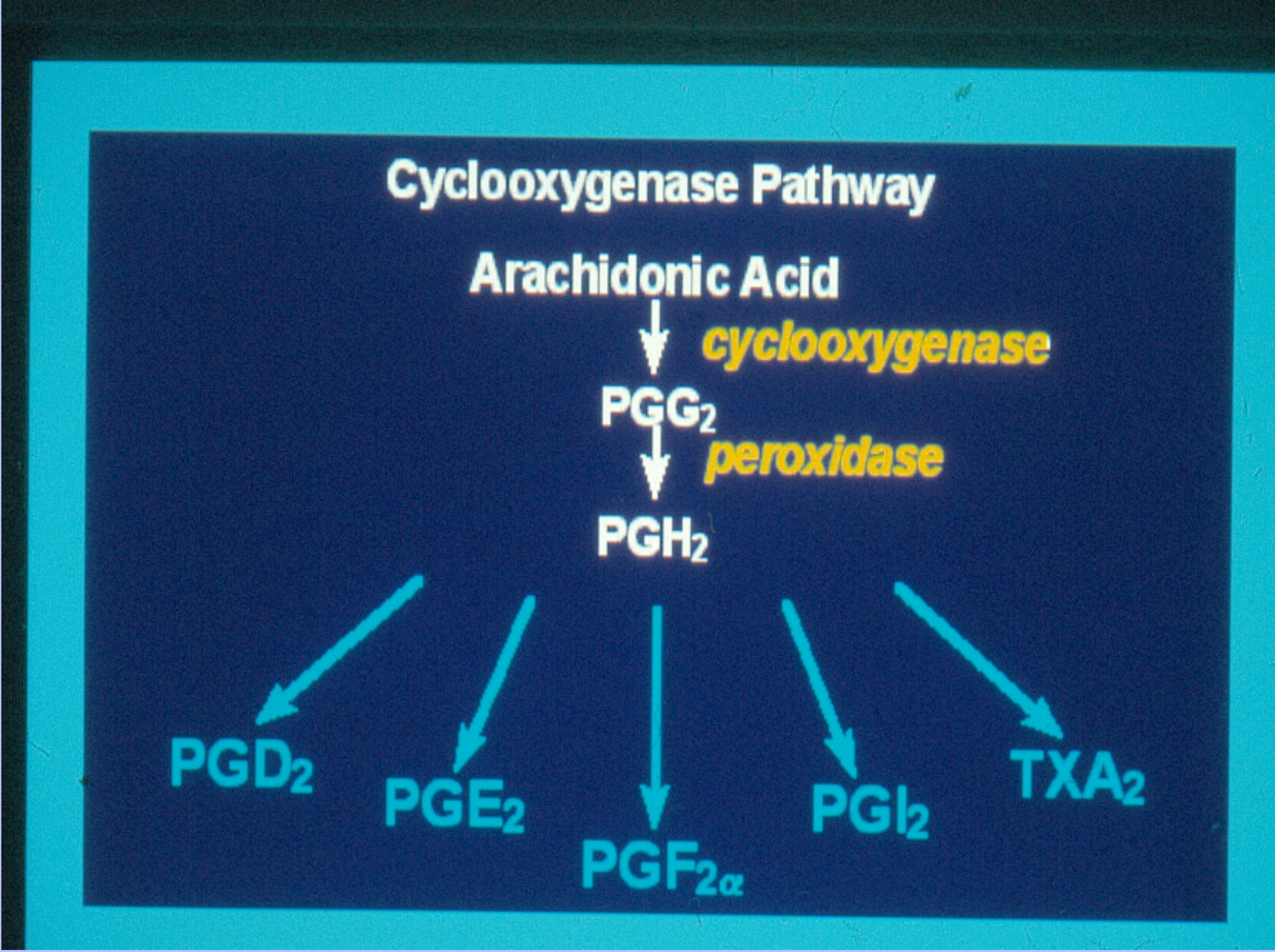
Ibuprofen

Ibuprofen and related compounds block the hydrophobic channel by which arachidonate enters the cyclooxygenase active site.

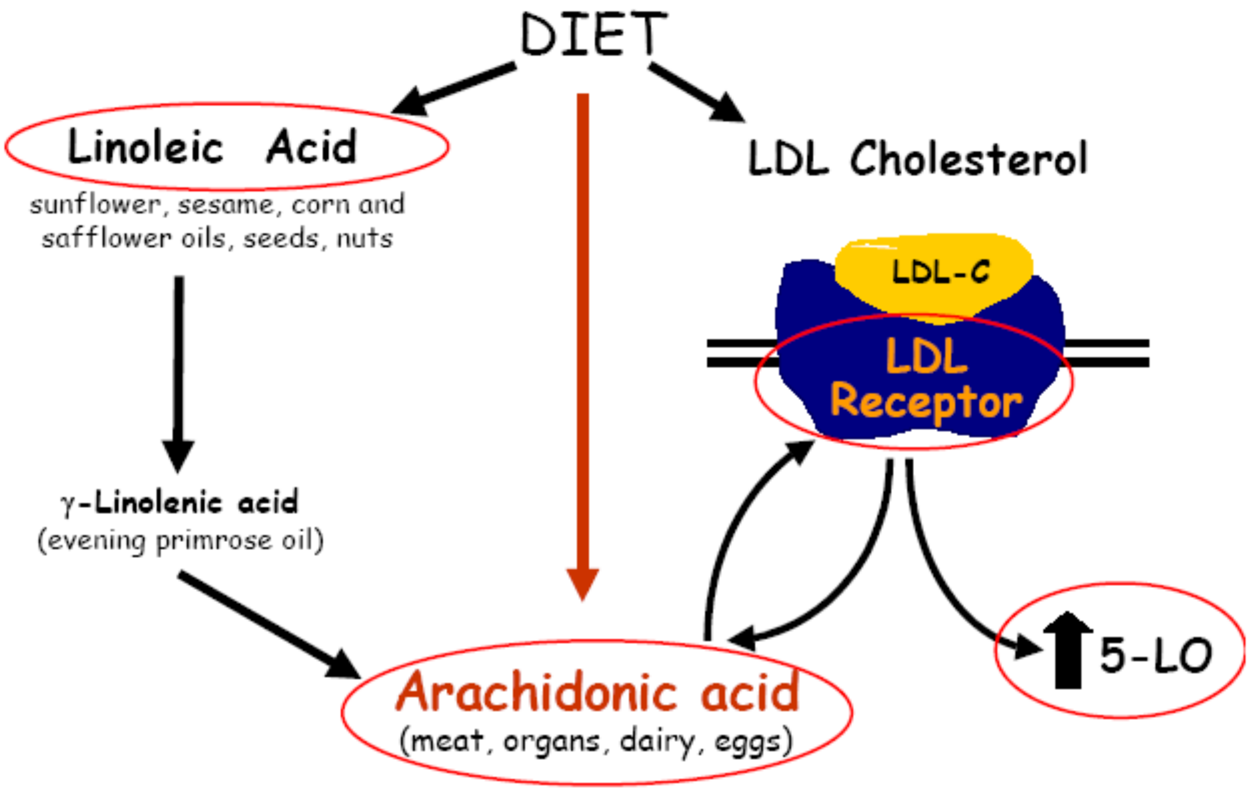
Cyclooxygenase Pathway

- Prostaglandins
- Prostacyclin
- Thromboxane


Cyclooxygenase
Arachidonic Acid
cyclooxygenase
PGG2
peroxidase
PGH2
PGH2 synthase
or
PG endoperoxide synthase
or
"cyclooxygenase"


Cyclooxygenase Pathway
Arachidonic Acid
cyclooxygenase
PGG2
peroxidase
PGH2
PGD2
PGE2
PGF2α
PGI2
TXA2

Dietary AA - the key nutritional determinant in regulating AA levels



Constitutive Form PGH_2 Synthase

- ✓ Found in many (most) cell types
- ✓ Important in the gut for production of PGs, which inhibit gastric acid secretion

Prostaglandin Receptors

Some prostaglandins activate heterotrimeric **G Proteins** via **7-helix** plasma membrane **receptors**.

Some of these G proteins activate formation of **cAMP**; others activate phosphatidylinositol signal pathways leading to intracellular **Ca^{++}** release.

Another prostaglandin receptor, **PPARγ**, is related to a family of nuclear receptors with transcription factor activity.

Eicosanoid Receptors Nomenclature

DP - receptor for PGD_2

EP - receptors for PGE_2

FP - receptor for $PGF_{2\alpha}$

IP - receptor for PGI_2

TP - receptor for TXA_2

Lipoxygenase

The 1st step of the **Linear Pathway** for synthesis of **leukotrienes** is catalyzed by **Lipoxygenase**.

Mammalian organisms have a family of Lipoxygenase enzymes that catalyze oxygenation of various polyunsaturated fatty acid at different sites. Many of the products have signal roles.

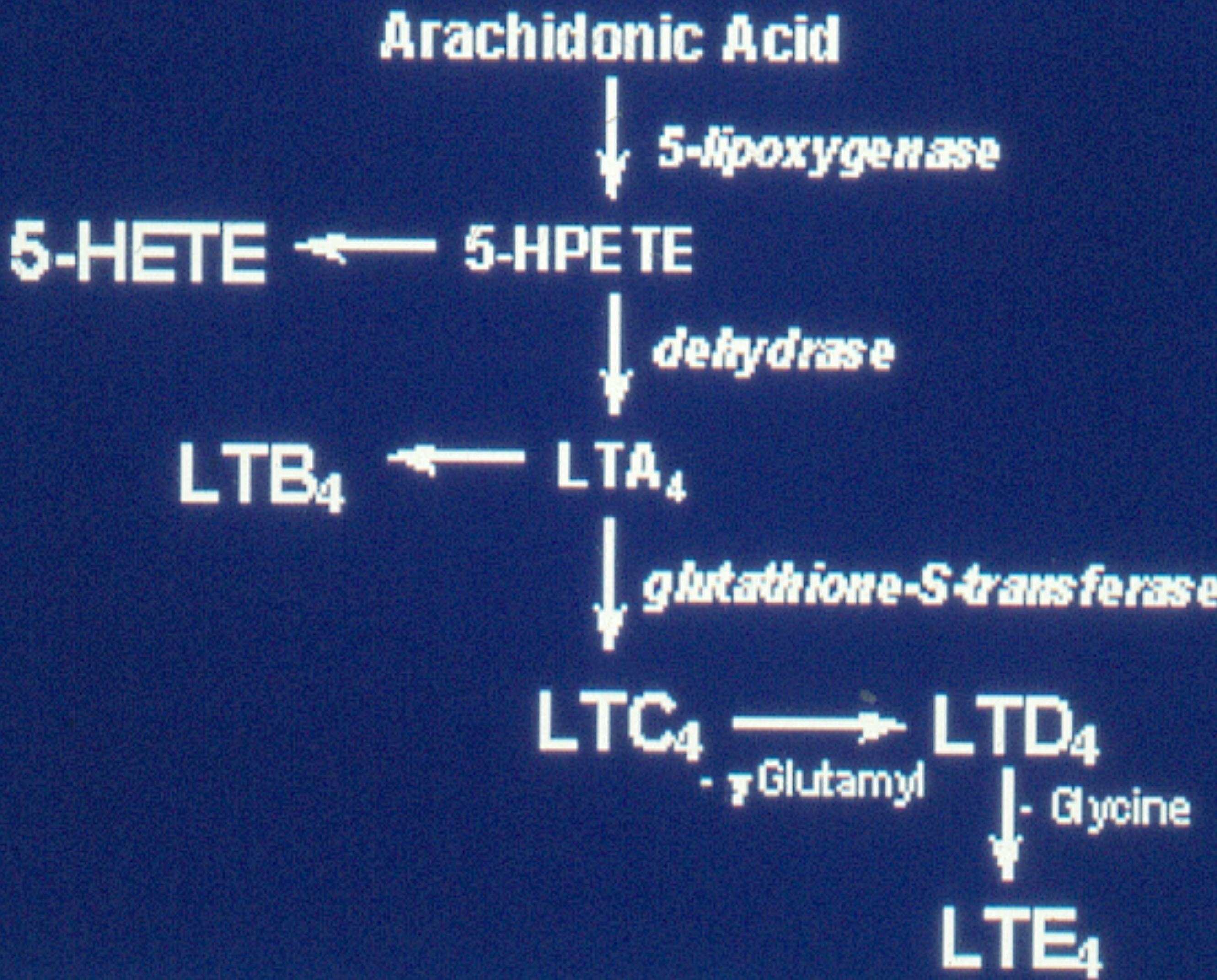
Lipoxygenase Pathways

- Leukotrienes
- Lipoxins
- HETEs, HPETEs

Lipoxygenases

- 5-lipoxygenase
- 12-lipoxygenases
- 15-lipoxygenases

Lipoxygenase Pathway



5-Lipoxygenase Pathway

Arachidonic Acid

↓ *5-lipoxygenase*

5-HPETE

↓

Leukotrienes

Sites of Action of Lipoxygenase Products

- Leukocytes
- Platelets
- Smooth muscle
- Many other tissues / cells

5-Lipoxygenase (5-LO) Pathway in Human Diseases

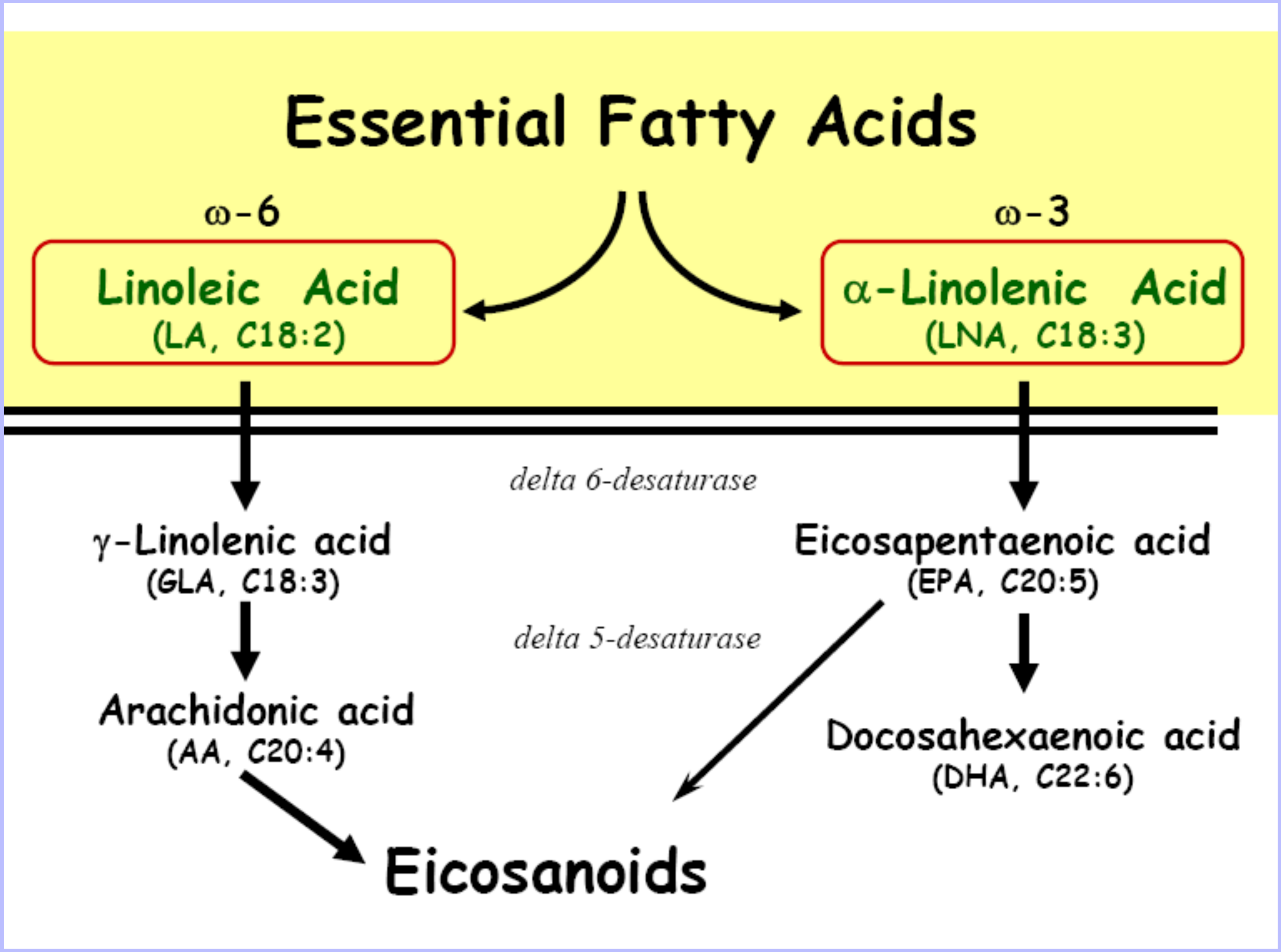
Inflammatory conditions

- Asthma
- Inflammatory bowel disease
- Psoriasis

Atherosclerosis

- Myocardial infarction
- Stroke
- Aneurysm

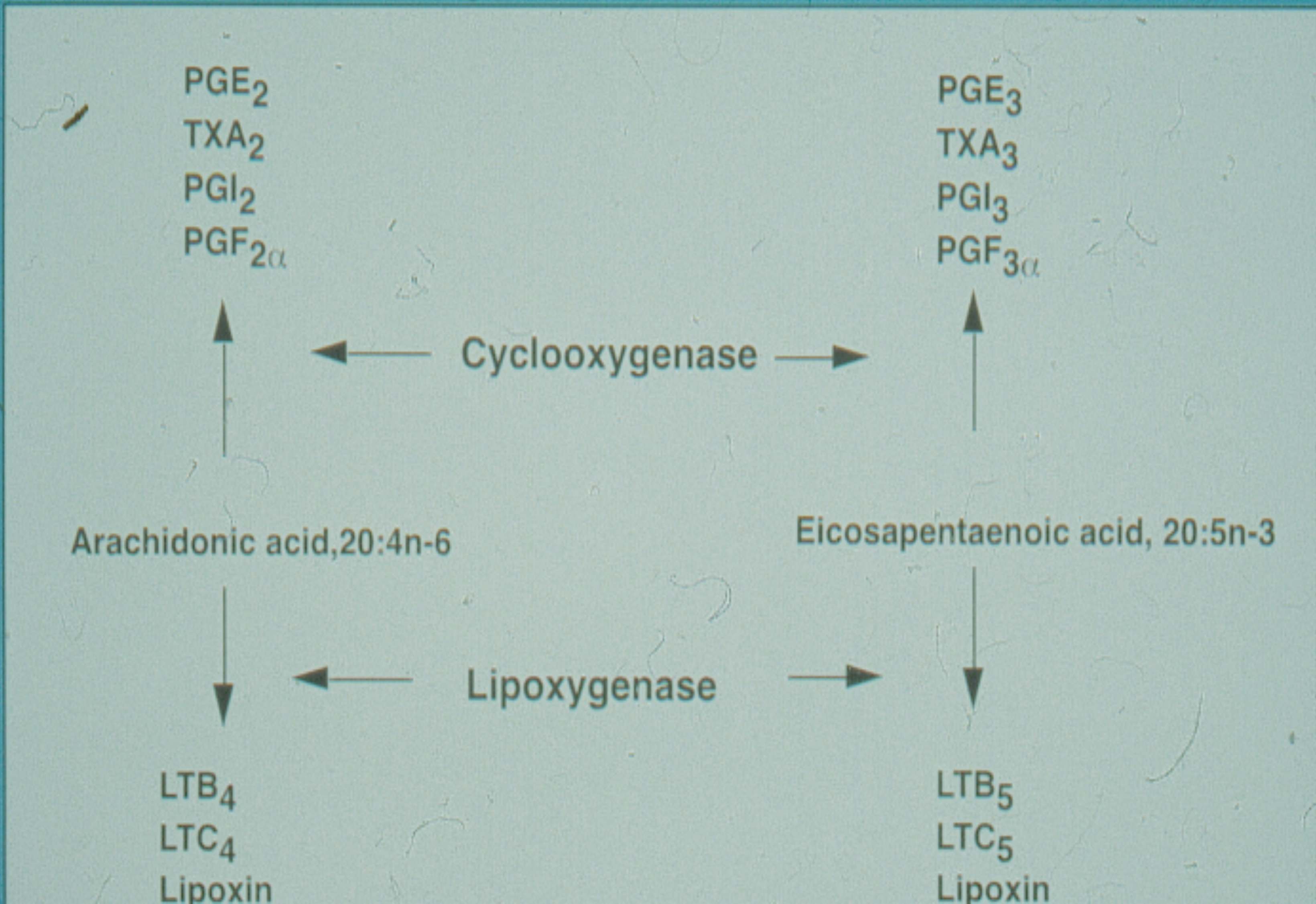
- Cancer
  - Lung (Avis et al., 1996; Mao JT , 2004)
  - Prostate (Gupta S, 2001; Matsuyama M, 200
  - Pancreas (Hennig R et al., 2002)
  - Colon (Ohd JF et al., 2003)
  - Bladder (Yoshimura R et al., 2003)
  - Testis (Yoshimura R et al., 2004)
  - Esophagus (Chen X et al., 2004)
  - High-grade astrocytomas (Nathoo et al., in review)

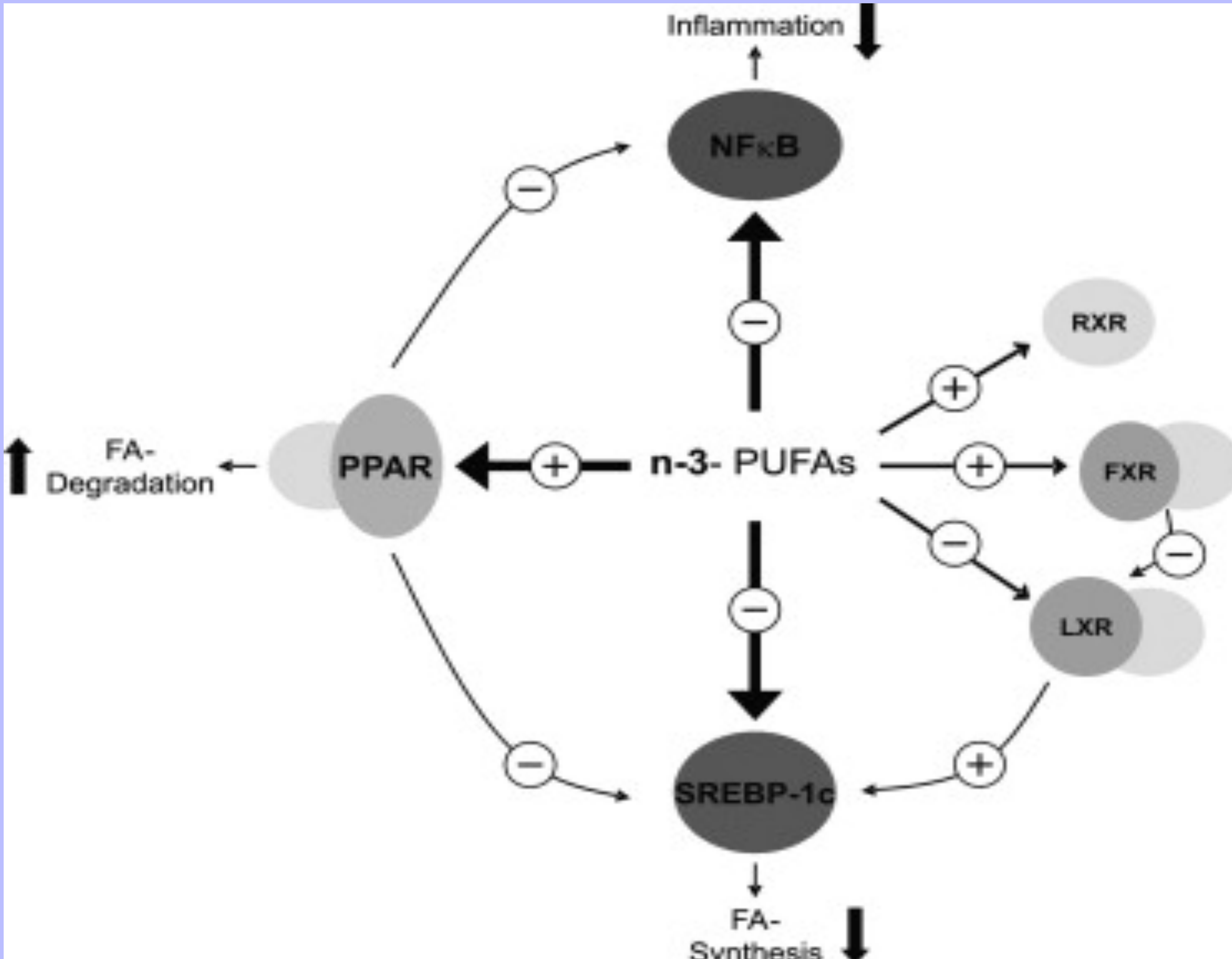

Essential Fatty Acids
ω-6
Linoleic Acid
(LA, C18:2)
ω-3
α-Linolenic Acid
(LNA, C18:3)
delta 6-desaturase
γ-Linolenic acid
(GLA, C18:3)
Eicosapentaenoic acid
(EPA, C20:5)
delta 5-desaturase
Arachidonic acid
(AA, C20:4)
Docosahexaenoic acid
(DHA, C22:6)
Eicosanoids

Main function of Eicosanoids

N-6 fatty acids			N-3 fatty acids		
Arachidonic acid			Eicosapentaenoic acid		
TxA_2	Platelet aggregation	+	TXA_3	Platelet aggregation	
	Vasocontriction	+		Vasocontriction	
PGI_2	Anti-aggregation	+	PGI_3	Anti-aggregation	+
	Vasodilatation	+		Vasodilatation	+
LTB_4	Aggregation	+++	LTB_5	Aggregation	+
	Adhesion	+++		Adhesion	+
	Permeability	+++		Permeability	+

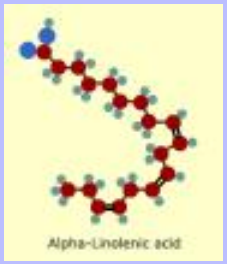
Competition between arachidonic and eicosapentaenoic acids for cyclooxygenase and lipoxygenase




Inflammation
NFκB
RXR
FA-
Degradation
PPAR
n-3- PUFAs
FXR
LXR
SREBP-1c
FA-
Synthesis

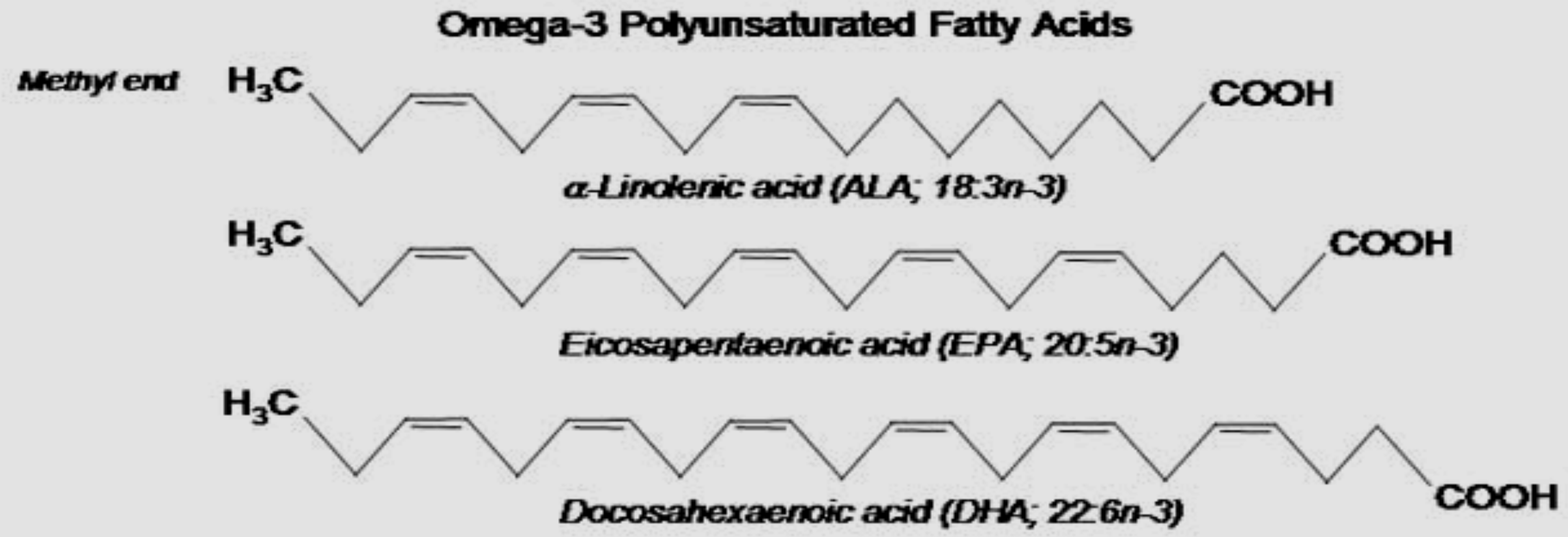
Omega 3 Fatty Acids

Alpha-linolenic acid (ALA)



- Scientific abbreviation is 18:3n-3
- The first part (18:3) suggests that ALA is an 18-carbon fatty acid with 3 double bonds
- The second part (n-3) tells you that ALA is an omega-3 fatty acid
- It is required for health, but cannot be synthesized in humans
- Must be obtained from the diet

Structures of the Omega-3 Fatty Acids



Alpha-linolenic Acid

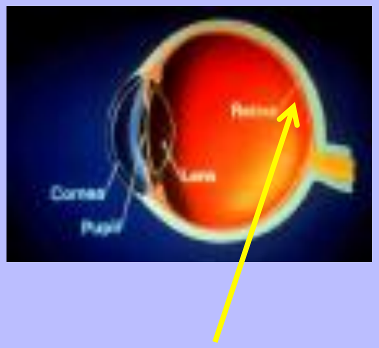
- Humans can synthesize other omega-3 fatty acids from ALA:

- Eicosapentaenoic acid (EPA): 20:5n-3
- Docosahexaenoic acid (DHA): 22:6n-3

- These two are usually referred to as marine-derived omega-3 fatty acids because they are abundant in certain species of fish

- Whereas, ALA is considered a plant-derived omega-3 fatty acid

Docosahexaenoic acid (DHA)



- Found in very high concentrations in the cell membranes of the retina
- It conserves and recycles DHA even when omega-3 fatty acid intake is low
- Studies in animals indicate that DHA is required for the normal development and function of the retina

Disease Prevention:
Impaired Visual and Neural Development

- Because the last trimester of pregnancy is a critical period for the accumulation of DHA in the brain and retina, preterm infants are particularly vulnerable to adverse effects of insufficient DHA on visual and neural development

- Although preterm infants can synthesize DHA from ALA, they can’t synthesize enough to prevent declines in plasma and cellular DHA levels without additional dietary intake

- Preterm infants fed formulas with DHA added had significantly improved measures of visual function compared to preterm infants fed DHA-free formulas in 5 out of 5 randomized controlled trials

Fish Consumption
And Coronary Heart Disease

- One study followed 1,822 men for 30 years and found that mortality from CHD was 38% lower in men who consumed an average of at least 35 g (1.2 ounces) of fish daily than in men who did not eat fish, while mortality from myocardial infarction (MI) was 67% lower

ALA Consumption

And Coronary Heart Disease

- In a prospective study of 43,757 male health professionals followed for 6 years, a relatively small increase in ALA intake (1% of total energy) was associated with a 59% decrease in the risk of acute MI
- Women who consumed oil and vinegar salad dressings 5-6 times weekly had a risk of fatal CHD that was 54% lower than those who rarely consumed it even after adjusting the analysis for vegetable intake
- Although the evidence is limited, it is indicated that increased ALA intakes may decrease the risk for CHD, especially in populations with relatively low levels of fish consumption

CHD Treatment

- Results of randomized controlled trials in individuals with documented coronary heart disease suggest a beneficial effect of dietary and supplemental omega-3 fatty acids

- Therefore, the American Heart Association has recommended that individuals with documented CHD consume 1 g/d of EPA and DHA combined

Omega 3 fatty acids and cardiovascular disease

Epidemiology

Very low mortality among the Greenland Inuits compared with Denish people

They consume 10gm Omega 3 per 3000kcal

High plasma DHA, EPA
Low ARA
Low platelet activity

Kromnann N *et al* Acta Med Scand 208, 401-406, 1980
Bjerregaard P et al Int J. Epidemiol 17, 514-519, 1988

Fish Consumption
And Sudden Cardiac Death

- Several studies have found inverse relationships between fish consumption and sudden cardiac death

- In a prospective study, omega-3 fatty acid intakes equivalent to two fatty fish meals per week were associated with a 50% decrease in the risk of primary cardiac arrest

- Plasma levels of EPA and DHA were found to be inversely related to the risk of sudden death, supporting the idea that omega-3 fatty acids are at least partially responsible for the beneficial effect of fish consumption and sudden cardiac death

Fish Consumption

And Stroke

- A stroke is a result of impaired blood flow to a region of the brain, which may be due to obstruction of a blood vessel by a blood clot (thrombotic or ischemic stroke) or the rupture of a blood vessel (hemorrhagic stroke)

- Even though the effects of increased omega-3 fatty acid intake and the incidence of stroke have not been studied as thoroughly as the relationship with CHD, what is available suggests that increased fish intake may decrease the risk of thrombotic or ischemic stroke but not hemorrhagic

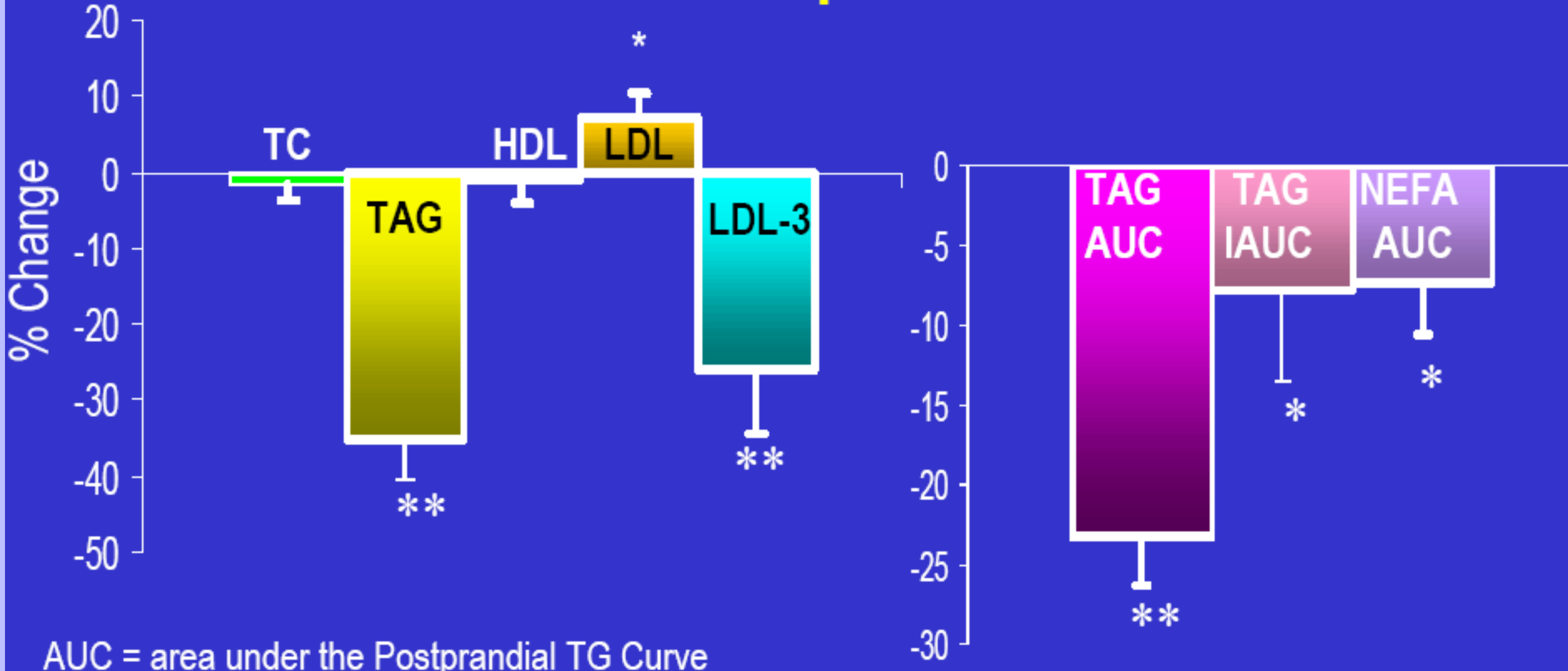
Intervention studies on CVD with omega 3 fatty acids

Supplementation of Omega 3 has beneficial effects on CVD patients

Ref:

1. Burr ML et al Lancet 2, 757-761, 1989
2. Trial et al Lancet 354, 447-455, 1999

Effect of Fish Oil on Fasting and Postprandial Lipids

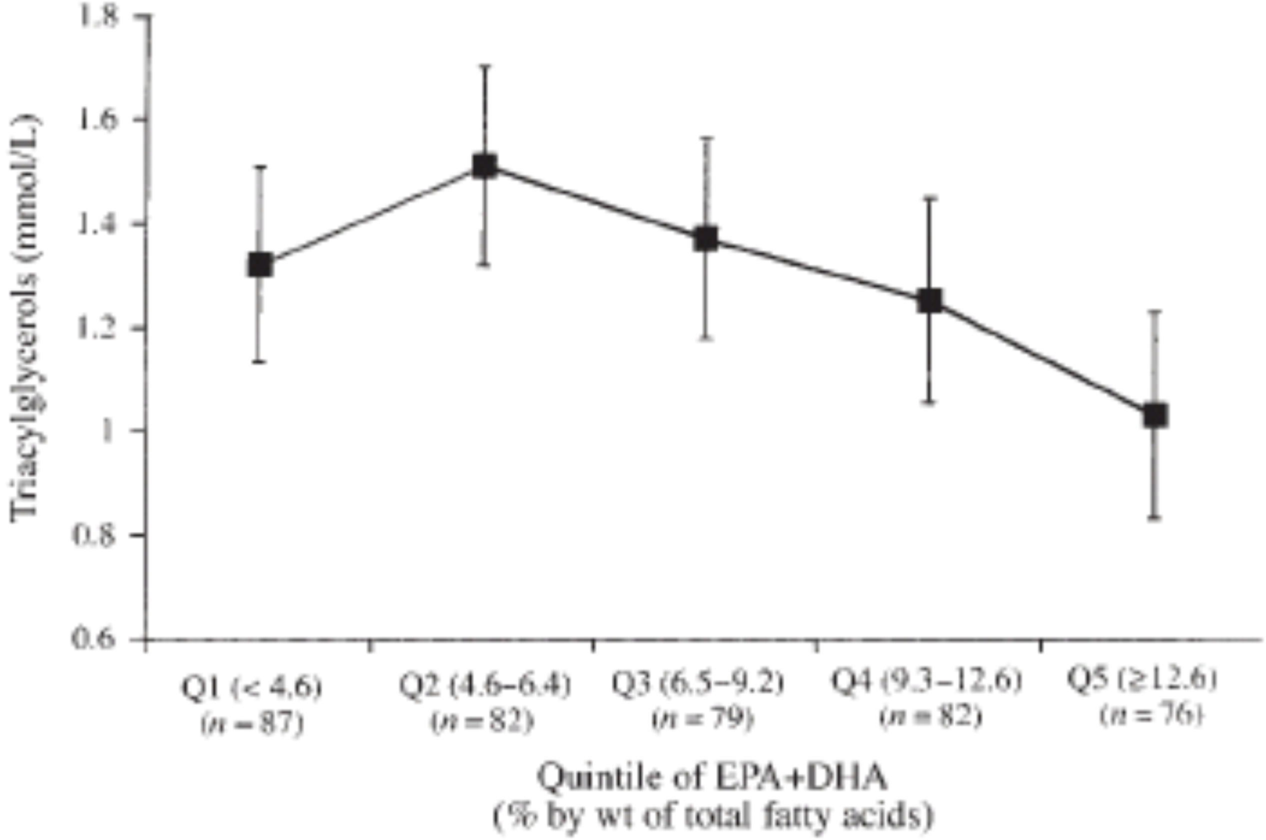


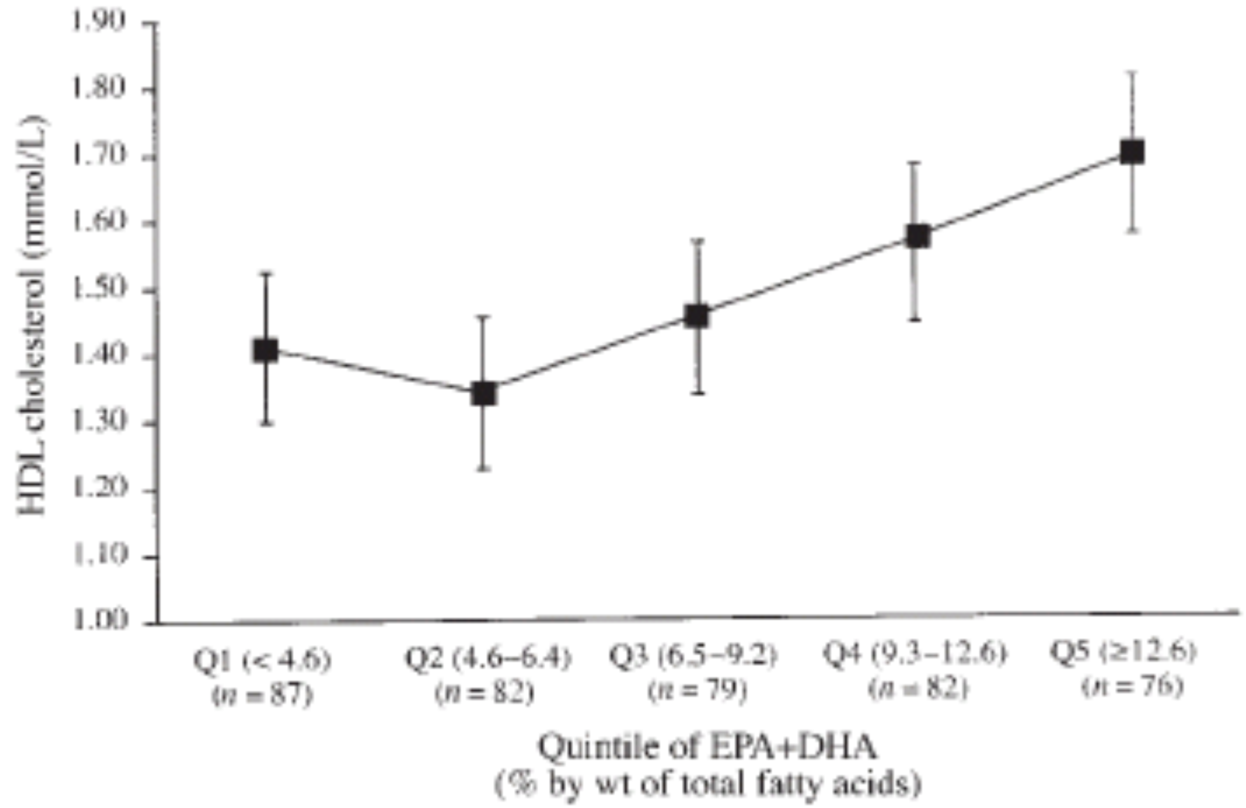
AUC = area under the Postprandial TG Curve

IAUC = Incremental area under the PP TG curve

* $p < 0.05$ ** $p < 0.001$

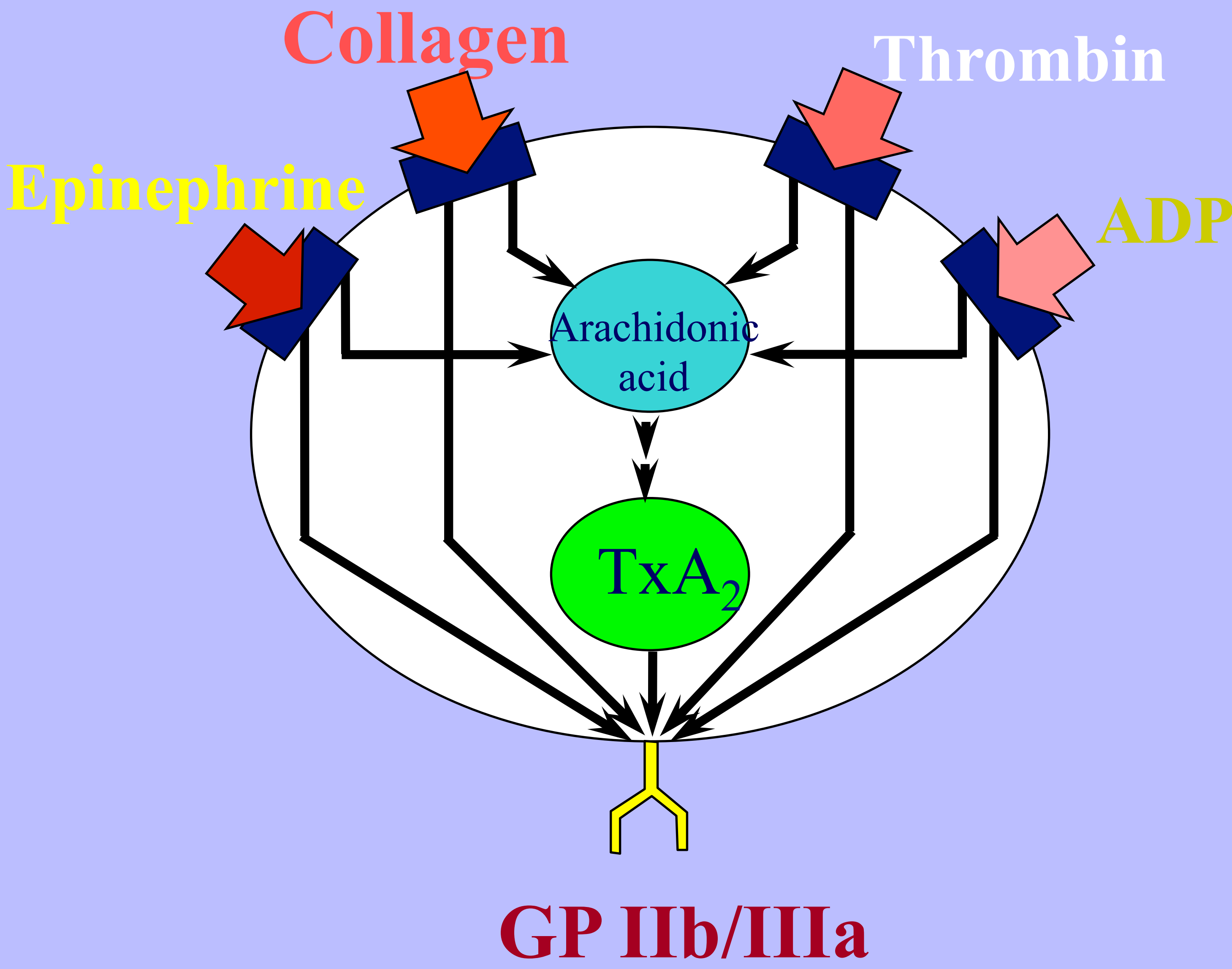
Minihane et al., 2000a

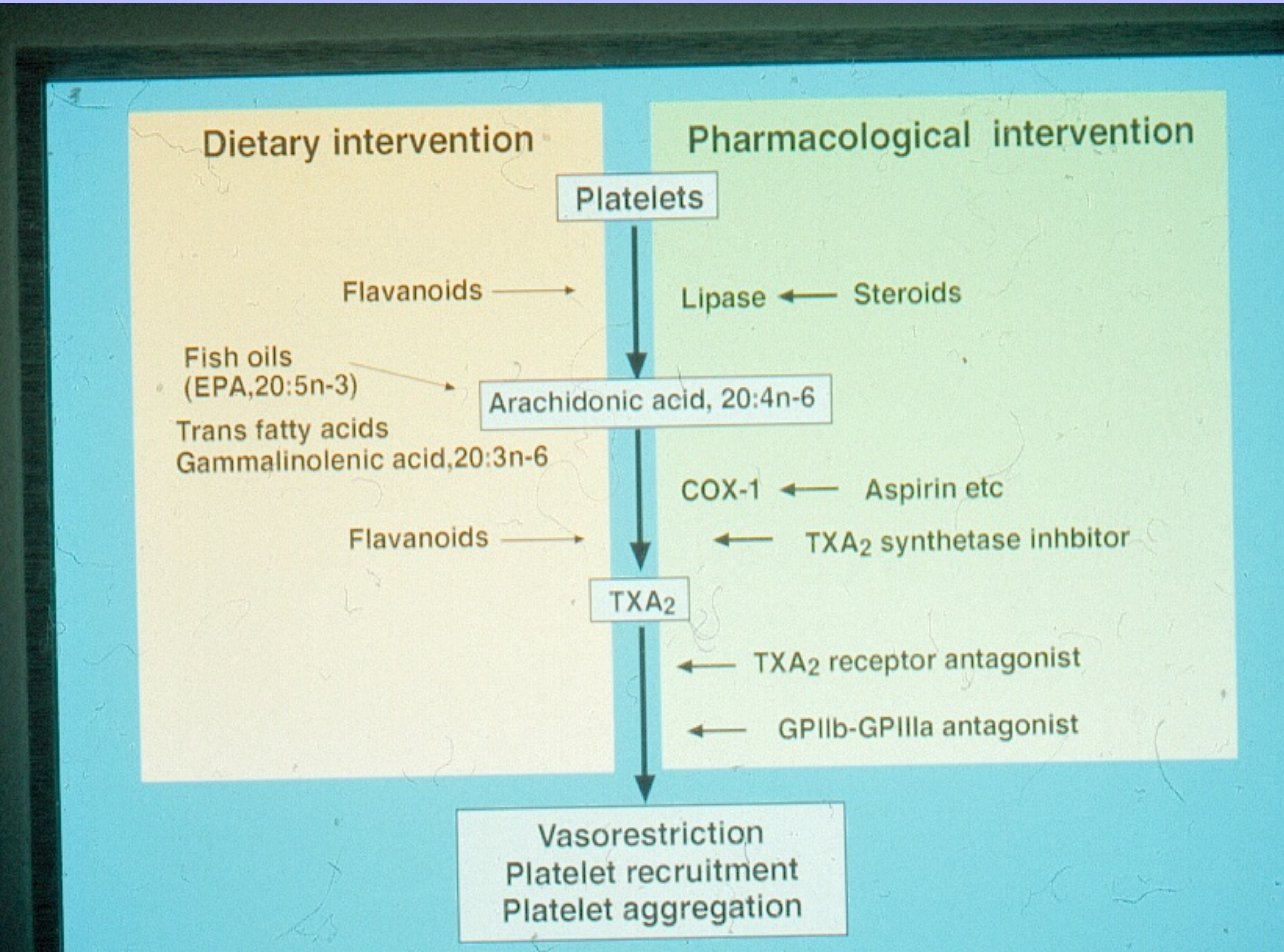

1.8
1.6
1.4
1.2
1
0.8
0.6
Triacylglycerols (mmol/L)
Q1 (< 4.6)
(n = 87)
Q2 (4.6–6.4)
(n = 82)
Q3 (6.5–9.2)
(n = 79)
Q4 (9.3–12.6)
(n = 82)
Q5 (≥12.6)
(n = 76)
Quintile of EPA+DHA
(% by wt of total fatty acids)



Dewailly et al Am J Clin Nutr, 74, 464-473, 2001

Platelet Activation Pathways




Dietary intervention
Pharmacological intervention
Platelets
Flavanoids
Lipase
Steroids
Fish oils
(EPA,20:5n-3)
Arachidonic acid, 20:4n-6
Trans fatty acids
Gammalinolenic acid,20:3n-6
COX-1
Aspirin etc
Flavanoids
TXA2 synthetase inhbitor
TXA2
TXA2 receptor antagonist
GPIIb-GPIIIa antagonist
Vasorestriction
Platelet recruitment
Platelet aggregation

Omega 3 fatty acids and CVD risk factors

Coagulation and platelet function

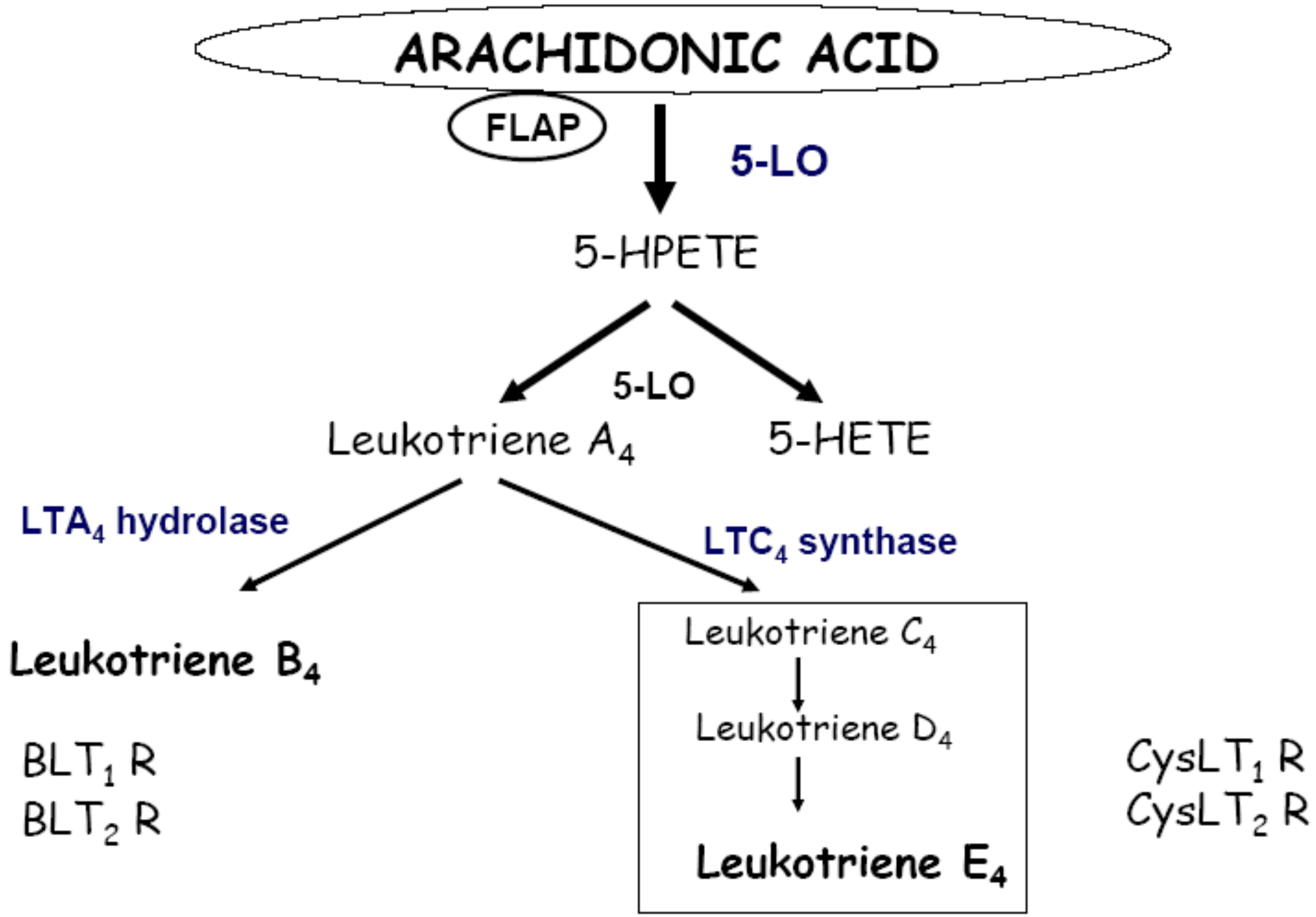
Blood pressure

Plasma lipoproteins and triglycerides
(Fasting and postpranidal)

Ventricular arrhythmias

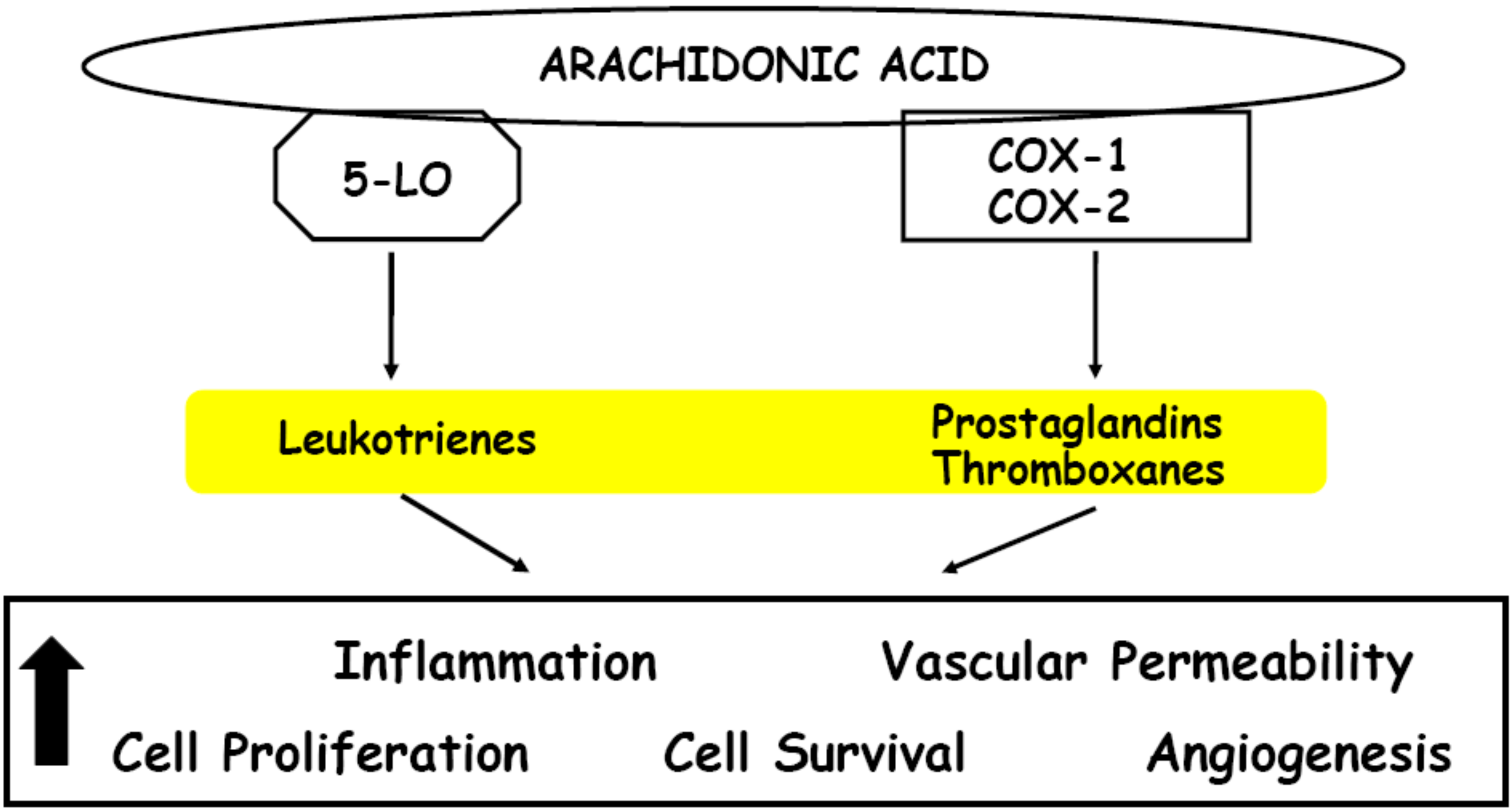
Cancer

- Marine-derived fatty acids have been found to inhibit proliferation and promote apoptosis in breast, prostate, and colon cancer cell lines cultured outside the body
- Studies in animal models of cancer also indicate that increased intake of EPA and DHA decreases the occurrence and progression of mammary, prostate, and intestinal tumors
- However, in humans few have demonstrated significant inverse relationships between fish or omega-3 fatty acid intake and the risk for breast, prostate, or colorectal cancers

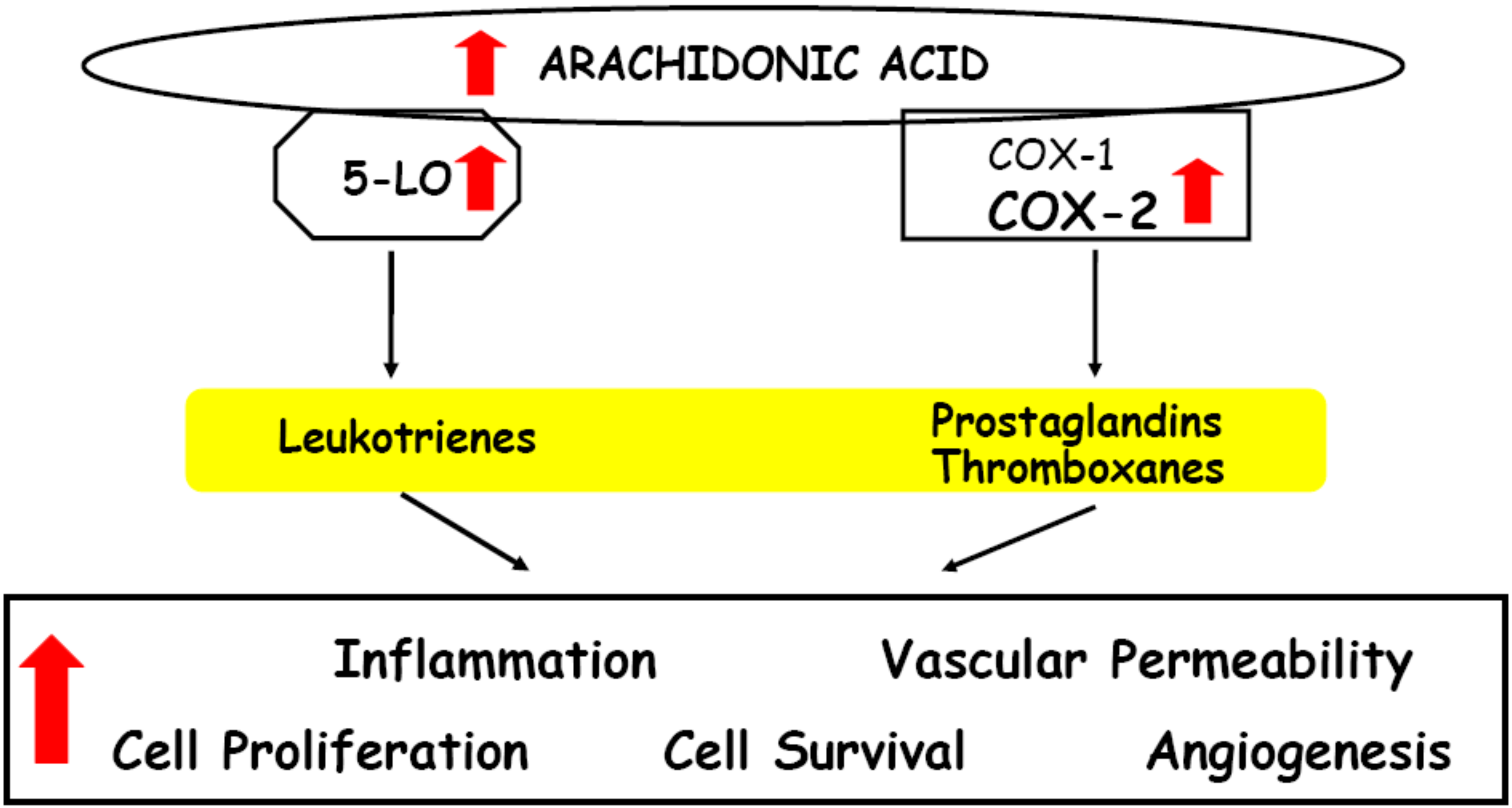


ARACHIDONIC ACID
FLAP
5-LO
5-HPETE
5-LO
Leukotriene A_4
5-HETE
LTA_4 hydrolase
LTC_4 synthase
Leukotriene B_4
Leukotriene C_4
Leukotriene D_4
Leukotriene E_4
BLT_1 R
BLT_2 R
$CysLT_1$ R
$CysLT_2$ R

Eicosanoids – Important Mediators of Peritumoral Brain Edema

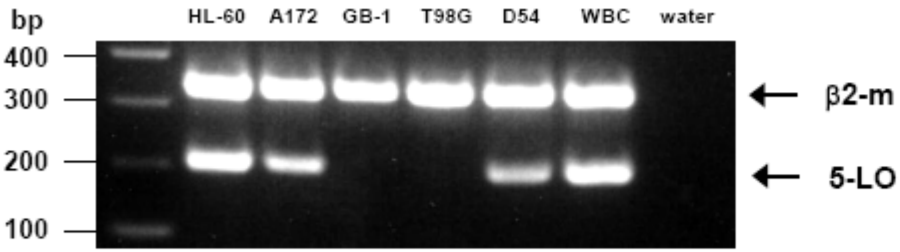


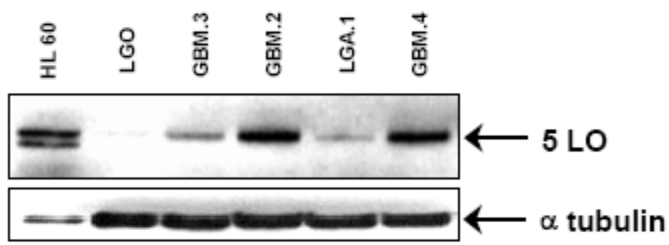
Increased Eicosanoid Metabolism in GBM

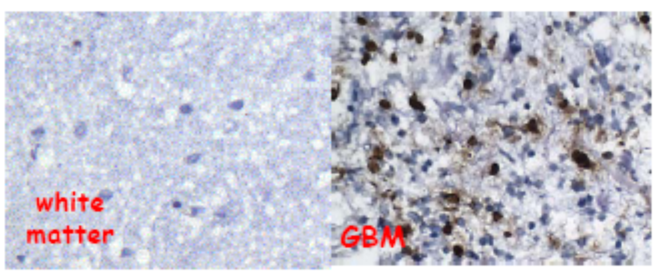


Nathoo N et al: 2004

5-LO is Overexpressed in High-grade Astrocytomas

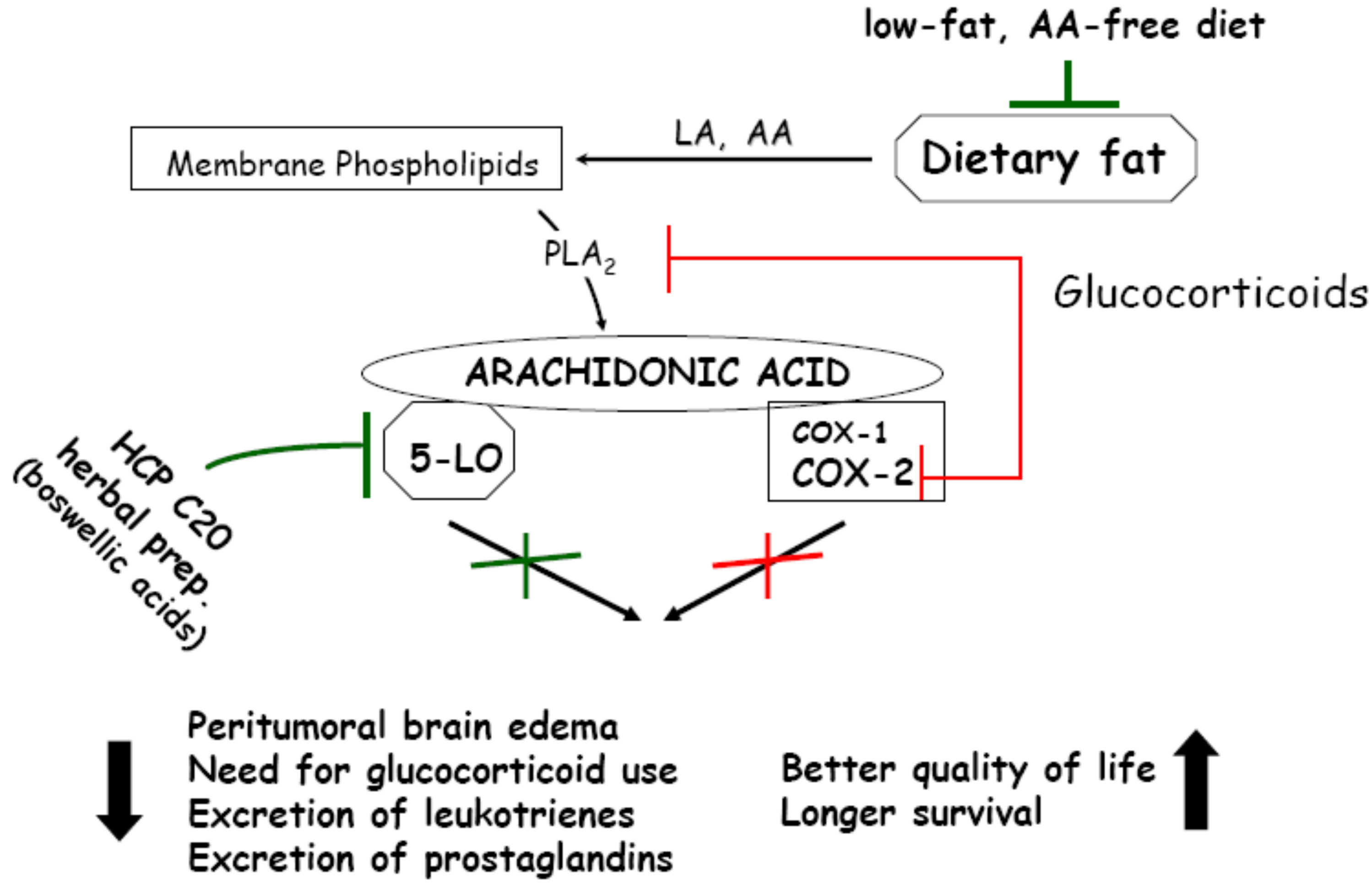






- Patients with astrocytomas whose tumors expressed 5-LO protein were:
  - significantly older
  - had lower pre-op Karnofsky Performance Status (KPS)
  - shorter survival

Nathoo N et al., in press



low-fat, AA-free diet
LA, AA
Membrane Phospholipids
Dietary fat
PLA2
Glucocorticoids
ARACHIDONIC ACID
5-LO
COX-1
COX-2
HCP C20
herbal prep.
(boswellic acids)
Peritumoral brain edema
Need for glucocorticoid use
Excretion of leukotrienes
Excretion of prostaglandins
Better quality of life
Longer survival

Diabetes Mellitus

- Cardiovascular diseases are the leading causes of death in individuals with diabetes
- Hypertriglyceridemia (fasting serum TG of 200 mg/dl or higher) is a common lipid abnormality in individuals with Type 2 diabetes
- A number of randomized controlled trials have found that fish oil supplementation significantly lowers serum triglyceride levels in diabetic individuals

Diabetes Mellitus

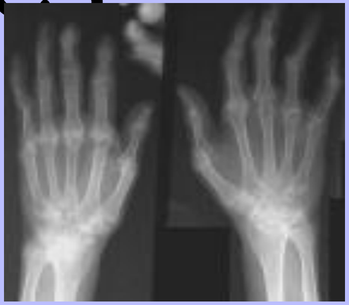
- But, few control trials have examined the effect of fish oil supplementation on cardiovascular disease outcomes in diabetics

- One prospective study, following 5103 women diagnosed with type 2 DM but free of cardiovascular disease at the start of the study, found decreased risks

- Those with higher fish intakes were associated with significantly decreased risks of CHD over the 16 years that the study lasted for, suggesting that increasing EPA and DHA levels may be beneficial to diabetic individuals, especially those with elevated serum triglycerides

Inflammatory Diseases

Rheumatoid arthritis

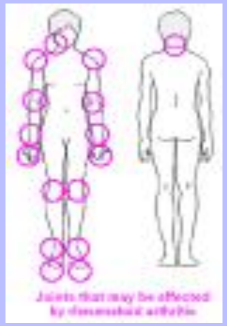


- Rheumatoid arthritis is the most common systemic inflammatory rheumatic (joint) disease
- Studies have been conducted to determine the effects of omega-3 fatty acids on rheumatoid arthritis
- Clinical benefits were observed at a minimum dose of 3 g/day of EPA + DHA, and were not apparent until at least 12 weeks of supplementation

Inflammatory Diseases

Rheumatoid arthritis

- Some investigators report that patients taking omega-3 fatty acid supplementation were able to <u>lower</u> their doses of nonsteroidal anti-inflammatory drugs (NSAIDS), but not all findings on this issue were consistent



Inflammatory Bowel Disease

Ulcerative colitis and Crohn's Disease

- Clinical trial results were less consistent with inflammatory bowel diseases than in patients with rheumatoid arthritis

- A significantly higher proportion of Crohn's disease patients supplemented with 2.7 g/day of EPA + DHA remained in remission over a one-year period than those given placebo

Ileocecal region →

Inflammatory Bowel Disease
Ulcerative colitis and Crohn's Disease

- In 3 randomized controlled trials of EPA + DHA supplementation in Ulcerative colitis patients, significant improvements were reported in at least one outcome measure, including decreased corticosteroid use, decreased production of inflammatory mediators, and improvements in disease activity scores, histology scores, and weight gain

Crohn's disease

Ulcerative Colitis

Asthma

- Although there is some evidence that omega-3 fatty acid supplementation can decrease the production of inflammatory mediators in asthmatic patients, evidence that omega-3 fatty acid supplementation decreases the clinical severity of asthma in controlled trials has been inconsistent

Major Depression

And Bipolar Disorder

- Several small studies have found omega-3 fatty acid levels to be lower in the plasma and fat of individuals suffering from depression compared to controls
- In one study conducted, for 30 individuals, with bipolar disorder, consuming large amounts of EPA (6.2 g/d) and DHA (3.4 g/d), they had a significantly longer period of remission than those on an olive oil placebo over a 4 month period
- Patients who took the EPA + DHA supplement also experienced less depression than those who took the placebo

Major Depression

And Bipolar Disorder

- Although these very limited pilot studies produce somewhat optimistic results, larger and long-term randomized trial are needed to determine the efficacy of marine-derived omega-3 fatty acid supplementation on major depression

Schizophrenia

- Schizophrenia is a chronic disabling brain disorder that affects approximately 1% of the population

- A pilot study in 45 schizophrenic patients found that the addition of 2 g/day of EPA to standard antipsychotic therapy was superior to the addition of a 2 g/day to DHA or a placebo in decreasing residual symptoms

- Although limited evidence does suggest that EPA supplementation may be a useful adjunct to antipsychotic therapy in schizophrenic patients, larger long-term studies addressing clinically relevant outcomes are needed

Physiological Effects of 20 & 22-Carbon N3-PUFA.

• Plasma Lipids:	Lowers triglycerides
• Liver:	Suppresses lipogenesis Increases fatty acid oxidation
• Heart:	Anti-arrhythmia
• Skeletal Muscle:	Improves insulin sensitivity
• Immune:	Anti-inflammatory
• Retina:	Enhances visual acuity
• CNS:	Neural Development Cognitive functions

Dietary omega-3 Fatty acids as possible modifiers of morbidity

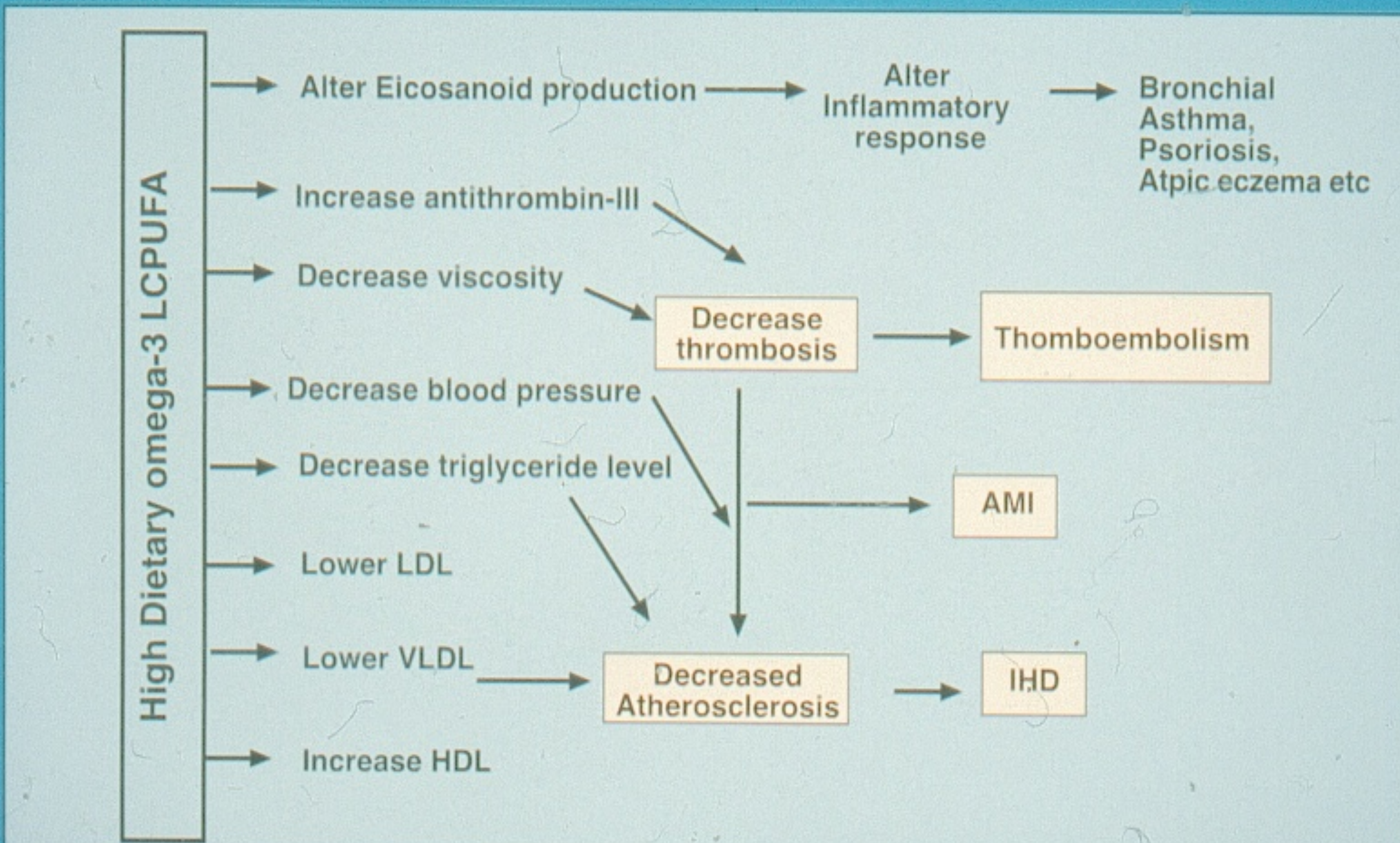


TABLE 1

Ethnic differences in fatty acid concentrations in thrombocyte phospholipids and percentage of all deaths from cardiovascular disease[1]

	Europe and United States	Japan	Greenland Eskimos
		%	
Arachidonic acid (20:4n−6)	26	21	8.3
Eicosapentaenoic acid (20:5n−3)	0.5	1.6	8.0
n−6:n−3	50	12	1
Mortality from cardiovascular disease	45	12	7

[1] Data modified from reference 33.

Changes in consumption of n-3 and n-6 fatty acids in the past

Sources of n-6/n-3 fatty acids	Years	Ratio
n-6 to n-3 ratio (Vegetables)	BC	1:1
n-6 to n-3 ratio (Vegetables)	>1900	10:1
n-6 to n-3 ratio (Fish)	>1900	20:1

Adapted from Simopoulos, Am. J. Clin. Nutr. 54, 438-463, 1991

Appropriate balance between dietary n-6 and n-3 fatty Acids are required to produce not only to produce membrane function, but also for eicosanoid production and gene expression for cell function

Recommendations

For optimum benefit, the omega 3 and omega 6 ratio Should be between ¼ and 1/10 , preferably around 1/5.

At the present moment they recommend a regular Omega 3 LCPUFA intake of 0.9 -1 gm per day

PUFA GUIDELINES

Source	N-3/N-6 Ratio	N-3 recommendn	EPA/DHA
Nordic Nutrition		0.5% (1-2 g/day)	
British Nutrition Fnd	1:6		0.5% (1.1g/day)
National Nutrition Council, NO		0.5% (1-2 g/day)	
FDA			1 g/day)
EU	1:4.5 -1.5:6	0.5% (1-2 g/day)	

Dietary intakes (% of energy) of total fat and fatty acid clusters in the Nordic countries in 1997-2002 according to national food consumption surveys.

	Denmak	Finland	Iceland	Norway	Sweden
Years	*2000-2002*	2002	*2002*	*1997*	1997-98
Total fat	*33*	33.6	*35.3*	*31*	34
SFA	*14.3*	14.0	*14.7*	*12.1*	14
TFA	*1.2*	0.5	*1.4*	*<1*	1
MUFA	*11.5*	11.2	*11.2*	*10.8*	12
PUFA	*4.7*	5.1	*4.7*	*5.4*	4.5
n-6/n-3	*4.2*	4.0	*3*	*5.5*	5

Plant Sources of Omega-3 Fatty Acids

Plant Sources of Omega-3 Fatty Acids

Food (serving size)	Omega-3 (g)	Omega-6 (g)
	6.6	**1.6**
Flax seed oil, 1 Tbsp.	**1.6**	**3.2**
Canola oil, 1 Tbsp.	**1.4**	**7.6**
Walnut oil, 1 Tbsp.	**1.0**	**7.0**
Soy oil, 1 Tbsp.		
Nuts and Seeds	**3.2**	**0.8**
Flax seeds, ground, 2 Tbsp.	**1.0**	**5.4**
Walnuts (English), 2 Tbsp.		
Vegetables, Fruits, and Legumes	**1.1**	**7.8**
Soybeans, cooked, 1 cup	**0.7**	**5.0**
Tofu, firm, ½ cup	**0.4**	**2.9**
Tofu, medium, ½ cup	**0.4**	**2.9**
Soy milk, 1 cup	**0.2**	**0.2**
Berries, 1 cup	**0.2**	**0.2**
Peas, ½ cup	**0.05**	**0.05**
Legumes, ½ cup	**0.1**	**0.03**
Grains		
Oat germ, 2 Tbsp.		
Wheat germ, 2 Tbsp.	**0.2**	**1.6**
	0.1	**0.8**

n-3 fatty acids content of common animal source

Source	EPA+DHA (g/100g)
Mackerel	2.5
Salmon	1.8
Herring	1.6
Tuna	1.6
Pork	0.7
Lamb (leg)	0 .5
Beef	0.25

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