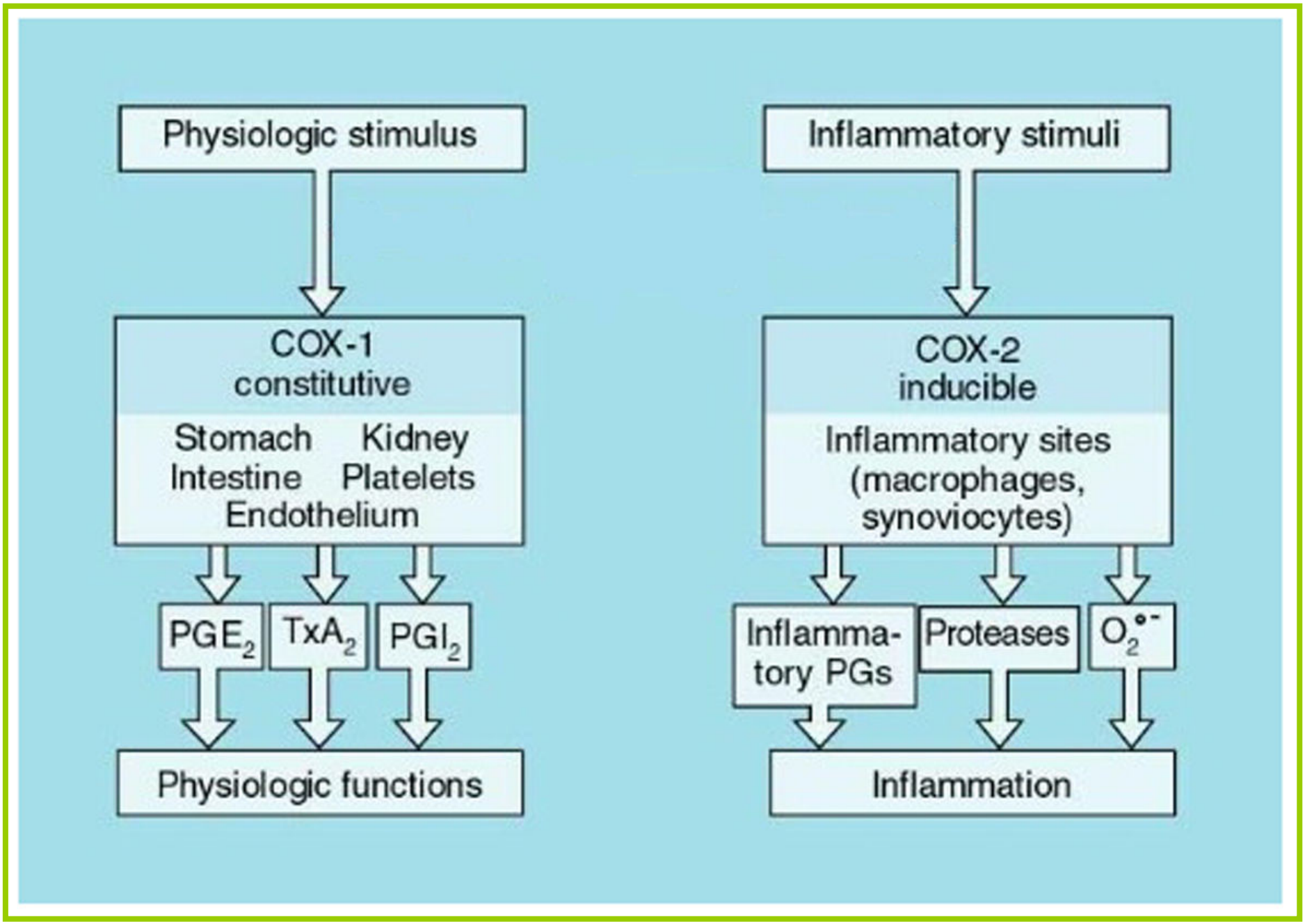
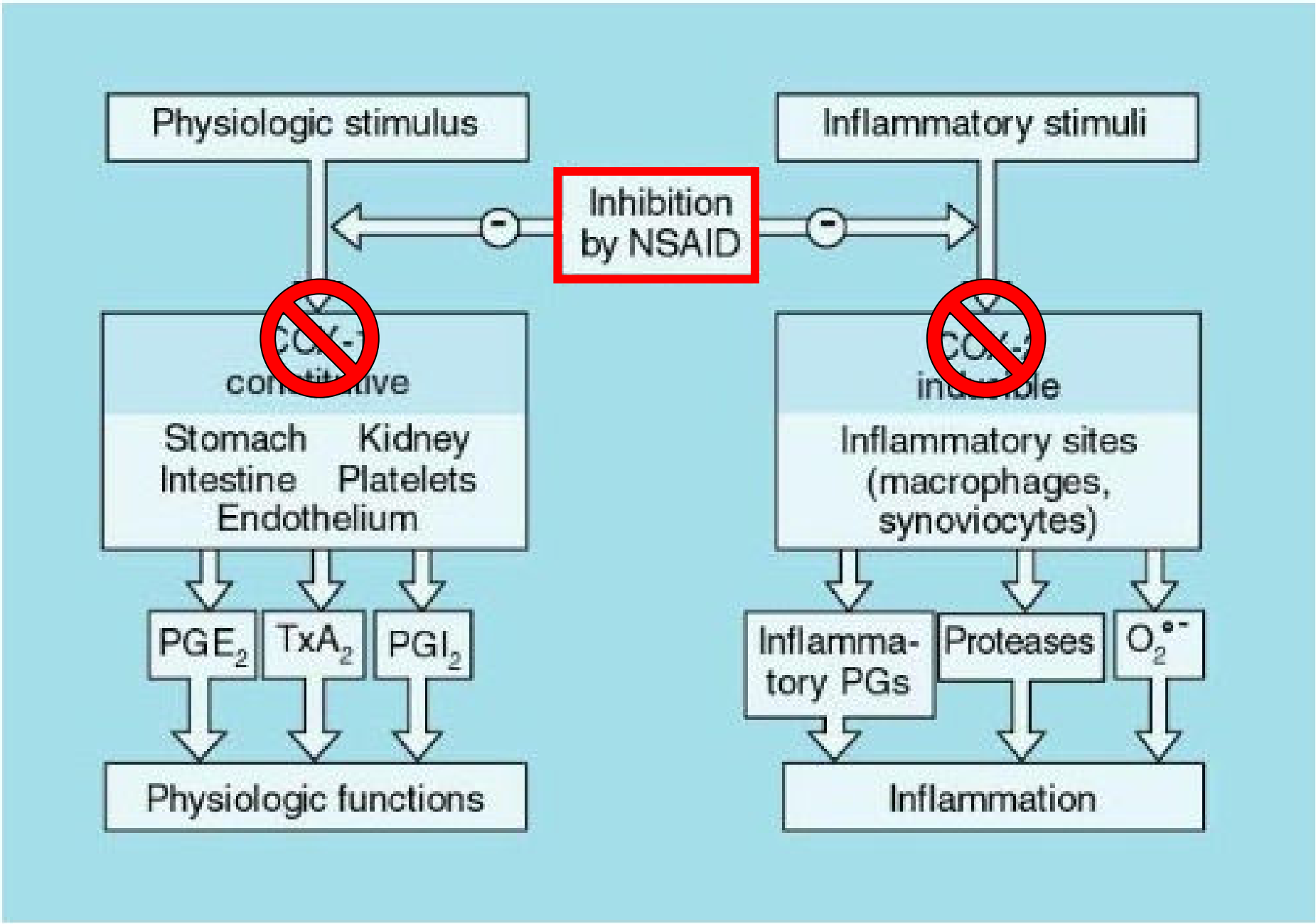
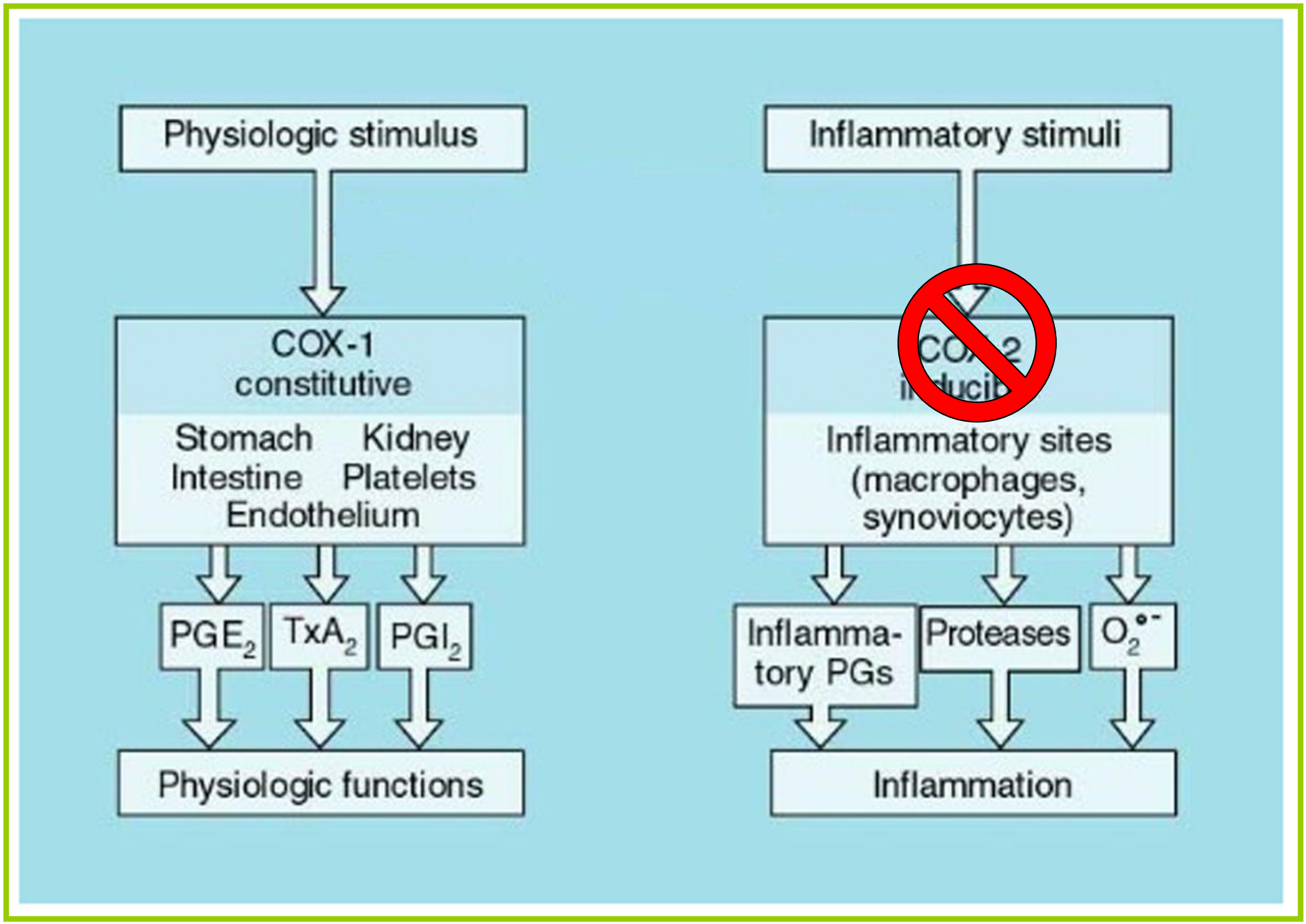
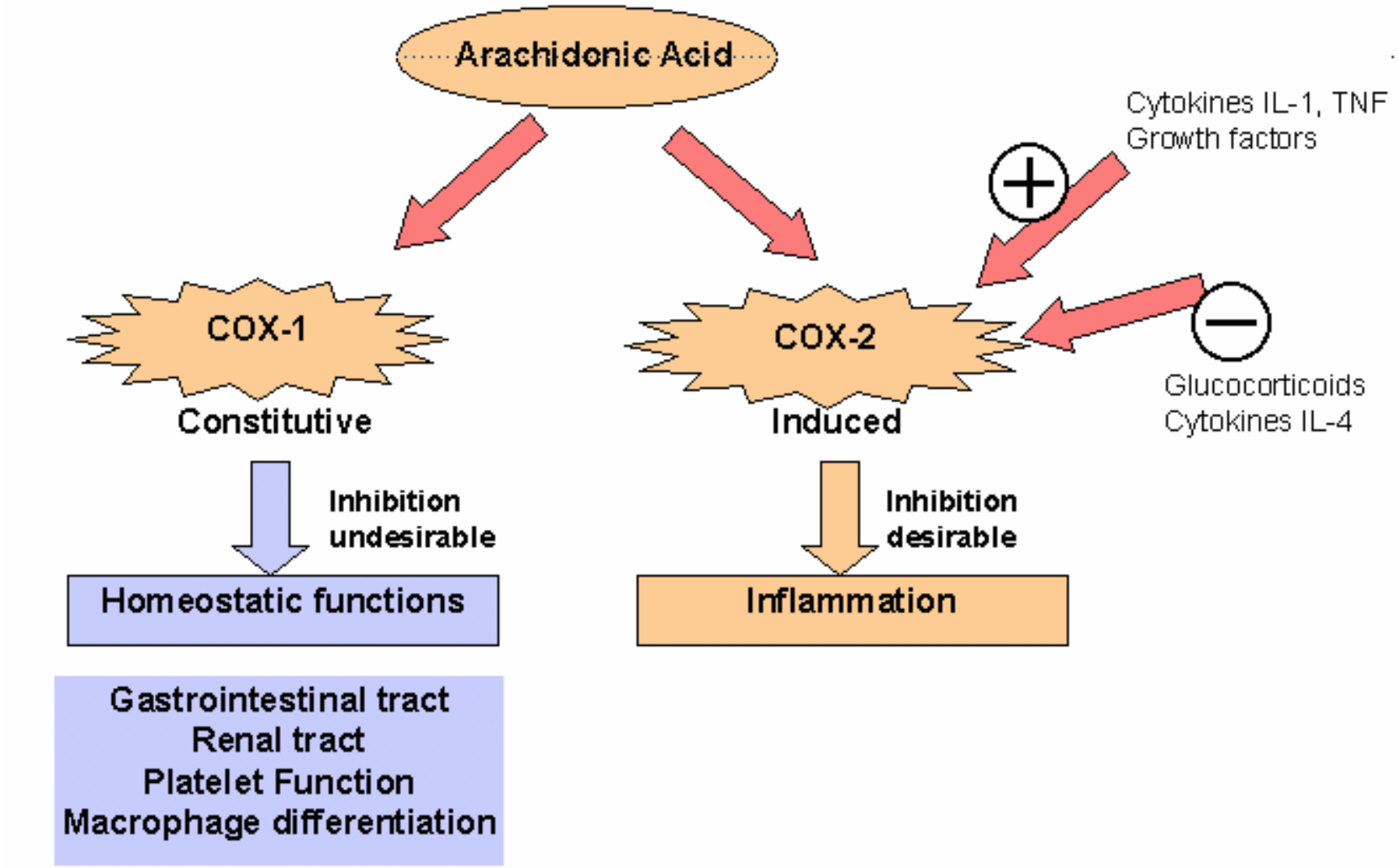
COX-2
(cyclooxygenase-2)

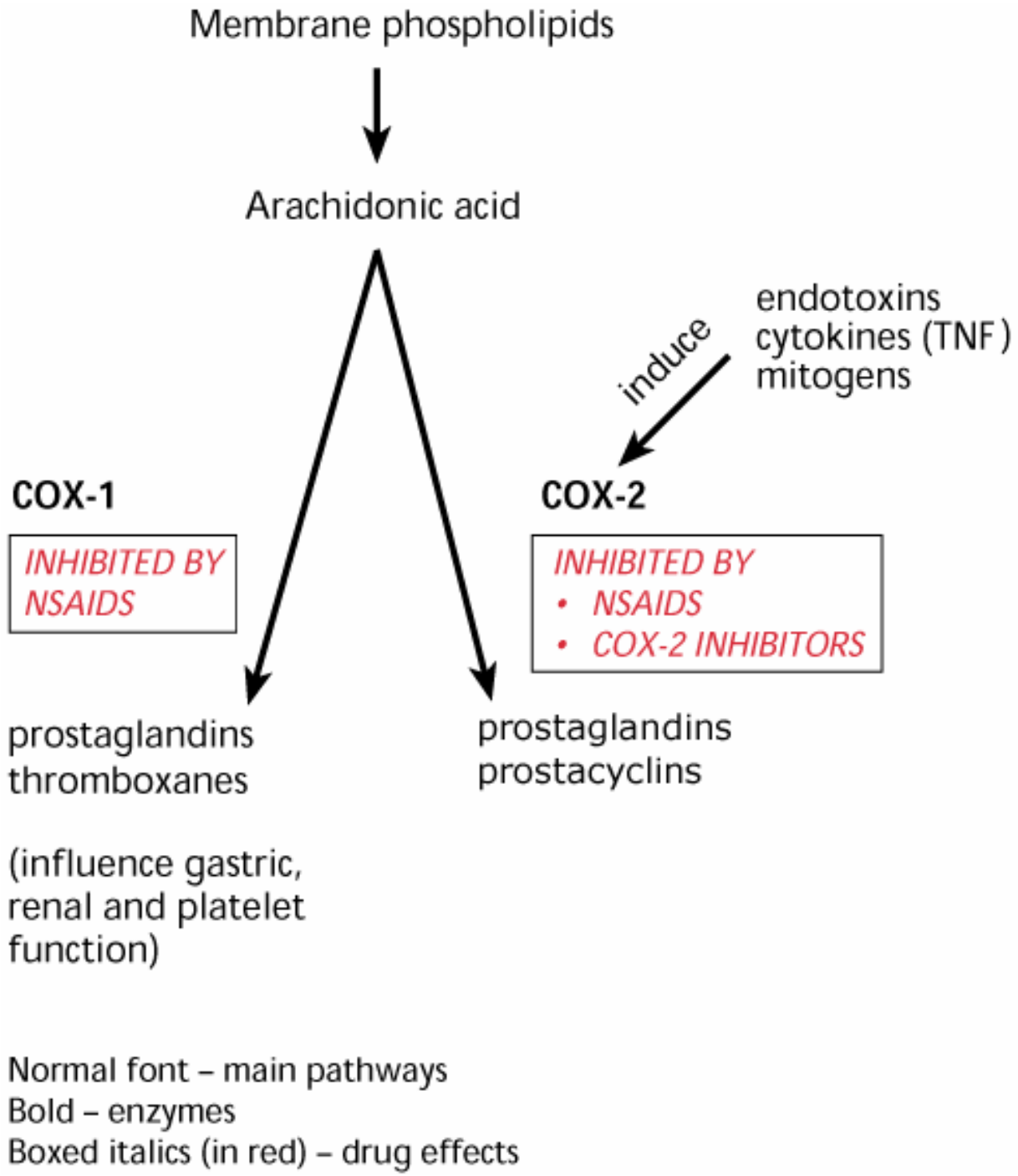
울산의대 한기훈


Physiologic stimulus
COX-1
constitutive
Stomach
Kidney
Intestine
Platelets
Endothelium
PGE2
TxA2
PGI2
Physiologic functions
Inflammatory stimuli
COX-2
inducible
Inflammatory sites
(macrophages,
synoviocytes)
Inflamma-
tory PGs
Proteases
O2°-
Inflammation


Physiologic stimulus
Inflammatory stimuli
Inhibition by NSAID
Stomach
Kidney
Intestine
Platelets
Endothelium
Inflammatory sites (macrophages, synoviocytes)
PGE2
TxA2
PGI2
Inflamma-tory PGs
Proteases
O2•-
Physiologic functions
Inflammation


Physiologic stimulus
COX-1
constitutive
Stomach
Kidney
Intestine
Platelets
Endothelium
PGE2
TxA2
PGI2
Physiologic functions
Inflammatory stimuli
Inflammatory sites
(macrophages,
synoviocytes)
Inflamma-
tory PGs
Proteases
O2°-
Inflammation


Arachidonic Acid
Cytokines IL-1, TNF
Growth factors
COX-1
COX-2
Glucocorticoids
Cytokines IL-4
Constitutive
Induced
Inhibition
undesirable
Inhibition
desirable
Homeostatic functions
Inflammation
Gastrointestinal tract
Renal tract
Platelet Function
Macrophage differentiation



Normal font – main pathways
Bold – enzymes
Boxed italics (in red) – drug effects

20-carbon arachidonic acid
("eicos" is from the Greek word eikosi, the number 20)

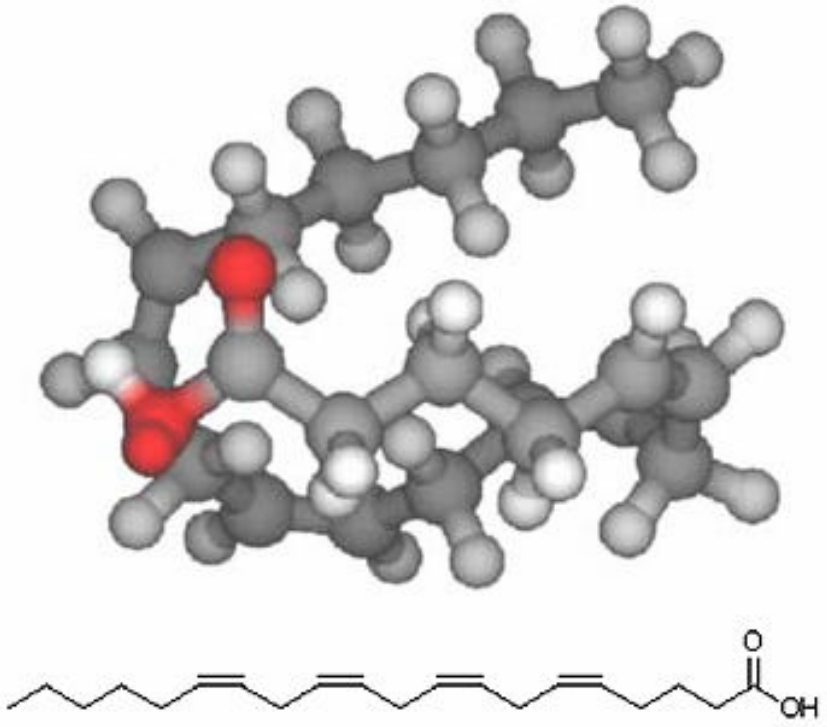
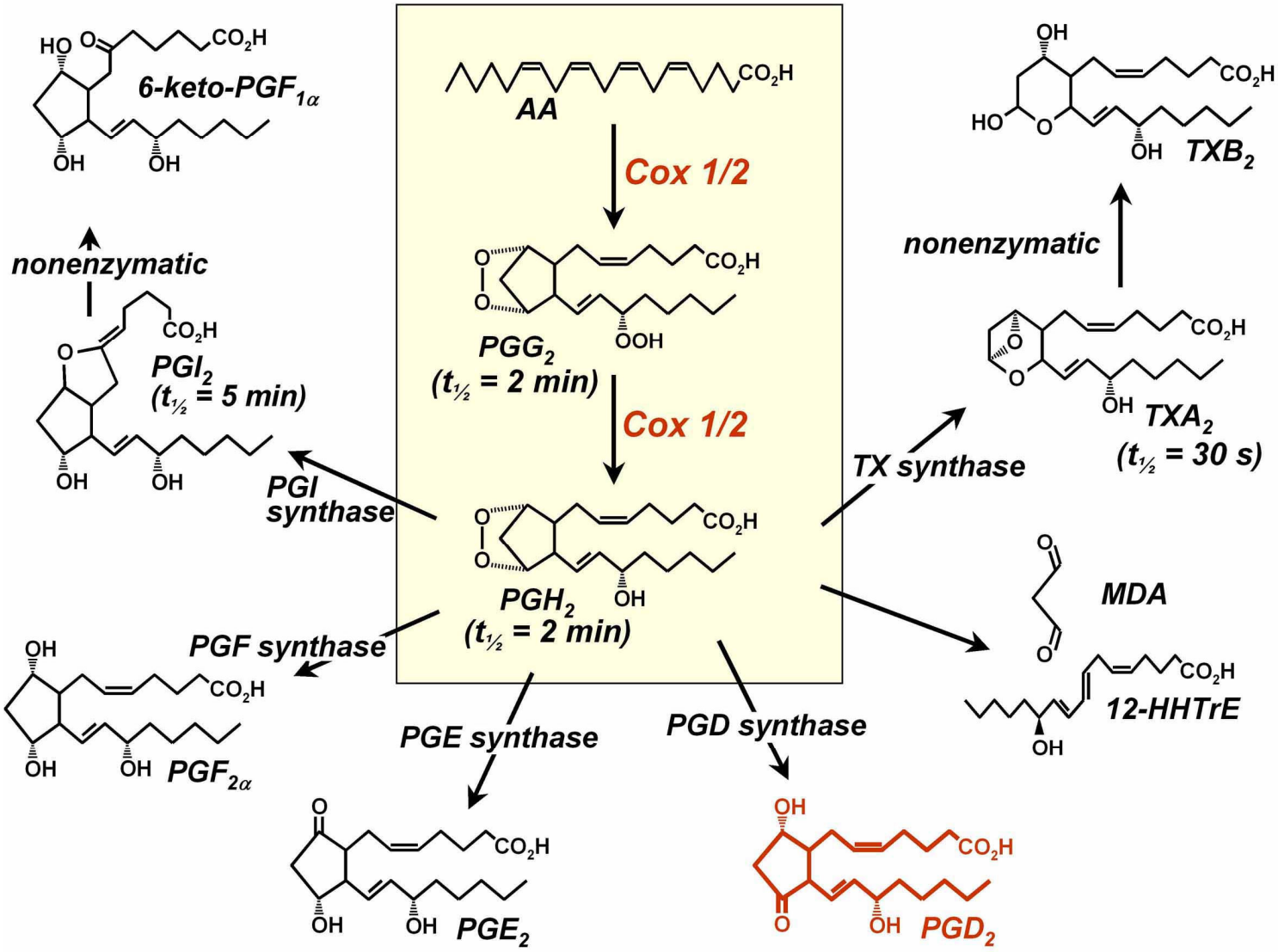
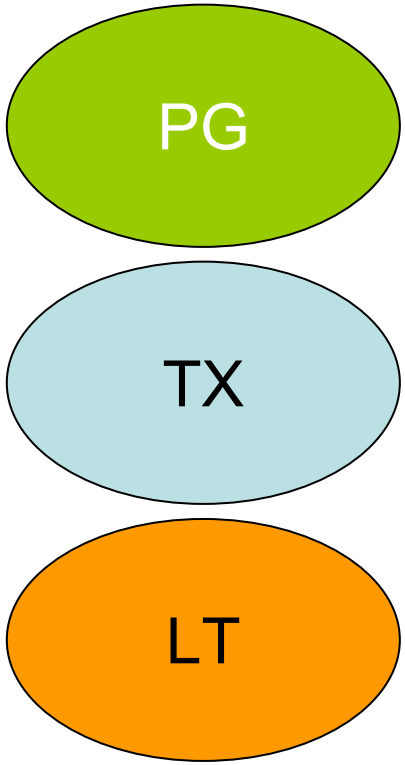


Figure 1: Arachidonic acid: three dimensional representation, top; chemical structure diagram, bottom. The molecule is a long chain of CH and CH2 units, terminated by the acid unit (COOH). There are 20 carbons in a linear chain that is folded as indicated in the 3-D representation.

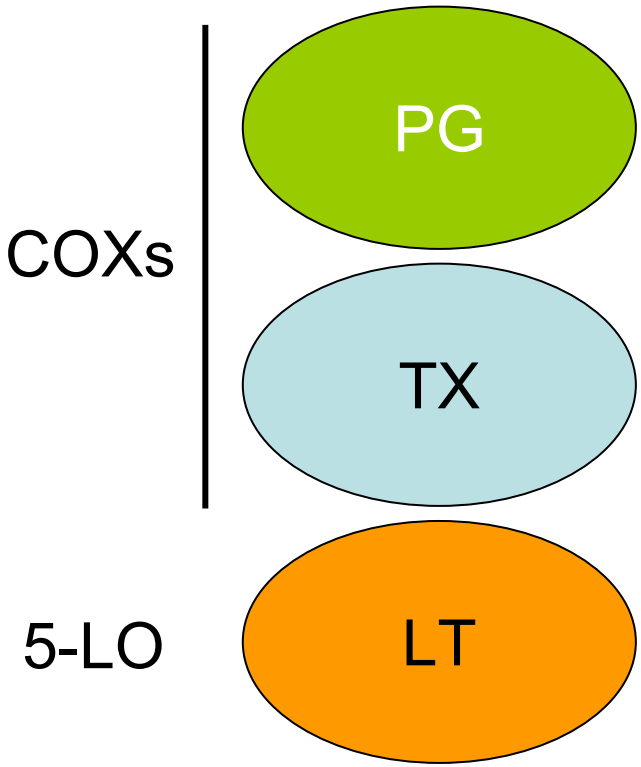
Biosynthesis of prostaglandins by cyclooxygenases



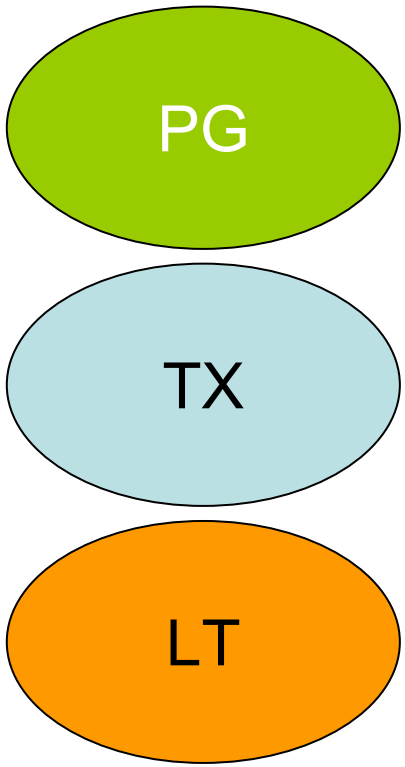
20-carbon acid



20-carbon acid



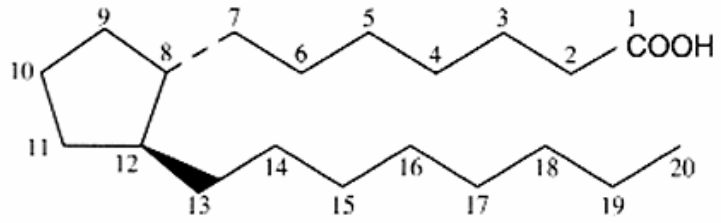
20-carbon acid



Platelet aggregation
vasodilation/constriction

Platelet aggregation
vasoconstriction

Secretion of cytokines (IFN-gamma, IL-1,2)
Immune reaction



Prostanoic Acid

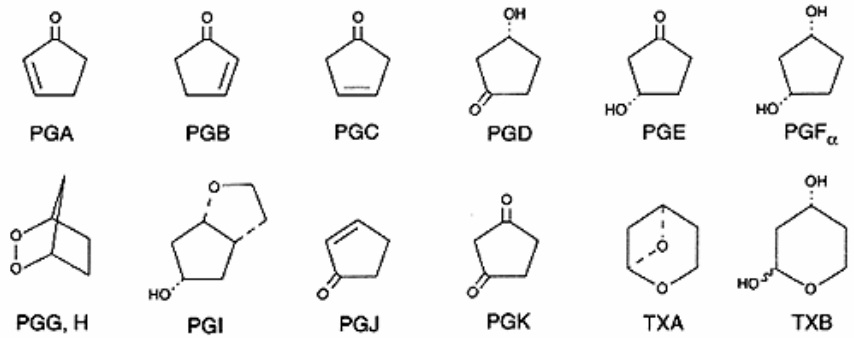


Figure 2: Prostaglandins and thromboxanes. Prostanoic acid is the basic prostanoid molecule, and the ring structure (top) varies to yield the different groups of prostaglandins and thromboxanes (bottom). These are all formed from arachidonic acid by the action of the COX enzymes.

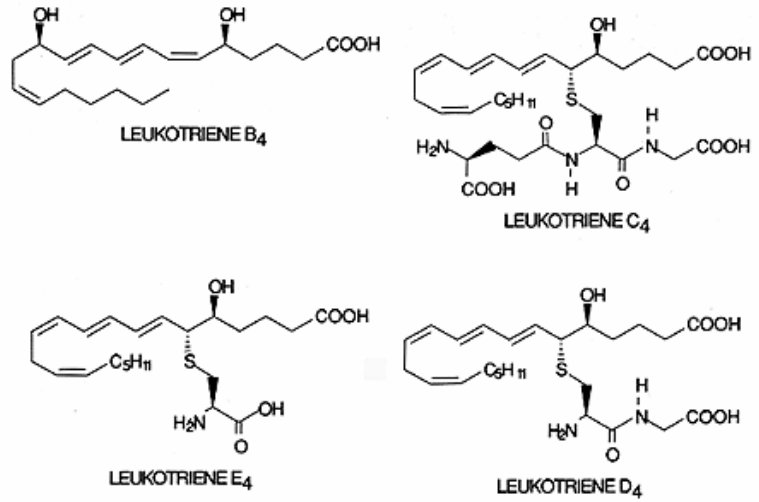


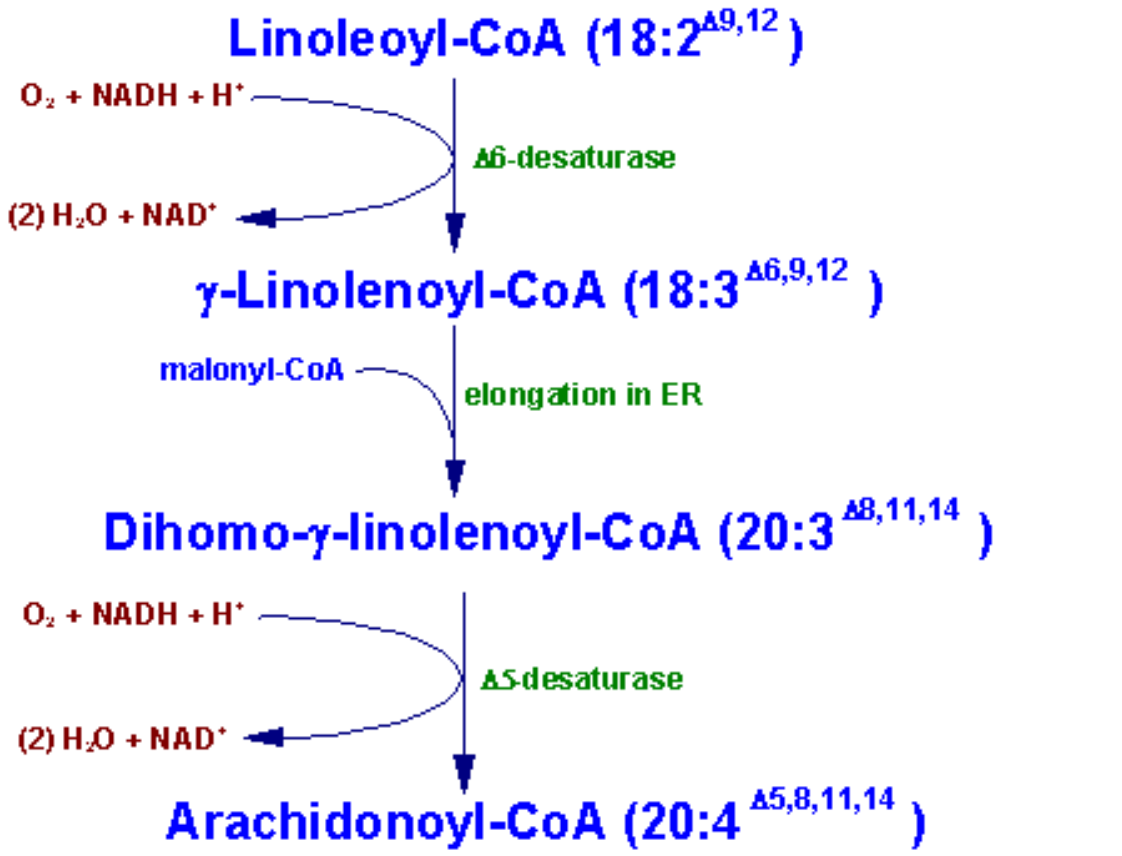
Figure 3: Leukotrienes; these are formed from arachidonic acid by action of the LOX enzymes.

Affected Part	Effects of Specific Prostanoids
Vascular smooth muscle	PGE_s & PGI_2 → smooth muscle dilation → vasodilation PGF_{2a} & TXA_2 → vasoconstriction
GI tract smooth muscle	PGI_2, PGF_2 & PGI_2 → smooth muscle contraction → cramps PGE → decreased gastric acid secretion & ulceration
Lung smooth muscle	PGI_2 & PGE_2 → vasodilation & constriction, respectively TXA_2 is a vasoconstrictor & bronchoconstrictor PGFs contract while PGE_s relax respiratory smooth muscle
Platelets	PGE_1 & PGI_2 → decreased platelet aggregation TXA_2 → increased platelet aggregation
Reproductive organs	PGE_2 & PGF_{2a} → uterine contractions initiate & stimulate labor; menstrual pain
Kidneys	PGE regulates arteriolar tone, compensatory vasodilatation, maintains normal blood flow, increased glomerular filtration rate
Inflammatory processes	fever: PGE_s act on thermoregulatory center in brain → increased body temperature pain: PGs → sensitize pain receptors to stimulation → increased pain PGs promote vasodilation & increased vascular permeability

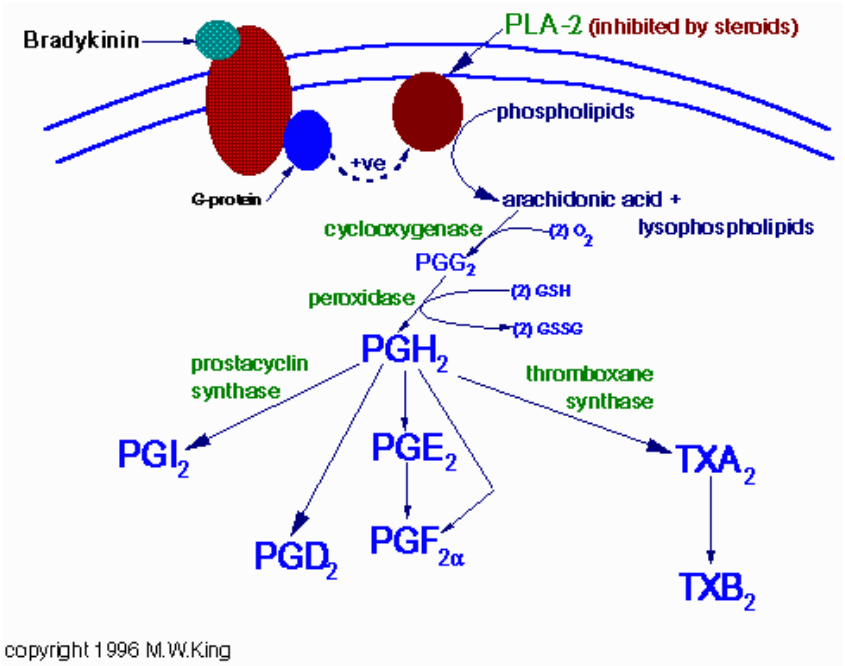
Eicosanoid	Major Site(s) of Synthesis	Major Biological Activities
PGD_2	mast cells	inhibits platelet and leukocyte aggregation, decreases T-cell proliferation and lymphocyte migration and secretion of IL-1&ALPHA; and IL-2; induces vasodilation and production of cAMP
PGE_2	kidney, spleen, heart	increases vasodilation and cAMP production, enhancement of the effects of bradykinin and histamine, induction of uterine contractions and of platelet aggregation; decreases T-cell proliferation and lymphocyte migration and secretion of IL-1&ALPHA; and IL-2
PGF2α	kidney, spleen, heart	increases vasoconstriction, bronchoconstriction and smooth muscle contraction
PGH_2	many sites	a short-lived precursor to thromboxanes A_2 and B_2, induction of platelet aggregation and vasoconstriction
PGI_2	heart, vascular endothelial cells	inhibits platelet and leukocyte aggregation, decreases T-cell proliferation and lymphocyte migration and secretion of IL-1&ALPHA; and IL-2; induces vasodilation and production of cAMP
TXA_2	platelets	induces platelet aggregation, vasoconstriction, lymphocyte proliferation and bronchoconstriction
TXB_2	platelets	induces vasoconstriction
LTB_4	immune cells*	induces leukocyte chemotaxis and aggregation, vascular permeability, T-cell proliferation and secretion of INF-&gamma , IL-1 and IL-2
LTC_4	immune cells*	component of SRS-A**, induces vasodilation, vascular permeability and bronchoconstriction and secretion of INF-&gamma
LTD_4	immune cells*	predominant component of SRS-A, induces vasodilation, vascular permeability and bronchoconstriction and secretion of INF-&gamma
LTE_4	mast cells and basophils	component of SRS-A**, induces vasodilation and bronchoconstriction

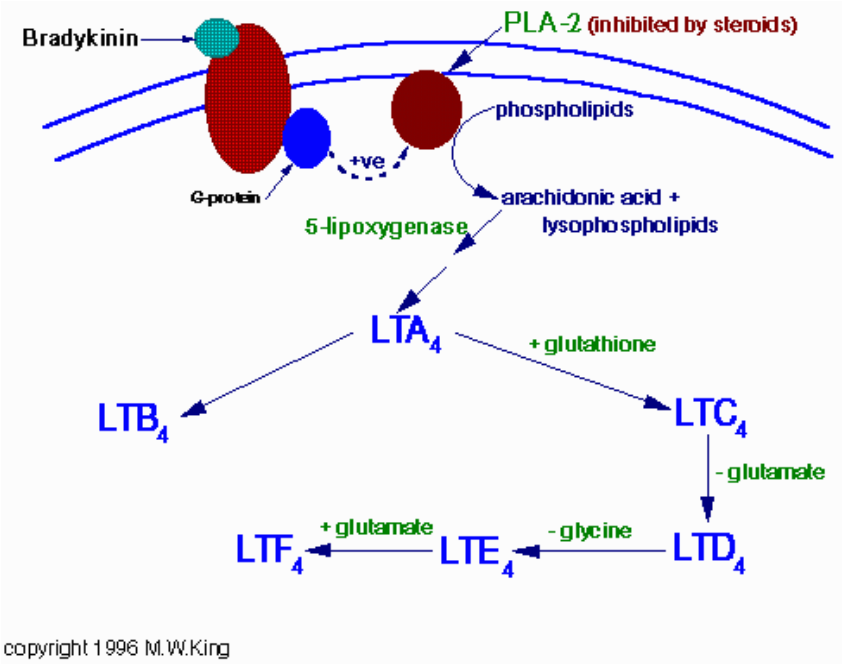
* mainly from immune cells, such as monocytes, basophils, alveolar macrophages, neutrophils, eosinophils, mast cells, epithelial cells;
** SRS-A = slow-reactive substance of anaphylaxis

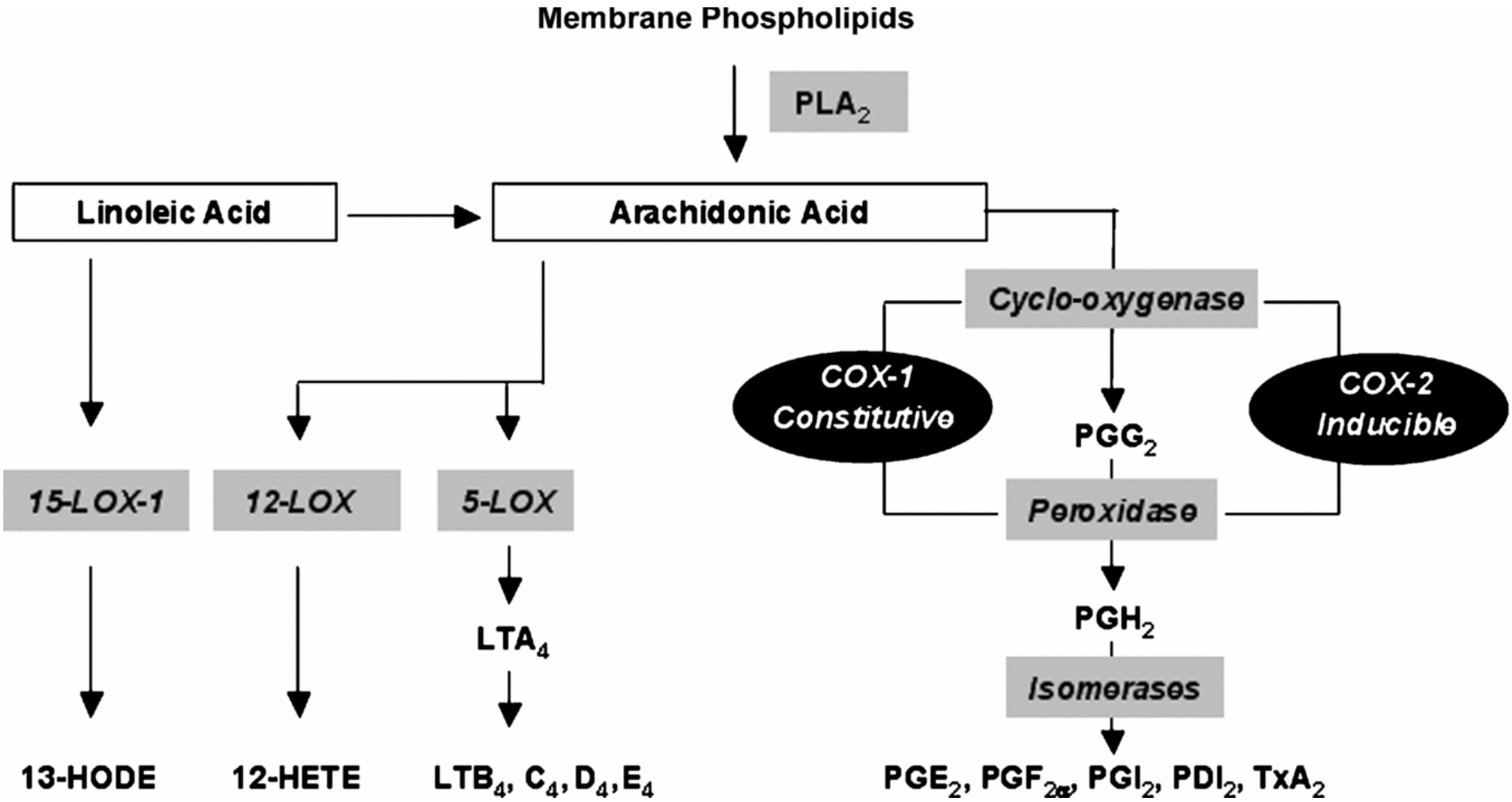
Phospholipid to AA



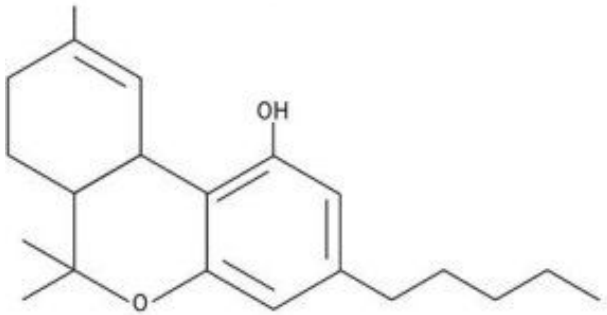
Phospholipid to AA by PLA2



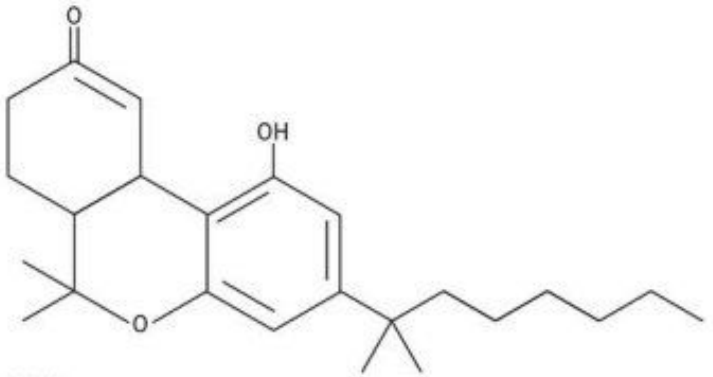



Membrane Phospholipids
PLA2
Linoleic Acid
Arachidonic Acid
Cyclo-oxygenase
COX-1
Constitutive
COX-2
Inducible
PGG2
Peroxidase
PGH2
Isomerases
15-LOX-1
12-LOX
5-LOX
LTA4
13-HODE
12-HETE
LTB4, C4, D4, E4
PGE2, PGF2α, PGI2, PDI2, TxA2

Cannabinoids currently licensed for clinical use

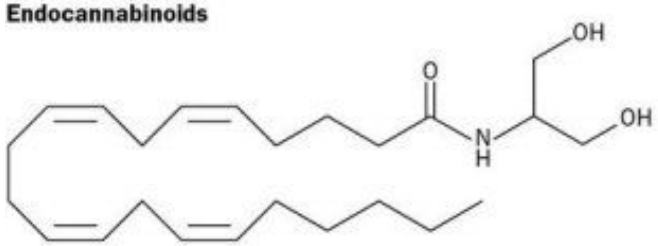


THC

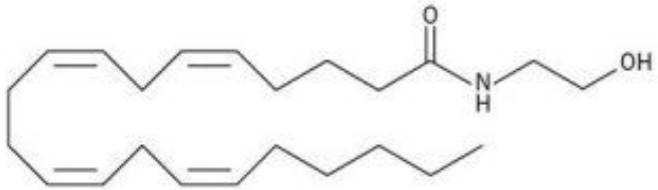


Nabilone

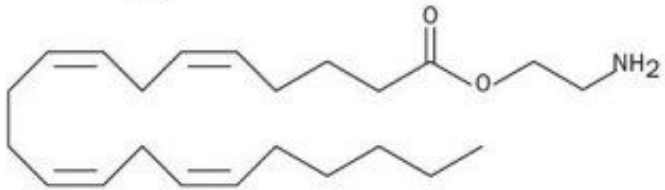
Endocannabinoids



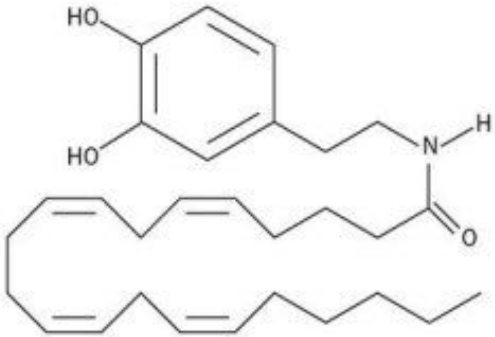
2-archidonoylglycerol



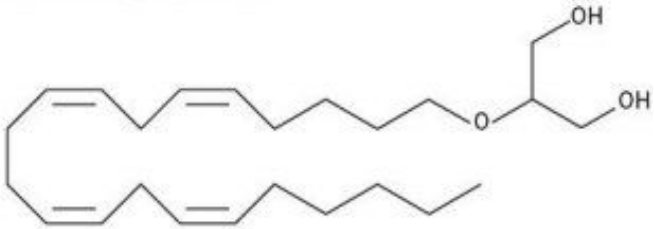
2-archidonoylglycerol



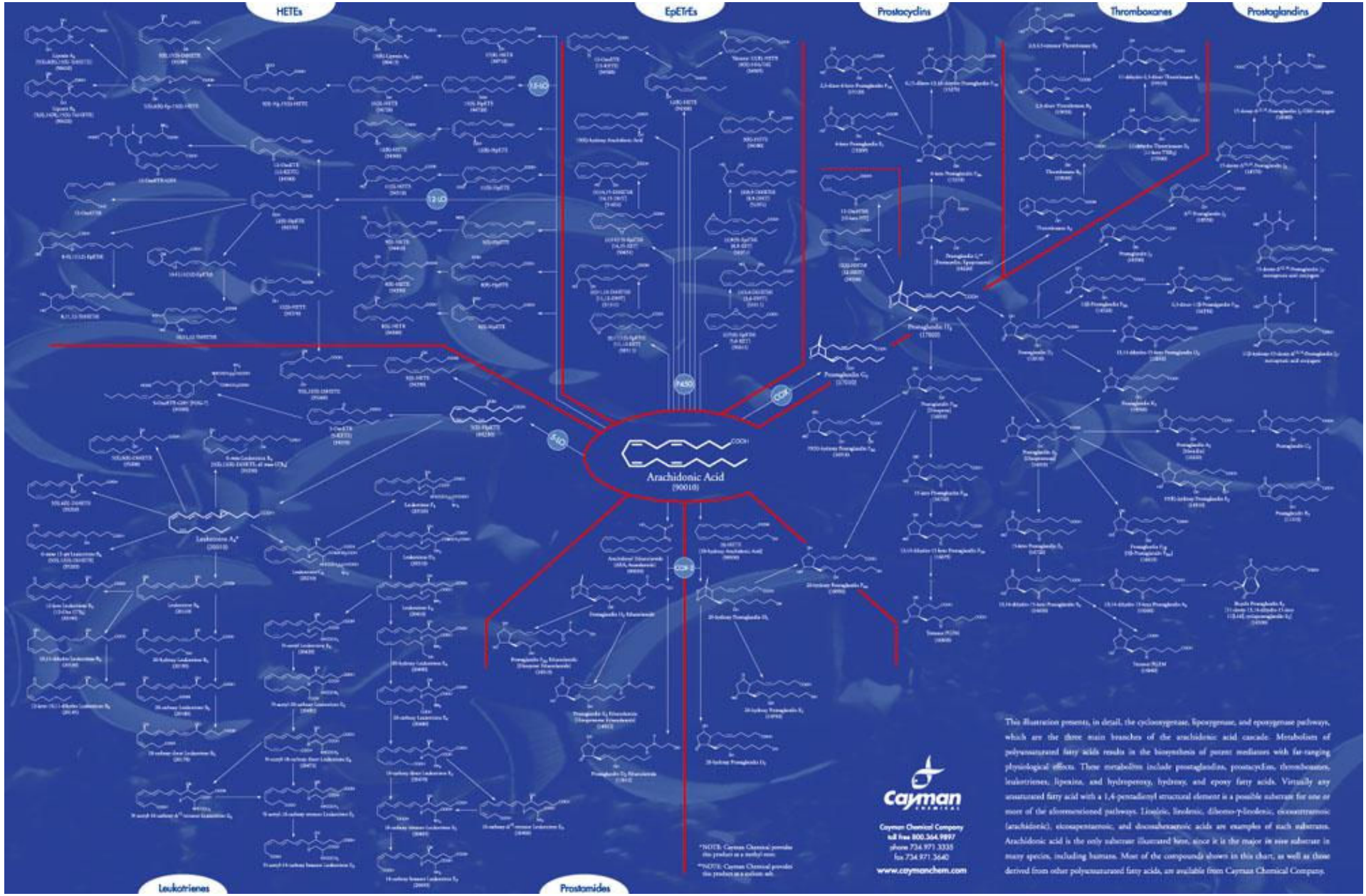
Virodhamine

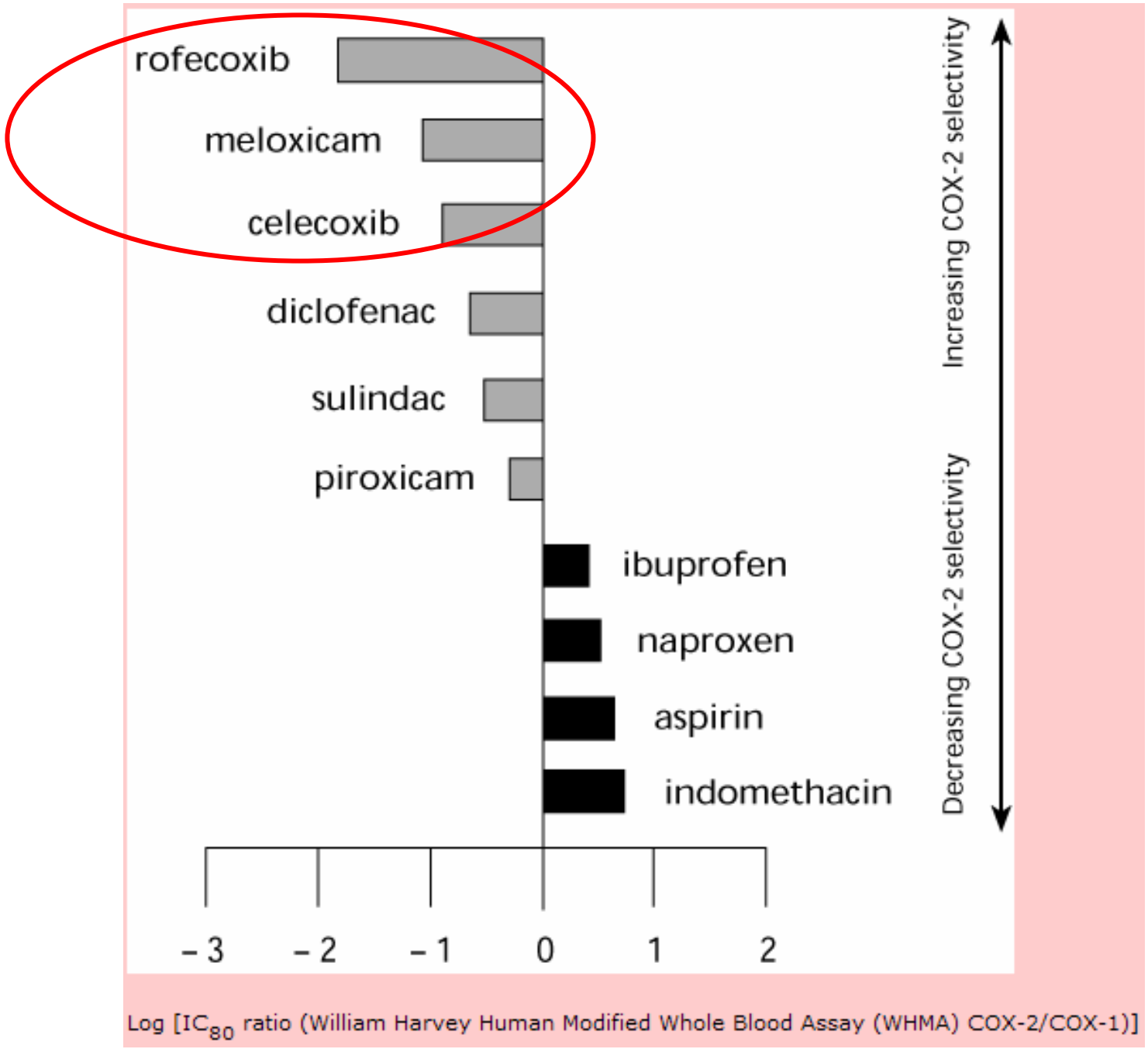


N-archidonoyldopamine



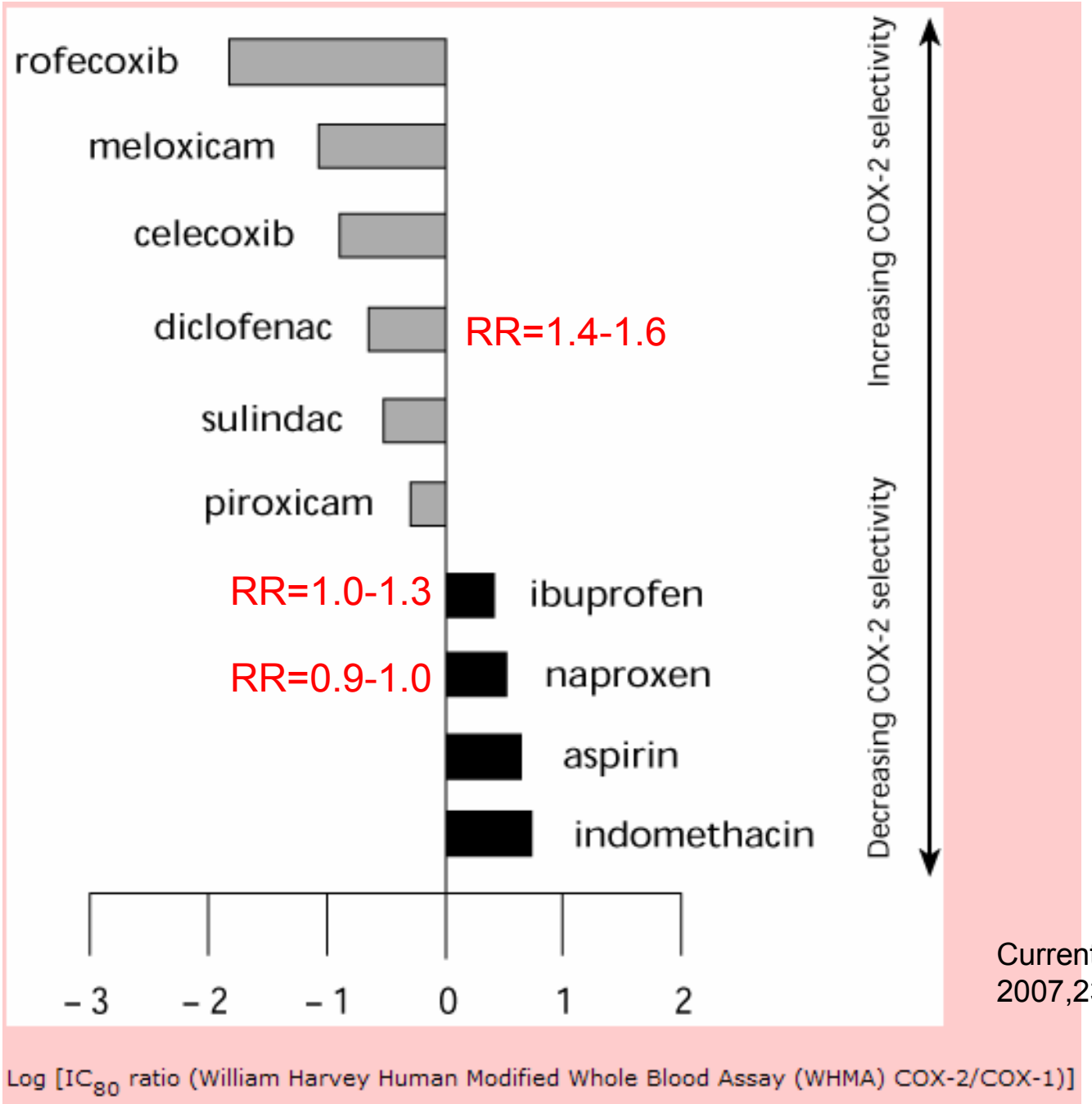
Noladin ether


HETEs
EpETrEs
Prostacyclins
Thromboxanes
Prostaglandins
Arachidonic Acid
(90010)
Leukotrienes
Prostamides
Cayman
Cayman Chemical Company
toll free 800.364.9897
phone 734.971.3335
fax 734.971.3640
www.caymanchem.com
This illustration presents, in detail, the cyclooxygenase, lipoxygenase, and epoxygenase pathways, which are the three main branches of the arachidonic acid cascade. Metabolism of polyunsaturated fatty acids results in the biosynthesis of potent mediators with far-ranging physiological effects. These metabolites include prostaglandins, prostacyclins, thromboxanes, leukotrienes, lipoxins, and hydroperoxy, hydroxy, and epoxy fatty acids. Virtually any unsaturated fatty acid with a 1,4-pentadienyl structural element is a possible substrate for one or more of the aforementioned pathways. Linoleic, linolenic, dihomo-γ-linolenic, eicosatetraenoic (arachidonic), eicosapentaenoic, and docosahexaenoic acids are examples of such substrates. Arachidonic acid is the only substrate illustrated here, since it is the major in vivo substrate in many species, including humans. Most of the compounds shown in this chart, as well as those derived from other polyunsaturated fatty acids, are available from Cayman Chemical Company.


rofecoxib
meloxicam
celecoxib
diclofenac
sulindac
piroxicam
ibuprofen
naproxen
aspirin
indomethacin
Increasing COX-2 selectivity
Decreasing COX-2 selectivity
– 3
– 2
– 1
0
1
2
Log [IC80 ratio (William Harvey Human Modified Whole Blood Assay (WHMA) COX-2/COX-1)]

Selective inhibition of COX-2

- 明
  - 선택적 염증반응, 신혈관생성, 세포증식 저해
  - 위장관 출혈 보호
  - 신기능 보호
- 暗
  - 혈전의 증가



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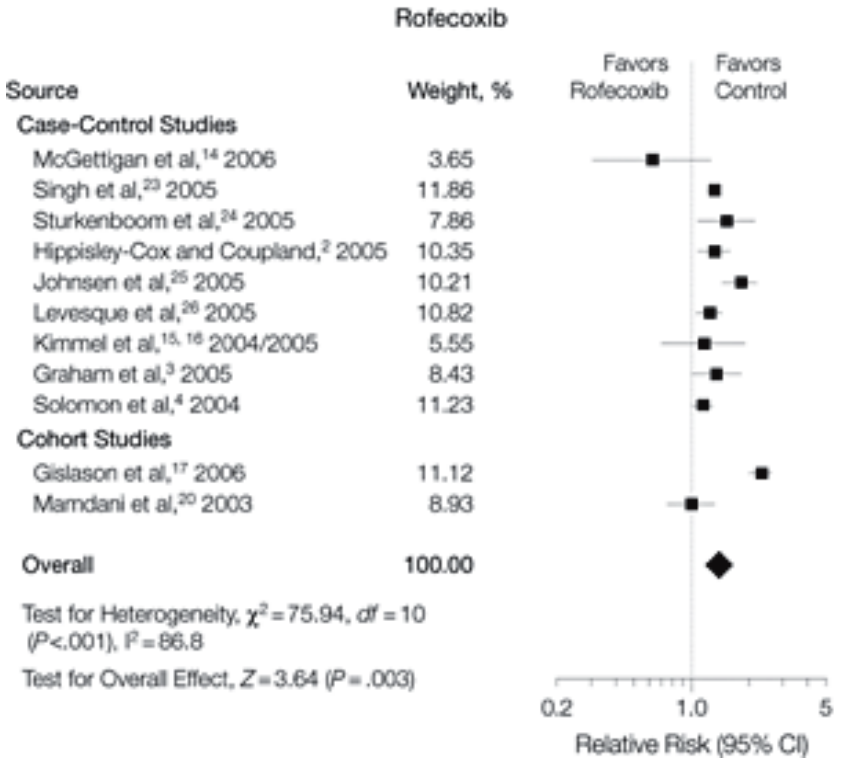
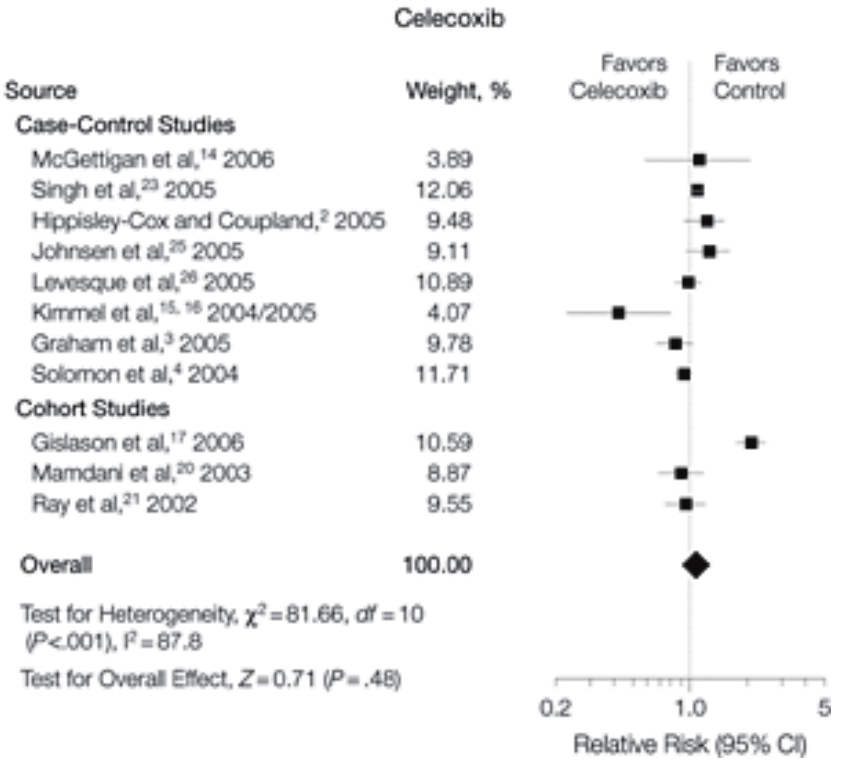
2007,23:617-24

Failure of COX-2 inhibition

- 위장관출혈 예방효과가 생각보다 좋지 않다
- 심혈관질환을 증가시킨다
- rofe~; VIGOR study, APPROVe trial
- cele~; Adenoma Prevention with Celecoxib trial
- cele~ (neutral) ; ADAT trial and other observational studies
- lumira and etori~; TARGET and MEDAL
- 초기 (1-3개월) 심혈관발생이 증가
- 용량의존적인듯 함
- 심혈관질환의 위험이 높은 그룹일 수록 호발
- 신기능 보호효과가 없다

Point Estimates and Summary Relative Risks for Cardiovascular Events With Rofecoxib and Celecoxib

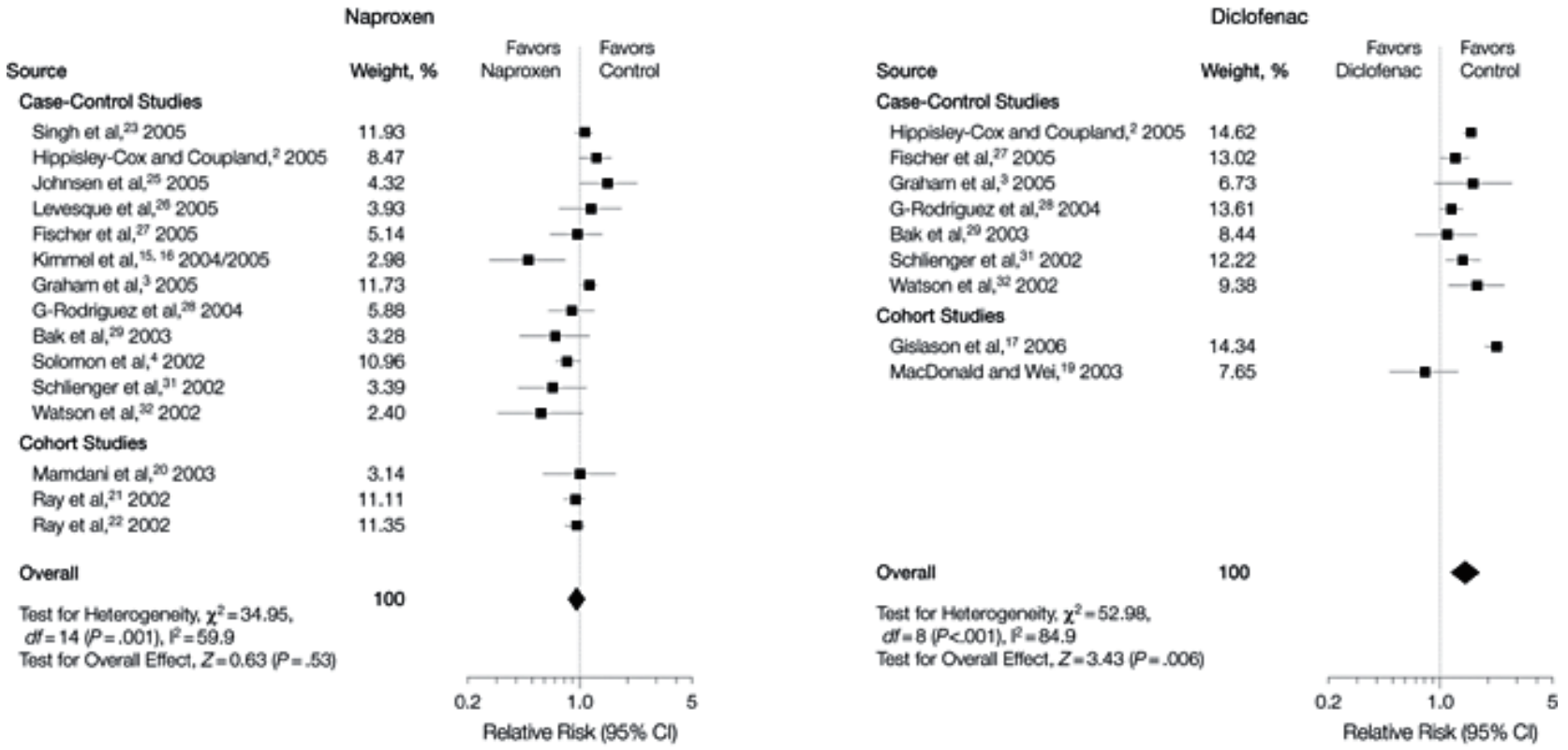




McGettigan, P. et al. JAMA 2006;296:1633-1644.

JAMA

Point Estimates and Summary Relative Risks for Cardiovascular Events With Naproxen and Diclofenac



McGettigan, P. et al. JAMA 2006;296:1633-1644.

JAMA

Results of Case-Control and Cohort Studies Reporting on Cardiovascular Risks With Cyclooxygenase 2 Inhibitors

Table 3. Results of Case-Control and Cohort Studies Reporting on Cardiovascular Risks With Cyclooxygenase 2 Inhibitors

Source	Relative Risk (95% Confidence Interval)				
	All Celecoxib	All Rofecoxib	Rofecoxib ≤25 mg/d	Rofecoxib >25 mg/d	Meloxicam
Case-control studies that reported on COX-2 inhibitors					
Hippisley-Cox and Coupland,[2] 2005	1.21 (0.96-1.54)	1.32 (1.09-1.61)	NR	NR	NR
Graham et al,[3] 2005	0.84 (0.67-1.04)	1.34 (0.98-1.82)	1.23 (0.98-1.71)	3.00 (1.09-8.31)	NR
Solomon et al,[4] 2004	0.93 (0.84-1.02)	1.14 (1.00-1.31)	1.21 (1.01-1.44)*	1.70 (1.07-2.71)†	NR
McGettigan et al,[14] 2006	1.11 (0.59-2.11)	0.63 (0.31-1.28)	NR	NR	NR
Kimmel et al,[15,16] 2004/5	0.43 (0.23-0.79)	1.16 (0.70-1.93)	NR	NR	NR
Singh et al,[23] 2005‡	1.09 (1.02-1.15)	1.32 (1.22-1.42)	NR	NR	1.37 (1.05-1.78)
Sturkenboom et al,[24] 2005‡	NR	1.52 (1.08-2.15)	NR	2.32 (1.2-4.4)§	NR
Johnsen et al,[25] 2005	1.25 (0.97-1.62)	1.80 (1.47-2.21)	NR	NR	NR
Levesque et al,[26] 2005	0.99 (0.85-1.16)	1.24 (1.05-1.46)	1.2 (1.02-1.43)	1.73 (1.09-2.76)	1.06 (0.49-2.30)
Garcia Rodriguez et al,[28] 2004	NR	NR	NR	NR	0.97 (0.60-1.56)
Summary relative risk	1.01 (0.90-1.13)	1.31 (1.18-1.46)	1.21 (1.08-1.36)	1.89 (1.43-2.51)	1.25 (1.00-1.55)
Cohort studies that reported on COX-2 inhibitors					
Gislason et al,[17] 2006‖	2.06 (1.73-2.45)	2.29 (1.99-2.65)	2.17 (1.86-2.54)	3.31 (2.37-4.61)	NR
Mamdani et al,[20] 2003	0.90 (0.70-1.20)	1.0 (0.80-1.40)	NR	NR	NR
Ray et al,[21] 2002	0.96 (0.76-1.21)	NR	1.03 (0.78-1.35)	1.70 (0.98-2.95)	NR
Summary relative risk	1.22 (0.69-2.16)	1.53 (0.68-3.44)	1.51 (0.73-3.13)	2.46 (1.29-4.71)	NR
Case-control and cohort studies combined risk estimates	1.06 (0.91-1.23)	1.35 (1.15-1.59)	1.33 (1.00-1.79)	2.19 (1.64-2.91)	1.25 (1.00-1.55)

Abbreviations: COX, cyclooxygenase; NR, not reported.
*vs Celecoxib ≤ 200 mg/d; author's reported risk was similar compared with no current nonsteroidal anti-inflammatory drug.
†vs Celecoxib > 200 mg/d; author's reported risk was similar compared with no current nonsteroidal anti-inflammatory drug.
‡Published abstract only.
§"Twice the recommended dose"; odds ratio reported only for cerebrovascular ischemia; no elevation in risk for cardiovascular ischemia but odds ratio not reported.
‖Data for combined end point of death/recurrent acute myocardial infarction provided by study author.

McGettigan, P. et al. JAMA 2006;296:1633-1644.

Results of Case-Control and Cohort Studies Reporting on Cardiovascular Risks With Nonselective NSAIDs

Table 4. Results of Case-Control and Cohort Studies Reporting on Cardiovascular Risks With Nonselective NSAIDs

Source	Naproxen	Diclofenac	Ibuprofen	Indomethacin	Any/Other NSAIDs	Piroxicam
Hippisley-Cox and Coupland,[2] 2005	1.27 (1.01-1.60)	1.55 (1.39-1.72)	1.24 (1.11-1.39)	NR	1.21 (1.20-1.44)*	NR
Graham et al,[3] 2005	1.14 (1.00-1.30)	1.60 (0.92-2.79)	1.06 (0.96-1.17)	1.30 (1.06-1.59)	1.13 (1.01-1.27)*	NR
McGettigan et al,[14] 2006	NR	NR	0.98 (0.53-1.81)	NR	0.57 (0.41-1.09)†	NR
Kimmel et al,[15,16] 2004/5	0.48 (0.28-0.82)‡	NR	0.52 (0.39-0.69)	NR	0.61 (0.52-0.71)†	NR
Singh et al,[23] 2005§	1.08 (0.95-1.22)	NR	1.11 (1.01-1.22)	1.71 (1.36-2.17)	1.12 (1.06-1.19)o	NR
Johnsen et al,[25] 2005	1.50 (0.99-2.29)	NR	NR	NR	1.68 (1.52-1.85)*	NR
Levesque et al,[26] 2005	1.17 (0.75-1.84)	NR	NR	NR	1.00 (0.73-1.37)†	NR
Fischer et al,[27] 2005	0.96 (0.66-1.38)	1.23 (1.00-1.51)	1.16 (0.92-1.46)	1.36 (0.82-2.25)	1.07 (0.96-1.19)†	0.95 (0.53-1.69)
Garcia Rodriguez et al,[28] 2004	0.89 (0.64-1.24)	1.18 (0.99-1.40)	1.06 (0.87-1.29)	0.86 (0.87-1.32)	0.95 (0.77-1.18)*	1.25 (0.69-2.2)
Bak et al,[29] 2003	0.7 (0.4-1.1)	1.1 (0.7-1.17)	1.3 (1.0-1.6)	1.40 (0.80-2.40)	1.2 (1.1-1.4)†	NR
Solomon et al,[30] 2002	0.84 (0.72-0.98)	NR	1.02 (0.88-1.18)	NR	1.00 (0.92-1.08)†	0.5 (0.2-1.3)
Schlienger et al,[31] 2002	0.68 (0.42-1.13)	1.38 (1.08-1.77)	1.17 (0.87-1.58)	1.03 (0.58-1.85)	1.17 (0.99-1.37)†	1.65 (0.78-3.49)
Watson et al,[32] 2002	0.57 (0.31-1.06)	1.68 (1.14-2.49)	0.74 (0.35-1.55)	NR	1.47 (1.00-2.16)*	NR
Garcia Rodriguez et al,[33] 2004	NR	NR	NR	NR	1.45 (1.18-1.79)†	NR
Summary relative risk	0.96 (0.84-1.10)	1.36 (1.21-1.54)	1.06 (0.95-1.18)	1.30 (1.07-1.60)	1.10 (0.98-1.24)	1.06 (0.70-1.59)
Adjusted date cohort studies that reported on NSAIDs						
Gíslason et al,[17] 2006‖	NR	2.19 (1.93-2.49)	1.39 (1.27-1.53)	NR	1.33 (1.21-1.46)*	NR
Curtis et al,[18] 2003	NR	NR	0.84 (0.70-1.01)	NR	0.96 (0.86-1.06)*	NR
MacDonald and Wei,[19] 2003	NR	0.80 (0.49-1.31)	1.73 (1.05-2.84)	NR	1.03 (0.77-1.37)*	NR
Mamdani et al,[20] 2003	1.0 (0.6-1.7)	NR	NR	NR	1.2 (0.9-1.4)*	NR
Ray et al,[21] 2002	0.93 (0.82-1.06)	NR	0.91 (0.78-1.06)	NR	NR	NR
Ray et al,[22] 2002	0.95 (0.82-1.09)	NR	1.15 (1.02-1.28)	NR	1.03 (0.92-1.16)	NR
Summary relative risk	0.94 (0.85-1.04)	1.36 (0.51-3.65)	1.12 (0.90-1.38)		1.10 (0.95-1.29)	
Case-control and cohort studies combined risk estimates	0.97 (0.87-1.07)	1.40 (1.16-1.70)	1.07 (0.97-1.18)	1.30 (1.07-1.60)	1.10 (1.00-1.21)	1.06 (0.70-1.59)

Abbreviations: NR, not reported; NSAID, nonsteroidal anti-inflammatory drug.
*NSAIDs other than those reported on individually.
†All NSAIDs.
‡vs Celecoxib≤ 200 mg/d.
§Published abstract only.
‖Data for combined end point of death/recurrent acute myocardial infarction provided by study author.

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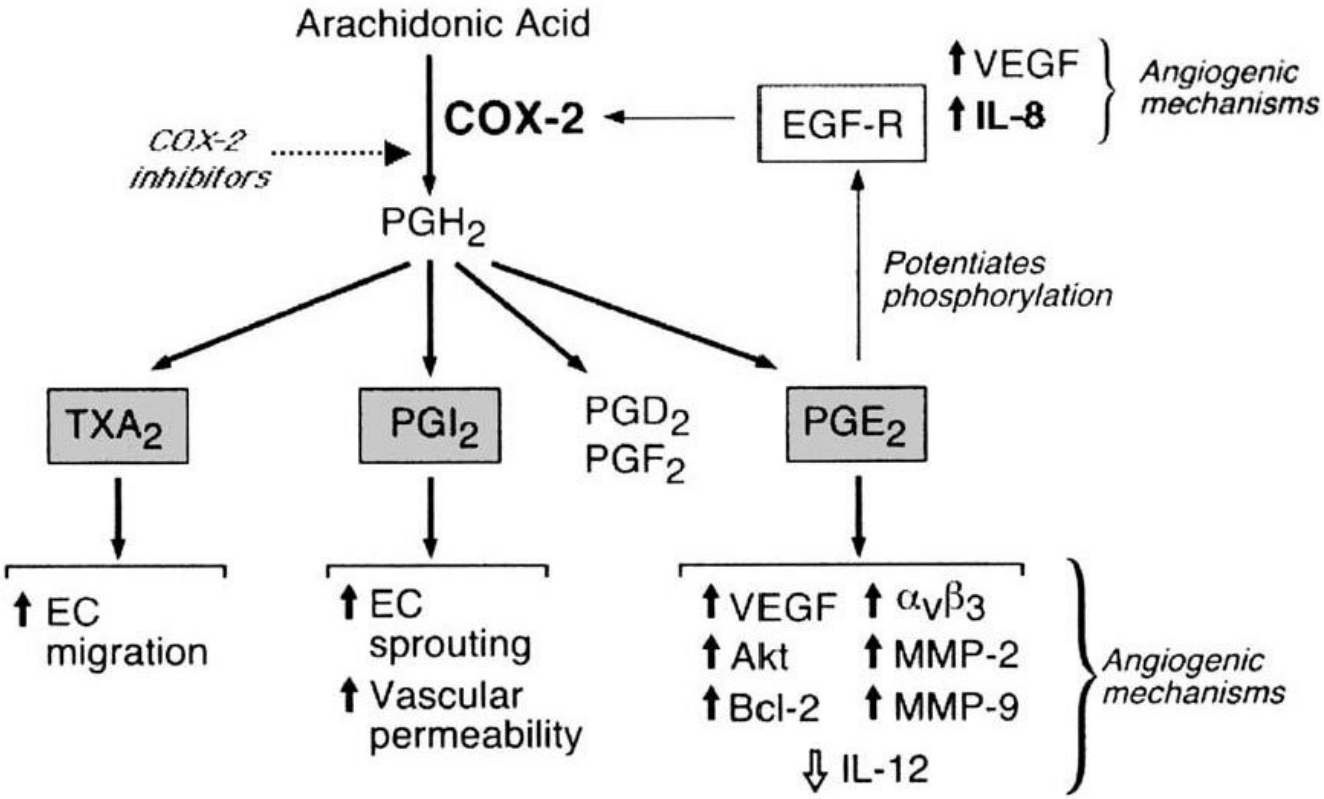
COX-2 inhibition is nothing for a COX-2 inhibitor ?
Why is only celecoxib still in the US market ?



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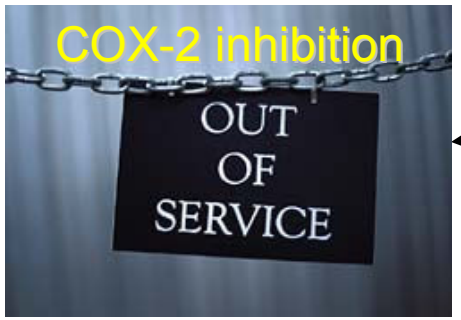

PKG activation
NFkB activation inhibition
Bcl-XL production inhibition
PPAR delta activation inhibition
PPAR gamma activation

감사합니다