HISTAMIN
&
AUTAKOIDS

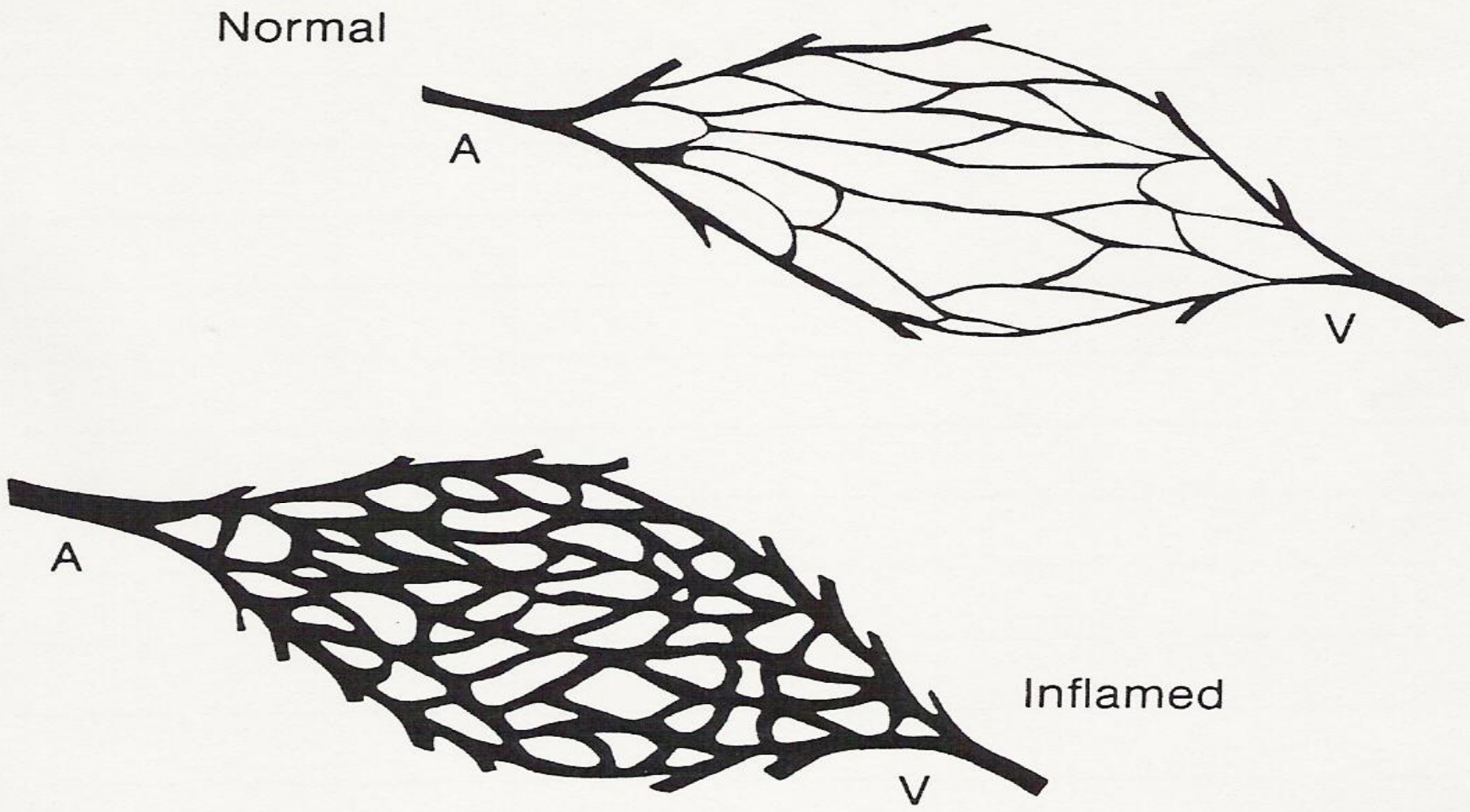


Figure 1–4 Increase in blood flow associated with inflammation. *(A)* Arteriole; *(V)* venule.

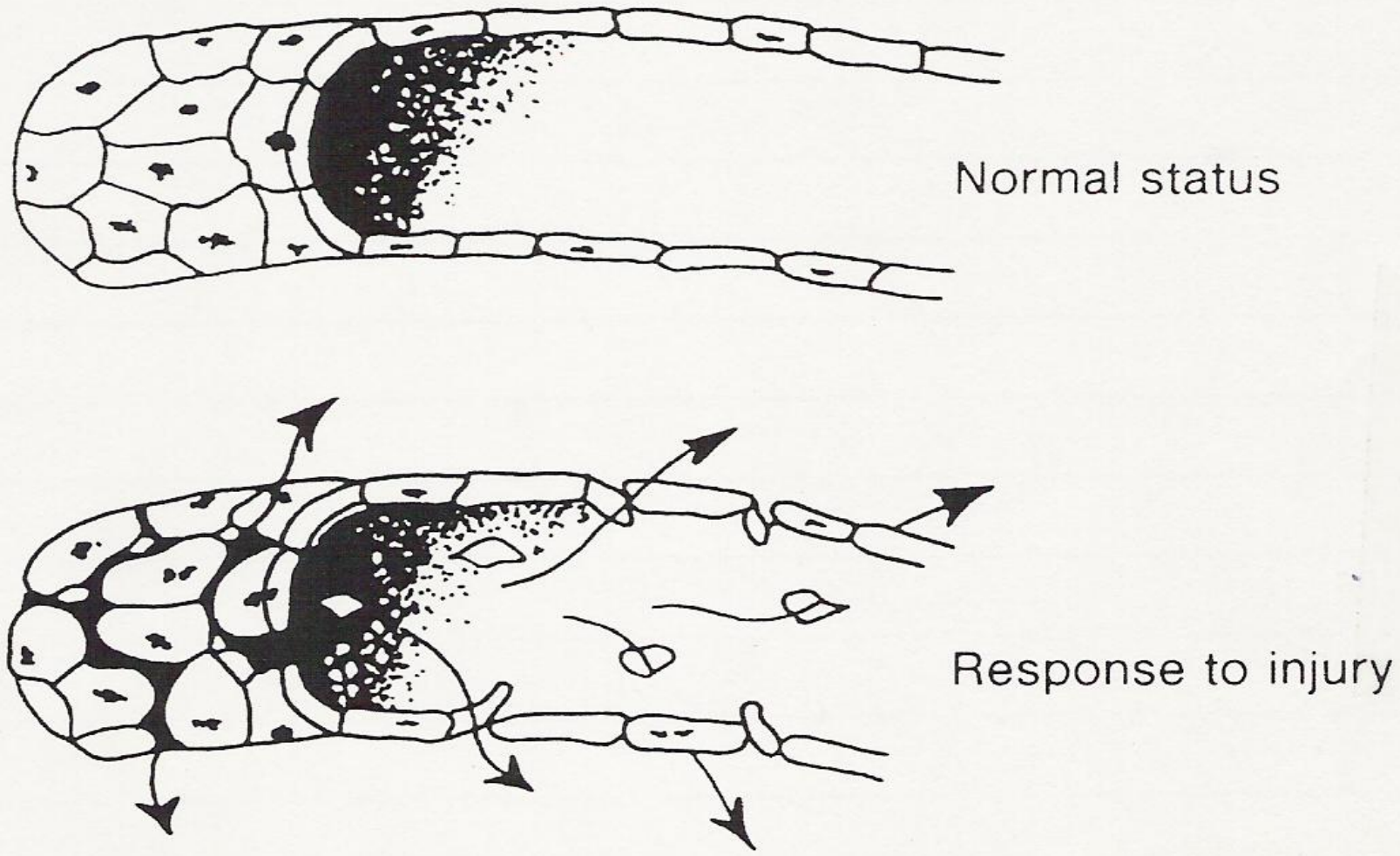


Figure 1–5 Intercellular gaps.

Vascular Changes in Inflammation

- Mediators of blood flow and vascular permeability changes

- vasoactive amines (histamine, serotonin)
- vasoactive peptides (bradykinin)
- vasoactive lipids (prostaglandins, leukotrienes)

Mediators of leukocyte chemotaxis

- leukotriene B4
- Eosinophil chemotactic factor of anaphylaxis

Tissue damage in Inflammation and Autoimmune Disease

- Generation of reactive oxygen species (O_2-, H_2O_2, HOCl) and proteolytic enzymes (collagenases, elastase) by phagocytic cells
- Cytotoxic complement proteins
- Cell- mediated and humeral immune responses
- Release of pro-inflammatory cytokines

HISTAMIN

- **Komponen bisa/racun serangga/tumbuhan**
- **Tersimpan di Mast Cell & Basofil**

  (di lokasi trauma: hidung, mulut, kaki)
- **Release:**

  1. Respon Imun

  Immediate (Type I) Allergic Reaction

  Inflamasi akut

  2. Respon Kimia (gol. Amine: morfin)

Physiologic effects of histamine

- Smooth Muscle
- Vascular
- Bronchiolar
- Gut

- Cutaneous effects
- Secretory Epithelia
- GI

EFEK: - Triple Response: merah, edema, nyeri

- Shock anafilaktik

- Rangsang ujung saraf tepi nyeri, gatal H1

- Vasodilatasi + edema jaringan nadi tensi

- Bronkokonstriksi provocatif test

- Kontraksi otot polos: H2

GI : peristalsis diare

Uterus : aborsi

Lambung: sekresi HCl

- Pengelolaan:

1. Antagonis Fisiologis: epinefrin

2. Antagonis Reseptor : CTM, Burimamide anti-H2

3. Release Inhibitor: Cromolin, Nedocromil

H1 ANTAGONIS

Gen 1: sedatif, blok reseptor otonom

Gen 2: <<sedatif (distribusi di CNS<<)

- p.o. absorbsi cepat (peak 1-2 jam, durasi 4-6 jam)
- Metabolisme di hepar
- Efek:
  - sedasi
  - anti-nausea/ anti-emetik
  - anti-Parkinson (Bromokriptin: anti-kolinergik)
  - anti-kolinergik (Etanolamine, Etilendiamine)
  - α-adrenoceptor blocker: hipotensi postural (Fenotiazin, Prometazin)
  - Serotonin blocker (Siproheptadin)
  - Anestesi lokal (Difenhidramin, Prometazin)

First vs. Second Generation H1 antagonists

- Many first generation H1 antagonists interact with other receptor types

- diphenhydramine – muscarinic receptors
- Promethazine – dopamine, muscarinic, α1
- Cyproheptadine – serotonergic receptors

Second Generation H1 antagonists are:

- highly selective for H1 receptors
- do not penetrate the blood-brain barrier; less sedation
- Have long half-lives
- Are primarily indicated for allergic rhinitis

Some Uses for H1 antagonists

- Allergic rhinitis – e.g.chlorpheniramine, loratidine
- Motion sickness – eg. meclizine, chlorcyclizine
- Hypnotic agents – e.g.doxylamaine, diphenhydramine
- Pruritis –e.g. hydroxyzine
- Serum sickness- e.g. promethazine
- Anti-emetics- e.g. promethazine
- Antitussive – e.g. diphenhydramine
- Carcinoid tumors (serotonin-mediated) – cyproheptadine
- Allergic conjuctivitis – e.g. levocobastine

Drugs	Usual Adult Dose	Anticholinergic Activity	Comments
FIRST-GENERATION ANTIHISTAMINES			
Ethanolamines			
Carbinoxamine (Clistin)	4–8 mg	+++	Slight to moderate sedation
Dimenhydrinate (salt of diphenhydramine) (Dramamine)	50 mg	+++	Marked sedation; anti-motion sickness activity
Diphenhydramine (Benadryl, etc)	25–50 mg	+++	Marked sedation; anti-motion sickness activity
Doxylamine	1.25–25 mg	nd	Marked sedation; now available only in OTC "sleep aids"
Ethylaminediamines			
Pyrilamine (Neo-Antergan)	25–50 mg	+	Moderate sedation; component of OTC "sleep aids"
Tripelennamine (PBZ, etc)	25–50 mg	+	Moderate sedation
Piperazine derivatives			
Hydroxyzine (Atarax, etc)	15–100 mg	nd	Marked sedation
Cyclizine (Marezine)	25–50 mg	–	Slight sedation; anti-motion sickness activity
Meclizine (Bonine, etc)	25–50 mg	–	Slight sedation; anti-motion sickness activity

Alkylamines			
Brompheniramine (Dimetane, etc)	**4–8 mg**	**+**	**Slight sedation**
Chlorpheniramine (Chlor-Trimeton, etc)	**4–8 mg**	**+**	**Slight sedation; common component of OTC "cold" medication**
Phenothiazine derivatives			
Promethazine (Phenergan, etc)	**10–25 mg**	**+++**	**Marked sedation; antiemetic**
Miscellaneous			
Cyproheptadine (Periactin, etc)	**4 mg**	**+**	**Moderate sedation; also has antiserotonin activity**
SECOND-GENERATION ANTIHISTAMINES			
Piperidines			
Fexofenadine (Allegra)	**60 mg**	**–**	**Lower risk of arrhythmia**
Miscellaneous			
Loratadine (Claritin)	**10 mg**	**–**	**Longer action**
Cetirizine (Zyrtec)	**5–10 mg**	**–**	

Penggunaan Klinis

- Reaksi Alergi: rinitis, urtikaria
  asma ? (tidak efektif)

- Motion sickness
  - Gen 1: difenhidramin/ dimenhidrinat, prometazin
    sikloserin, meclizine: less sedatif
  - Obat lain : skopolamin
  - +efedrin/amfetamin: >>efek

- Nausea/Vomiting pd kehamilan
  piperasin : teratogenik

Toksisitas

mirip keracunan Atropin

eksitasi, konvulsi, koma

- Astemizole, Terfenadine aritmia

pada penderita hepar

interaksi dg ketokonazole, makrolid

juice anggur

dilarang di USA

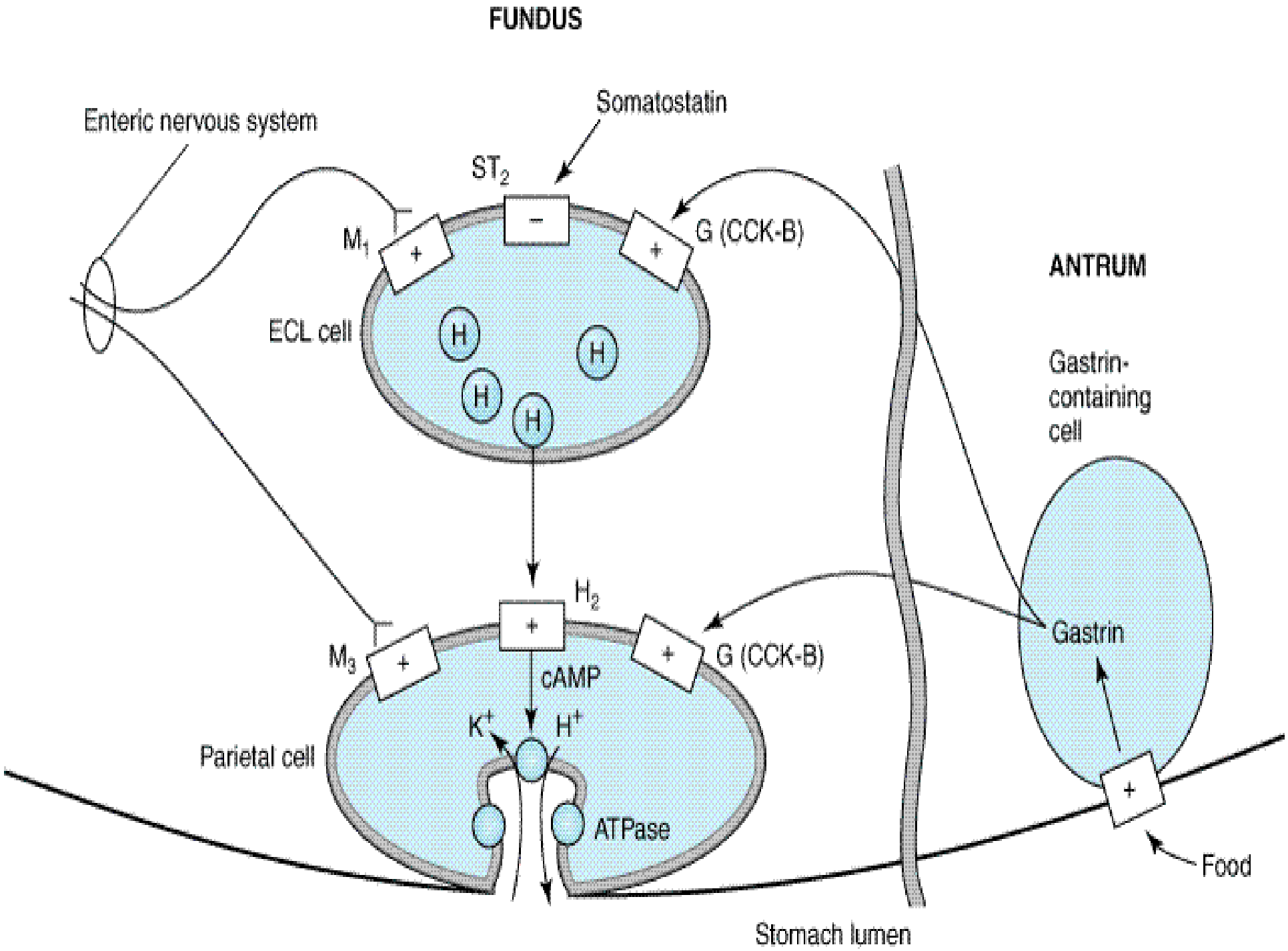
H2 ANTAGONIS

- Cimetidine
- Ranitidine
- Famotidine
- Nizatidine

- Mengurangi sekresi HCl lambung
- Menghambat enzim hepar

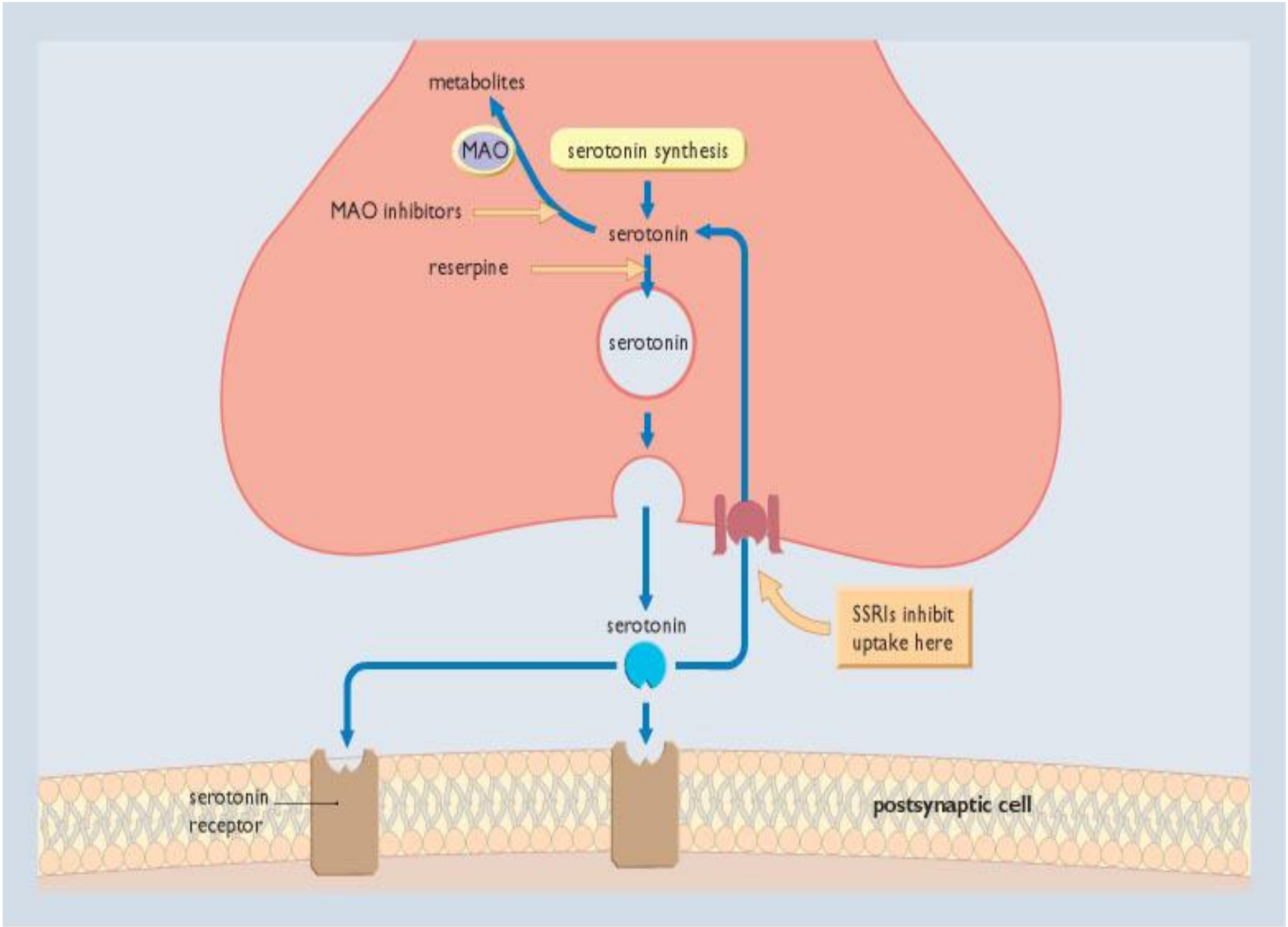
Clinical uses for H2 receptor Antagonists

- Gastric and duodenal ulcers
- Gastroesophageal reflux
- Erosive esophagitis
- Heartburn (available OTC)


FUNDUS
Enteric nervous system
Somatostatin
ST2
M1
G (CCK-B)
ANTRUM
ECL cell
H
Gastrin-containing cell
H2
M3
G (CCK-B)
Gastrin
cAMP
K+
H+
Parietal cell
ATPase
Food
Stomach lumen

SEROTONIN

- Komponen bisa/racun serangga
- CNS: mood, sleep, appetite, suhu, pain preception
  tensi, vomiting, migrain
- Vasokonstriksi + vasodilatasi otot & jantung
  trifasik: hipo-hiper-hipo
- GI: release asetilkolin peristalsis
- Otot: malignant hiperthermia (o.k. obat anestesi)
- MAOinhibitor + Serotonis Agonis
  = serotonin syndrome



Receptor Subtype	Distribution	Postreceptor Mechanism	Partially Selective Agonists	Partially Selective Antagonists
5-HT_{1A}	Raphe nuclei, hippocampus	Multiple, G_i coupling dominates	8-OH-DPAT	WAY100635
5-HT_{1B}	Substantia nigra, globus pallidus, basal ganglia	cAMP	CP93129	
5-$HT_{1Da,b}$	Brain	cAMP	Sumatriptan	
5-HT_{1E}	Cortex, putamen	cAMP		
5-HT_{1F}	Cortex, hippocampus	cAMP		
5-HT_{1P}	Enteric nervous system	G_o; slow EPSP	5-Hydroxyindalpine	Renzapride

5-HT_{2A}	**Platelets, smooth muscle, cerebral cortex, skeletal muscle**	**IP_3**	**-Methyl-5-HT**	**Ketanserin**
5-HT_{2B}	**Stomach fundus**	**IP_3**	**-Methyl-5-HT**	**SB204741**
5-HT_{2C}	**Choroid, hippocampus, substantia nigra**	**IP_3**	**-Methyl-5-HT**	**Mesulergine**
5-HT_3	**Area postrema, sensory and enteric nerves**	**Receptor is a Na^+-K^+ ion channel**	**2-Methyl-5-HT, *m*-chlorophenylbiguanide**	**Tropisetron, ondansetron, granisetron**
5-HT_4	**CNS and myenteric neurons, smooth muscle**	**cAMP**	**5-Methoxytryptamine, renzapride, metoclopramide**	
5-$HT_{5A,B}$	**Brain**	**cAMP**		
5-$HT_{6,7}$	**Brain**	**cAMP**		**Clozapine (5-HT_7)**

SEROTONIN AGONIS

- Buspirone
- Dexfenfluramin: anorexiogenik

  ESO: - hipertensi pulmonal

  - endokardial hiperplasia
- Sumatriptan: anti-migrain
- Cisapride: perangsang peristalsis

  ESO: jantung dilarang di USA
- Fluoksetine: anti-depresi

  sering disalahgunakan untuk anorexiogenik

SEROTONIN ANTAGONIS

- Reserpin: hambat storage
- Serotonin Reseptor Antagonis
  - Phenoksibensamin: long lasting blok
  - Alkaloid Ergot: partial agonis
  - Siproheptadin (antihistamin)
  - Ketanserine: hambat agregasi platelet, antihipertensi (α-blocker)
  - Ritanserin: tanpa α-blocker
  - Ondansentron: anti-nausea/ anti-vomiting pada pembedahan & kemoterapi kanker

ALKALOID ERGOT

- Dari jamur Claviceps purpurea pada biji-bijian
  isi: histamin, asetilkolin, tiramin, dsb
- Keracunan (ergotism):
  demensia, halusinasi, vasospasme/gangren
  kontraksi uterus (aborsi), konvulsi
- Absorbsi >> dengan kofein

Ergot Alkaloid	Adrenoceptor	Dopamine Receptor	Serotonin Receptor (5-HT_2)	Uterine Smooth Muscle Stimulation
Bromocriptine	–	+++	–	0
Ergonovine	+	+	– (PA)	+++
Ergotamine	– – (PA)	0	+ (PA)	+++
Lysergic acid diethylamide (LSD)	0	+++	– –, ++ in CNS	+
Methysergide	+/0	+/0	– – – (PA)	+/0

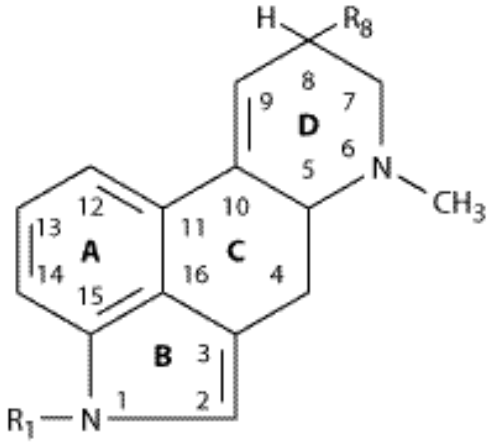
Penggunaan Klinik

- anti-migrain: ergotamine
- anti-hiperprolaktinemia (amenore, infertil):
  bromokriptin, cabergoline, pergolide
- Perdarahan post partum: ergonovin
- anti-Alzheimer ??

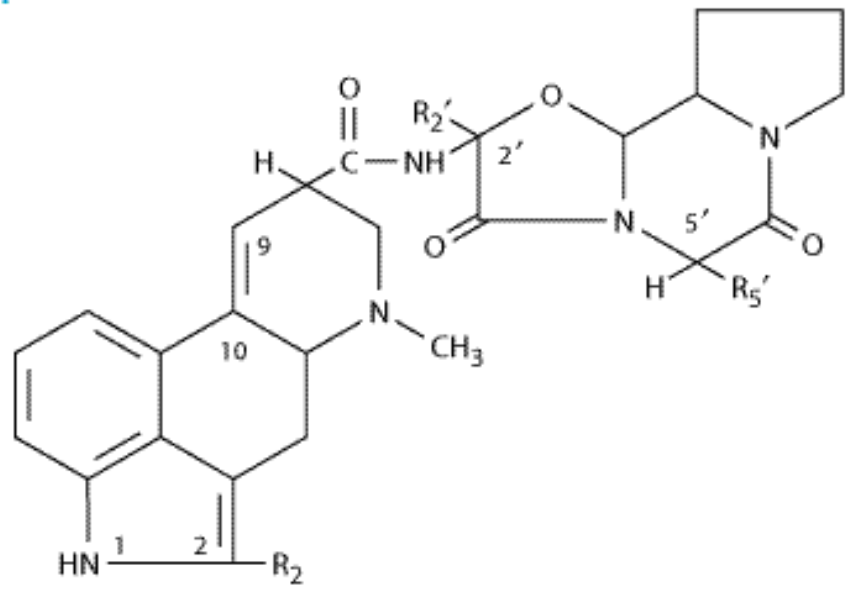
Intoksikasi:

- GI: diare, nausea, muntah
- Prolonged vasospasme….gangren

Amine alkaloids



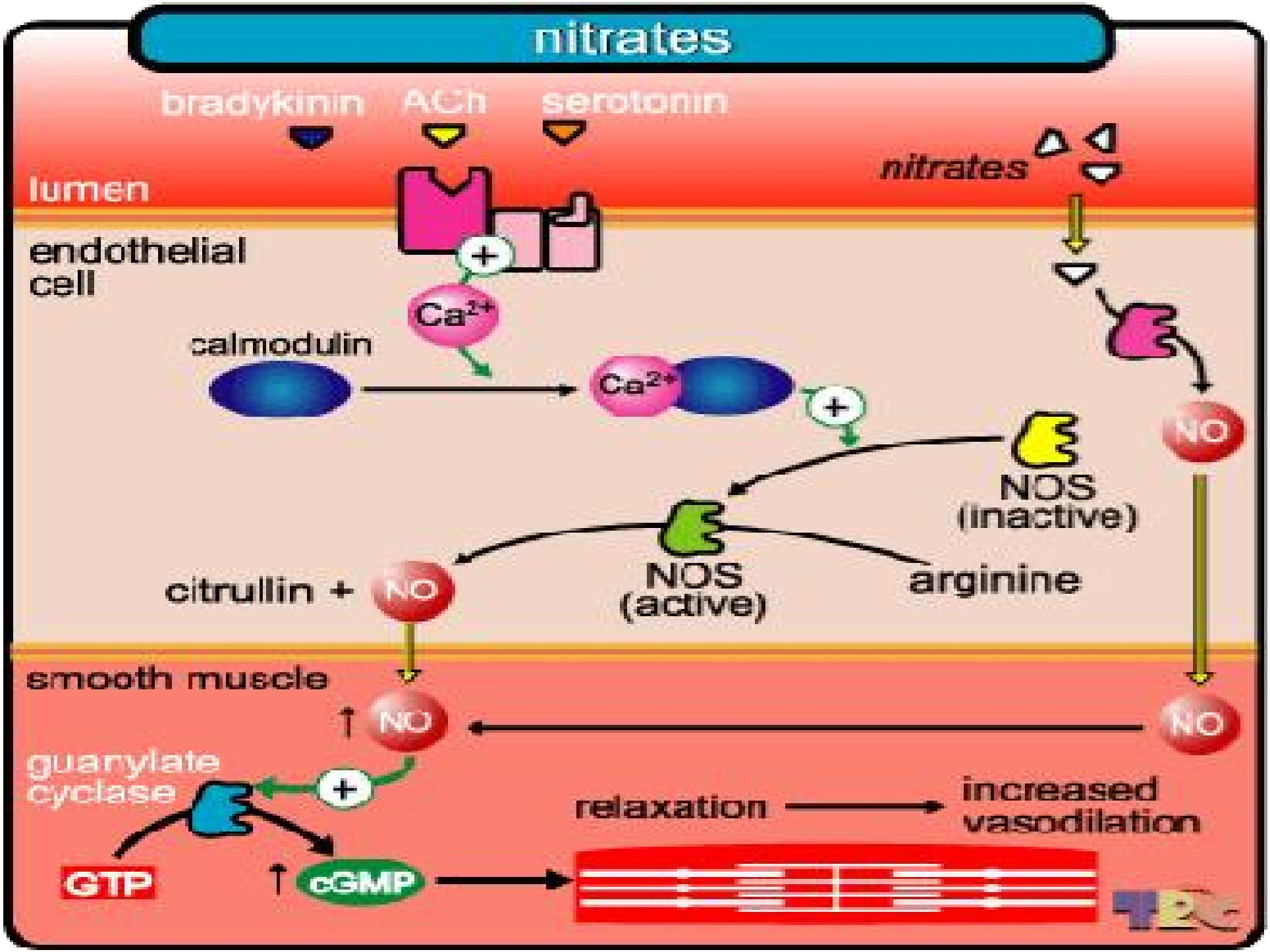
Peptide alkaloids



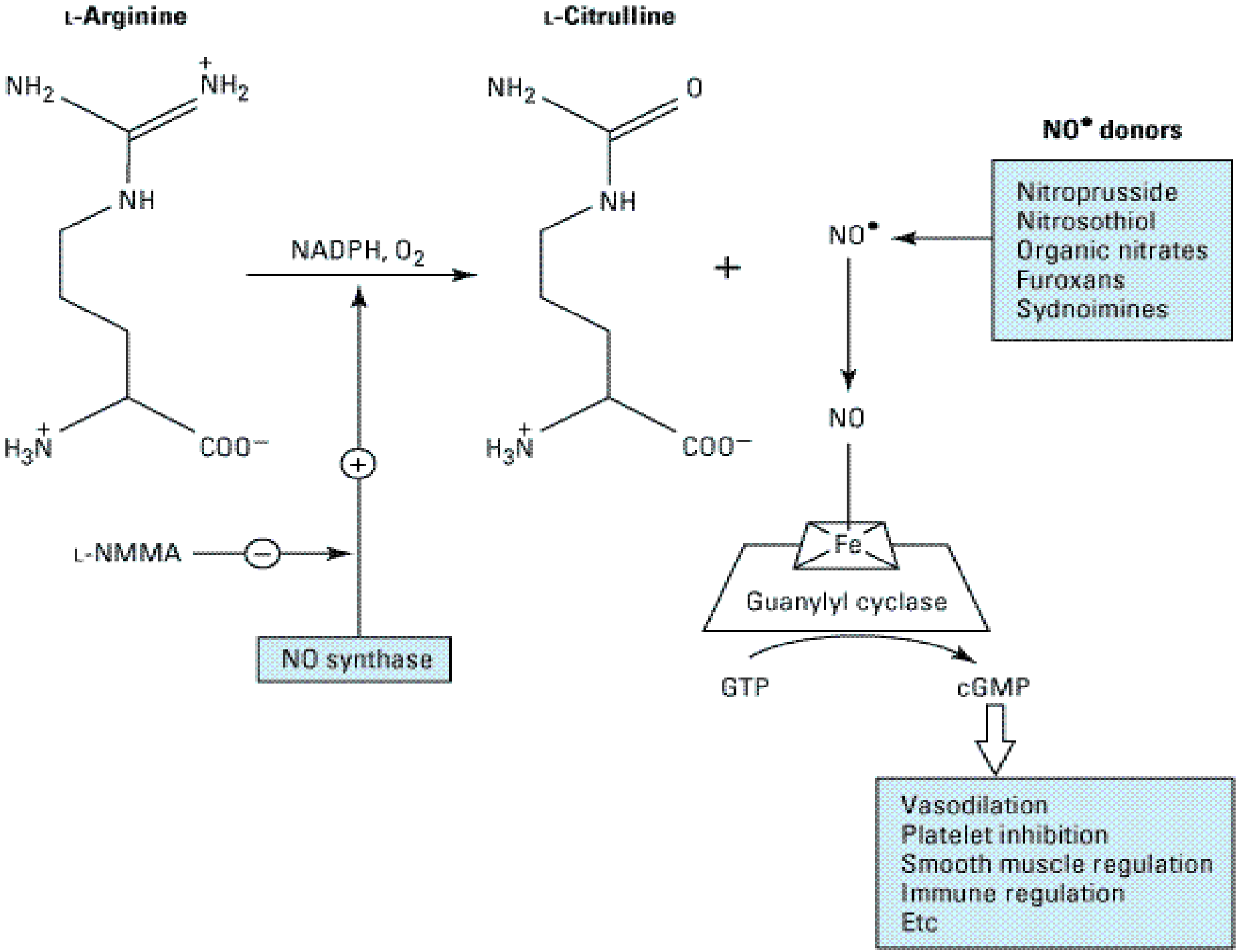
	R_1	R_8
6-Methylergoline	—H	—H
Lysergic acid	—H	—COOH
Lysergic acid diethylamide (LSD)	—H	—C(=O)—N(CH_2—CH_3)$_2$
Ergonovine (ergometrine)	—H	—C(=O)—CH(CH_2OH)—NHCHCH_3
Methysergide	—CH_3	—C(=O)—NH—CH(CH_2—CH_3)—

	R_2	R_2'	R_5'
Ergotamine[1]	—H	—CH_3	—CH_2—(benzene)
α-Ergocryptine	—H	—$CH(CH_3)_2$	—CH_2—$CH(CH_3)_2$
Bromocriptine	—Br	—$CH(CH_3)_2$	—CH_2—$CH(CH_3)_2$

NITRIC OXIDE, DONORS, & INHIBITORS: INTRODUCTION

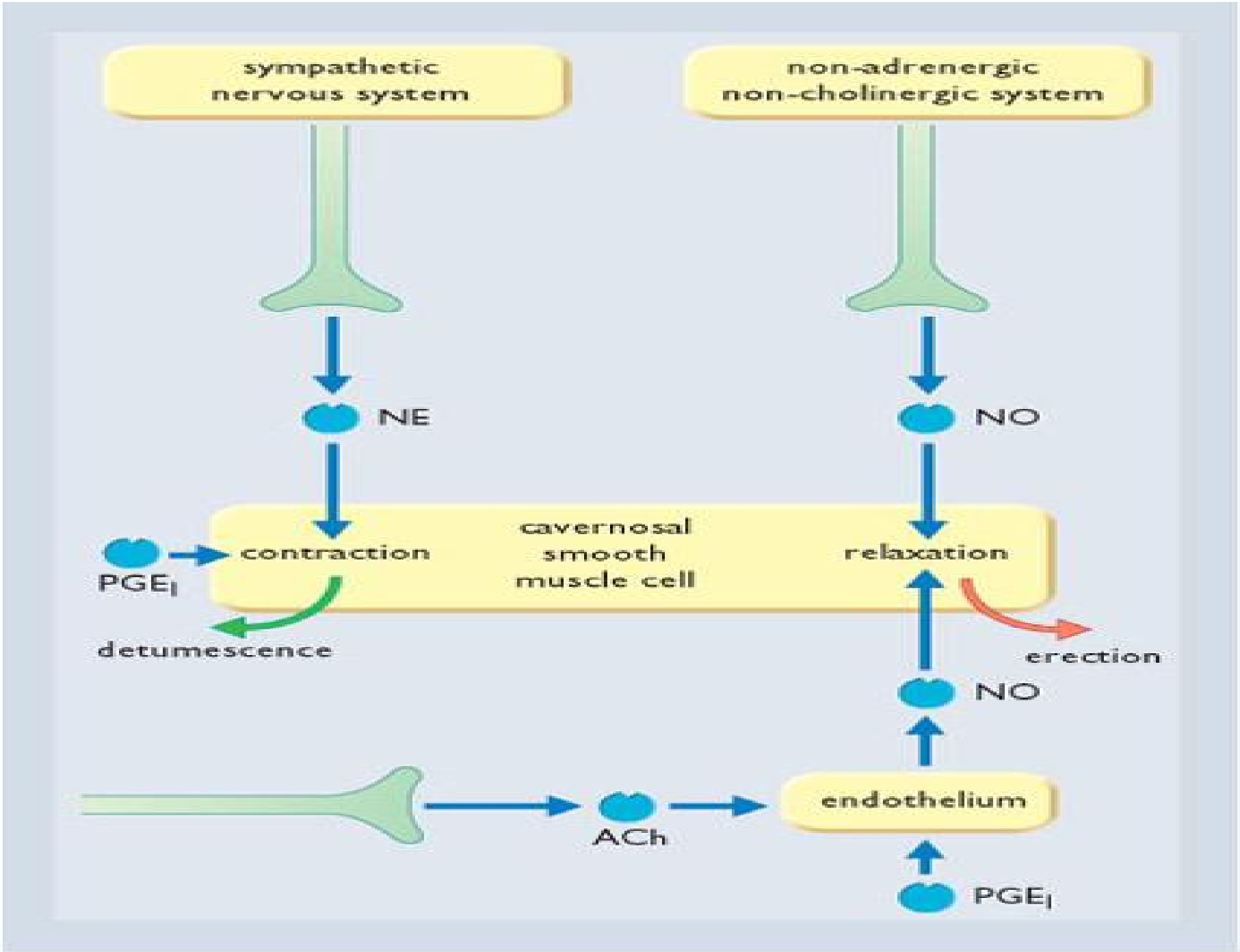

nitrates
bradykinin
ACh
serotonin
lumen
nitrates
endothelial cell
Ca2+
calmodulin
Ca2+
NO
NOS (inactive)
NOS (active)
arginine
citrullin +
NO
smooth muscle
NO
NO
guanylate cyclase
relaxation
increased vasodilation
GTP
cGMP

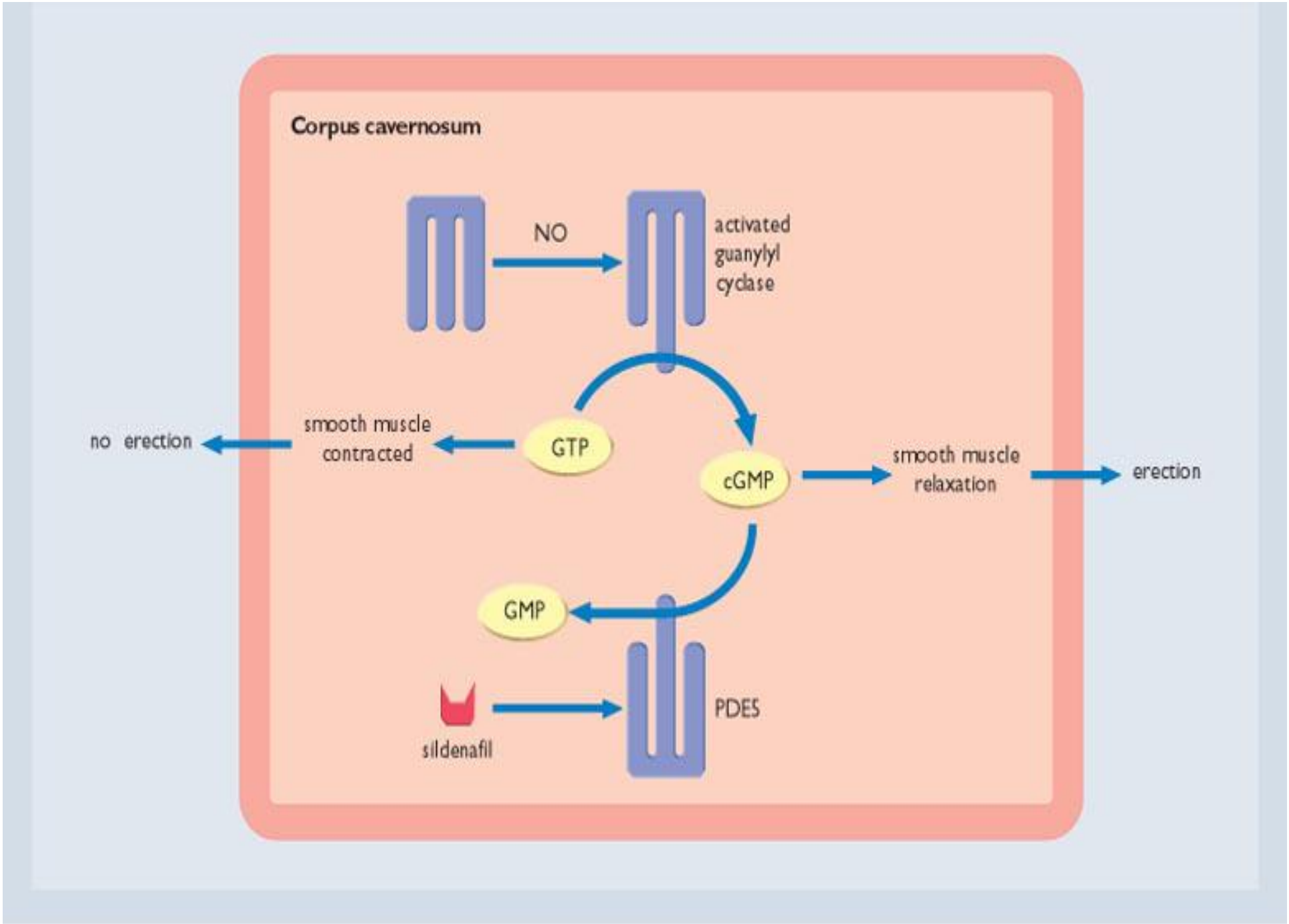
Property	NOS-1	NOS-2	NOS-3
Other names	nNOS (neuronal NOS)	iNOS (inducible NOS)	eNOS (endothelial NOS)
Tissue	Neuronal, epithelial cells	Macrophages, smooth muscle cells	Endothelial cells
Expression	Constitutive	Transcriptional induction	Constitutive
Calcium requirement	Yes	No	Yes
Chromosome	12	17	7
Approximate mass	150–160 kDa	125–135 kDa	133 kDa

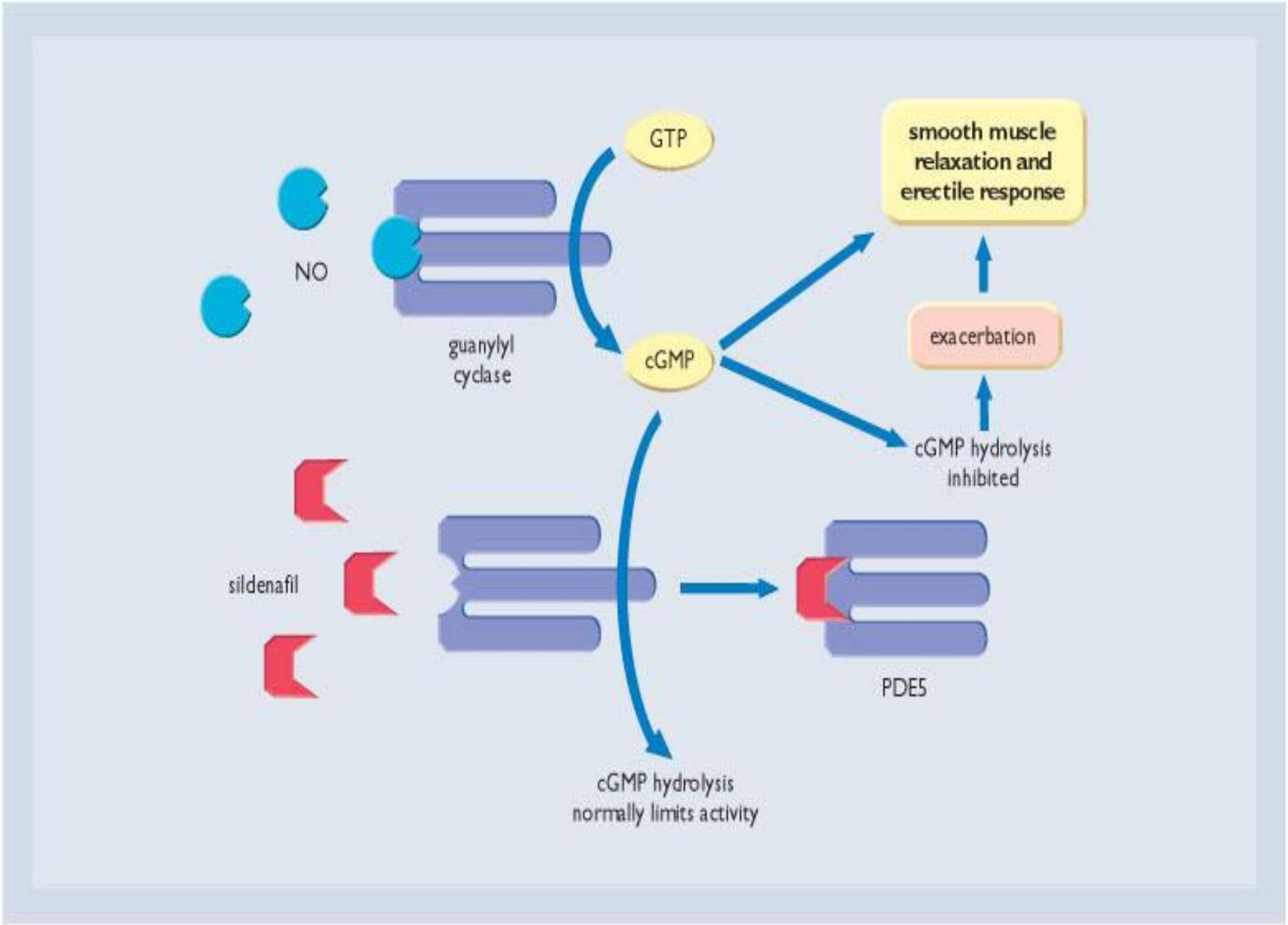

L-Arginine
L-Citrulline
NADPH, O2
L-NMMA
NO synthase
NO•
NO
NO• donors
Nitroprusside
Nitrosothiol
Organic nitrates
Furoxans
Sydnoimines
Fe
Guanylyl cyclase
GTP
cGMP
Vasodilation
Platelet inhibition
Smooth muscle regulation
Immune regulation
Etc

Name	Symbol	Known Function
Nitric oxide		Vasodilator, platelet inhibitor, immune regulator, neurotransmitter
Nitroxyl anion	NO^-	Smooth muscle relaxant
Nitrogen dioxide		Free radical, nitrosating agent, lung irritant
Nitrous oxide	N_2O	Anesthetic
Dinitrogen trioxide	N_2O_3	Nitrosating agent
Dinitrogen tetraoxide	N_2O_4	Nitrosating agent
Nitrite	NO_2^-	at acidic pH
Nitrate	NO_3^-	

Inhibitor	Mechanism	Comment
N^{g}–Monomethyl–L–arginine (L–NMMA)	NOS inhibition	May act as substrate in some tissues
N^{g}–Nitro–L–arginine methyl ester (L–NAME)	NOS inhibition	Less selective NOS inhibitor
7–Nitroindazole	NOS inhibition	Markedly selective for NOS–1 in vivo
S–Methylthiocitrulline	NOS inhibition	Partially selective for NOS–1
Heme	Nitric oxide scavenger	
Protein inhibitor of NOS	Unknown mechanism	Endogenous inhibitor found in brain







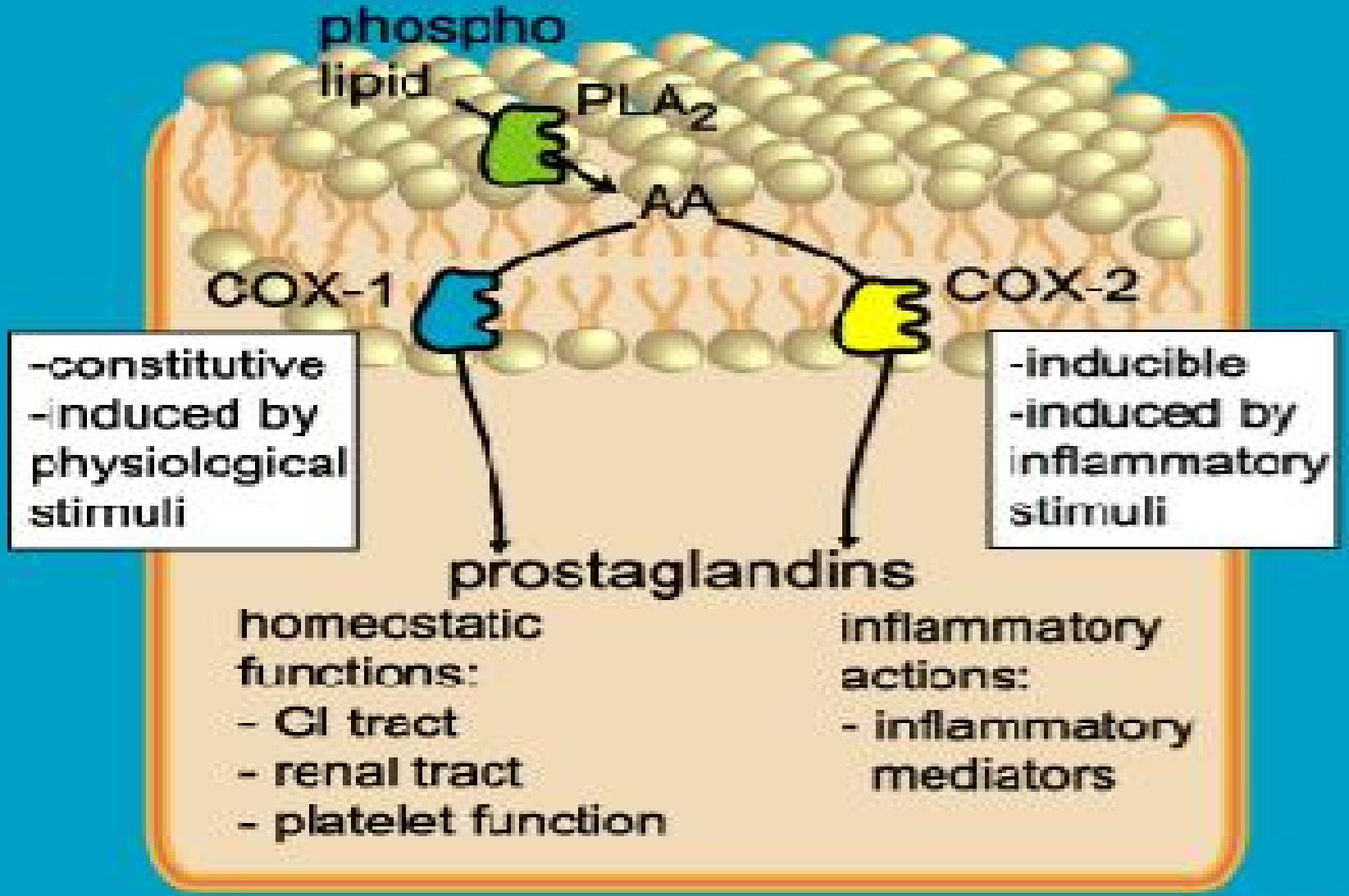
Licensed drugs withdrawn from the United States market 1996–2000

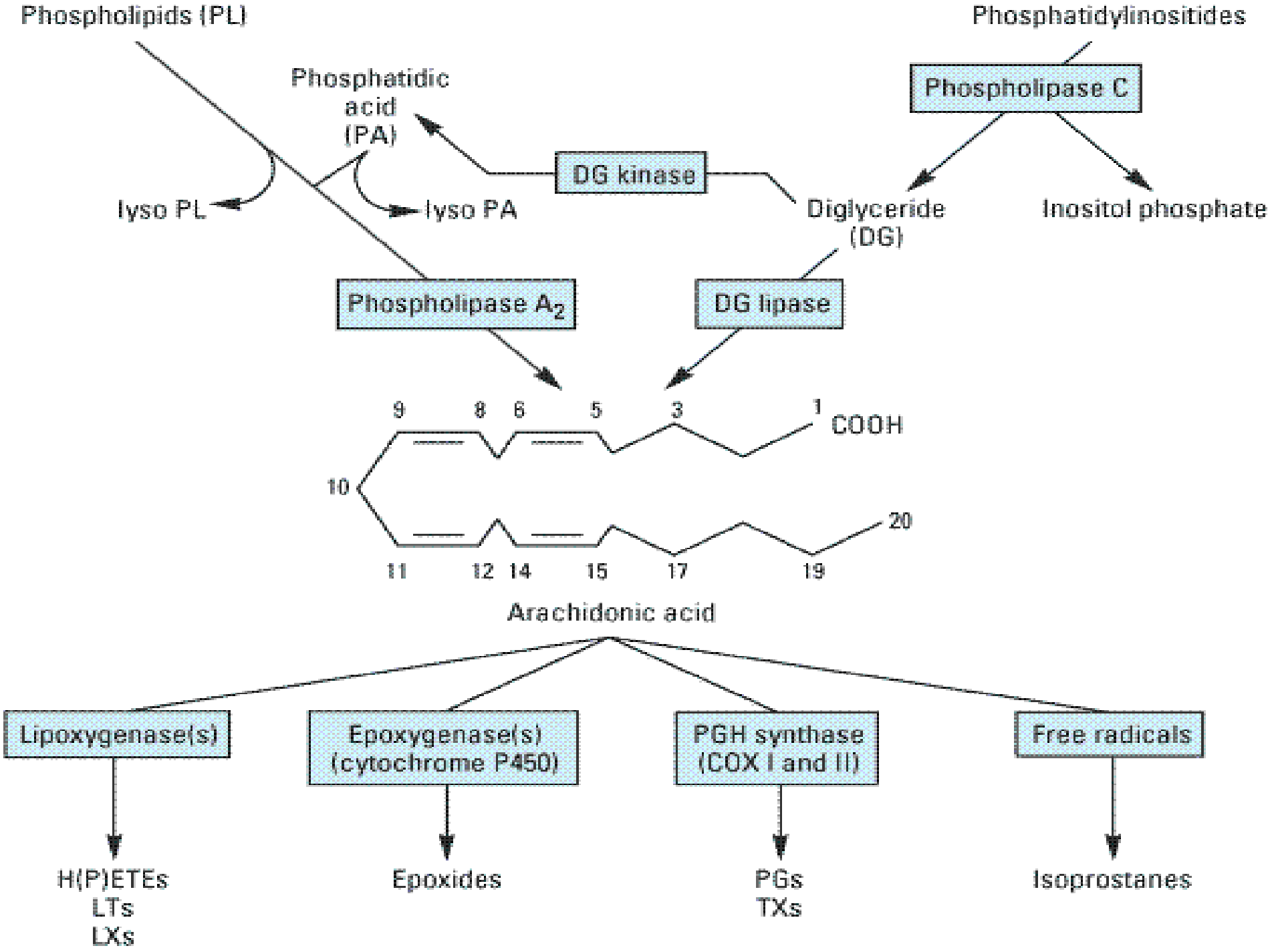
Drug	Use	Problem
Alosetron	Treating irritable bowel syndrome	Ischemic colitis
Phenylpropanolamine	Nasal decongestant	Hemorrhagic stroke
Troglitazone	Oral antidiabetic agent	Toxic to the liver
Cisapride	To increase gut motility	Arrhythmia
Grepafloxacin	Antibacterial	Severe cardiovascular events
Rotavirus vaccine	Protect against rotavirus diarrhea	Intussusception
Astemizole	Nonsedating antihistamine	Arrhythmia
Bromfenac sodium	Nonsteroidal anti-inflammatory	Severe hepatic failure
Mibefradil	Antihypertensive and anti-anginal	Potential for drug interactions
Terfenadine	Nonsedating antihistamine	Arrhythmia
Fenfluramine, dexfenfluramine	Anti-obesity agents	Heart valve disease
Chlormezanone	Sedative	Toxic epidermal necrolysis

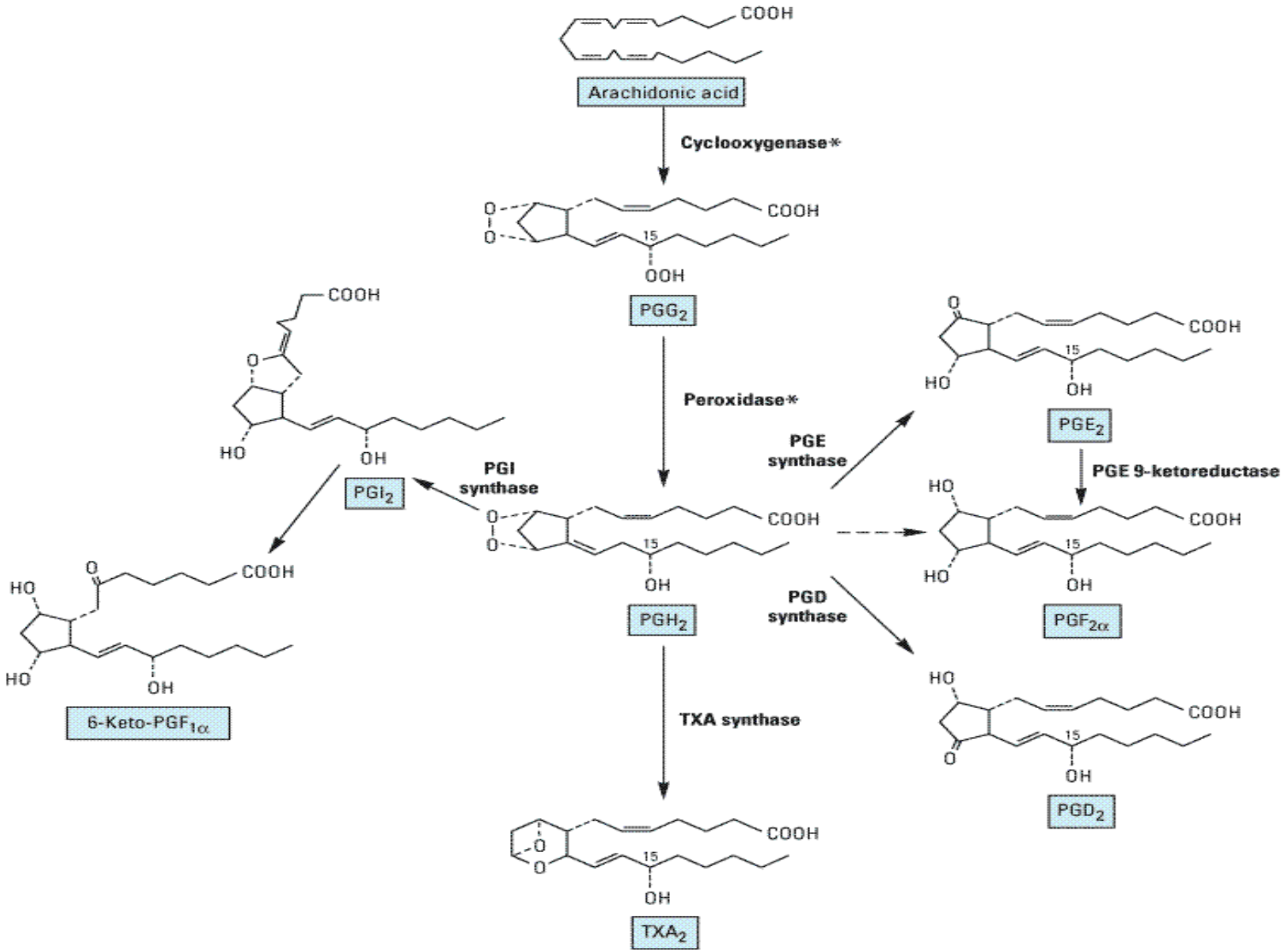
Lipid Autocoids

THE EICOSANOIDS: PROSTAGLANDINS, THROMBOXANES, LEUKOTRIENES, & RELATED COMPOUNDS: INTRODUCTION

prostaglandin synthesis




Phospholipids (PL)
Phosphatidylinositides
Phosphatidic acid (PA)
Phospholipase C
DG kinase
lyso PL
lyso PA
Diglyceride (DG)
Inositol phosphate
Phospholipase A2
DG lipase
9
8
6
5
3
1
COOH
10
20
11
12
14
15
17
19
Arachidonic acid
Lipoxygenase(s)
Epoxygenase(s) (cytochrome P450)
PGH synthase (COX I and II)
Free radicals
H(P)ETEs
LTs
LXs
Epoxides
PGs
TXs
Isoprostanes


COOH
Arachidonic acid
Cyclooxygenase*
O
O
COOH
15
OOH
PGG2
Peroxidase*
PGE synthase
PGI synthase
TXA synthase
PGD synthase
HO
OH
PGE2
PGE 9-ketoreductase
PGF2α
PGI2
6-Keto-PGF1α
PGH2
PGD2
TXA2

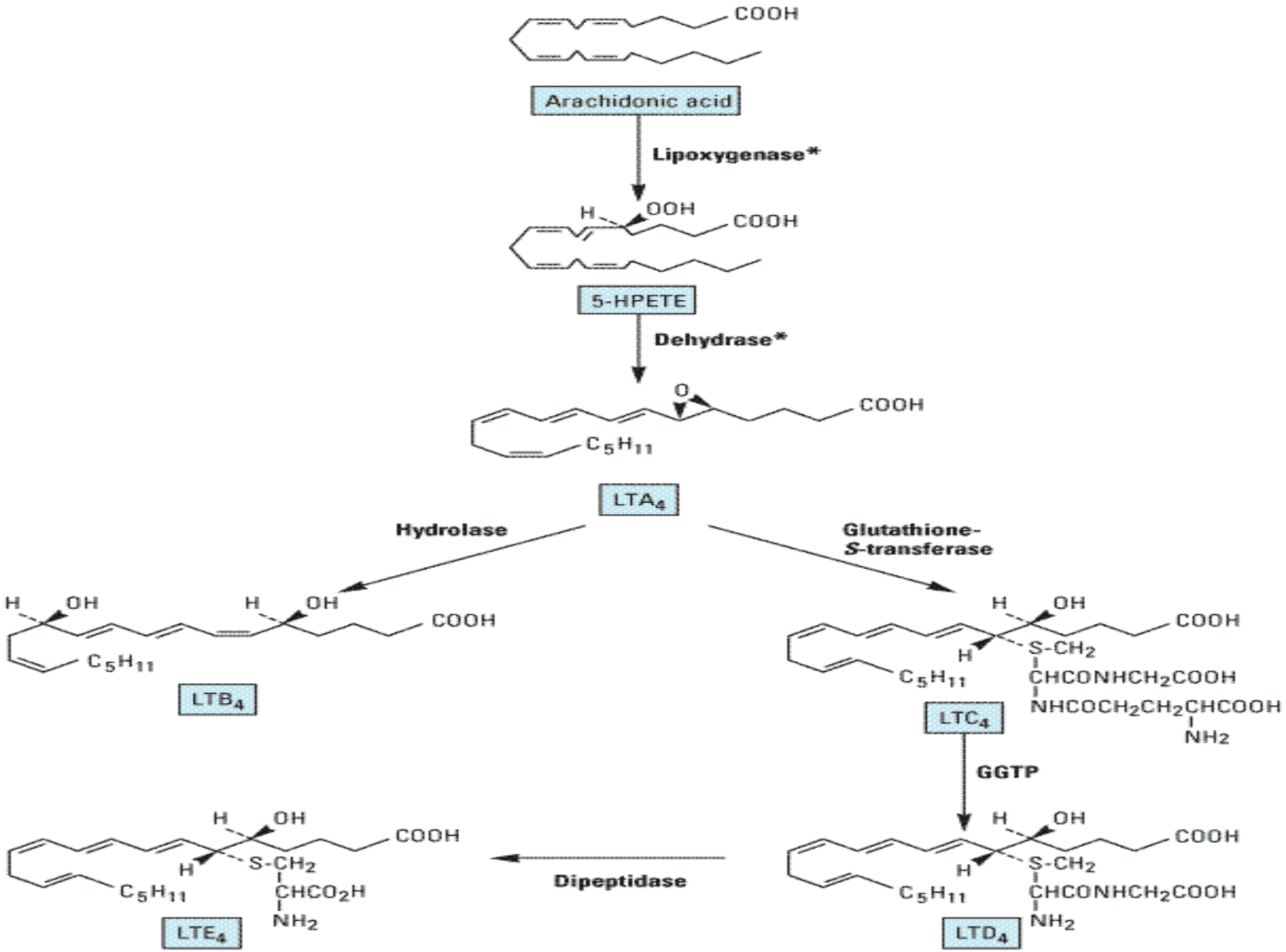

COOH
Arachidonic acid
Lipoxygenase*
H
OOH
COOH
5-HPETE
Dehydrase*
O
COOH
C_5H_{11}
LTA_4
Hydrolase
Glutathione-
S-transferase
H
OH
H
OH
COOH
C_5H_{11}
LTB_4
H
OH
COOH
H
S-CH_2
C_5H_{11}
CHCONHCH$_2$COOH
NHCOCH$_2$CH$_2$CHCOOH
NH_2
LTC_4
GGTP
H
OH
COOH
H
S-CH_2
C_5H_{11}
CHCONHCH$_2$COOH
NH_2
LTD_4
Dipeptidase
H
OH
COOH
H
S-CH_2
C_5H_{11}
$CHCO_2H$
NH_2
LTE_4

Figure 2–4 Formation of prostaglandin from arachidonic acid.

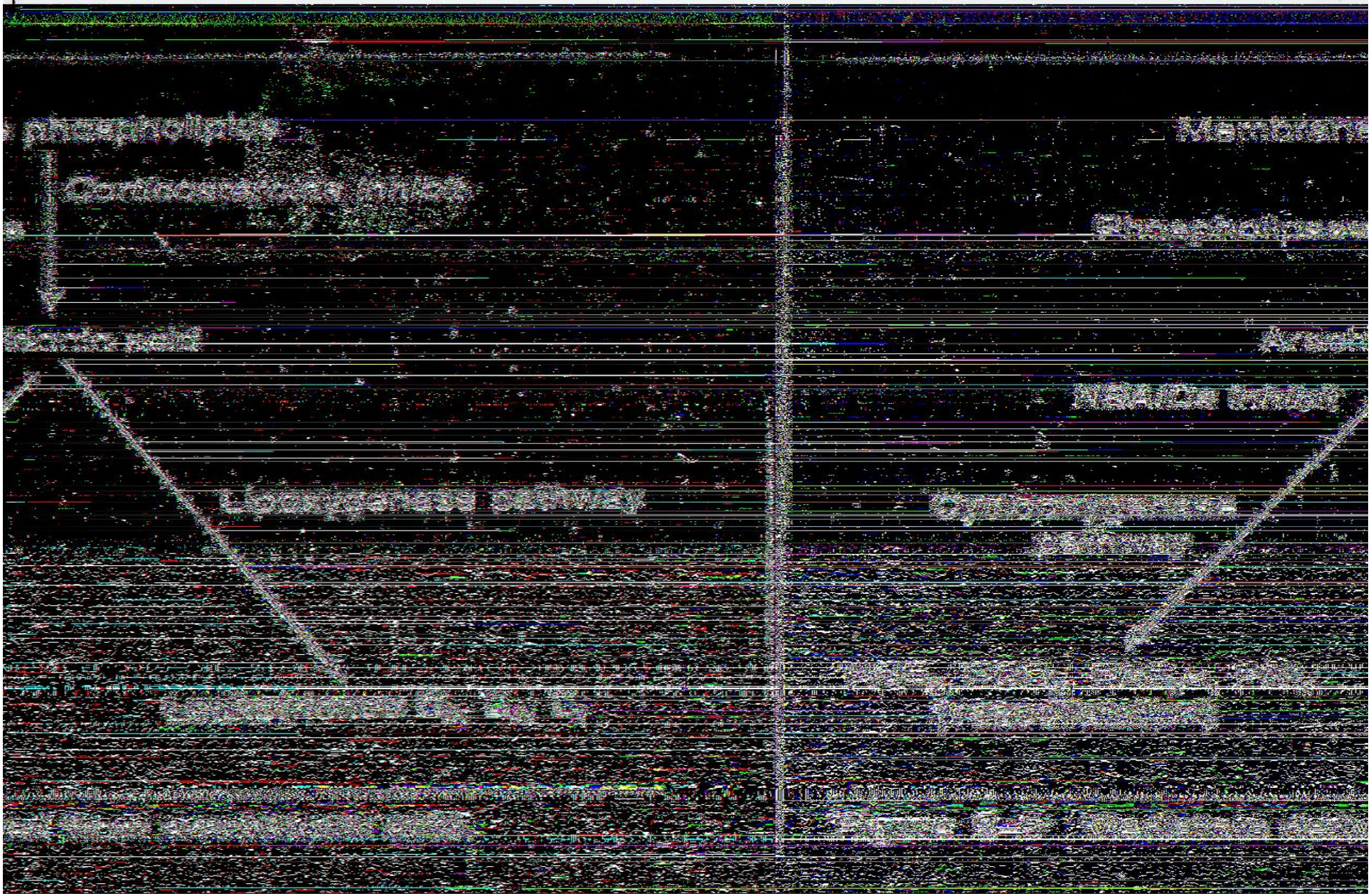
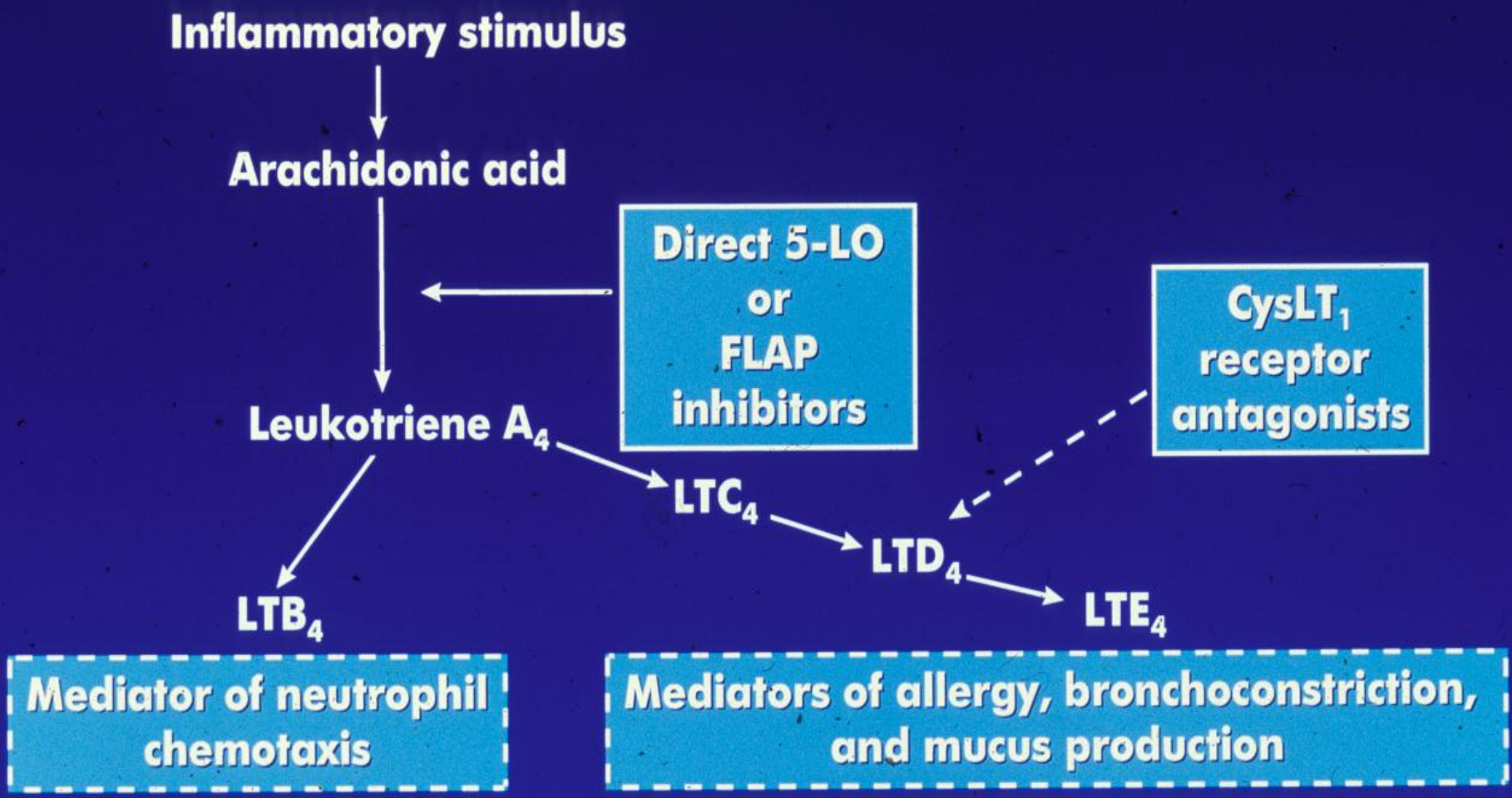


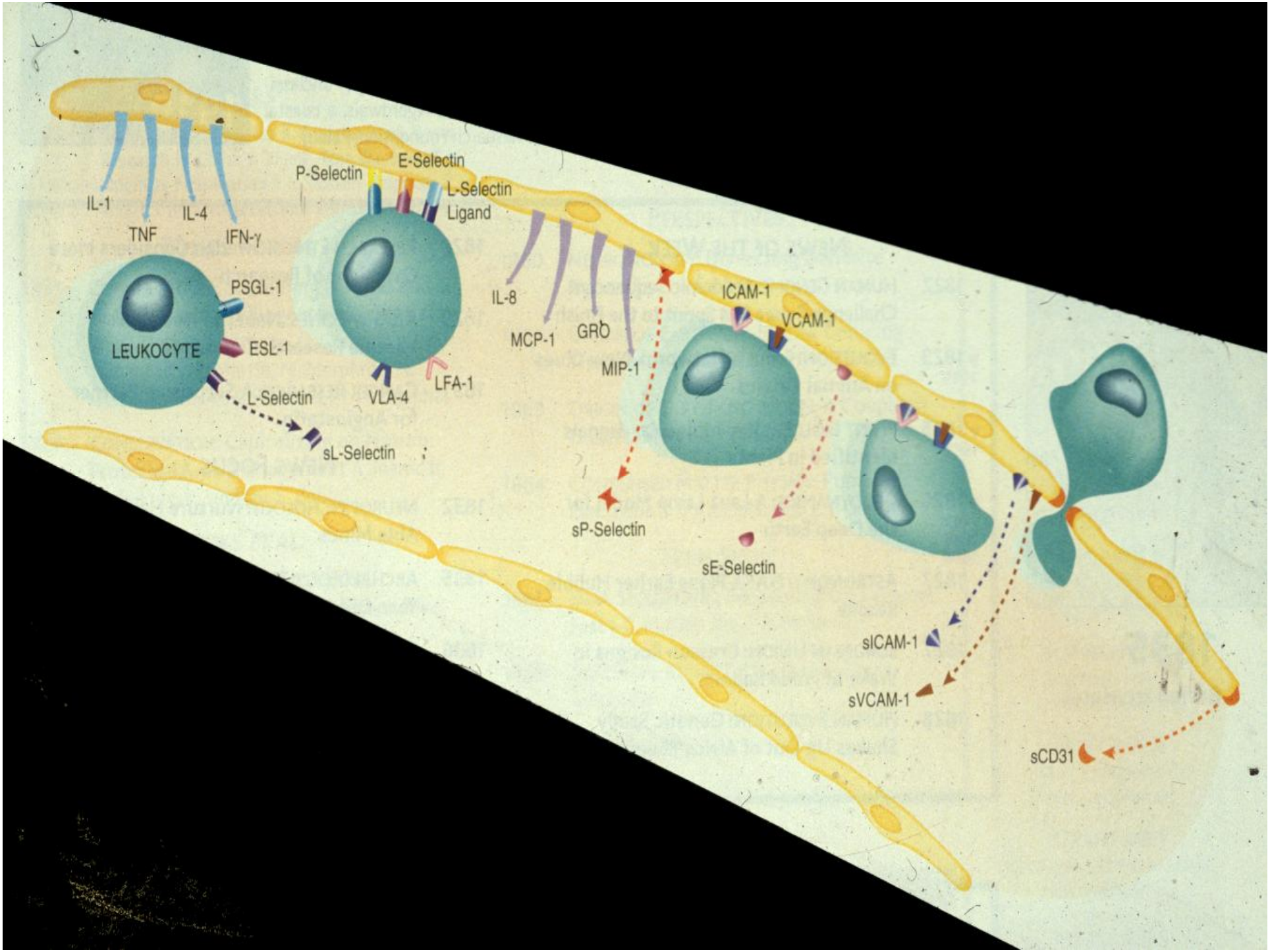
FIGURE 1
Illustration shows truncated bronchioles in gasping asthmatic patient, with typical histologic features, such as mucous plug formation, desquamation of epithelium, smooth muscle hypertrophy, vasodilation, and neutrophil and eosinophil infiltration. Other involved cells include macrophages, mast cells, basophils, and lymphocytes.

Depicted symbolically on the right is the antileukotriene zileuton blocking the production of leukotriene A4 (LTA4) and subsequent LTB4. It does so by preventing 5-lipoxygenase activating protein (FLAP) from presenting 5-lipoxygenase to arachidonic acid. Zafirlukast works differently, blocking *cys*LT receptors for LTC4, LTD4, and LTE4.

Mechanisms of Action



Adapted from Holgate ST et al. *J Allergy Clin Immunol.* 1996;*8(1)*:1-13; Henderson WR Jr. *Ann Allergy.* 1994;*72(3)*:272-278.


IL-1
TNF
IL-4
IFN-γ
P-Selectin
E-Selectin
L-Selectin
Ligand
PSGL-1
LEUKOCYTE
ESL-1
L-Selectin
sL-Selectin
VLA-4
LFA-1
IL-8
MCP-1
GRO
MIP-1
ICAM-1
VCAM-1
sP-Selectin
sE-Selectin
sICAM-1
sVCAM-1
sCD31

Strategies for Leukotriene Inhibition in Asthma

- 5-LO inhibitors, directly or via FLAP
  - Inhibit formation of LTB_4, LTC_4, LTD_4, and LTE_4
  - Decrease LTE_4 urinary excretion
- LT receptor antagonists
  - Selective, high-affinity $CysLT_1$ receptor antagonists
  - Oral, IV, and inhaled[5]

[5]Spector SL. *Ann Allergy Asthma Immunol.* 1995;75:463-470.

Clinical Features and Pharmacotherapy of Asthma

	Step 1 Mild Intermittent	Step 2 Mild Persistent	Step 3 Moderate Persistent	Step 4 Severe Persistent
Clinical Features				
Days with symptoms	≤2/week	3–6/week	Daily	Continual
Nights with symptoms	≤2/month	3–4/month	≥5/month	Frequent
PEFR or FEV1*	≥80%	≥80%	60%–80%	≤60%
PEF Variability	<20%	20–30%	>30%	>30%
Management				
Quick relief	← Short-acting inhaled beta$_2$ agonist as needed →			
Long-term control	None	Low-dose inhaled corticosteroids OR Cromolyn or Nedocromil OR Sustained-release theophylline OR Antileukotriene agent	Medium-dose inhaled corticosteroid OR Low-medium dose inhaled corticosteroid and long-acting bronchodilator† If needed: Medium-high dose inhaled corticosteroid and long-acting bronchodilator†	High-dose inhaled corticosteroid and long-acting bronchodilator† and long-term systemic corticosteroids#

**Expressed as a percent of predicted*

†Long-acting inhaled beta-agonist, sustained release theophylline, or beta-agonist tablets

#Attempt to reduce systemic steroid dose and maintain on high-dose inhaled corticosteroids

Source: Based on reference 21

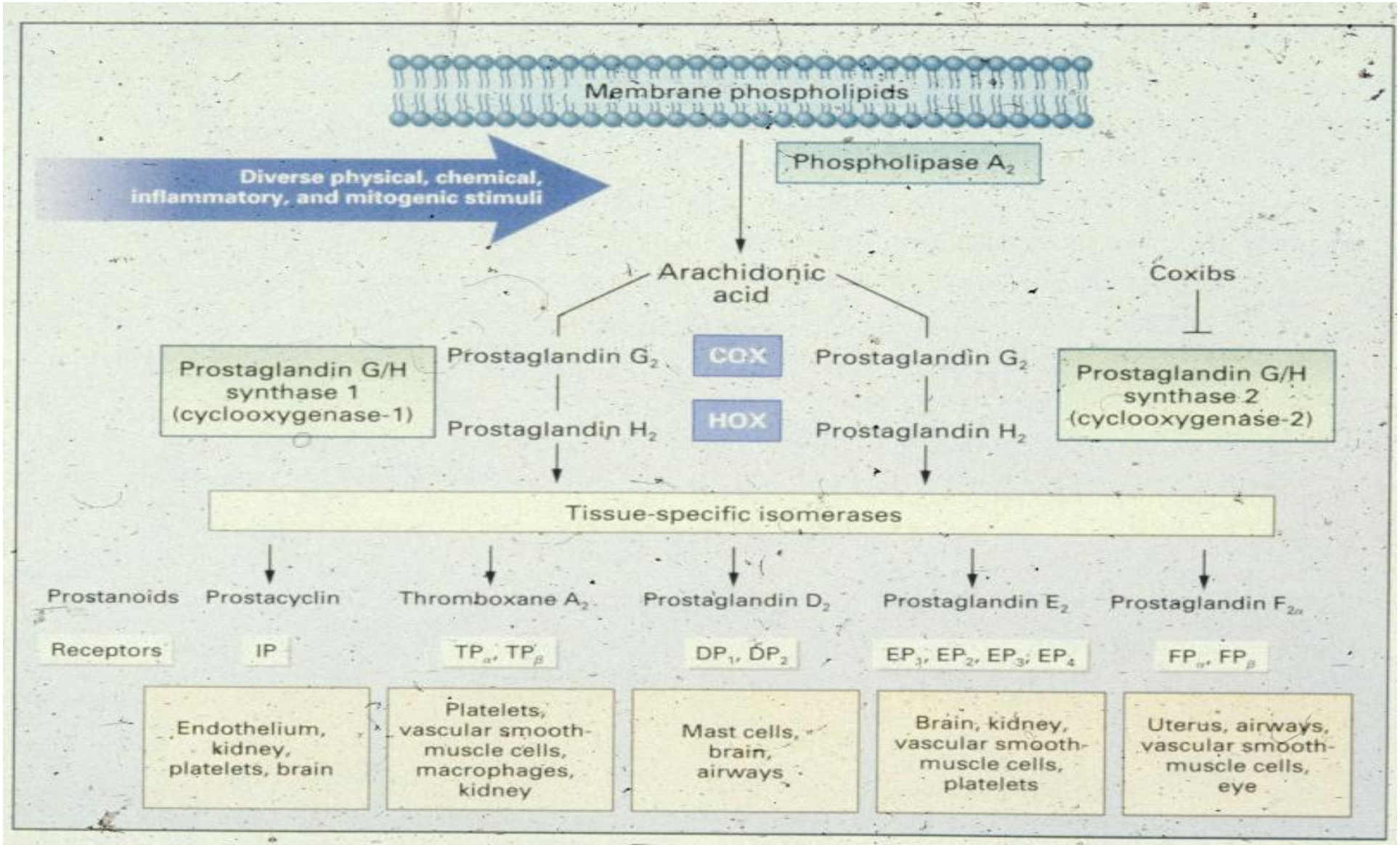
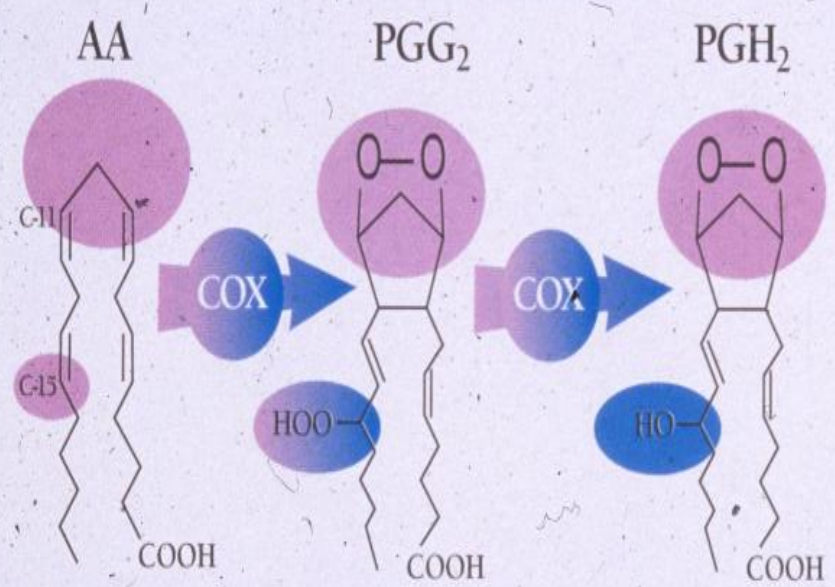


Figure 1. Production and Actions of Prostaglandins and Thromboxane.

Arachidonic acid, a 20-carbon fatty acid containing four double bonds, is liberated from the *sn*2 position in membrane phospholipids by phospholipase A_2, which is activated by diverse stimuli. Arachidonic acid is converted by cytosolic prostaglandin G/H synthases, which have both cyclooxygenase (COX) and hydroperoxidase (HOX) activity, to the unstable intermediate prostaglandin H_2. The synthases are colloquially termed cyclooxygenases and exist in two forms, cyclooxygenase-1 and cyclooxygenase-2. Coxibs selectively inhibit cyclooxygenase-2. Prostaglandin H_2 is converted by tissue-specific isomerases to multiple prostanoids. These bioactive lipids activate specific cell-membrane receptors of the superfamily of G-protein–coupled receptors. Some of the tissues in which individual prostanoids exert prominent effects are indicated. IP denotes prostacyclin receptor, TP thromboxane receptor, DP prostaglandin D_2 receptor, EP prostaglandin E_2 receptor, and FP prostaglandin $F_{2\alpha}$ receptor.



Prostanoid	Predominant location	Function
TxA_2 (Thromboxane A_2)	Platelets and monocytes	Platelet aggregation; broncho- and vasoconstriction; cellular proliferation
PGI_2 (Prostacyclin)	Vascular endothelium and subendothelium	Inhibition of platelet aggregation and adhesion; broncho- and vasodilation; cholesterol efflux from arterial cells; vascular leakage
PGD_2	Mast cells; PGD synthase also expressed in brain	Bronchospasm and allergic asthma; inhibition of platelet aggregation; sleep
PGE_2	Renal medulla, gastric mucosa, platelets, microvascular endothelium	Inhibition of sodium reabsorption; broncho- and vasodilation; uterine contraction; lymphocyte function; presynaptic adrenergic modulation
$PGF_{2\alpha}$	Brain, uterus	Bronchial and uterine contraction; uterine vasoconstriction; parturition

Figure 1. Prostanoid activities derived from COX activity. Prostaglandin G/H synthase (COX) is bifunctional: its *bis*-cyclooxygenase activity, directed both at C-11 and C-15 of arachidonic acid (AA), is indicated in purple; its hydroperoxidase activity, directed to the peroxide adduct at C-15 of prostaglandin G_2 (PGG_2), is indicated in blue.

Thromboxane vs. Prostacyclin

- Thromboxane (platelet) promotes platelet aggregation; prostacyclin (endothelium) inhibits platelet aggregation. Question: Why is low-dose aspirin such a potent antiplatelet agent?
- Thromboxane is a brochoconstrictor; Prostacyclin is a brochodilator.
- Thromboxane is a vasoconstrictor; Prostacyclin is a vasodilator

Prostaglandins (PGE2) and Inflammatory pain sensitization

- PGE2 has recently been shown to inhibit a glycine receptor (GlyR alpha3) in its action regulating central inflammatory pain sensation.
- GlyR alpha3 is expressed in the superficial layers of the spinal cord dorsal horn.

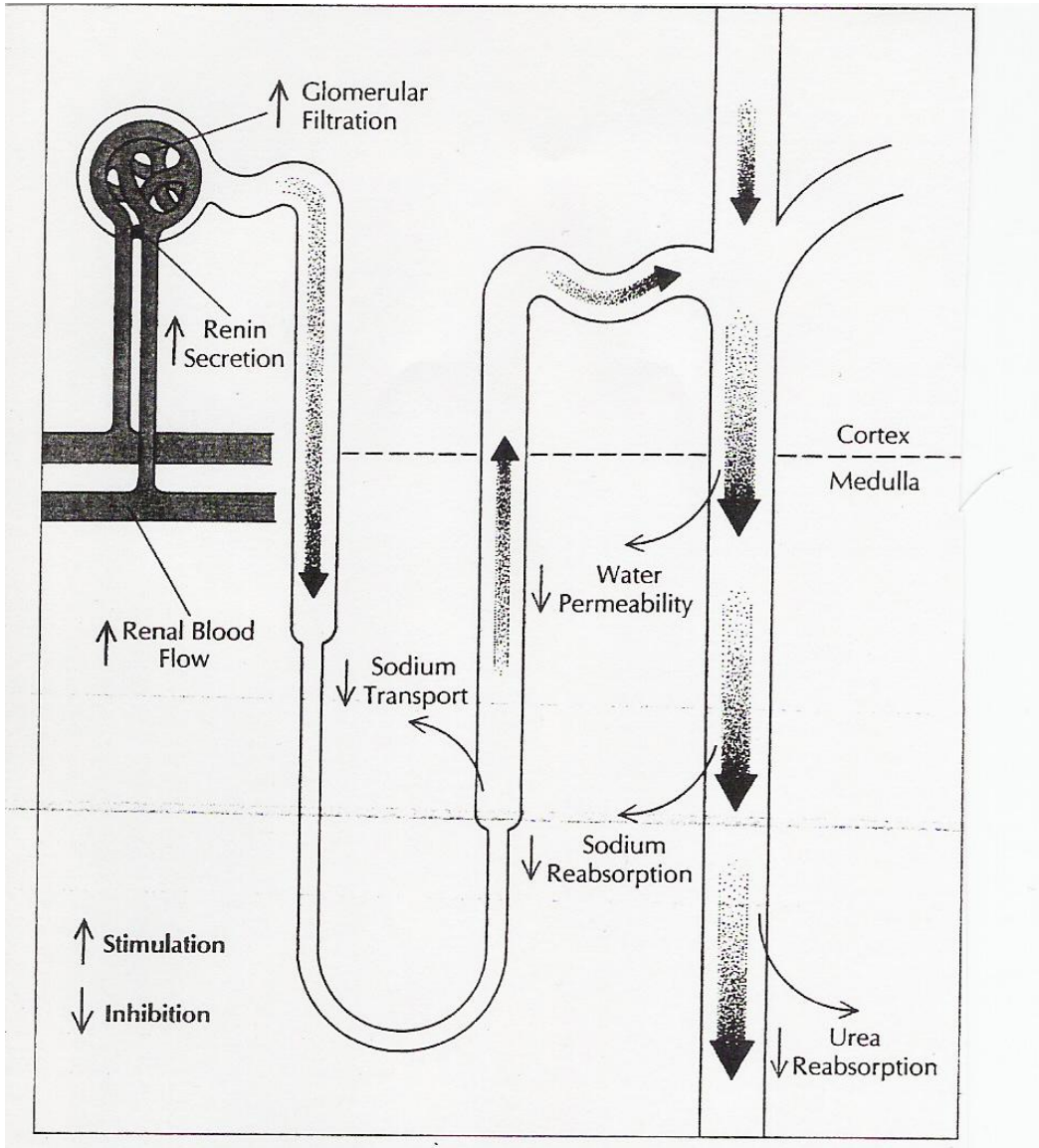
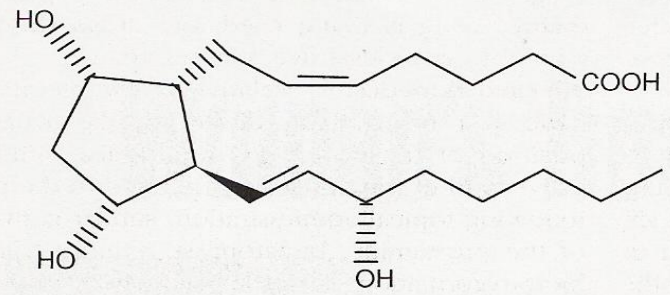


Figure 3. **Suppression of prostaglandin biosynthesis by NSAIDs may variously impair renal function. Prostaglandins synthesized in the renal cortex act locally to augment renin release from the juxtaglomerular cells and to increase both renal blood flow and glomerular filtration rate. In the medulla, prostaglandins increase renal blood flow, inhibit sodium transport from the thick ascending limb of Henle's loop, antagonize the action of vasopressin in the collecting duct, and inhibit reabsorption of urea and sodium from the duct.**

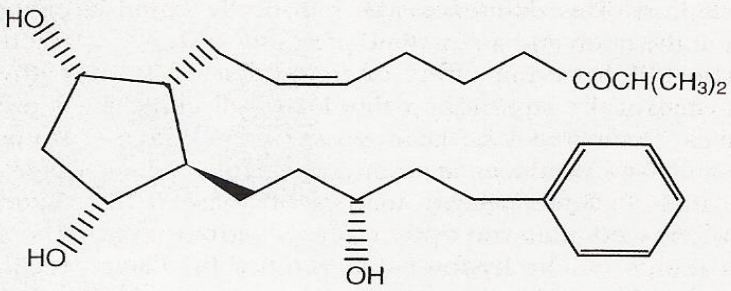
Indications for Prostaglandin analogues

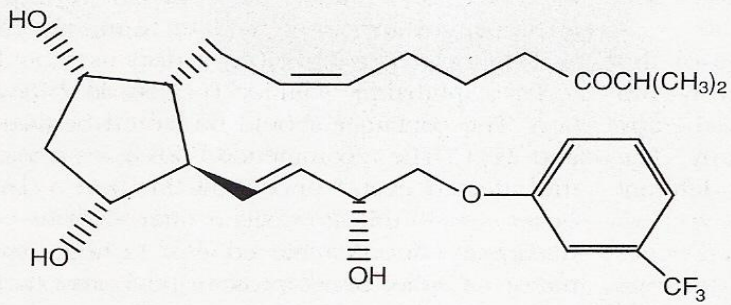
- Alprostadil- maintains a patent ductus arteriosus in the fetus; useful in treating erectile dysfunction
- Misoprostil – a PGE2 analogue used to treat NSAID-induced gastritis
- Carboprost; Dinoprostone – abortafacients, may be used to induce labor
- Lantanoprost – used in treating glaucoma



$PGF_{2\alpha}$

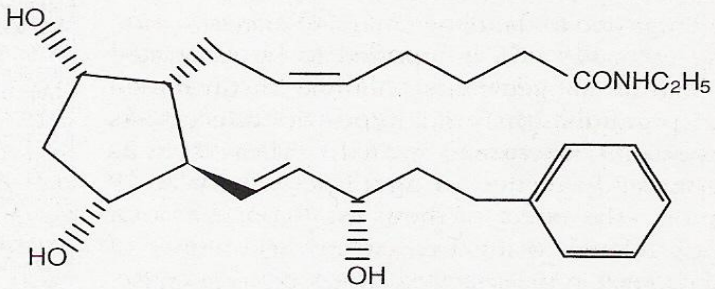
Latanoprost





Travoprost

Bimatoprost



Comparison of COX Enzyme Distribution

Location	COX-1	COX-2
Chondrocyte	X	X
Gastrointestinal tract	X	
Platelets	X	
Endothelial cells	X	
Renal medulla	X	
Renal cortex		X
Brain		X
Synovial tissue		X
Colorectal tumors		X
Breast cancer		X
Lung	X	
Liver	X	
Spleen	X	

References 21,22,28

Table 1. Inhibition of COX-1 and COX-2 in intact cells

Drug	IC_{50} values (μmol dl^{-3})		COX-2:COX-1	Refs
	COX-1	COX-2		
Piroxicam	0.0024	0.60	250	43
Aspirin	1.67	278	166	36
Indomethacin	0.028	1.68	60	43
Ibuprofen	4.85	72.8	15	36
Salicylate	254	725	2.8	36
Meloxicam	0.21	0.17	0.8	44

Bovine aortic endothelial cells were used for determining COX-1 activity; J774.2 macrophages were induced with lipopolysaccharide to expres
COX-2 (Refs 36, 43 and 44).

Table 2. Effects of cyclooxygenase inhibitors on ulcer formation and swelling of contralateral hind paw in rats with a vant arthritis.

Drug	COX-1 ID_{50} ulcer [mg kg^{-1} day^{-1}]	COX-2 ID_{50} swelling [mg kg^{-1} day^{-1}]	COX-2 : COX-1
Aspirin	32.4	198	6.1
Piroxicam	1.07	0.76	0.7
Indomethacin	2.35	0.67	0.3
Meloxicam	2.47	0.12	0.05

Data from Ref. 46.

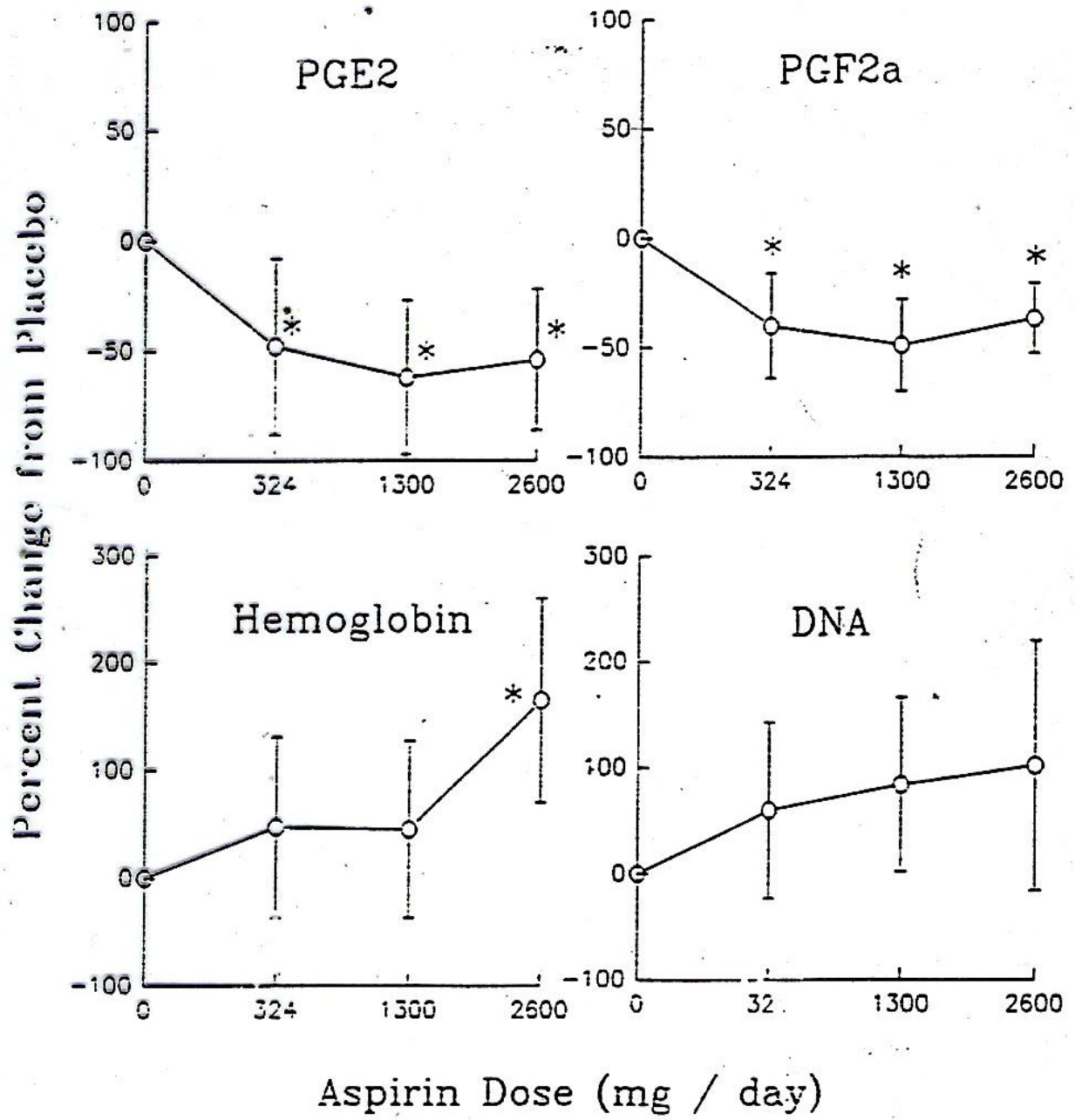


Figure 1. Effects of aspirin dose on gastric juice outputs. Results are expressed as a mean percent change from placebo for nine volunteers, with 95% CIs. Mean (± SE) outputs for the zero dose (placebo) were 108.9 ± 25.0 ng/h (PGE_2); 56.1 ± 9.4 ng/h (PGF_{2a}); 16.7 ± 5.6 mg/h (hemoglobin); and 436.4 ± 130.8 μg/h (DNA). * $P <$ 0.05 compared with placebo.

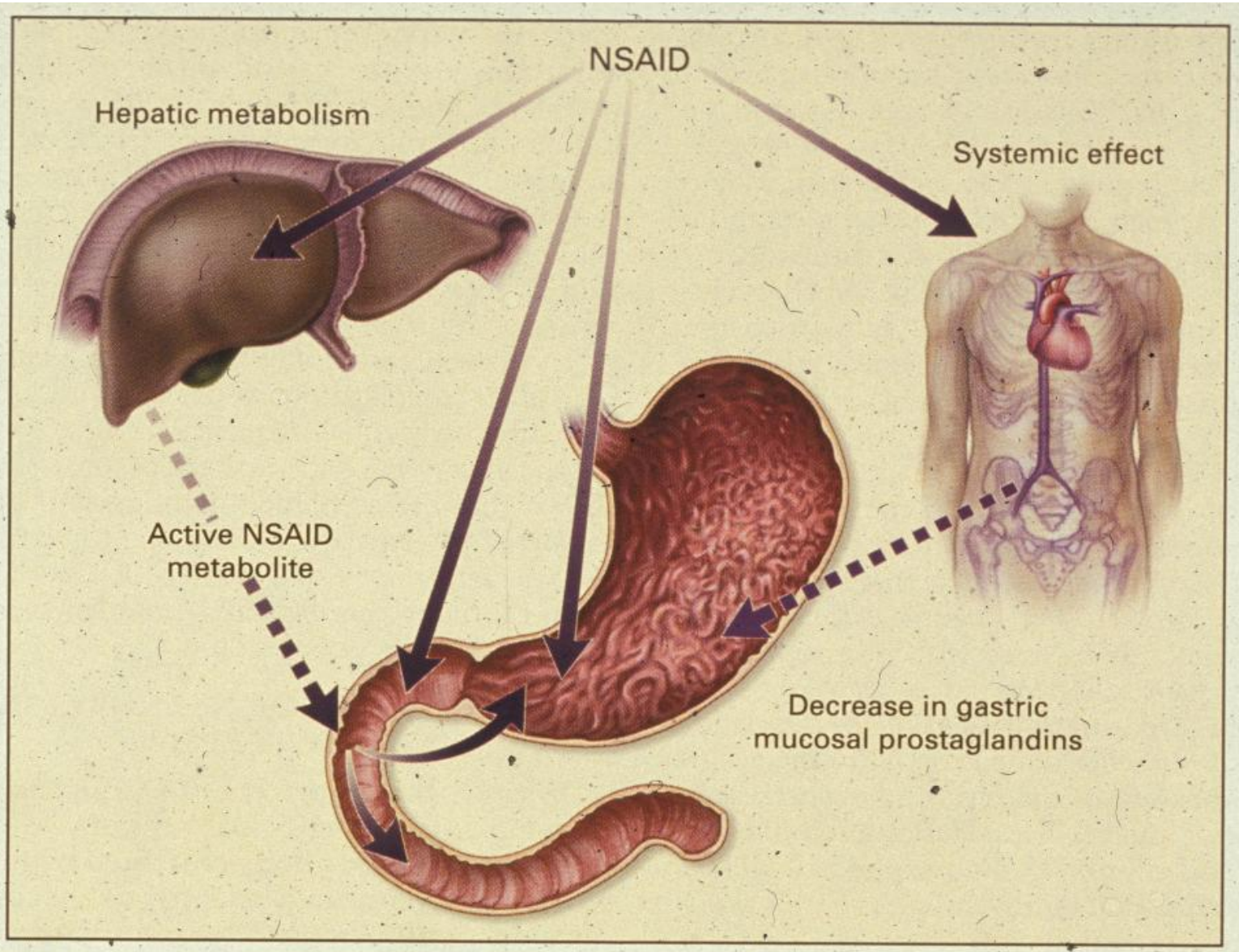


Figure 2. Mechanisms by Which NSAIDs Induce Gastroduodenal Mucosal Injury.

According to the dual-injury hypothesis of Schoen and Vender,[37] NSAIDs have direct toxic effects on the gastroduodenal mucosa (solid arrows) and indirect effects through active hepatic metabolites and decreases in mucosal prostaglandins (broken arrows). Hepatic metabolites are excreted into the bile and subsequently into the duodenum, where they cause mucosal damage to the stomach by duodenogastric reflux and mucosal damage to the small intestine by antegrade passage through the gastrointestinal tract. Adapted from Schoen and Vender.[37]

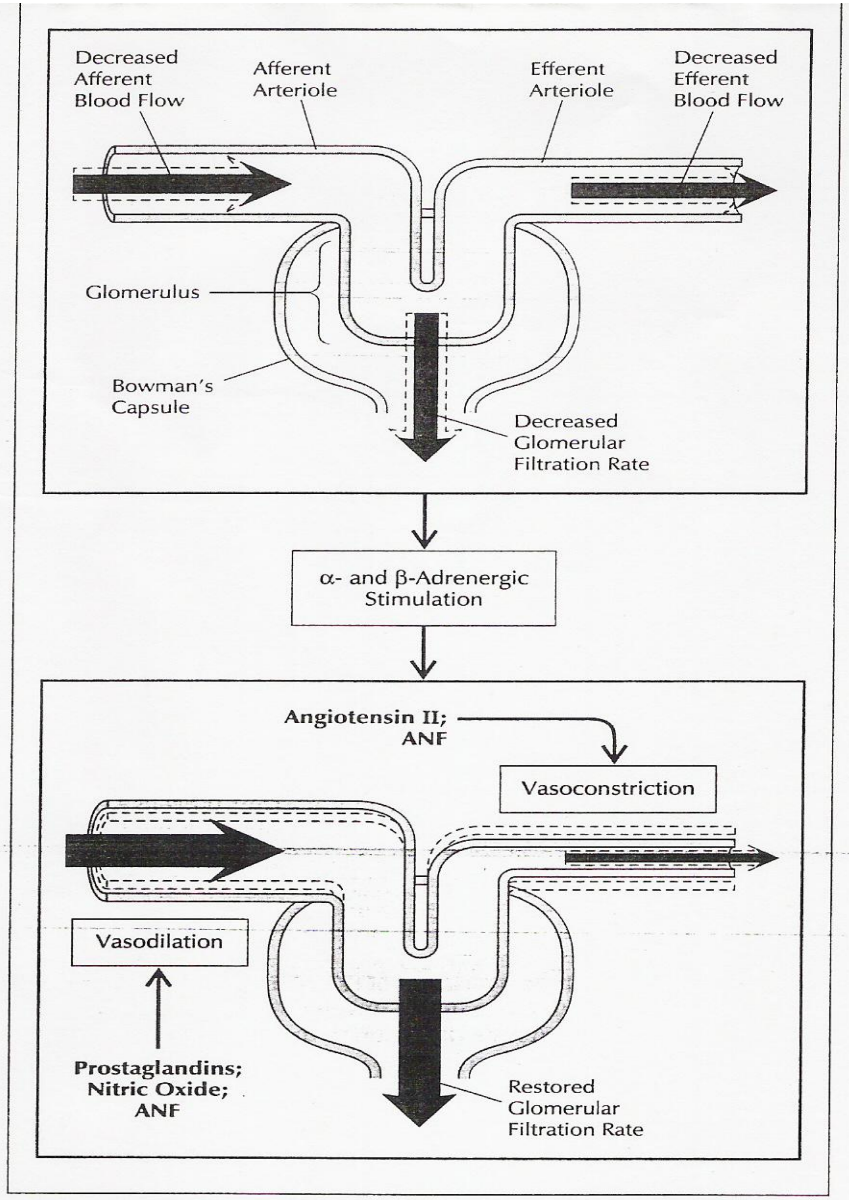


Figure 1. **With decreased renal perfusion, afferent and efferent arteriolar blood flow and glomerular capillary hydrostatic pressure and filtration rate are also decreased (top). To compensate, the adrenergic nervous system is stimulated, which in turn activates the renin-angiotensin system and production of prostaglandins (bottom). This increases afferent vasodilation by prostaglandins and vasoconstriction of efferent arterioles by angiotensin II. Other possibly relevant factors include nitric oxide, which induces afferent vasodilation, and atrial natriuretic factor, which increases efferent arteriolar resistance in association with afferent arteriolar relaxation.**

Aspirin (Acetyl Salicylic Acid)

- Irreversibly acetylates cyclooxygenase permanently disabling the enzyme
- Salicylate moiety competitively inhibits cyclooxygenase
- Aspirin displays dose-dependent kinetics
- Signs and symptoms of salicylate toxicity
- Dosing of aspirin differs greatly depending on the indication

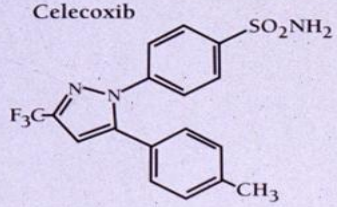
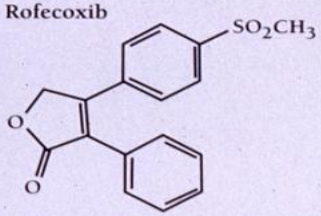
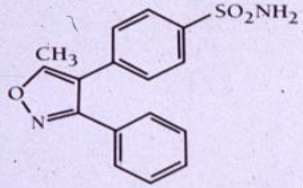
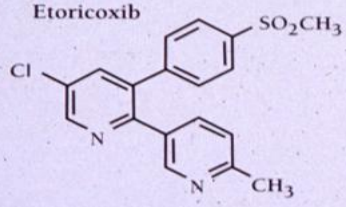
Celecoxib 	IC_{50}[a] (COX-1)	6.7 μM[b]
	IC_{50} (COX-2)	0.87 μM
	COX-2 Selectivity ratio[c]	7.6
Rofecoxib 	IC_{50} (COX-1)	18.8 μM
	IC_{50} (COX-2)	0.53 μM
	COX-2 Selectivity ratio	35
Valdecoxib 	IC_{50} (COX-1)	26.1 μM
	IC_{50} (COX-2)	0.87 μM
	COX-2 Selectivity ratio	30
Etoricoxib 	IC_{50} (COX-1)	116 μM
	IC_{50} (COX-2)	1.1 μM
	COX-2 Selectivity ratio	106

Figure 2. Structures and selectivity ratios of four coxibs as measured in human whole blood assays. In addition to the two COX-2 inhibitors that are currently on the market (i.e., celecoxib and rofecoxib), data are shown for two COX-2 inhibitors that are currently in clinical development (i.e., valdecoxib and etoricoxib).

[a] IC_{50} is the inhibitor concentration necessary to reduce COX rates by 50 percent.
[b] All data were obtained through the human whole blood assay (*17*).
[c] The selectivity of each compound for the COX-2 isoform is determined as the ratio IC_{50} (COX-1)/IC_{50} (COX-2).