FANS e PARACETAMOLO

Introduzione ai farmaci antipiretici e antinfiammatori

Diego Fornasari

Dipartimento di Biotecnologie Mediche e Medicina Traslazionale

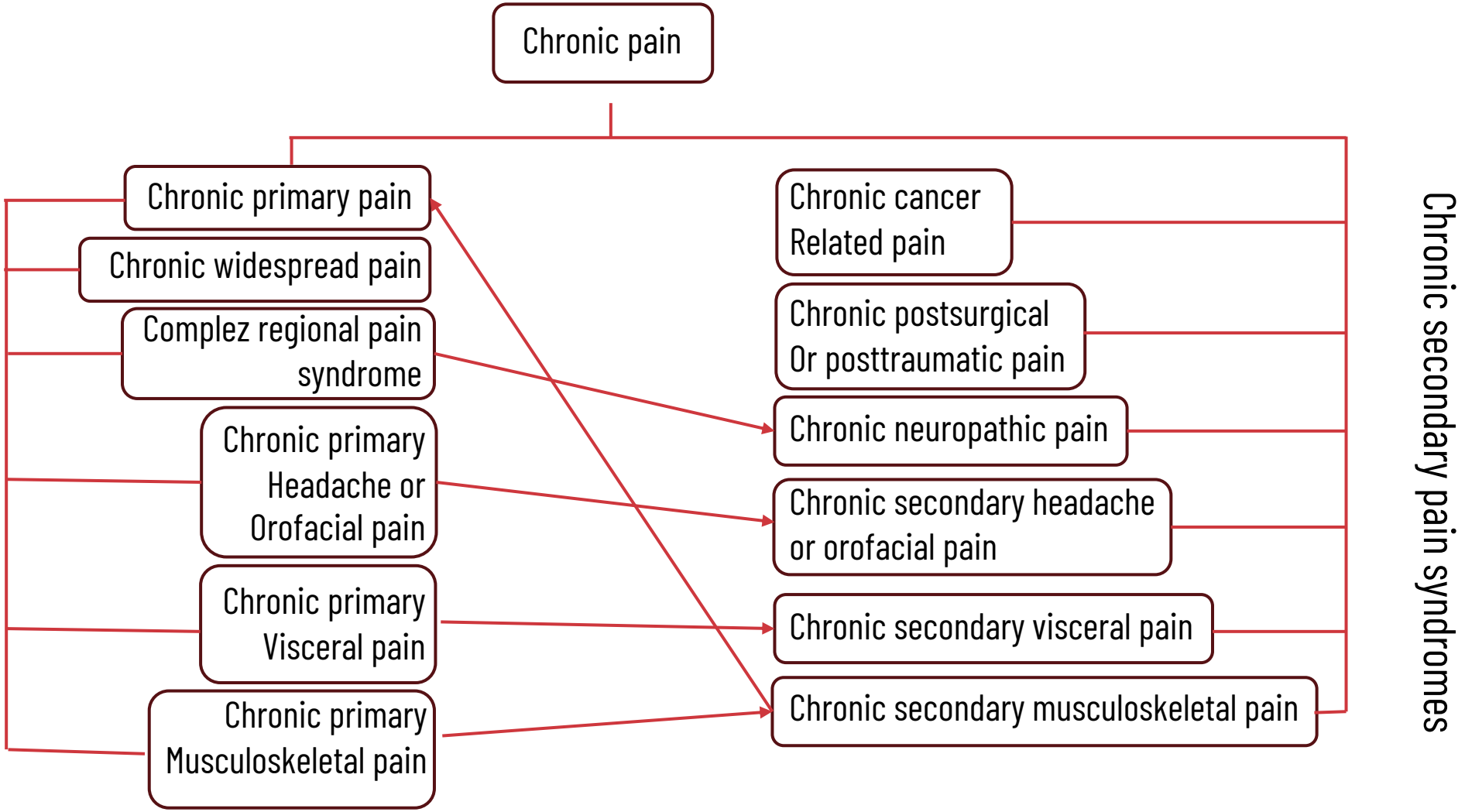
Università degli Studi di Milano «La Statale»

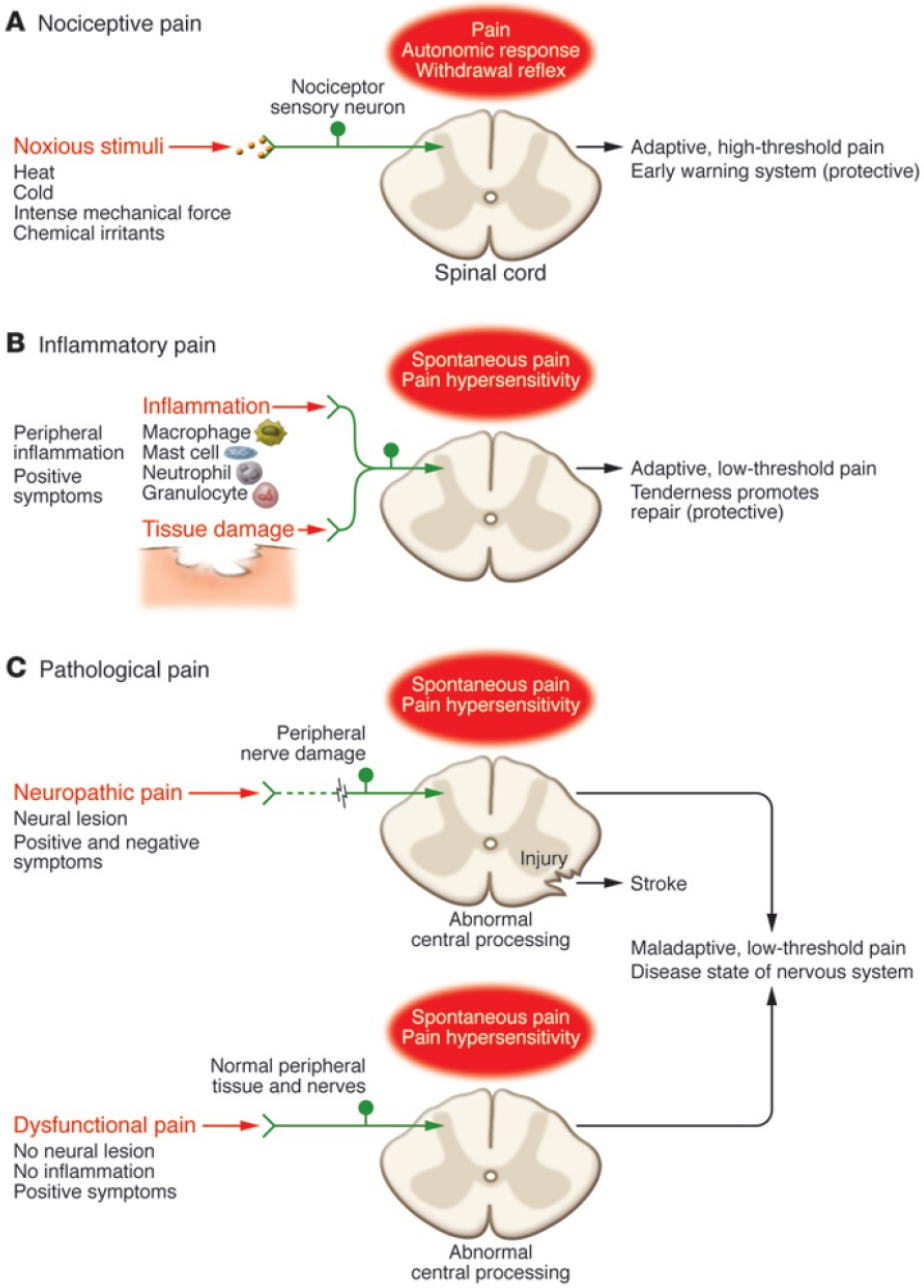
Narrative Review

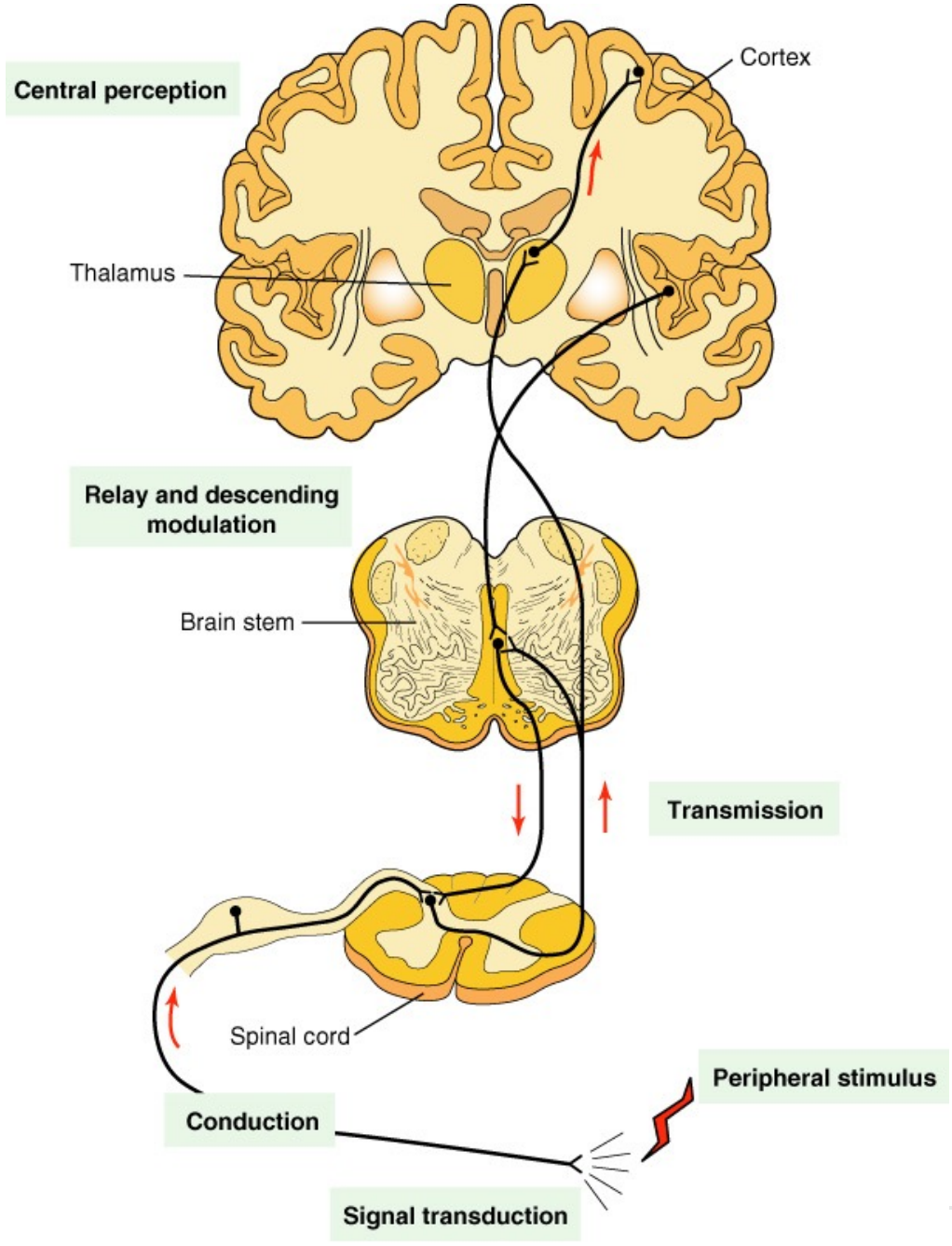
PAIN

Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the *International Classification of Diseases (ICD-11)*

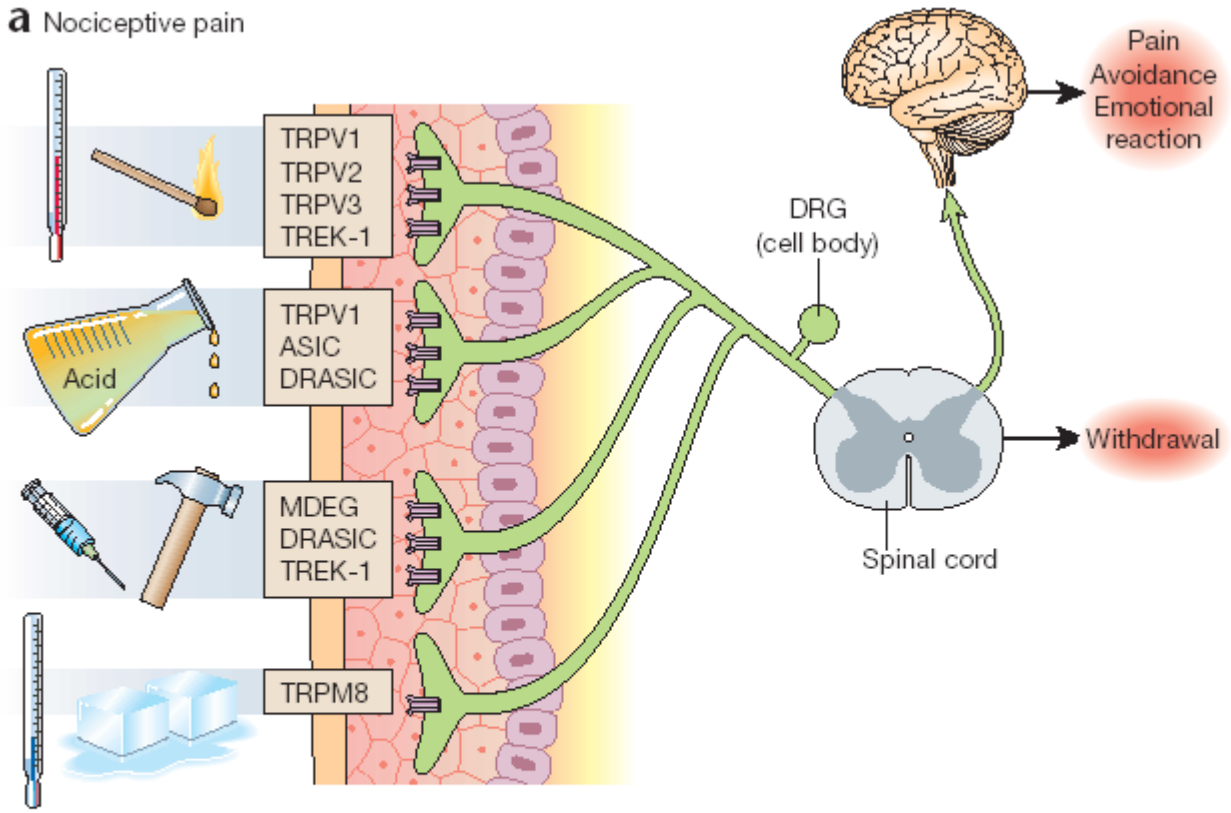
Rolf-Detlef Treede[a,*], Winfried Rief[b], Antonia Barke[b], Qasim Aziz[c], Michael I. Bennett[d], Rafael Benoliel[e], Milton Cohen[f], Stefan Evers[g], Nanna B. Finnerup[h,i], Michael B. First[j], Maria Adele Giamberardino[k], Stein Kaasa[l,m,n], Beatrice Korwisi[b], Eva Kosek[o], Patricia Lavand'homme[p], Michael Nicholas[q], Serge Perrot[r], Joachim Scholz[s], Stephan Schug[t,u], Blair H. Smith[v], Peter Svensson[w,x], Johan W.S. Vlaeyen[y,z,aa], Shuu-Jiun Wang[bb,cc]

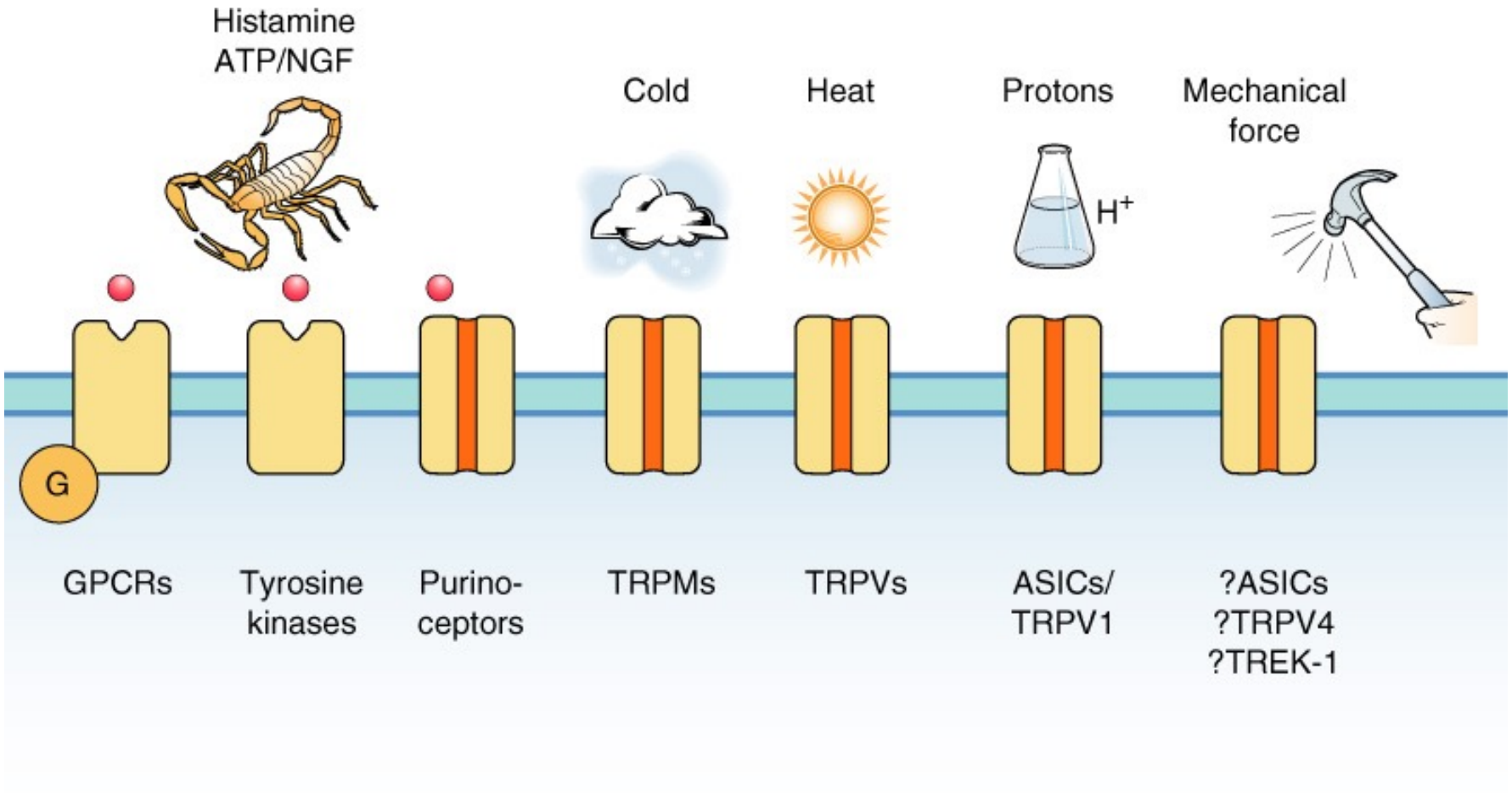

Chronic pain
Chronic primary pain
Chronic widespread pain
Complez regional pain syndrome
Chronic primary Headache or Orofacial pain
Chronic primary Visceral pain
Chronic primary Musculoskeletal pain
Chronic cancer Related pain
Chronic postsurgical Or posttraumatic pain
Chronic neuropathic pain
Chronic secondary headache or orofacial pain
Chronic secondary visceral pain
Chronic secondary musculoskeletal pain
Chronic secondary pain syndromes

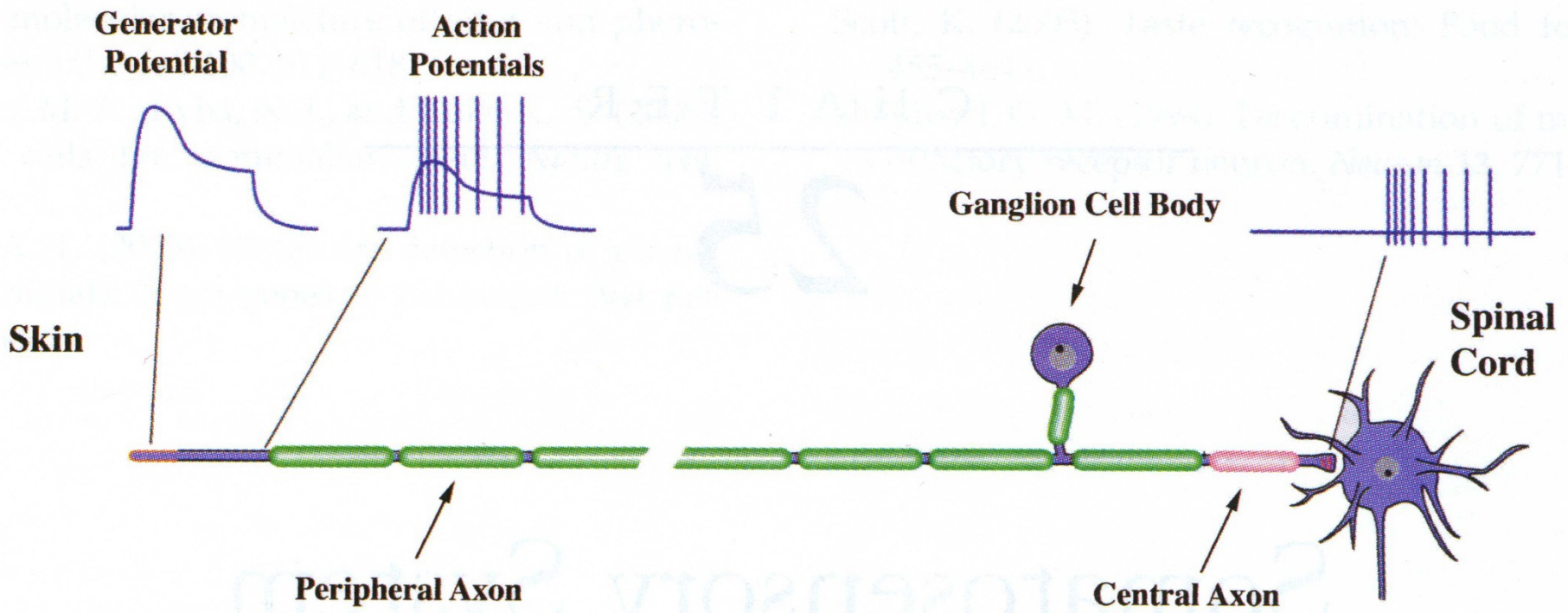

A Nociceptive pain
Pain
Autonomic response
Withdrawal reflex
Nociceptor
sensory neuron
Noxious stimuli
Heat
Cold
Intense mechanical force
Chemical irritants
Adaptive, high-threshold pain
Early warning system (protective)
Spinal cord
B Inflammatory pain
Spontaneous pain
Pain hypersensitivity
Inflammation
Peripheral
inflammation
Positive
symptoms
Macrophage
Mast cell
Neutrophil
Granulocyte
Tissue damage
Adaptive, low-threshold pain
Tenderness promotes
repair (protective)
C Pathological pain
Spontaneous pain
Pain hypersensitivity
Peripheral
nerve damage
Neuropathic pain
Neural lesion
Positive and negative
symptoms
Injury
Stroke
Abnormal
central processing
Maladaptive, low-threshold pain
Disease state of nervous system
Spontaneous pain
Pain hypersensitivity
Normal peripheral
tissue and nerves
Dysfunctional pain
No neural lesion
No inflammation
Positive symptoms
Abnormal
central processing

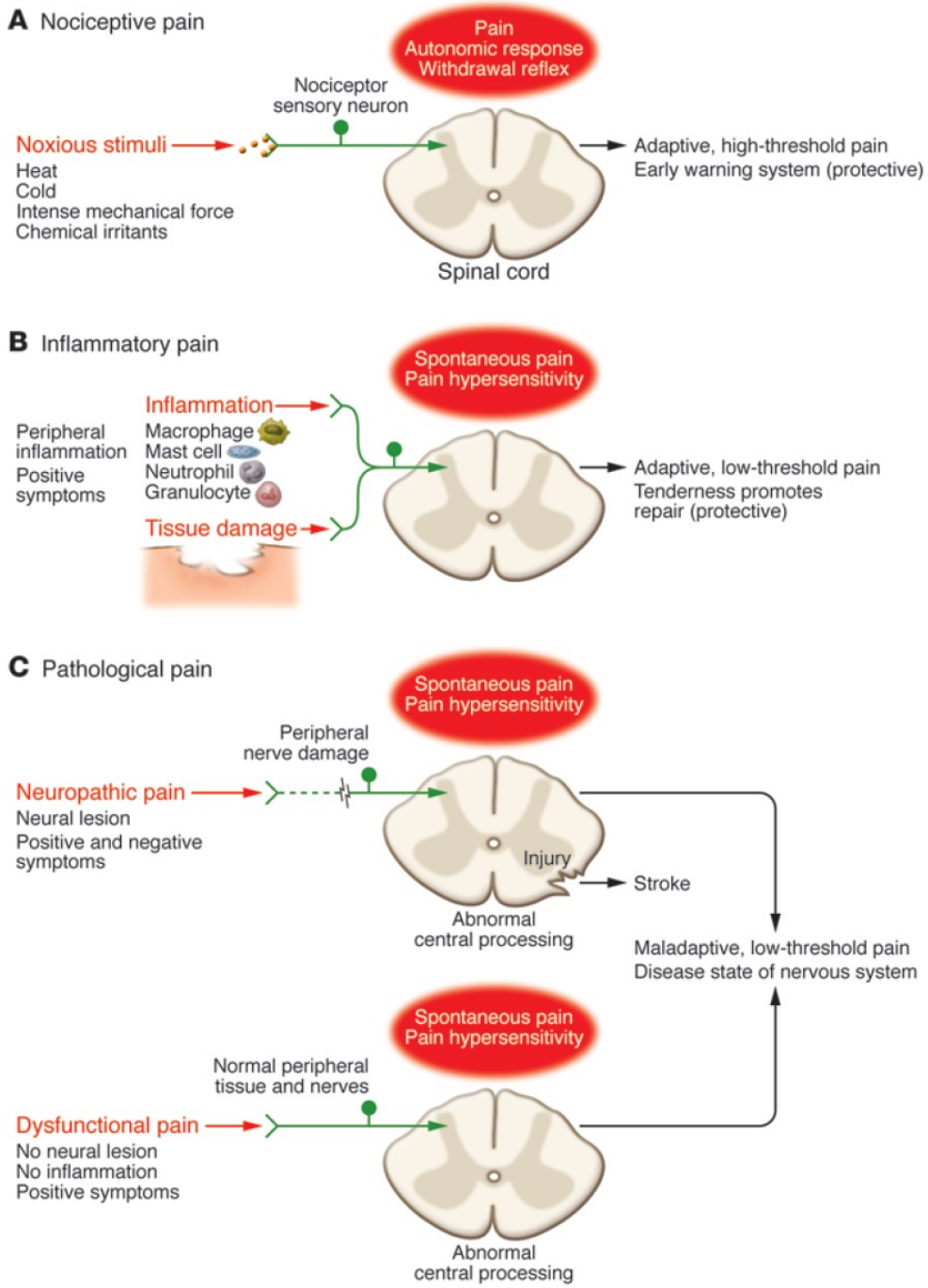


Trasduzione


a Nociceptive pain
TRPV1
TRPV2
TRPV3
TREK-1
TRPV1
ASIC
DRASIC
Acid
MDEG
DRASIC
TREK-1
TRPM8
DRG
(cell body)
Pain
Avoidance
Emotional
reaction
Withdrawal
Spinal cord

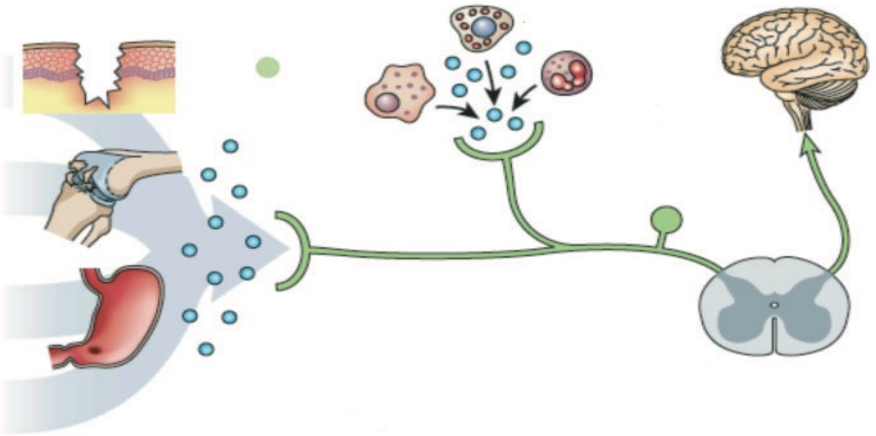


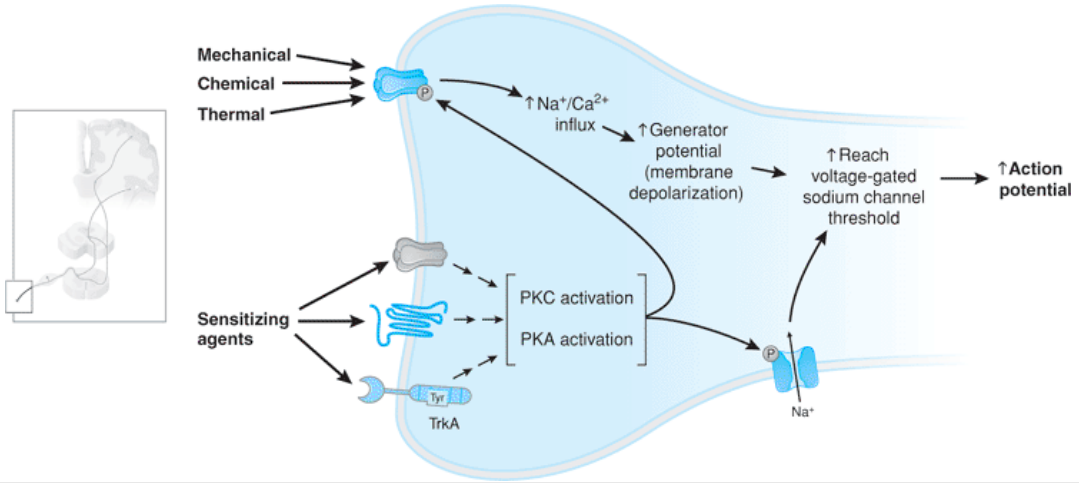

Generator Potential
Action Potentials
Skin
Ganglion Cell Body
Spinal Cord
Peripheral Axon
Central Axon


A Nociceptive pain
Pain
Autonomic response
Withdrawal reflex
Nociceptor
sensory neuron
Noxious stimuli
Heat
Cold
Intense mechanical force
Chemical irritants
Adaptive, high-threshold pain
Early warning system (protective)
Spinal cord
B Inflammatory pain
Spontaneous pain
Pain hypersensitivity
Inflammation
Peripheral
inflammation
Positive
symptoms
Macrophage
Mast cell
Neutrophil
Granulocyte
Tissue damage
Adaptive, low-threshold pain
Tenderness promotes
repair (protective)
C Pathological pain
Spontaneous pain
Pain hypersensitivity
Peripheral
nerve damage
Neuropathic pain
Neural lesion
Positive and negative
symptoms
Injury
Stroke
Abnormal
central processing
Maladaptive, low-threshold pain
Disease state of nervous system
Spontaneous pain
Pain hypersensitivity
Normal peripheral
tissue and nerves
Dysfunctional pain
No neural lesion
No inflammation
Positive symptoms
Abnormal
central processing

Dolore infiammatorio

Sensibilizzazione periferica





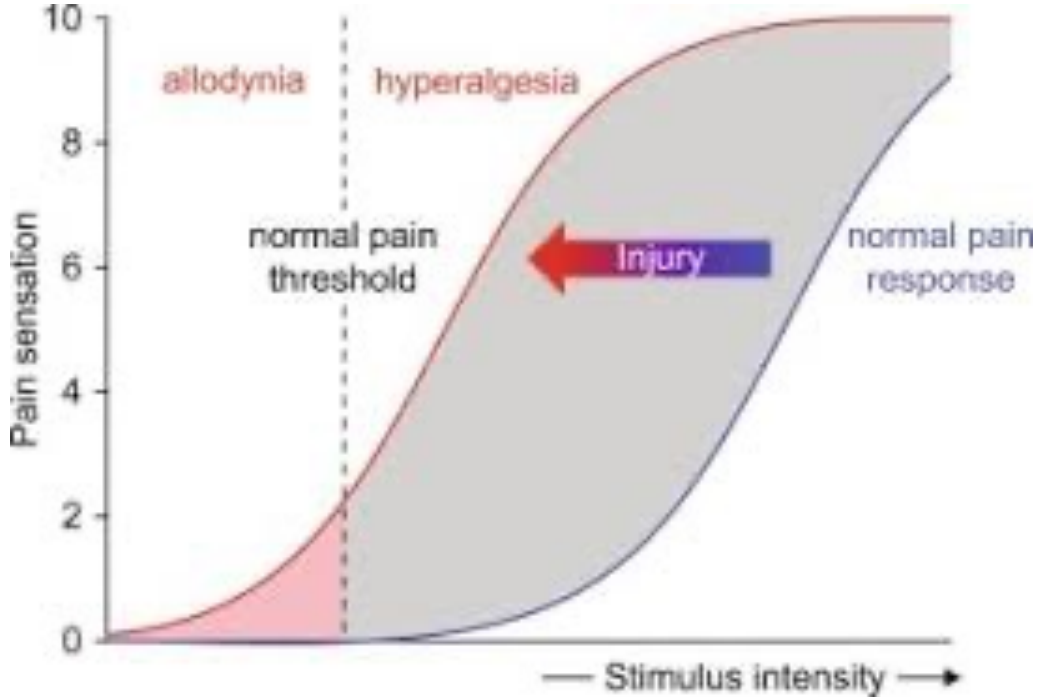
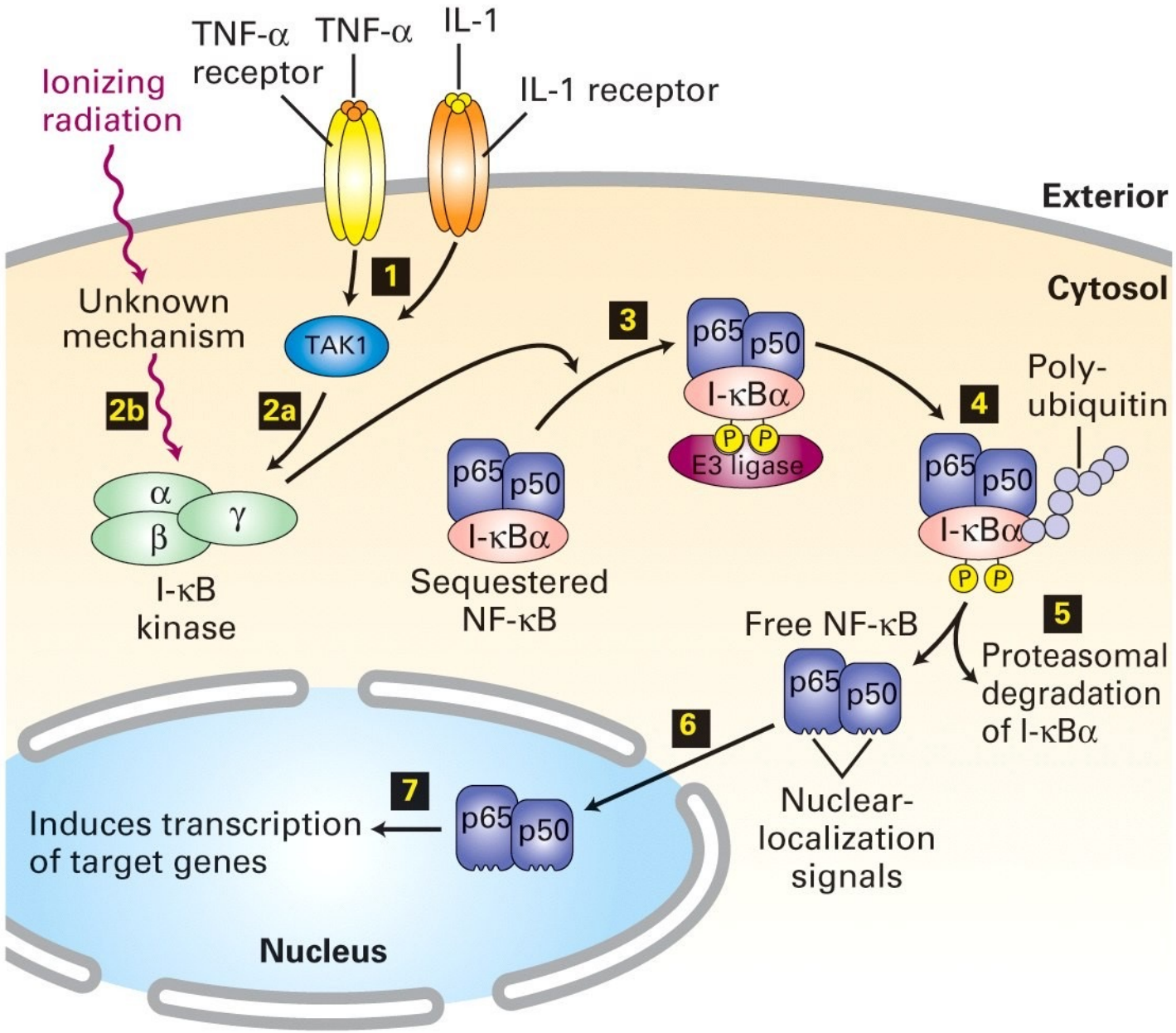
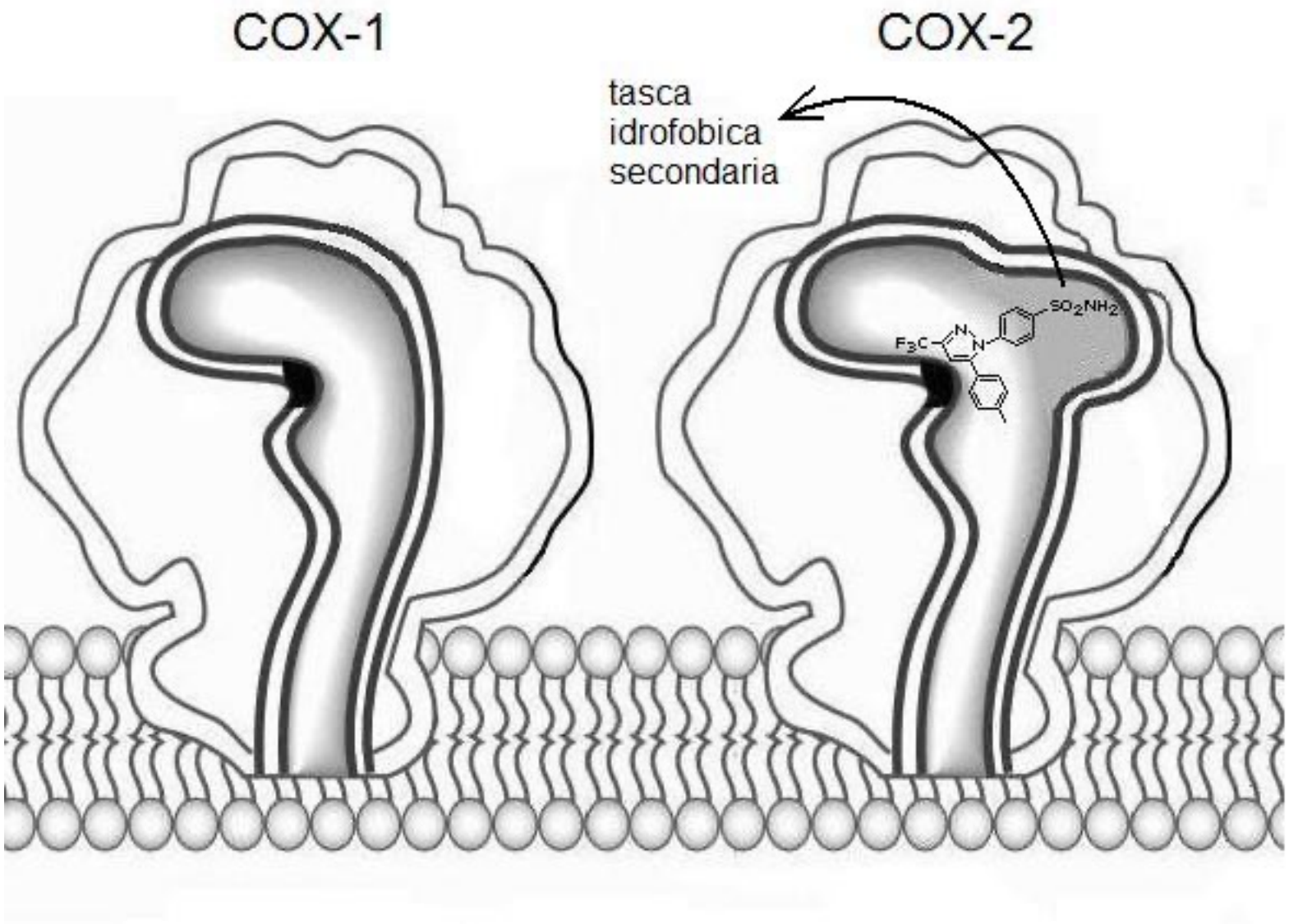

10
8
6
4
2
0
Pain sensation
allodynia
hyperalgesia
normal pain
threshold
Injury
normal pain
response
Stimulus intensity

Table 31–1 • GLUCOCORTICOSTEROID PREPARATIONS

	ANTI-INFLAMMATORY POTENCY	EQUIVALENT DOSE (mg)	SODIUM-RETAINING POTENCY	PLASMA HALF-LIFE (min)	BIOLOGIC HALF-LIFE (h)
Hydrocortisone	1	20	2+	90	8–12
Cortisone	0.8	25	2+	30	8–12
Prednisone	4	5	1+	60	12–36
Prednisolone	4	5	1+	200	12–36
Methylprednisolone	5	4	0	180	12–36
Triamcinolone	5	4	0	300	12–36
Betamethasone	20–30	0.6	0	100–300	36–54
Dexamethasone	20–30	0.75	0	100–300	36–54

From Garber EK, Targoff C, Paulus HE: In Paulus HE, Furst DE, Droomgoole SH (eds): Drugs for Rheumatic Diseases. New York, Churchill Livingstone, 1987, p 446.


TNF-α receptor
TNF-α
IL-1
IL-1 receptor
Ionizing radiation
Exterior
Cytosol
1
Unknown mechanism
TAK1
2b
2a
3
p65
p50
I-κBα
P
E3 ligase
Poly-ubiquitin
4
α
β
γ
I-κB kinase
Sequestered NF-κB
Free NF-κB
5
Proteasomal degradation of I-κBα
6
7
Induces transcription of target genes
Nuclear-localization signals
Nucleus


COX-1
COX-2
tasca
idrofobica
secondaria
SO_2NH_2
F_3C
N
N

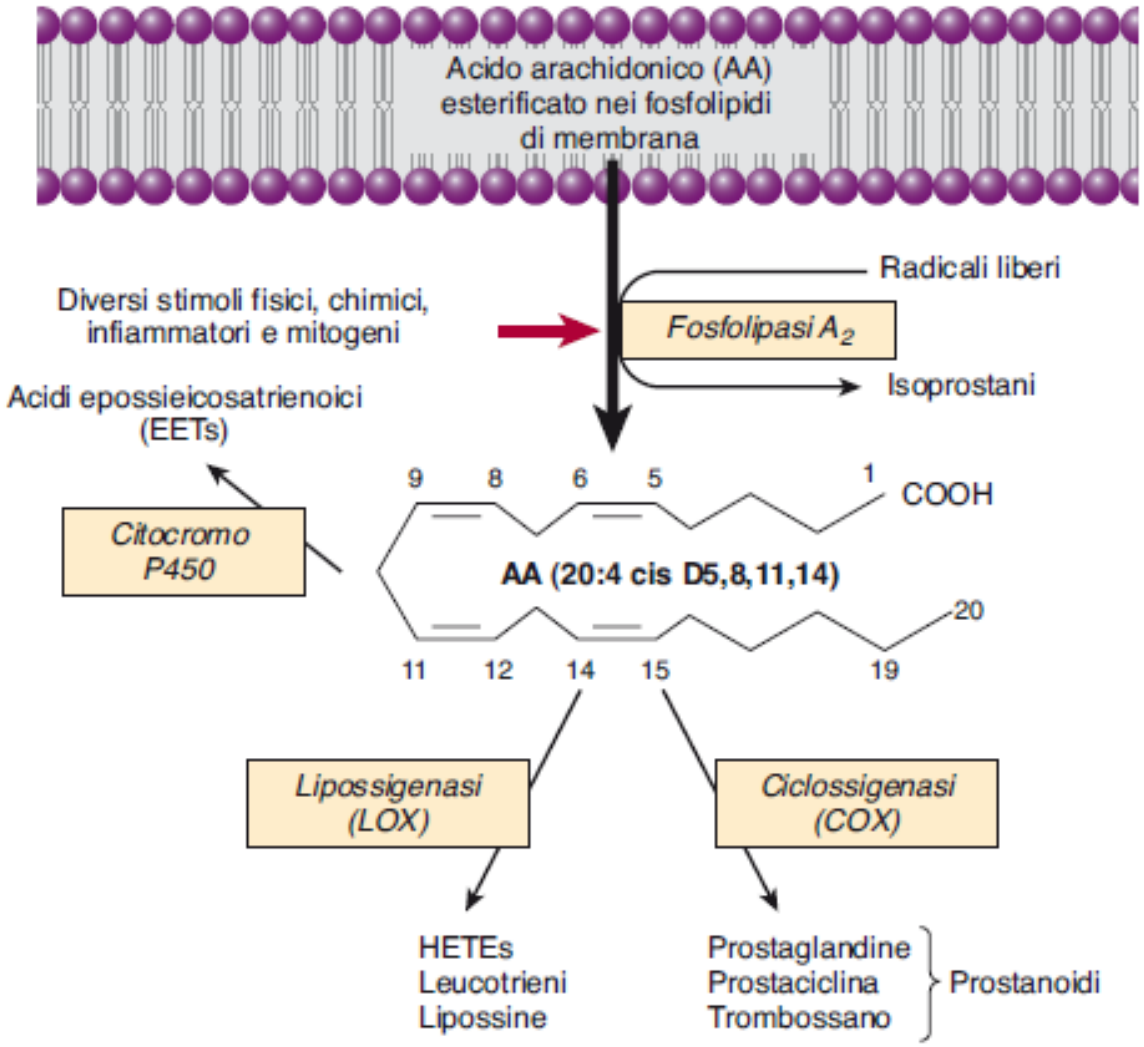
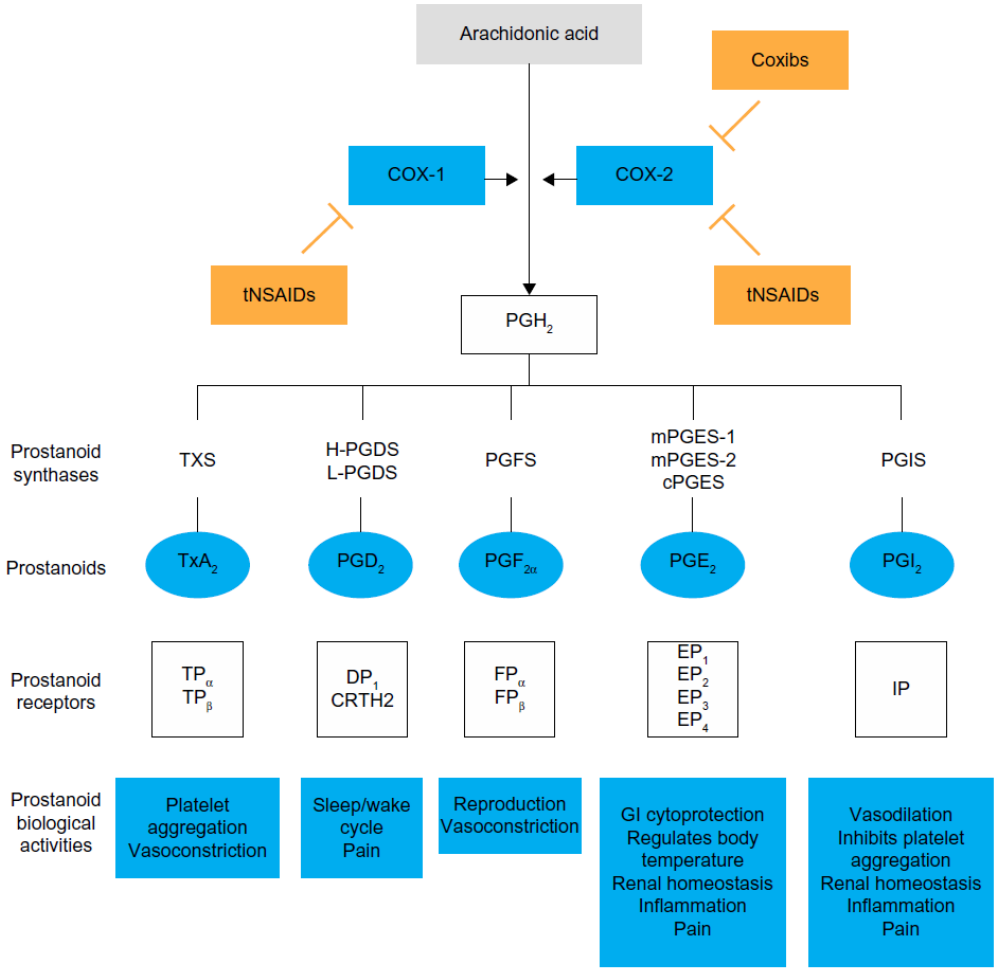


Figura 18-1. Vie metaboliche di rilascio e metabolismo dell'acido arachidonico.



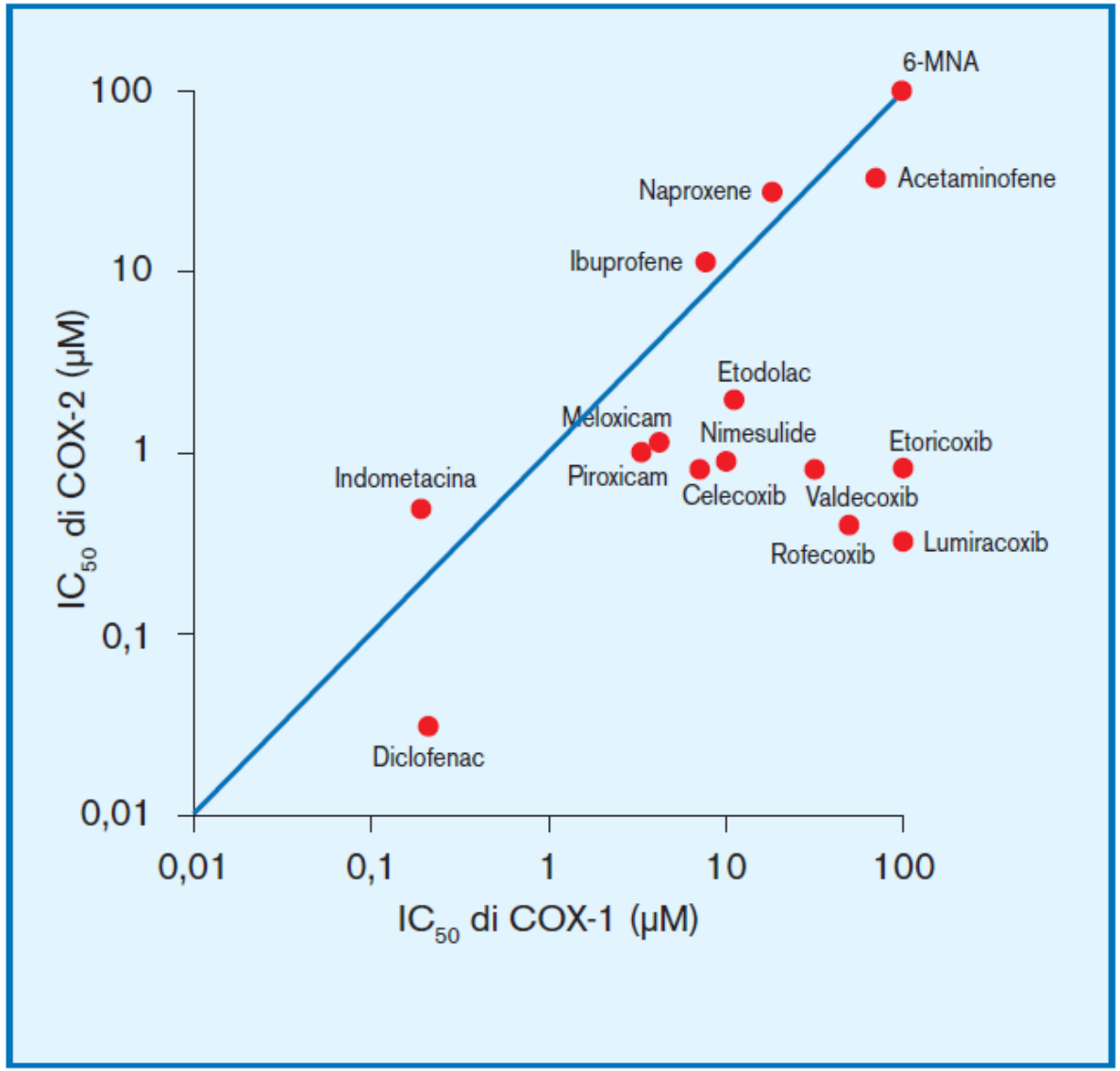
Notes: COX-I and COX-2 catalyze conversion of arachidonic acid into the intermediate metabolite PGH,, which is the rate-limiting step of prostanoid formation. The activity of different prostanoids in a tissue depends on the cell type-specific expression of their receptors and on their biosynthesis. NSAIDs and coxibs act by selectively inhibiting COX-I-dependent and/or COX-2-dependent prostanoid biosynthesis. 19.88-90

Abbreviations: COX, cyclooxygenase; PGES, cytosolic PGE, synchase; CRTH2, chemoattractant receptor-homologous molecule expressed on T helper 2 cells; DP, PGD2 receptor; EP, PGE receptor; FP, PGF receptor; GI, gastrointestinal; H-PGDS, hematopoietic PGD synthase; IP, PGI, receptor; L-PGDS, lipocalin-type PGD synthase; mPGES, membrane-associated PGE, synthase; PG, prostaglandin; PGFS, PGF synthase; PGIS, PGI, synthase; eNSAIDs, traditional non-steroidal anti-inflammatory drugs;

TP, TX receptor; TxA,, thromboxane Azi TXS, thromboxane synchase.

Farmaci	IC_{80}-COX-1 (μM)	IC_{80}-COX-2 (μM)
Aspirina	8,0	>100
Celecoxib	28	6,0
Diclofenac	1,0	0,27
Ibuprofene	58	67
Indometacina	0,46	5,0
Ketoprofene	1,0	22
Ketorolac	0,0034	0,4
Naproxene	110	260
Nimesulide	41	7,0
Rofecoxib	>100	6,0

IC_{80} concentrazione di farmaco necessaria per inibire l'80% dell'attività di COX-1 e COX-2


6-MNA
Acetaminofene
Naproxene
Ibuprofene
Etodolac
Meloxicam
Nimesulide
Etoricoxib
Indometacina
Piroxicam
Celecoxib
Valdecoxib
Rofecoxib
Lumiracoxib
Diclofenac
100
10
1
0,1
0,01
0,01
0,1
1
10
100
IC50 di COX-2 (μM)
IC50 di COX-1 (μM)

Nota 66

Un effetto analgesico si ottiene in genere in una settimana, mentre per un effetto antinfiammatorio completo (anche dal punto di vista clinico) servono spesso anche tre settimane. Se trascorso questo tempo non vi sono risultati, è bene tentare con un altro farmaco

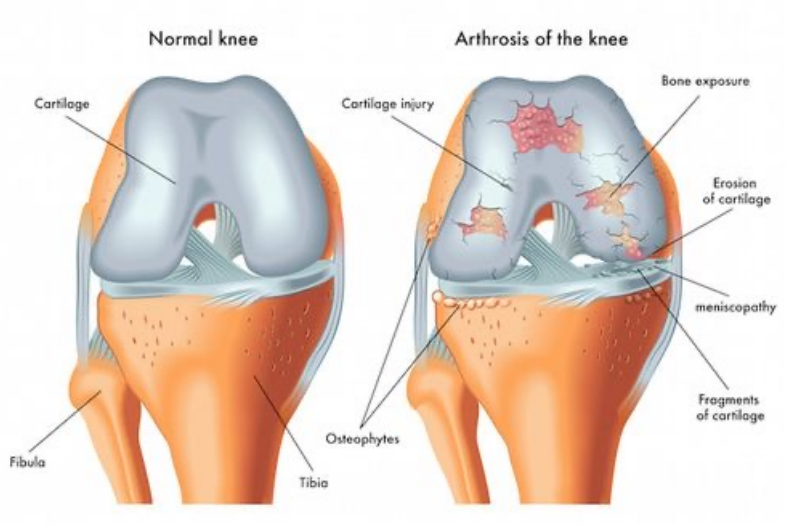
Faught et al. J Clin Pharmacol 2015;80:901-919.

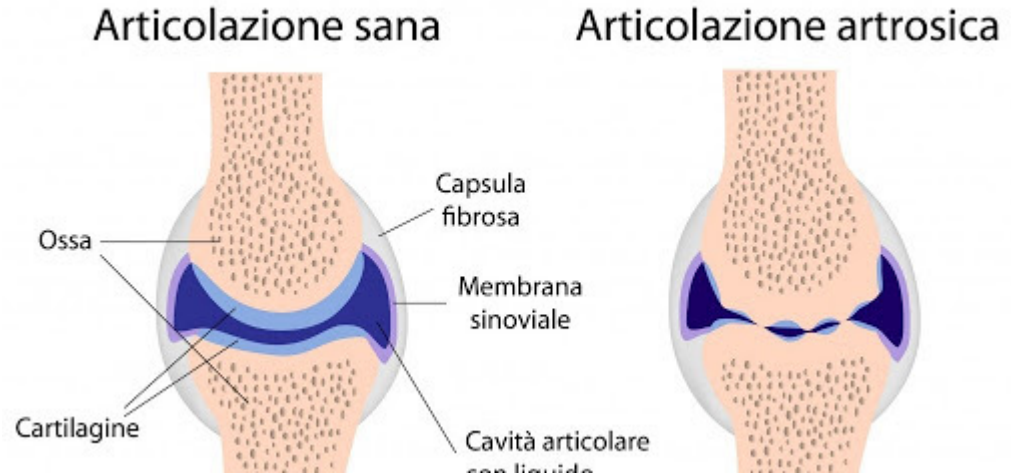
Farmaci antifiammatori non steroidei

FARMACO	REAZIONI AVVERSE	CONTROINDICAZIONI	CONSIDERAZIONI TERAPEUTICHE
FANS TRADIZIONALI (IBUPROFENE, DICLOFENAC, KETOPROFENE, KETOROLAC)	GASTROLESIVITA' AUMENTATO RISCHIO CARDIOVASCOLARE INSUFFICIENZA RENALE	CARDIOPATIA ISCHEMICA, INSUFFICIENZA RENALE, ULCERA PEPTICA	**INIBITORI NON SELETTIVI DELLA COX-1 E DELLA COX-2. ALCUNI POSSONO AVERE EFFETTI CENTRALI. ALCUNI HANNO ATTIVITA' ANCILLARI (PER.ES INIBIZIONE DELLA SOSTANZA P)**
INIBITORI PREFERENZIALI DELLA COX-2 (CELECOXIB, NIMESULIDE)	AUMENTATO RISCHIO CARDIOVASCOLARE RIDOTTA GASTROLESIVITA' INSUFFICIENZA RENALE	CARDIOPATIA ISCHEMICA, INSUFFICIENZA RENALE.	**INIBITORI SELETTIVI DELLA COX-2**
COXIB (ETORICOXIB)	AUMENTATO RISCHIO CARDIOVASCOLARE MODESTA GASTROLESIVITA' INSUFFICIENZA RENALE	CARDIOPATIA ISCHEMICA, INSUFFICIENZA RENALE.	

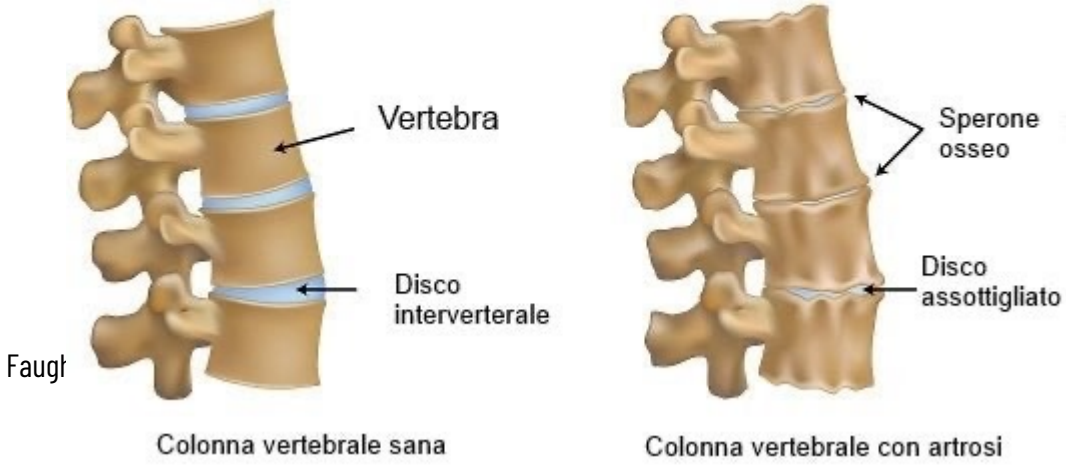
Dolore meccanico-strutturale

Dolore meccanico-strutturale



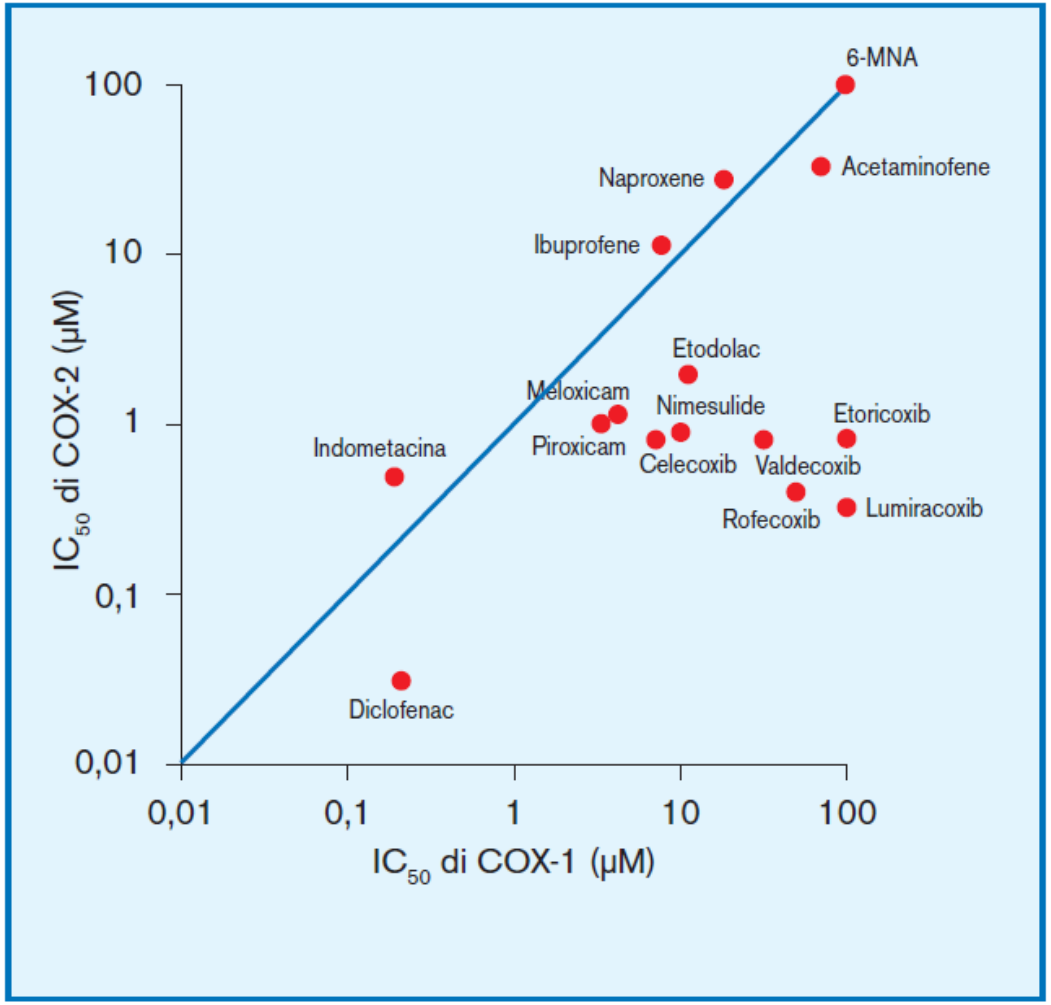


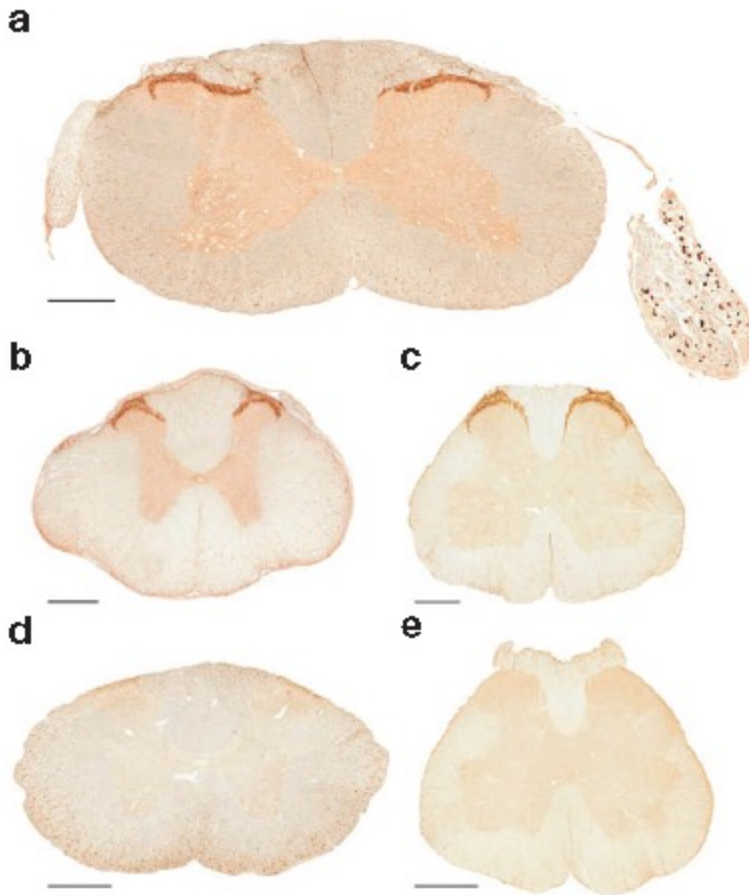
Artrosi della colonna vertebrale

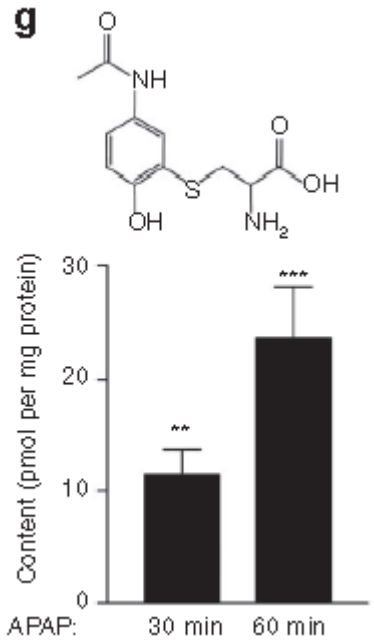


Faugh

E il paracetamolo?




a
b
c
d
e


g
O
NH
O
OH
S
OH
NH2
Content (pmol per mg protein)
30
20
10
0
**
***
APAP:
30 min
60 min

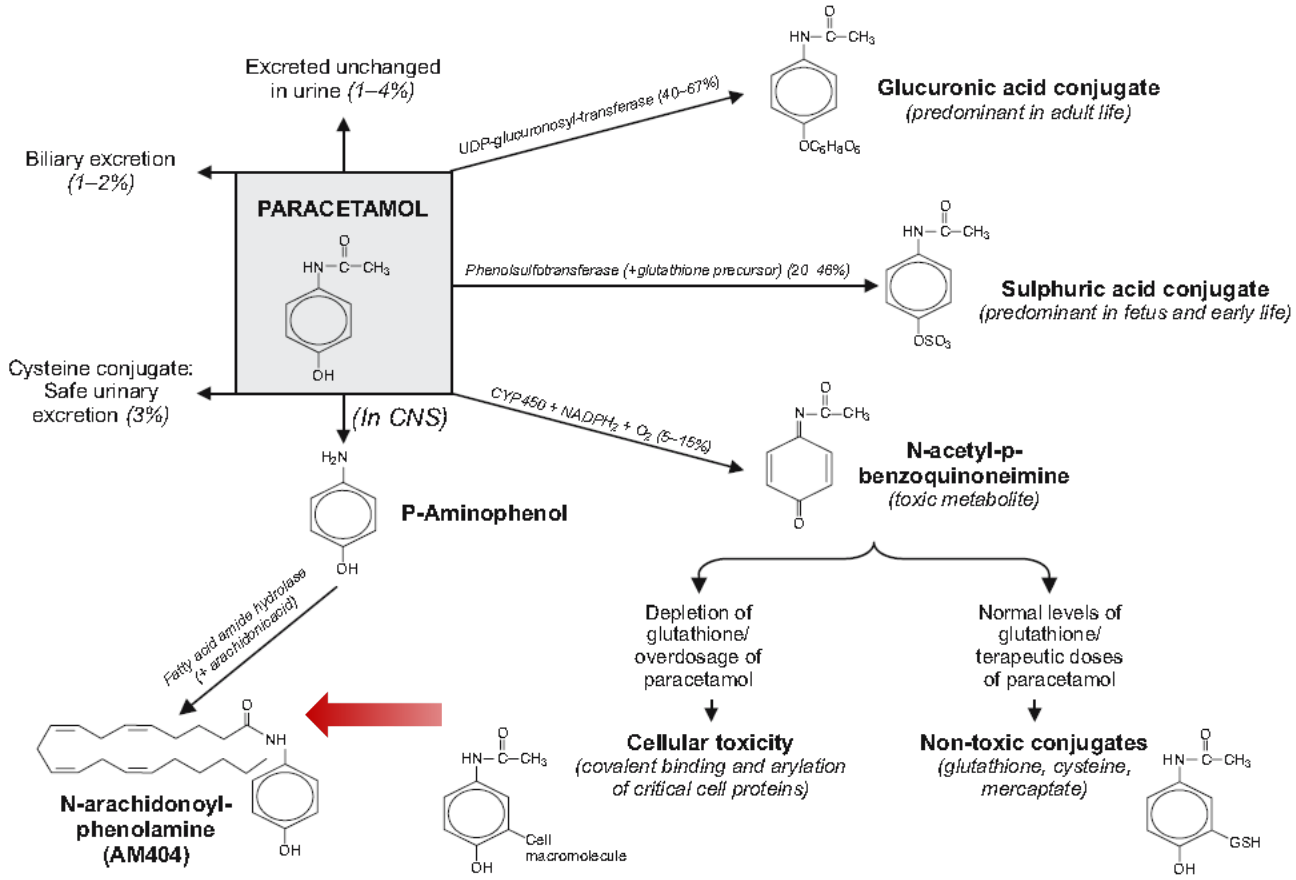
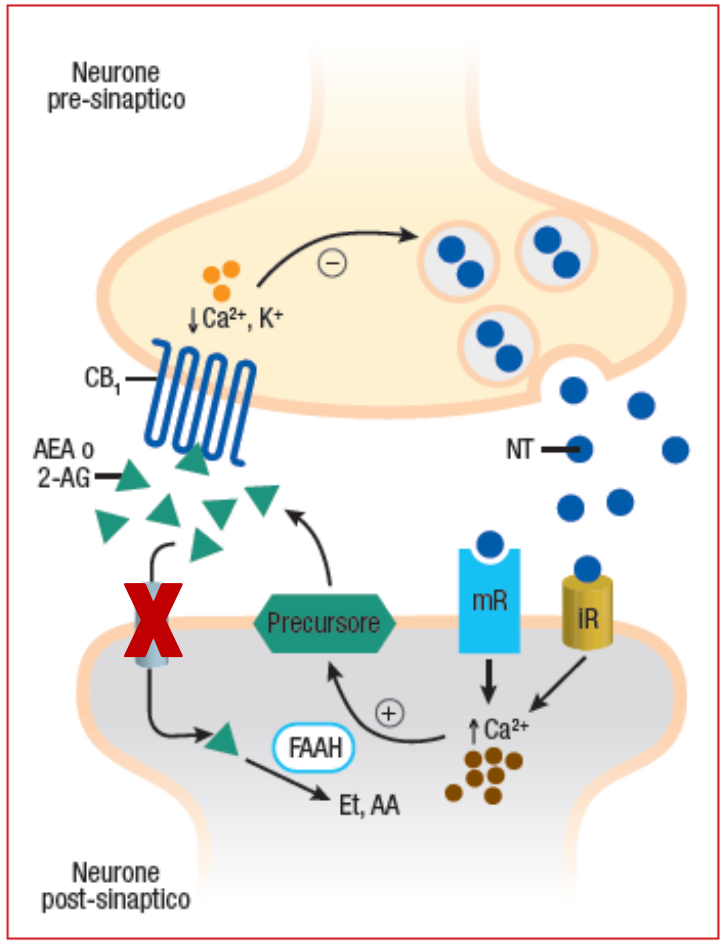
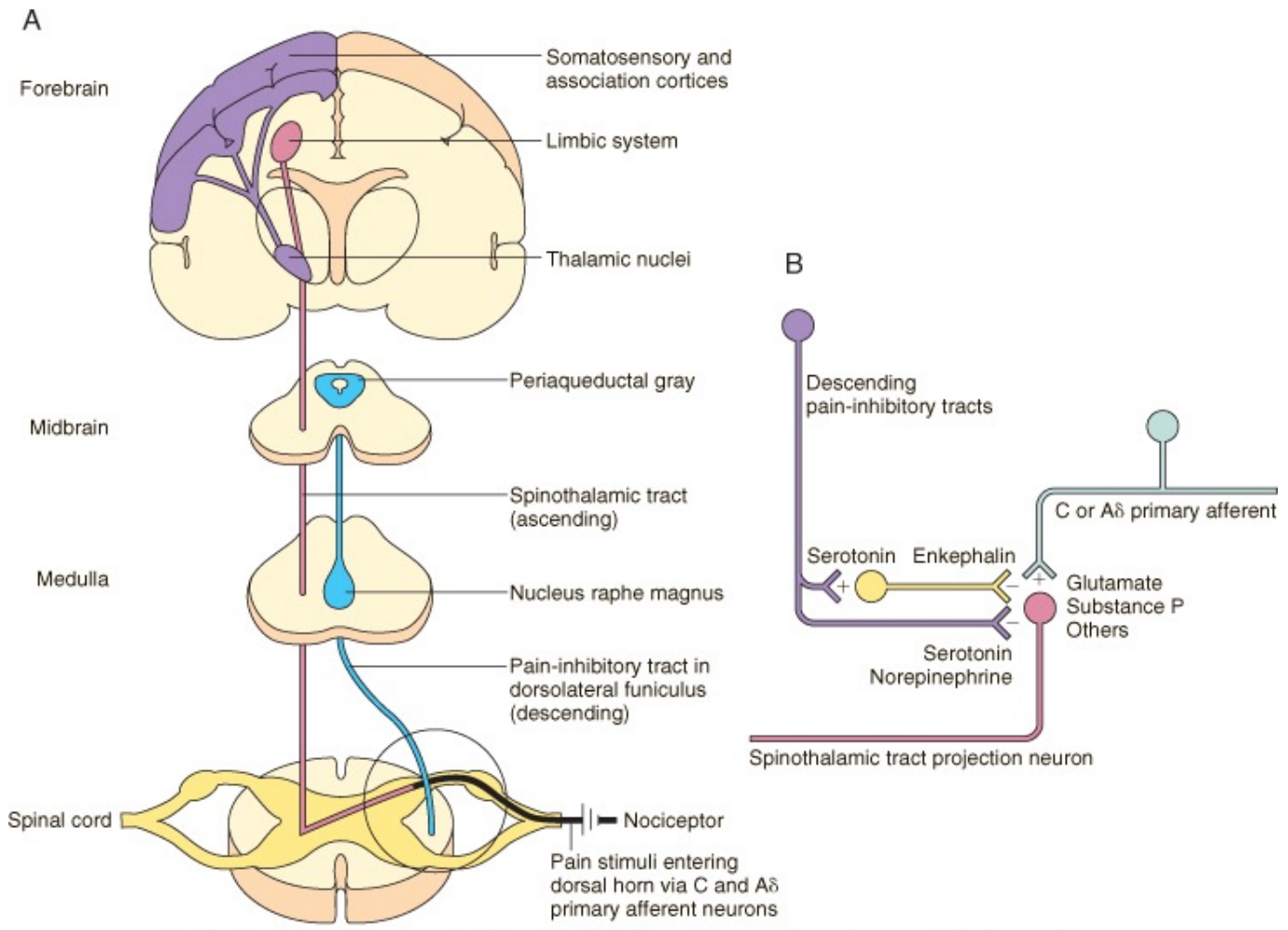


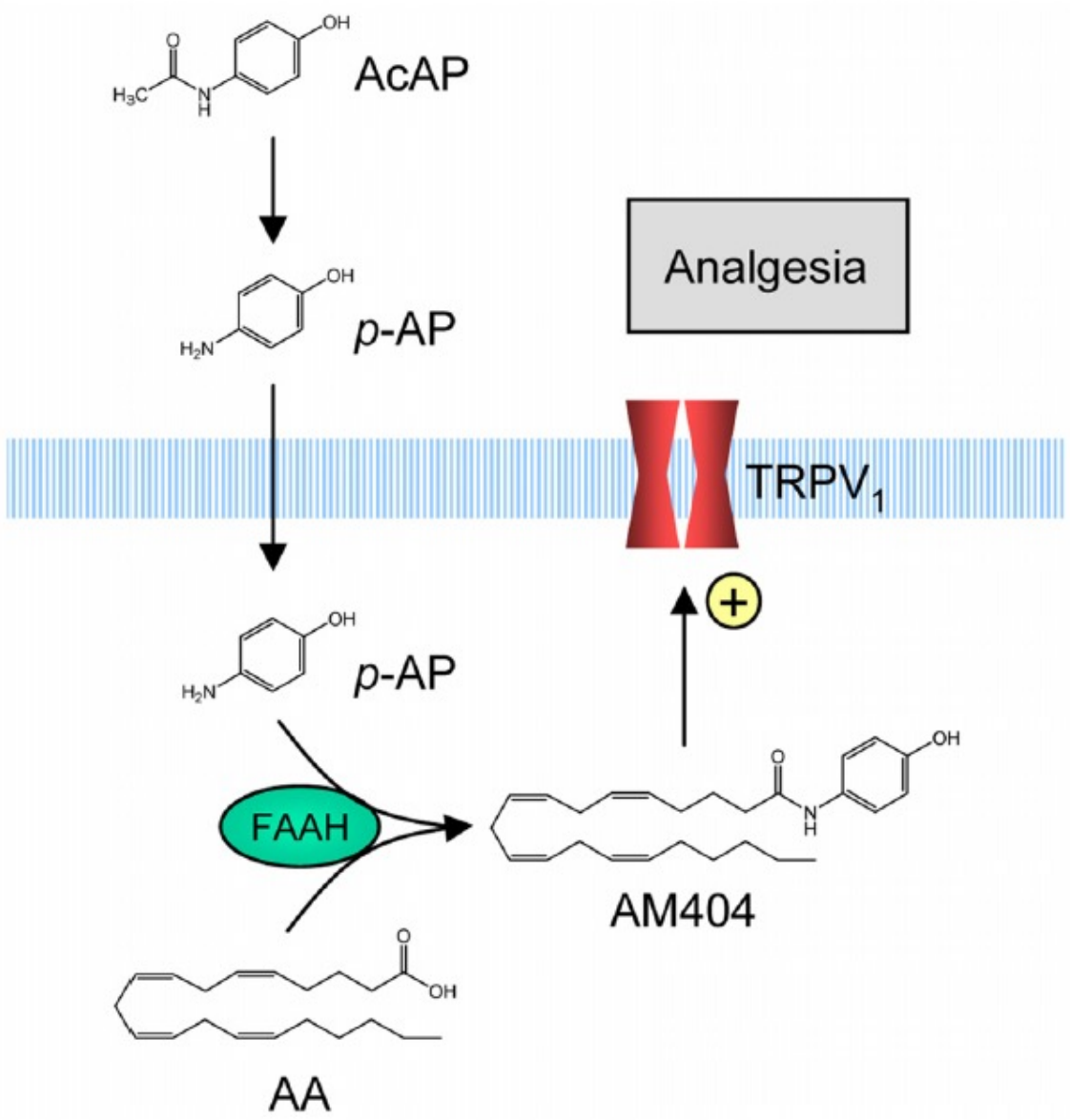
Fig. 3. Metabolism of paracetamol in humans.

Il sistema endocannabinoide

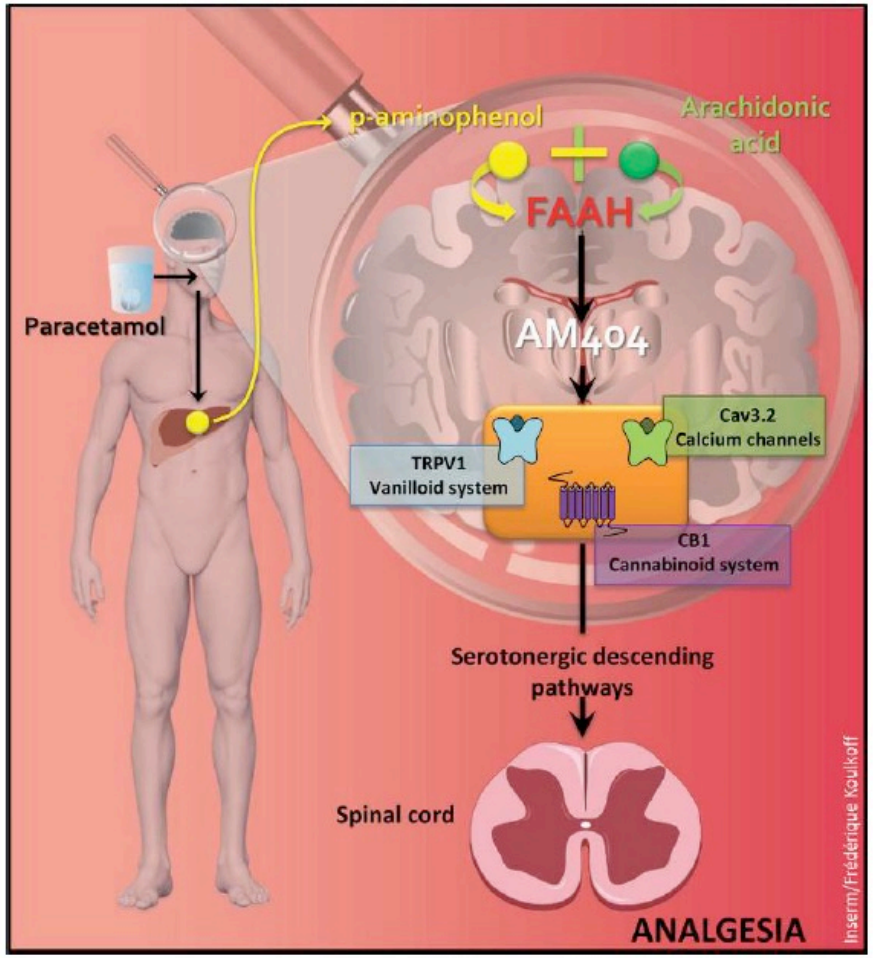


Via inibitoria discendente




AcAP
p-AP
Analgesia
TRPV1
p-AP
FAAH
AM404
AA

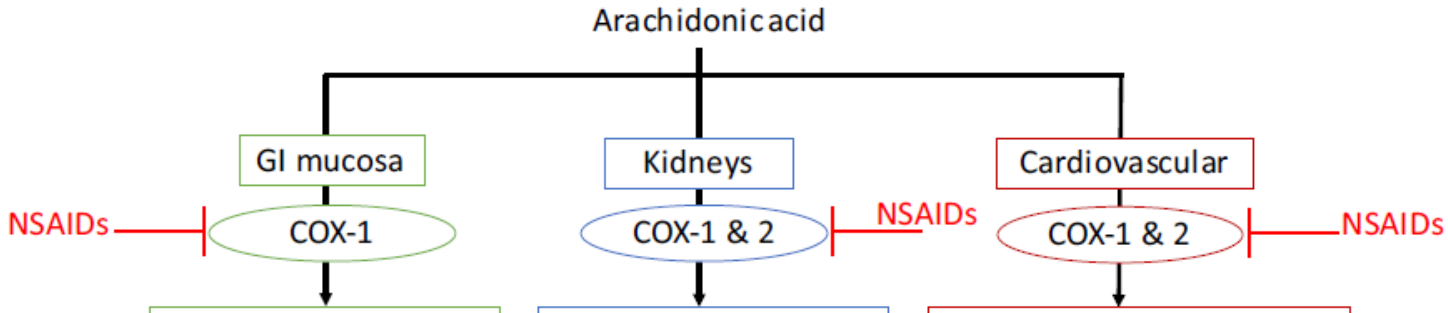
Proposed mechanisms for the antinociceptive effect of paracetamol



FROM THE EDITED VOLUME

Pain Relief - From Analgesics to Alternative Therapies

Edited by Cecilia Maldonado

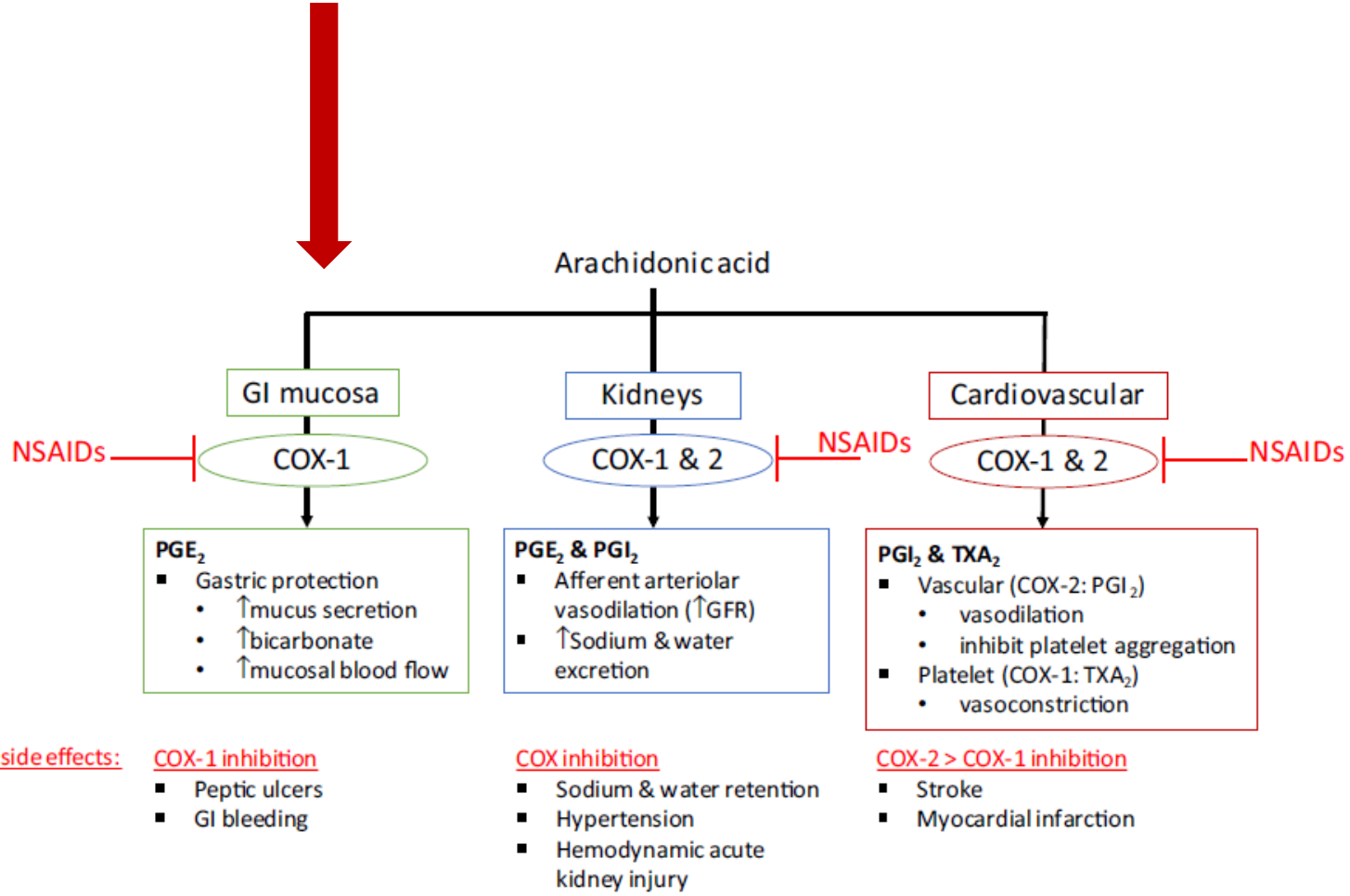


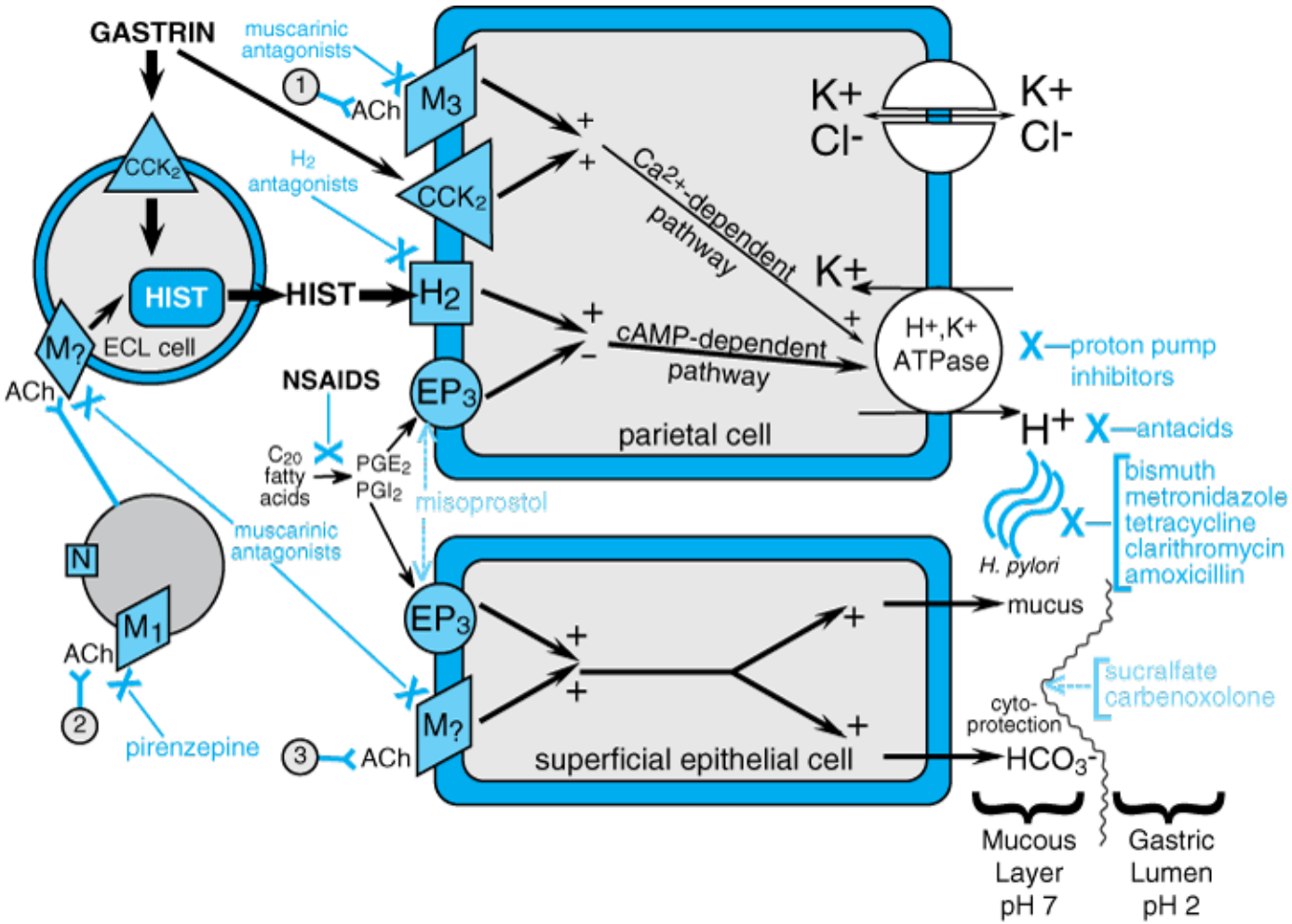
NSAID side effects:

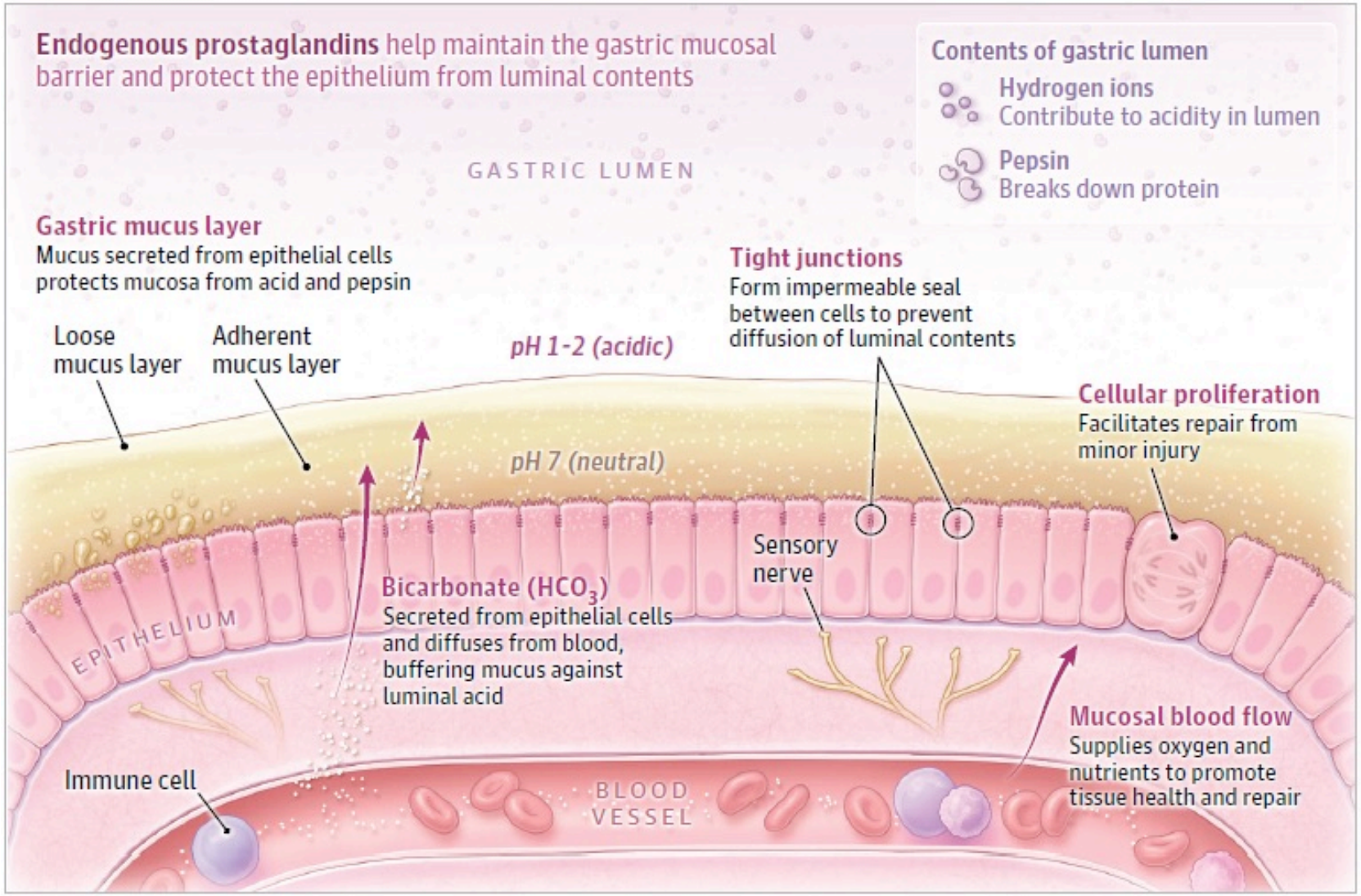
COX-1 inhibition
- Peptic ulcers
- GI bleeding

COX inhibition
- Sodium & water retention
- Hypertension
- Hemodynamic acute kidney injury

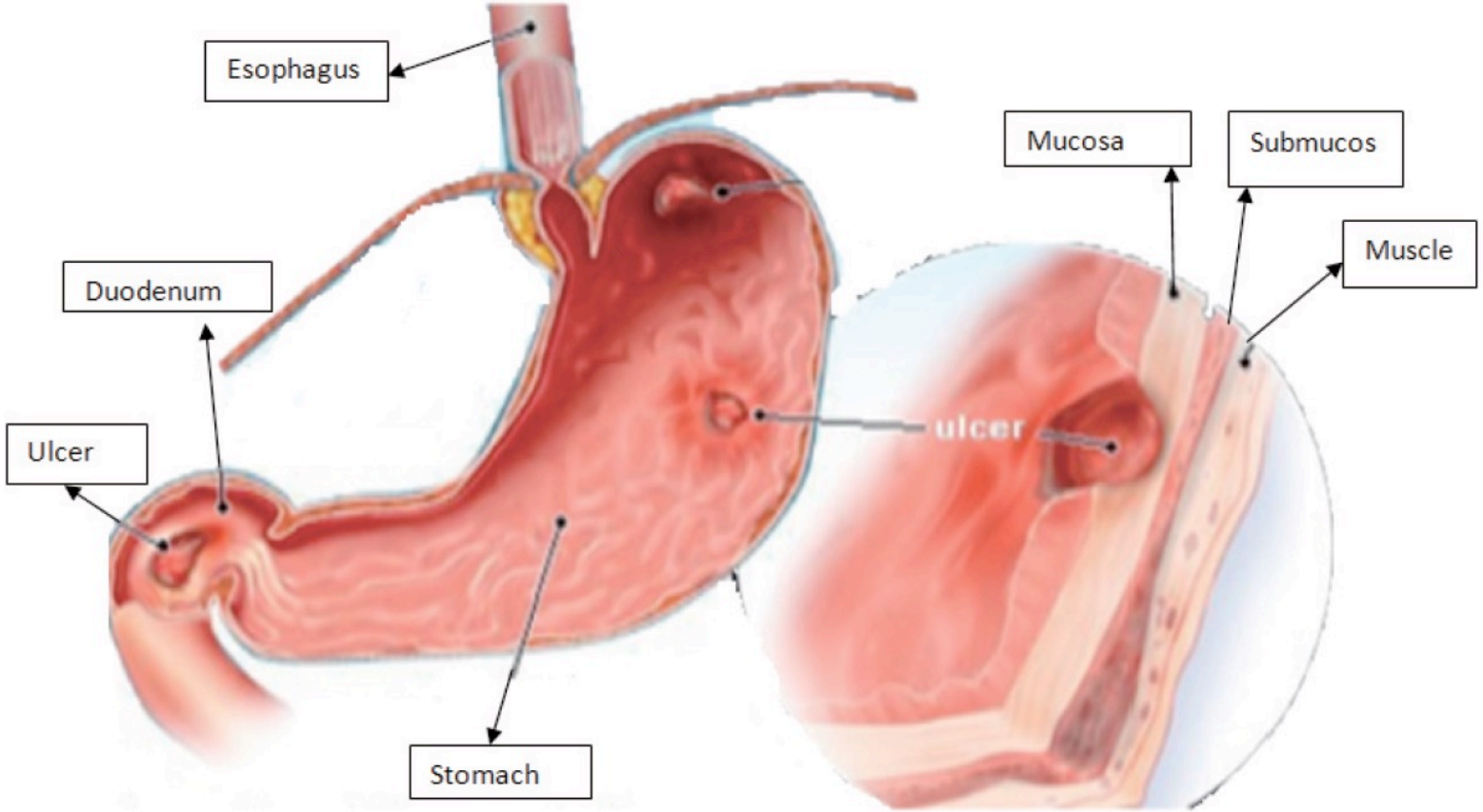
COX-2 > COX-1 inhibition
- Stroke
- Myocardial infarction

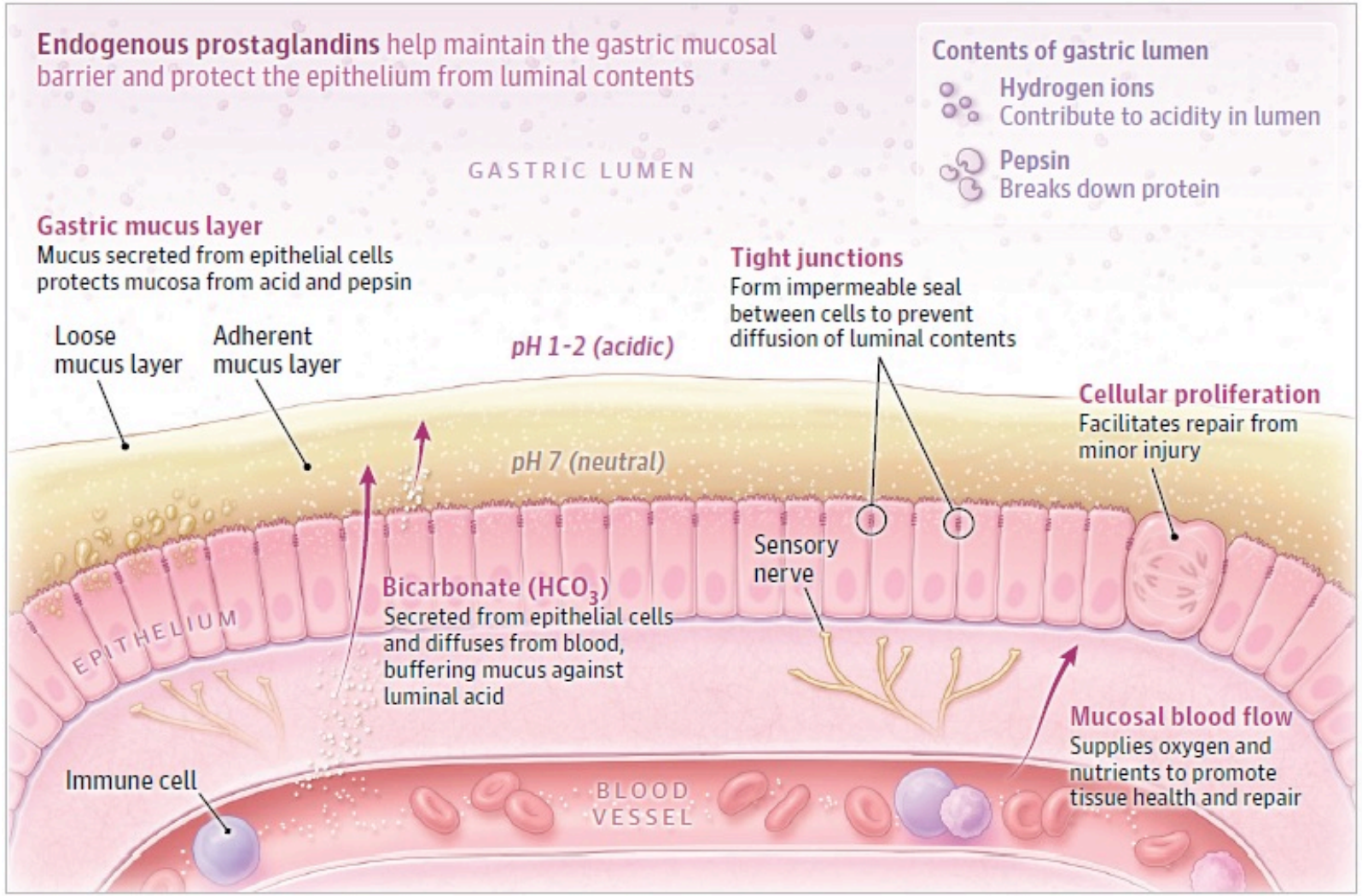

Arachidonic acid
GI mucosa
Kidneys
Cardiovascular
NSAIDs
COX-1
COX-1 & 2
NSAIDs
COX-1 & 2
NSAIDs
PGE2
Gastric protection
↑mucus secretion
↑bicarbonate
↑mucosal blood flow
PGE2 & PGI2
Afferent arteriolar vasodilation (↑GFR)
↑Sodium & water excretion
PGI2 & TXA2
Vascular (COX-2: PGI2)
vasodilation
inhibit platelet aggregation
Platelet (COX-1: TXA2)
vasoconstriction
NSAID side effects:
COX-1 inhibition
Peptic ulcers
GI bleeding
COX inhibition
Sodium & water retention
Hypertension
Hemodynamic acute kidney injury
COX-2 > COX-1 inhibition
Stroke
Myocardial infarction

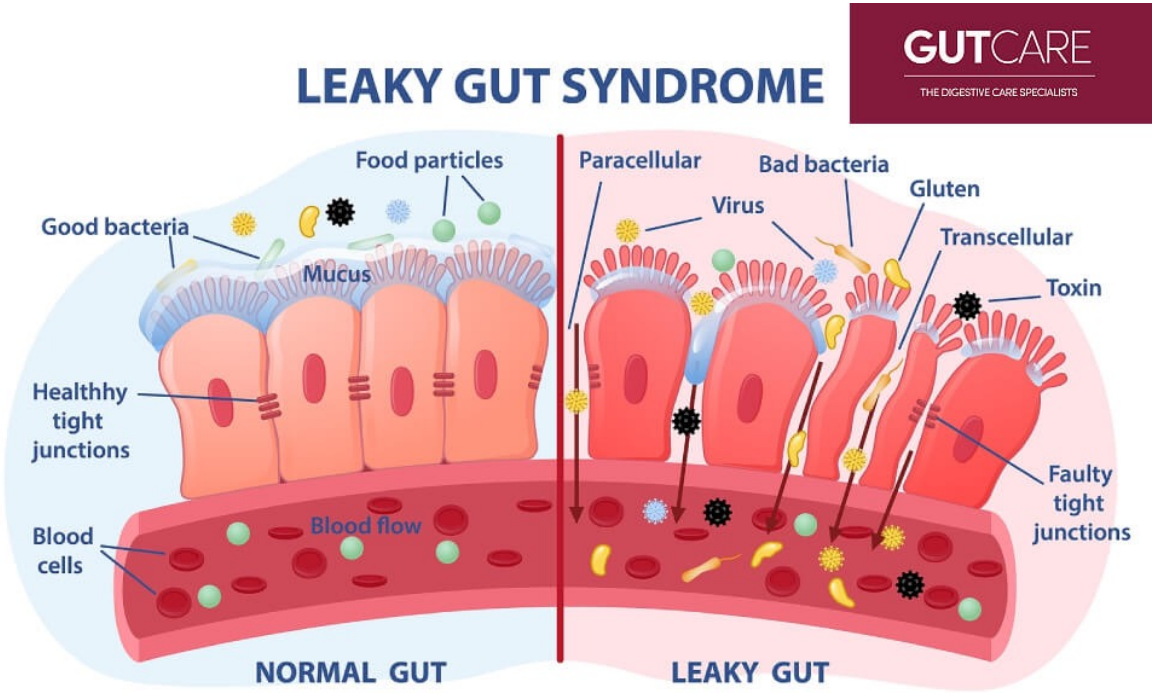


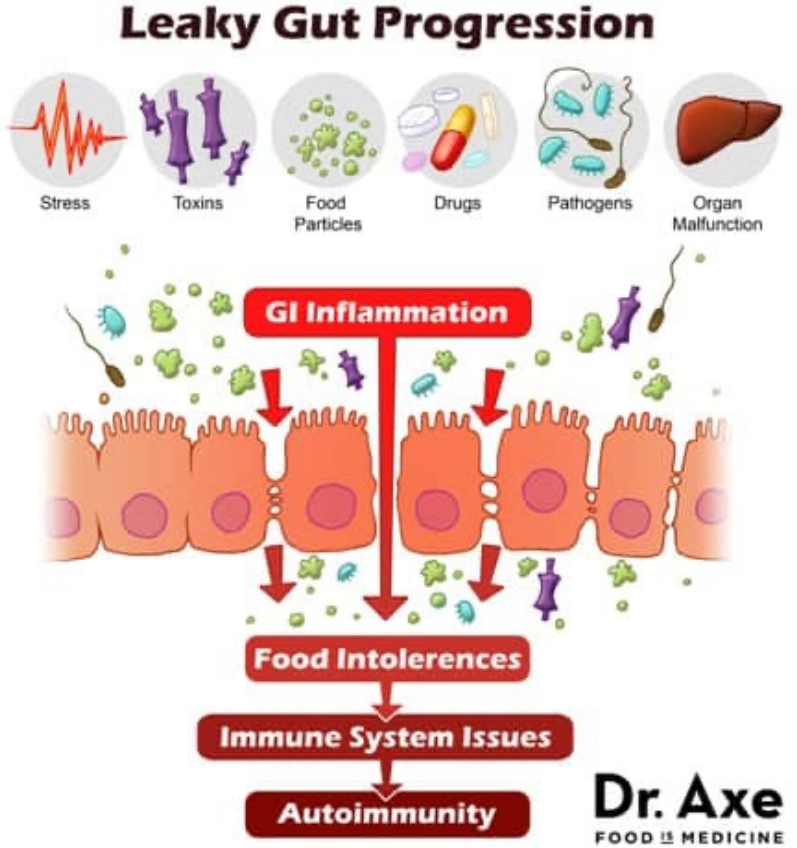

Endogenous prostaglandins help maintain the gastric mucosal barrier and protect the epithelium from luminal contents
Contents of gastric lumen
Hydrogen ions
Contribute to acidity in lumen
Pepsin
Breaks down protein
GASTRIC LUMEN
Gastric mucus layer
Mucus secreted from epithelial cells protects mucosa from acid and pepsin
Loose mucus layer
Adherent mucus layer
pH 1-2 (acidic)
Tight junctions
Form impermeable seal between cells to prevent diffusion of luminal contents
Cellular proliferation
Facilitates repair from minor injury
pH 7 (neutral)
Sensory nerve
Bicarbonate (HCO_3)
Secreted from epithelial cells and diffuses from blood, buffering mucus against luminal acid
EPITHELIUM
Mucosal blood flow
Supplies oxygen and nutrients to promote tissue health and repair
Immune cell
BLOOD VESSEL

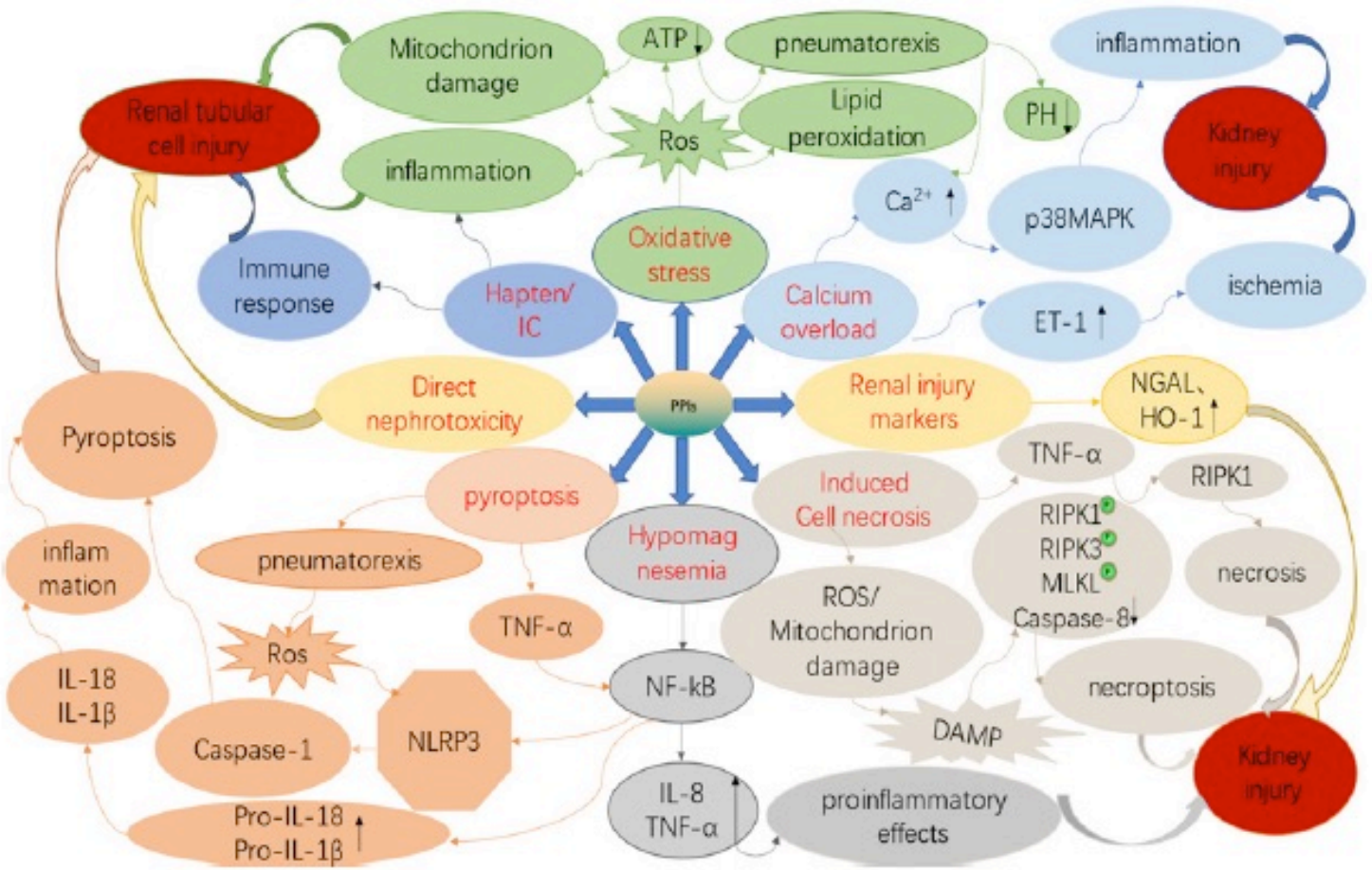
Peptic Ulcers

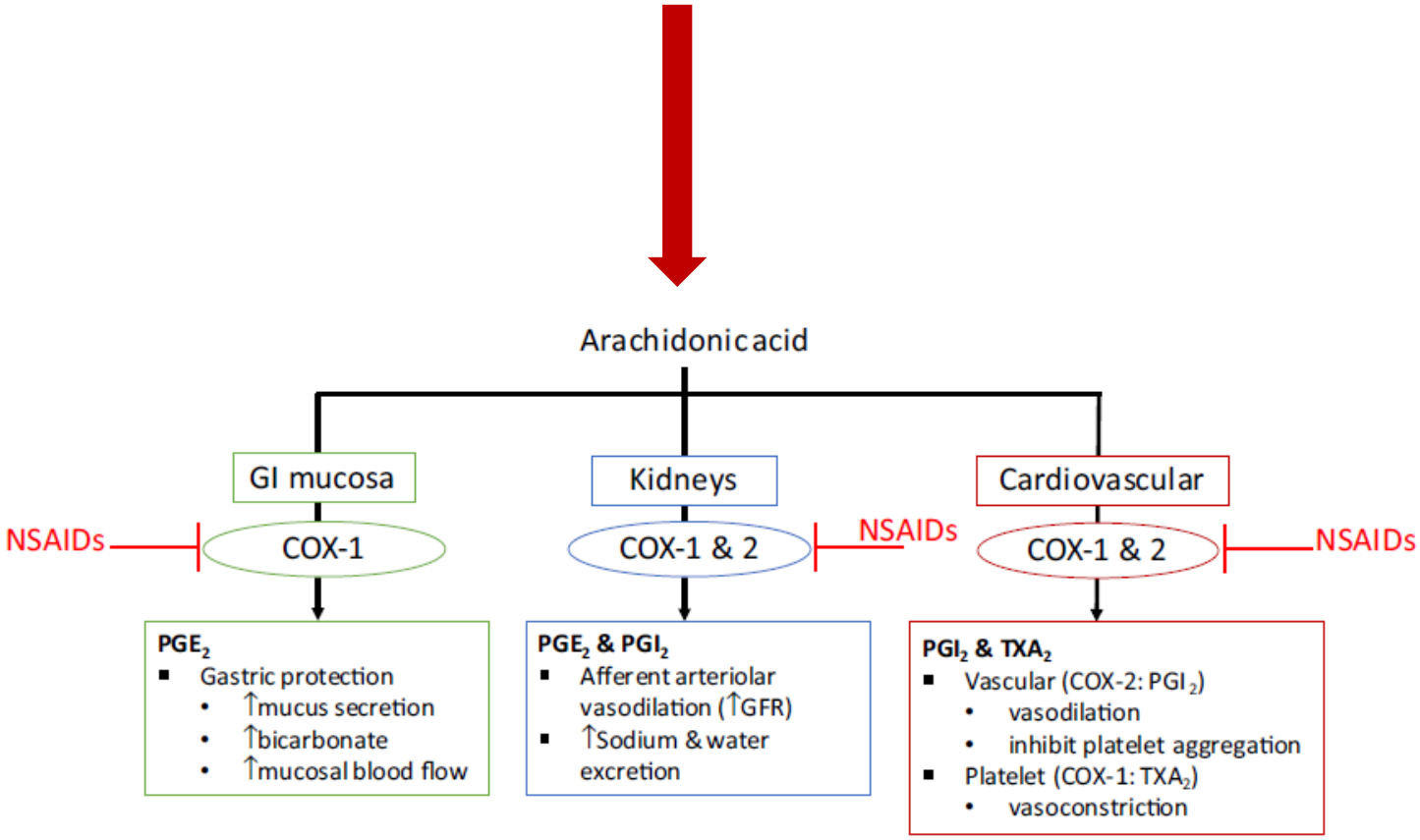


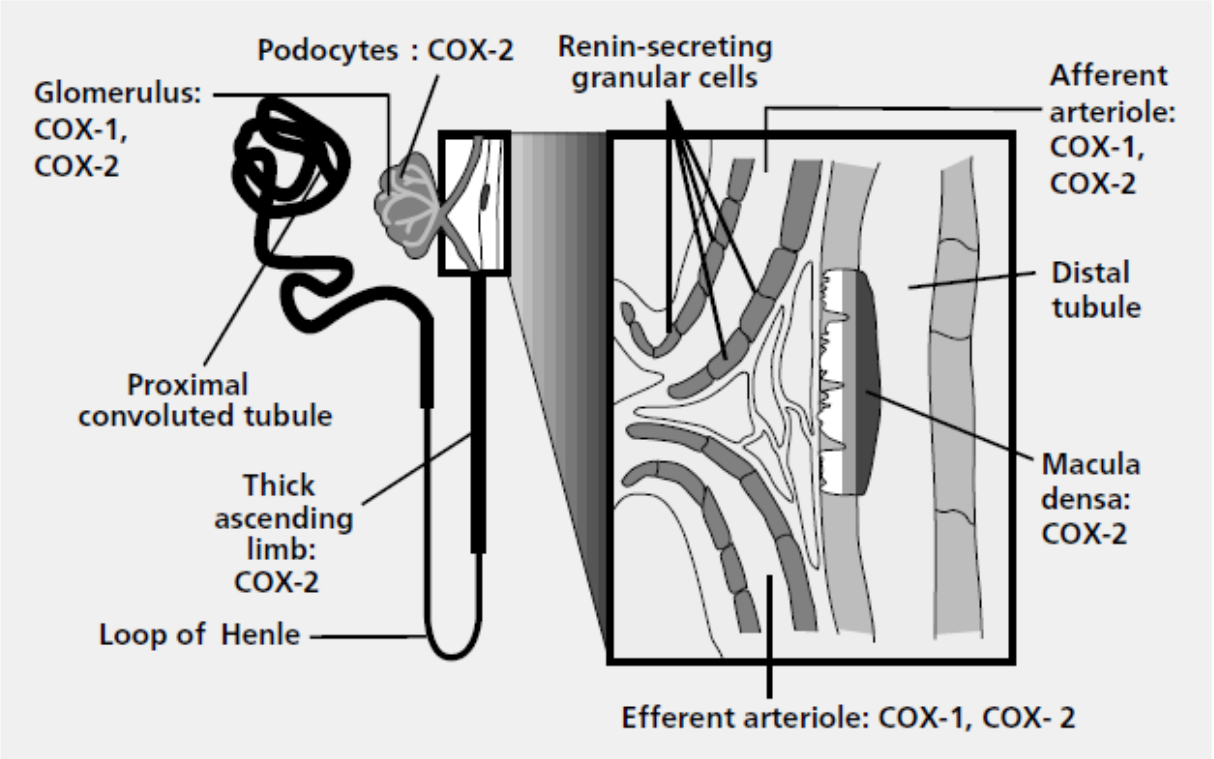

Endogenous prostaglandins help maintain the gastric mucosal barrier and protect the epithelium from luminal contents
Contents of gastric lumen
Hydrogen ions
Contribute to acidity in lumen
Pepsin
Breaks down protein
GASTRIC LUMEN
Gastric mucus layer
Mucus secreted from epithelial cells protects mucosa from acid and pepsin
Loose mucus layer
Adherent mucus layer
pH 1-2 (acidic)
Tight junctions
Form impermeable seal between cells to prevent diffusion of luminal contents
Cellular proliferation
Facilitates repair from minor injury
pH 7 (neutral)
Sensory nerve
Bicarbonate (HCO_3)
Secreted from epithelial cells and diffuses from blood, buffering mucus against luminal acid
EPITHELIUM
Mucosal blood flow
Supplies oxygen and nutrients to promote tissue health and repair
Immune cell
BLOOD VESSEL


LEAKY GUT SYNDROME
GUTCARE
THE DIGESTIVE CARE SPECIALISTS
Food particles
Paracellular
Bad bacteria
Virus
Gluten
Transcellular
Good bacteria
Mucus
Toxin
Healthhy tight junctions
Faulty tight junctions
Blood flow
Blood cells
NORMAL GUT
LEAKY GUT

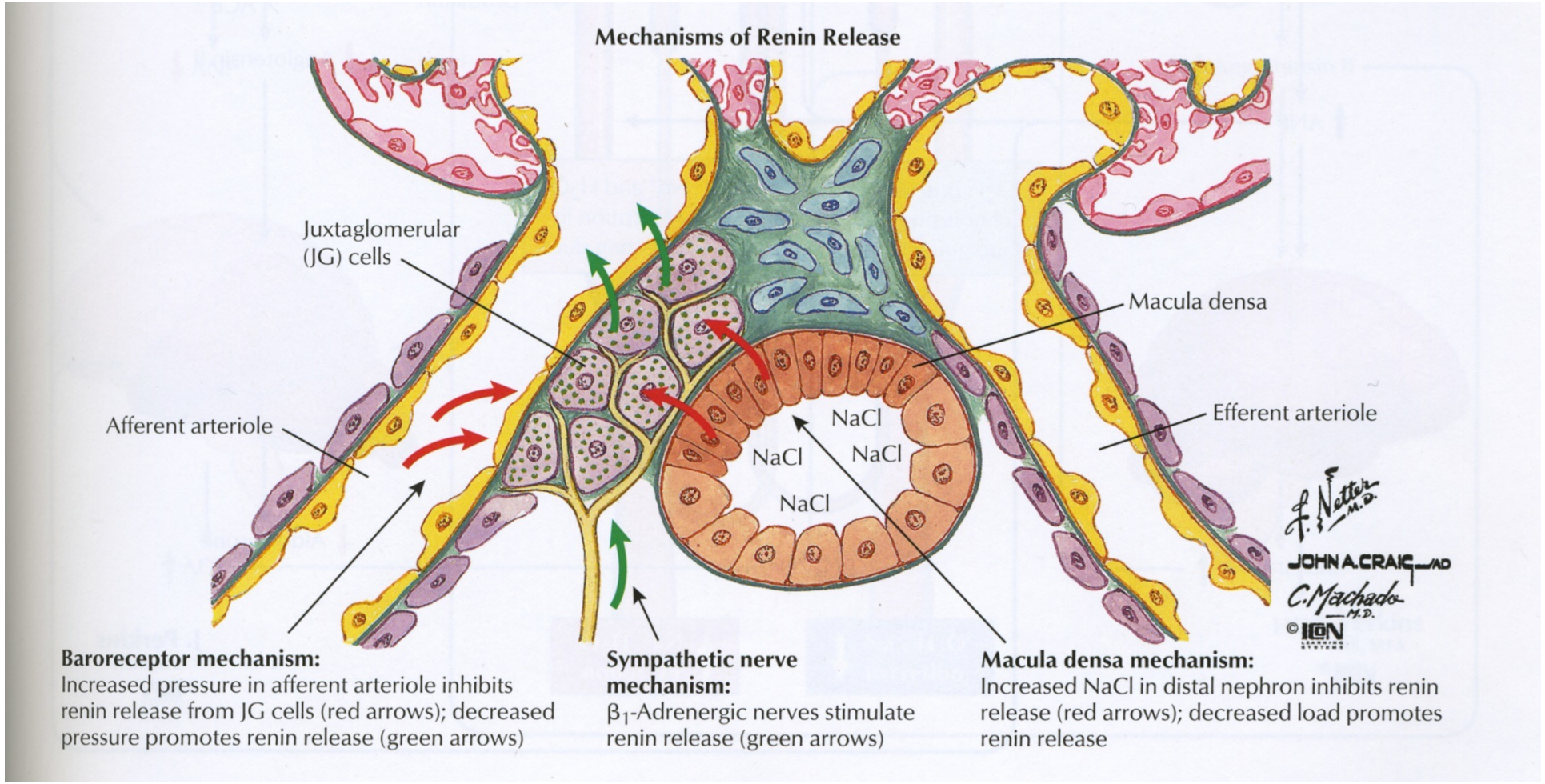

Leaky Gut Progression
Stress
Toxins
Food Particles
Drugs
Pathogens
Organ Malfunction
GI Inflammation
Food Intolerences
Immune System Issues
Autoimmunity
Dr. Axe
FOOD IS MEDICINE


Mitochondrion damage
ATP
pneumatorexis
inflammation
Renal tubular cell injury
Ros
Lipid peroxidation
PH
Kidney injury
inflammation
Ca2+
p38MAPK
Oxidative stress
Immune response
Hapten/ IC
Calcium overload
ET-1
ischemia
Direct nephrotoxicity
PPIs
Renal injury markers
NGAL、HO-1
Pyroptosis
TNF-α
RIPK1
pyroptosis
Induced Cell necrosis
RIPK1
RIPK3
MLKL
Caspase-8
inflam mation
pneumatorexis
Hypomag nesemia
necrosis
ROS/ Mitochondrion damage
Ros
TNF-α
IL-18
IL-1β
NF-kB
necroptosis
Caspase-1
NLRP3
DAMp
Kidney injury
IL-8
TNF-α
proinflammatory effects
Pro-IL-18
Pro-IL-1β

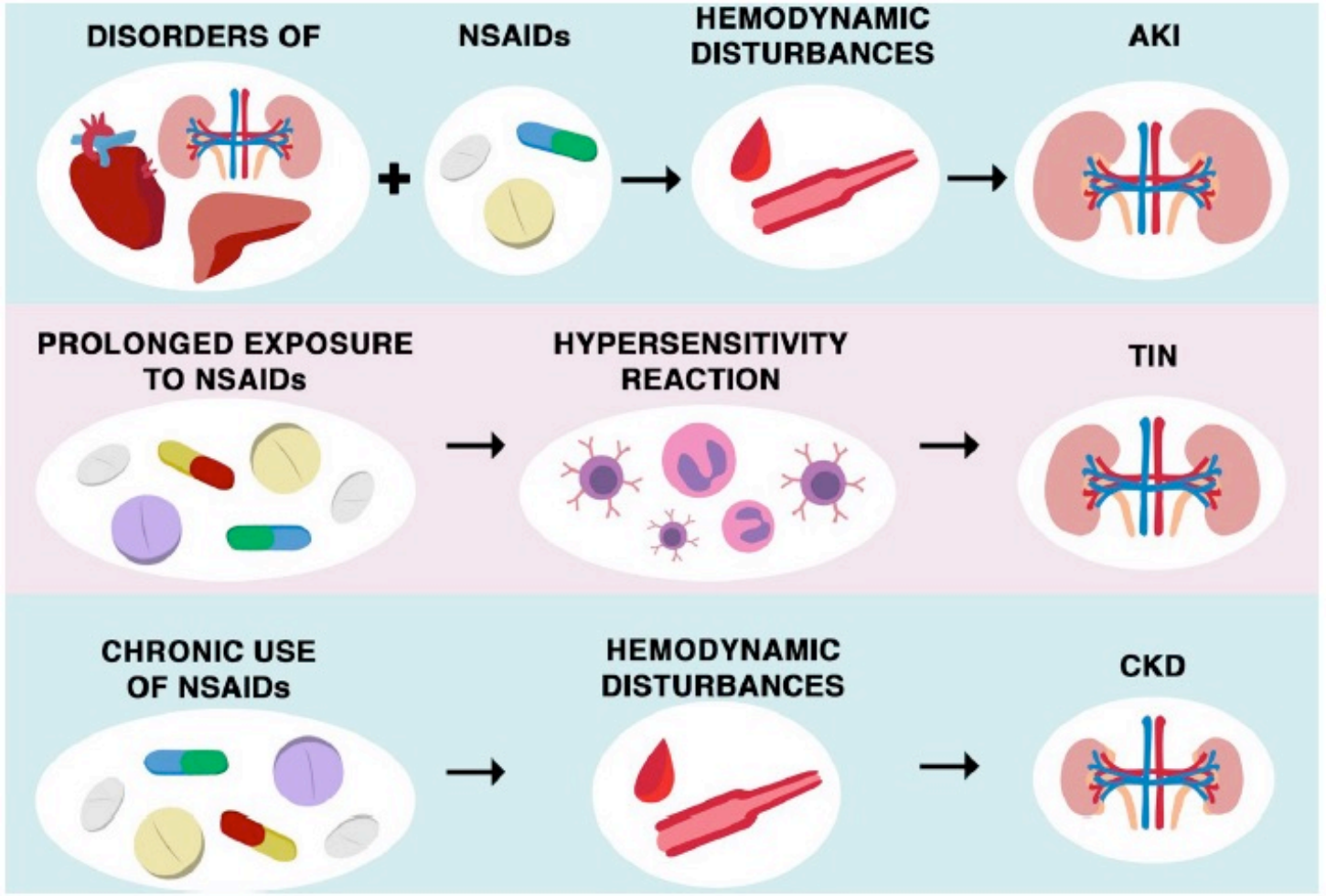

Arachidonic acid
GI mucosa
Kidneys
Cardiovascular
NSAIDs
COX-1
COX-1 & 2
NSAIDs
COX-1 & 2
NSAIDs
PGE2
Gastric protection
↑mucus secretion
↑bicarbonate
↑mucosal blood flow
PGE2 & PGI2
Afferent arteriolar vasodilation (↑GFR)
↑Sodium & water excretion
PGI2 & TXA2
Vascular (COX-2: PGI2)
vasodilation
inhibit platelet aggregation
Platelet (COX-1: TXA2)
vasoconstriction
NSAID side effects:
COX-1 inhibition
Peptic ulcers
GI bleeding
COX inhibition
Sodium & water retention
Hypertension
Hemodynamic acute kidney injury
COX-2 > COX-1 inhibition
Stroke
Myocardial infarction



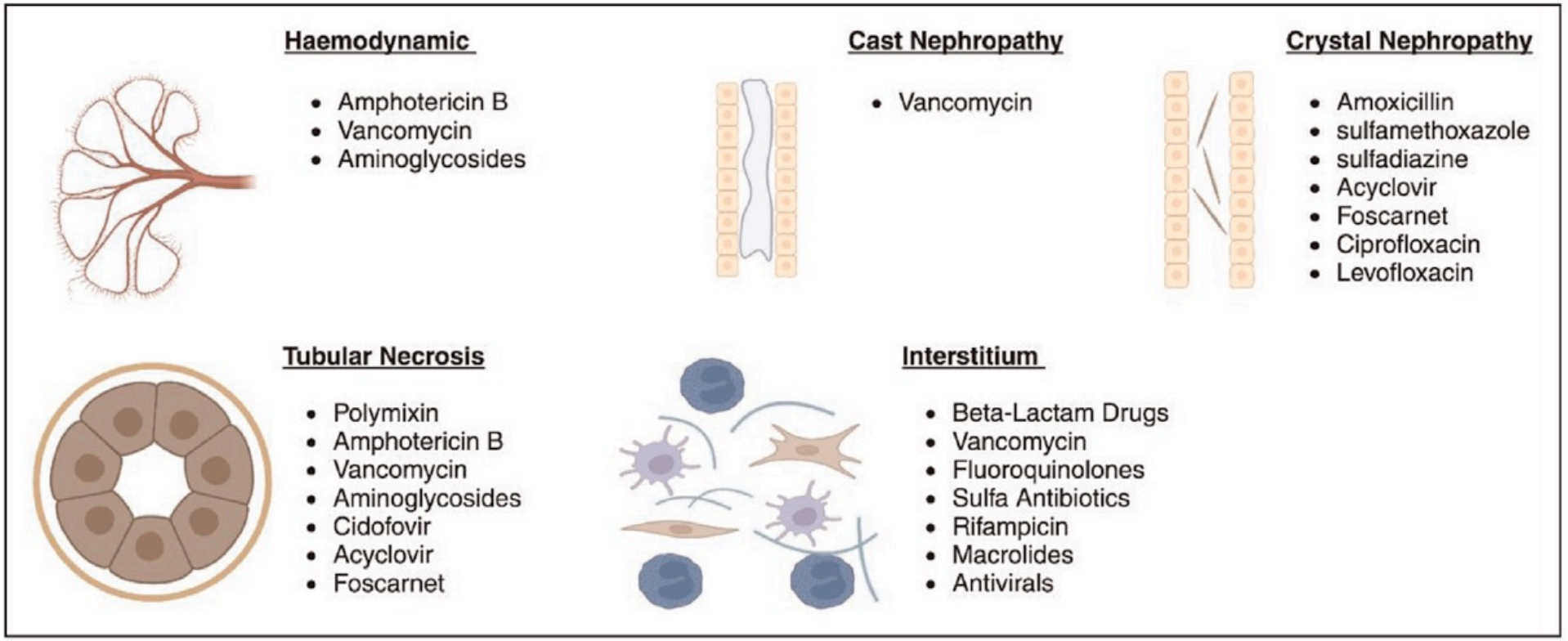
Cleveland Clinic Journal of Medicine

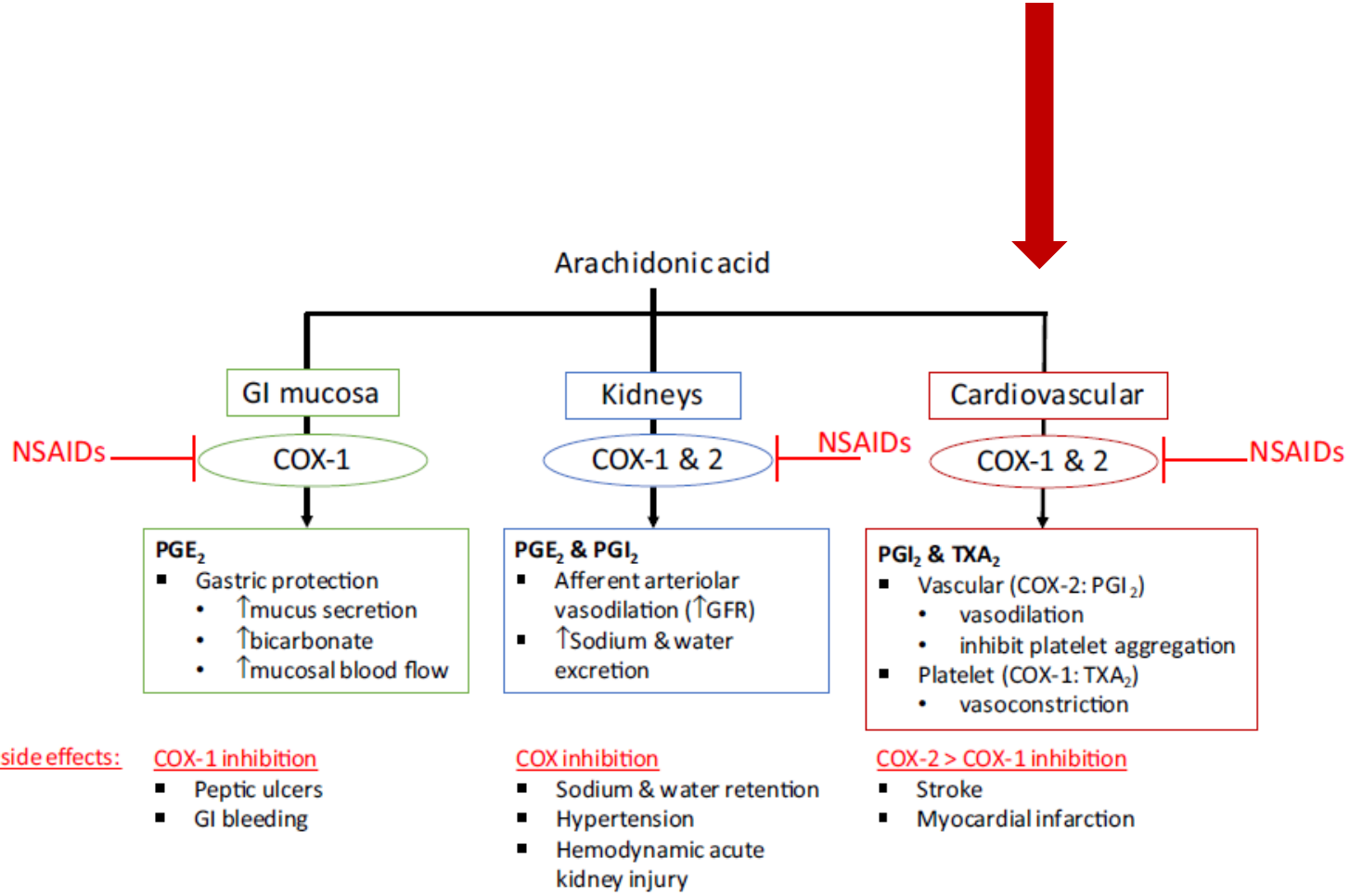

Mechanisms of Renin Release
Juxtaglomerular (JG) cells
Macula densa
Afferent arteriole
Efferent arteriole
NaCl
NaCl
NaCl
NaCl
F. Netter M.D.
JOHN A. CRAIG M.D.
C. Machado M.D.
© ICON
Baroreceptor mechanism:
Increased pressure in afferent arteriole inhibits renin release from JG cells (red arrows); decreased pressure promotes renin release (green arrows)
Sympathetic nerve mechanism:
β1-Adrenergic nerves stimulate renin release (green arrows)
Macula densa mechanism:
Increased NaCl in distal nephron inhibits renin release (red arrows); decreased load promotes renin release

Summarization of main renal pathomechanisms associated with NSAIDs usage



Some antimicrobials and their major pathophysiological mechanisms leading to drug-induced kidney injury




Arachidonic acid
GI mucosa
Kidneys
Cardiovascular
NSAIDs
COX-1
COX-1 & 2
NSAIDs
COX-1 & 2
NSAIDs
PGE2
Gastric protection
↑mucus secretion
↑bicarbonate
↑mucosal blood flow
PGE2 & PGI2
Afferent arteriolar vasodilation (↑GFR)
↑Sodium & water excretion
PGI2 & TXA2
Vascular (COX-2: PGI2)
vasodilation
inhibit platelet aggregation
Platelet (COX-1: TXA2)
vasoconstriction
NSAID side effects:
COX-1 inhibition
Peptic ulcers
GI bleeding
COX inhibition
Sodium & water retention
Hypertension
Hemodynamic acute kidney injury
COX-2 > COX-1 inhibition
Stroke
Myocardial infarction

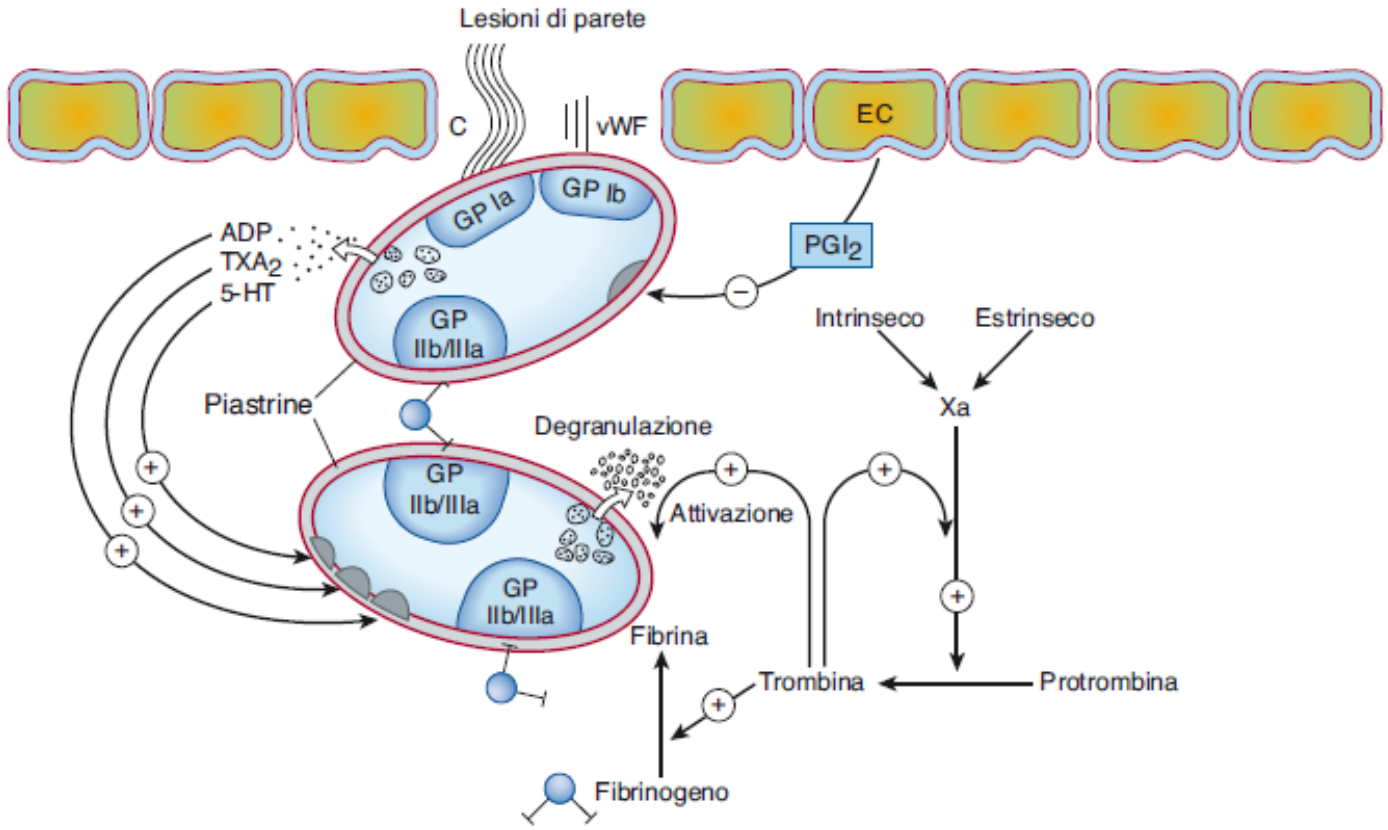
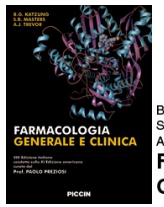
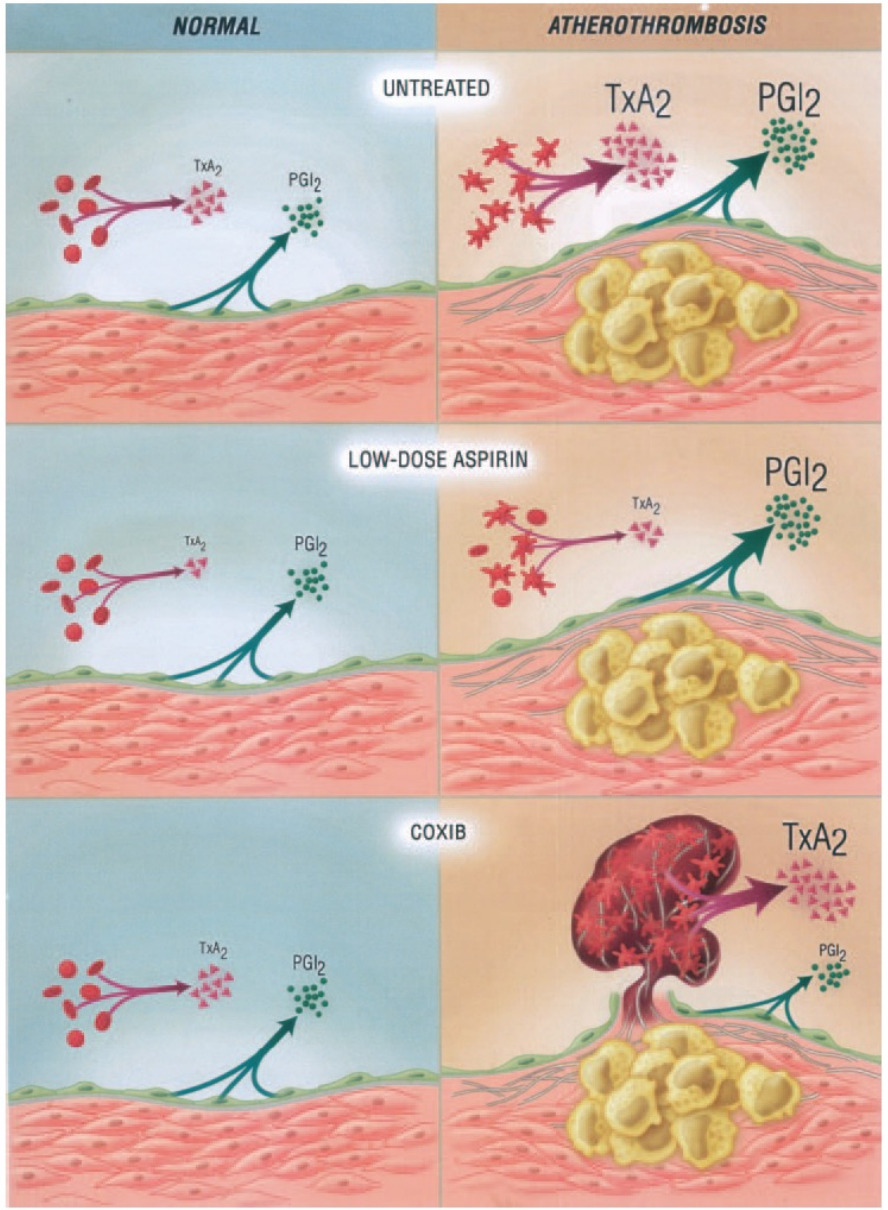


Figura 34-1. Formazione del trombo in sede di parete vasale danneggiata (EC, cellula endoteliale) e ruolo delle piastrine e dei fattori della coagulazione. Tra i recettori di membrana piastrinici vi sono il recettore glicoproteico (GP) Ia che lega il collageno (C), Ib che lega il fattore von Willebrand (vWF) e IIb/IIIa che lega il fibrinogeno ed altre macromolecole. La prostaciclina (PGI_2), ad azione antiaggregante piastrinica, viene rilasciata dall'endotelio. Tra le sostanze aggreganti rilasciate a seguito della degranulazione piastrinica vi sono l'ADP, il TXA_2 e la 5-HT. La formazione del fattore Xa è esemplificata nella fig. 34-2. (Ridisegnata e riprodotta, previo consenso, da Simoons ML, Decker JW: New directions in anticoagulant and antiplatelet treatment [Editorial], *Br Heart J* 1995; 74:337).



B.G.KATZUNG
S.B.MASTERS
A.J.TREVOR
FARMACOLOGIA GENERALE E CLINICA


NORMAL
ATHEROTHROMBOSIS
UNTREATED
TxA2
PGI2
LOW-DOSE ASPIRIN
COXIB

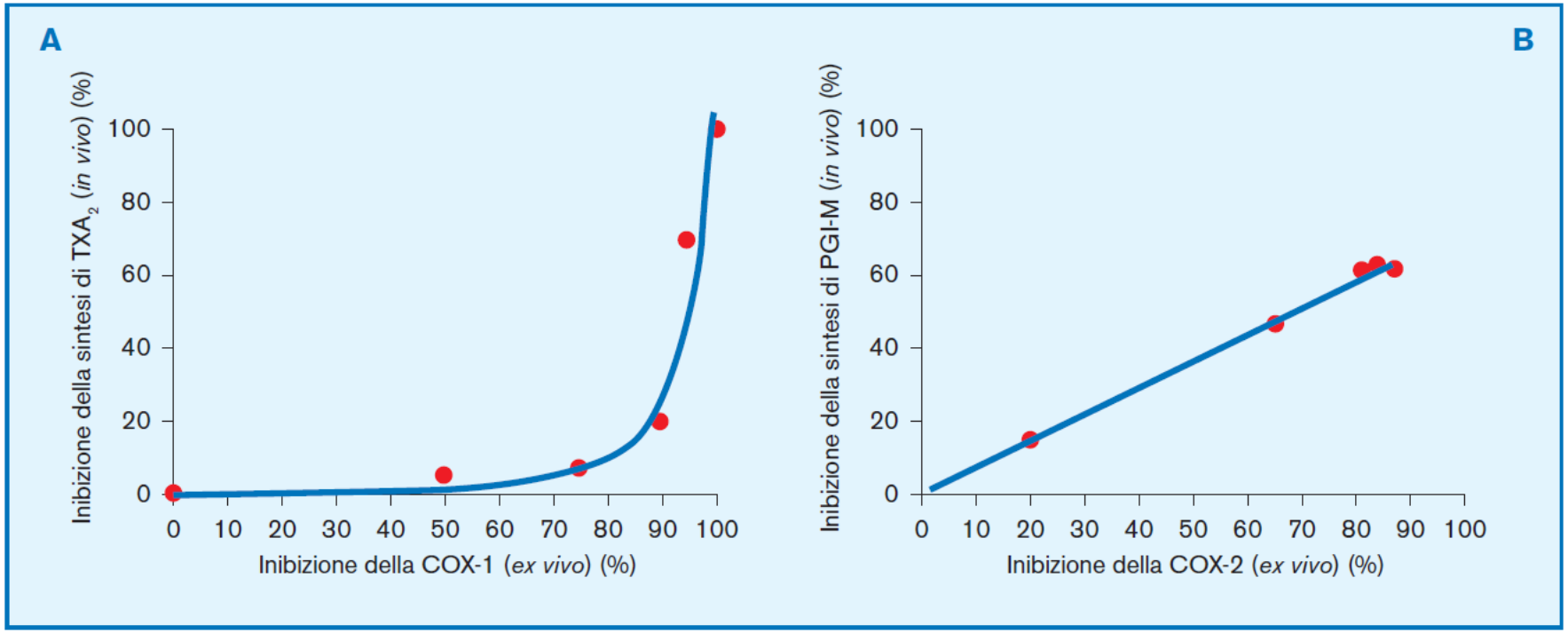
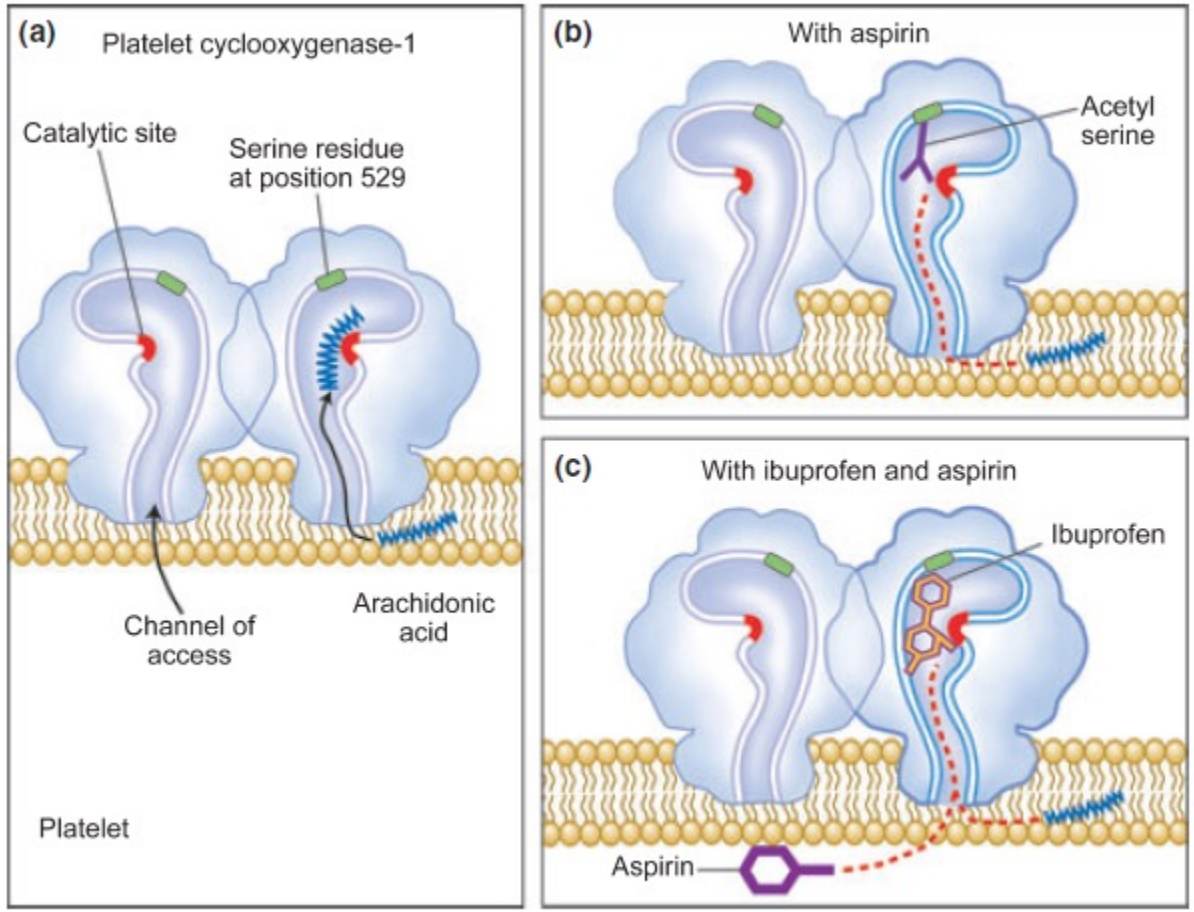
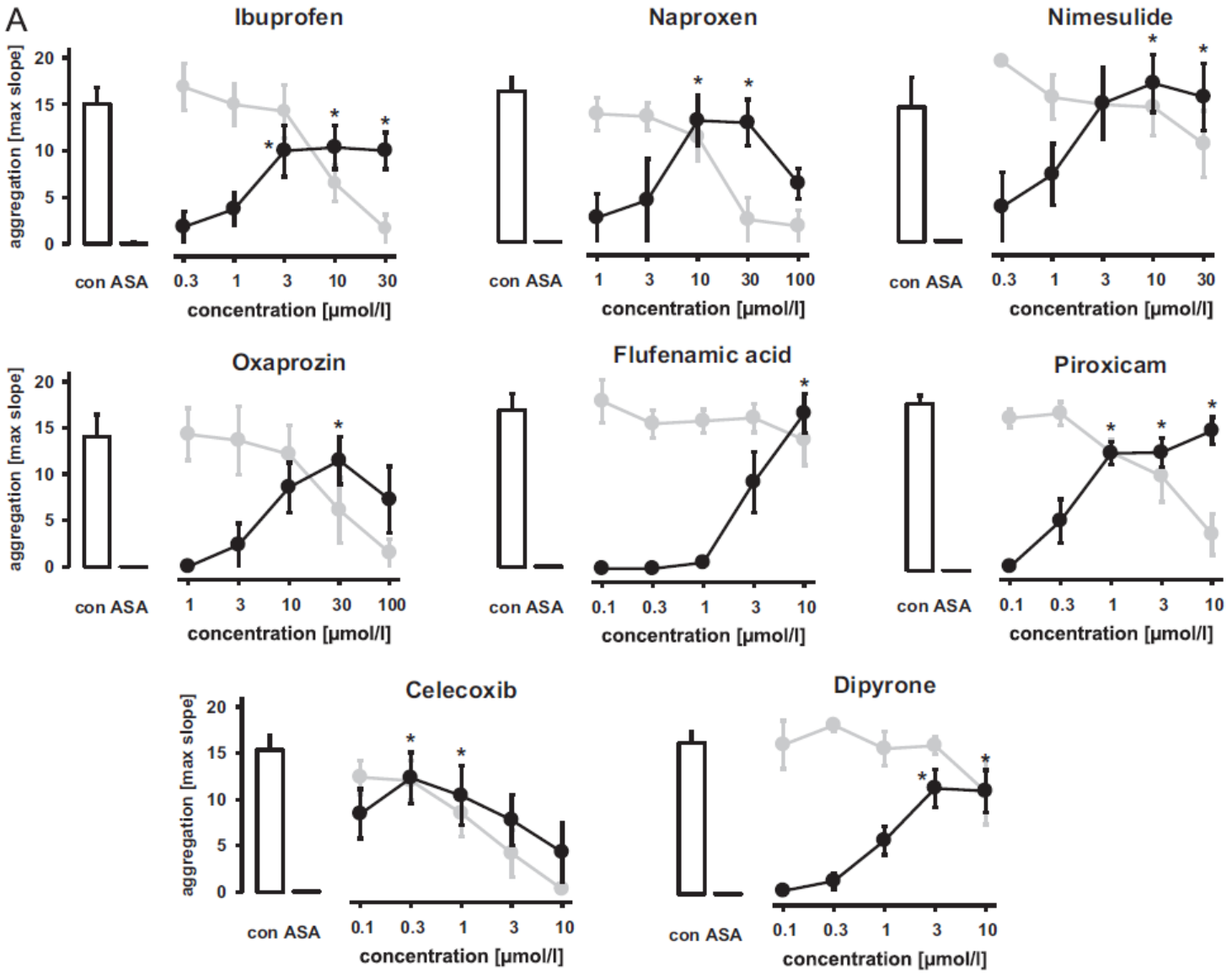
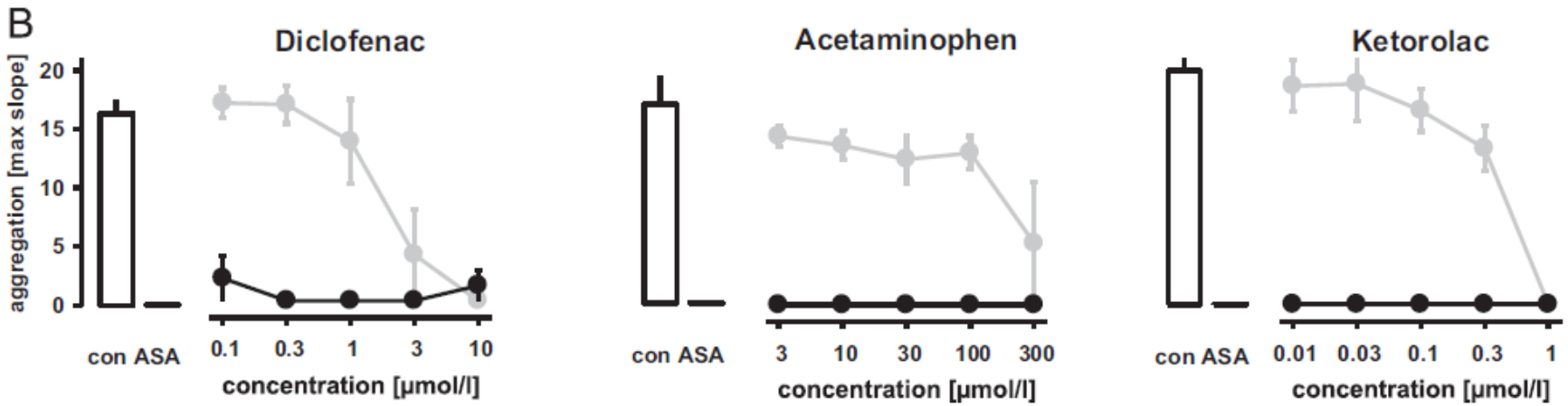
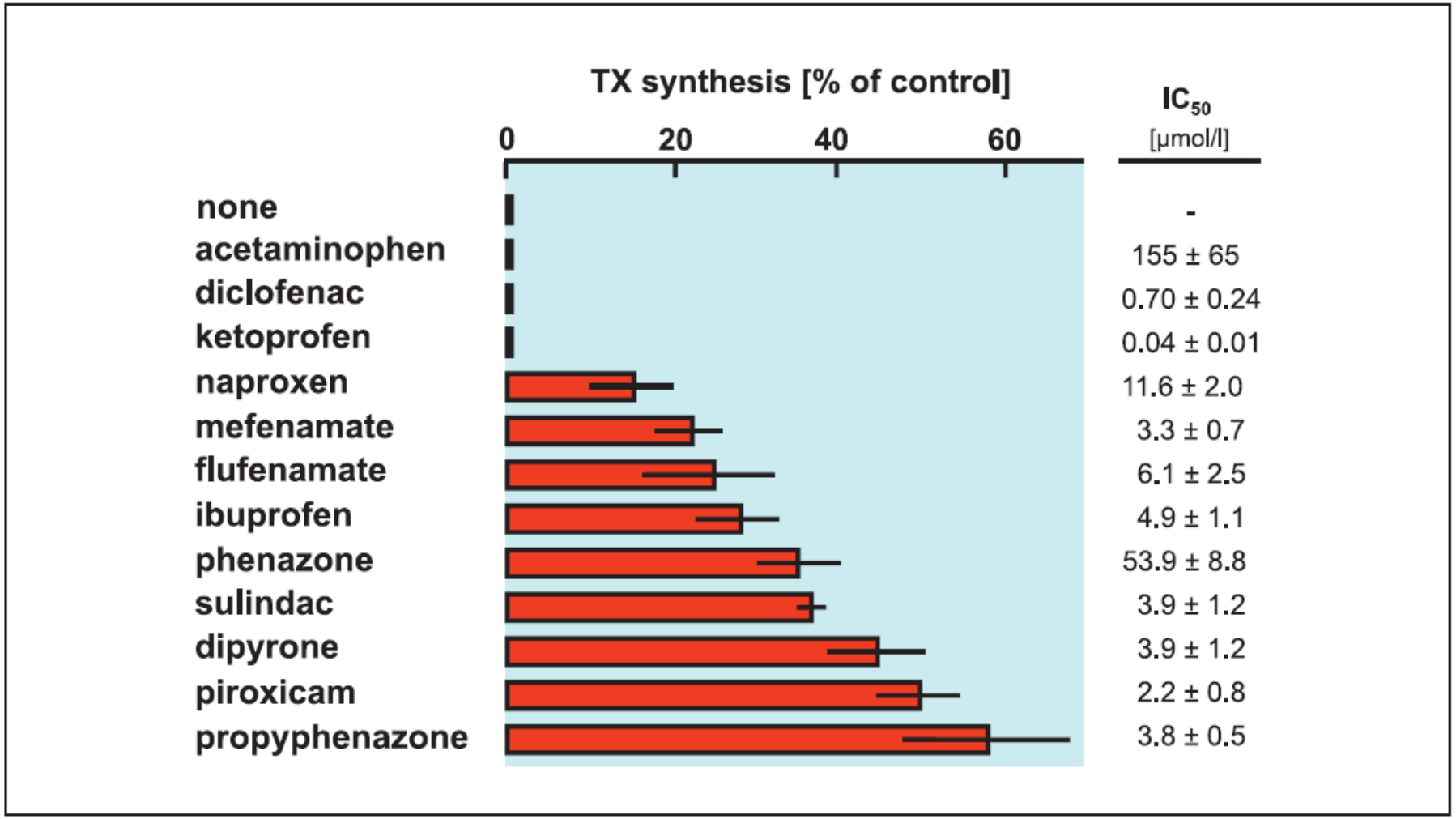


Figura 3. *Relazione tra la percentuale di inibizione delle COX-1 e delle COX-2 misurata su sangue intero e gli effetti anti-trombotici (**A**) e antinfiammatori (**B**) in vivo, misurati come inibizione della sintesi di tromboxano (TXA_2) e prostaciclina (PGI) (modificata da [8]). PGI-M, metabolita della prostaciclina*


(a)
Platelet cyclooxygenase-1
Catalytic site
Serine residue at position 529
Channel of access
Arachidonic acid
Platelet
(b)
With aspirin
Acetyl serine
(c)
With ibuprofen and aspirin
Ibuprofen
Aspirin


A
Ibuprofen
Naproxen
Nimesulide
Oxaprozin
Flufenamic acid
Piroxicam
Celecoxib
Dipyrone
aggregation [max slope]
con ASA
concentration [µmol/l]


B
Diclofenac
aggregation [max slope]
20
15
10
5
0
con ASA
0.1
0.3
1
3
10
concentration [µmol/l]
Acetaminophen
con ASA
3
10
30
100
300
concentration [µmol/l]
Ketorolac
con ASA
0.01
0.03
0.1
0.3
1
concentration [µmol/l]


TX synthesis [% of control]
0
20
40
60
IC50
[µmol/l]
none
-
acetaminophen
155 ± 65
diclofenac
0.70 ± 0.24
ketoprofen
0.04 ± 0.01
naproxen
11.6 ± 2.0
mefenamate
3.3 ± 0.7
flufenamate
6.1 ± 2.5
ibuprofen
4.9 ± 1.1
phenazone
53.9 ± 8.8
sulindac
3.9 ± 1.2
dipyrone
3.9 ± 1.2
piroxicam
2.2 ± 0.8
propyphenazone
3.8 ± 0.5

ORIGINAL WORK

History of Nonsteroidal Anti-inflammatory Drug Use and Functional Outcomes After Spontaneous Intracerebral Hemorrhage

Natasha Ironside[1,2*], Ching-Jen Chen[1], Victoria Dreyer[2], Dale Ding[3], Thomas J. Buell[1] and Edward Sander Connolly[1]

Conclusions: History of nonselective COX inhibition may affect functional outcomes in ICH patients. Pre-admission NSAID use did not appear to worsen the severity of presenting ICH or increase the risk of recurrent ICH. Additional clinical studies may be warranted to investigate the effects of pre-admission NSAID use on ICH outcomes.

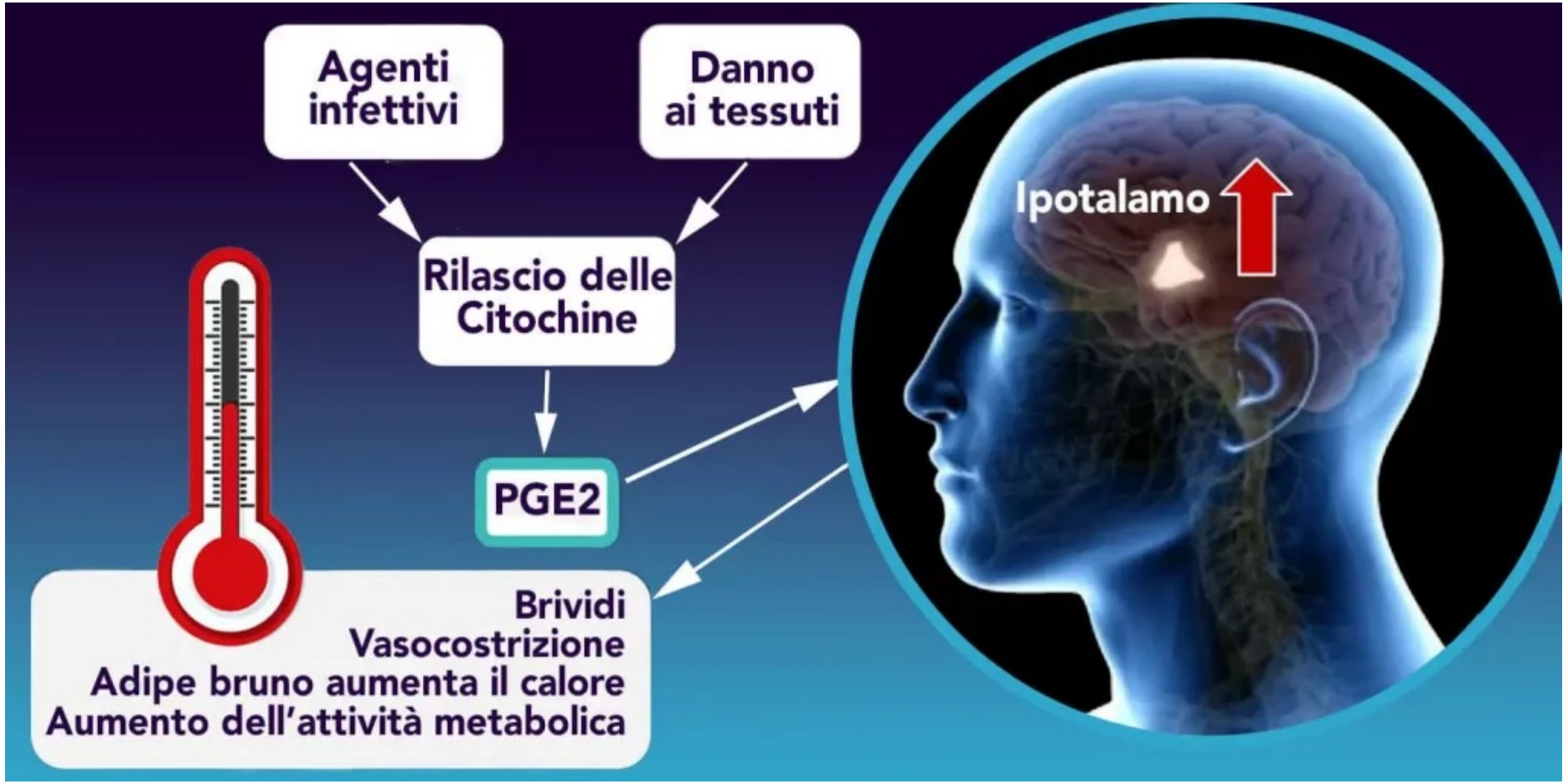
ORIGINAL ARTICLE

BJCP BRITISH PHARMACOLOGICAL SOCIETY

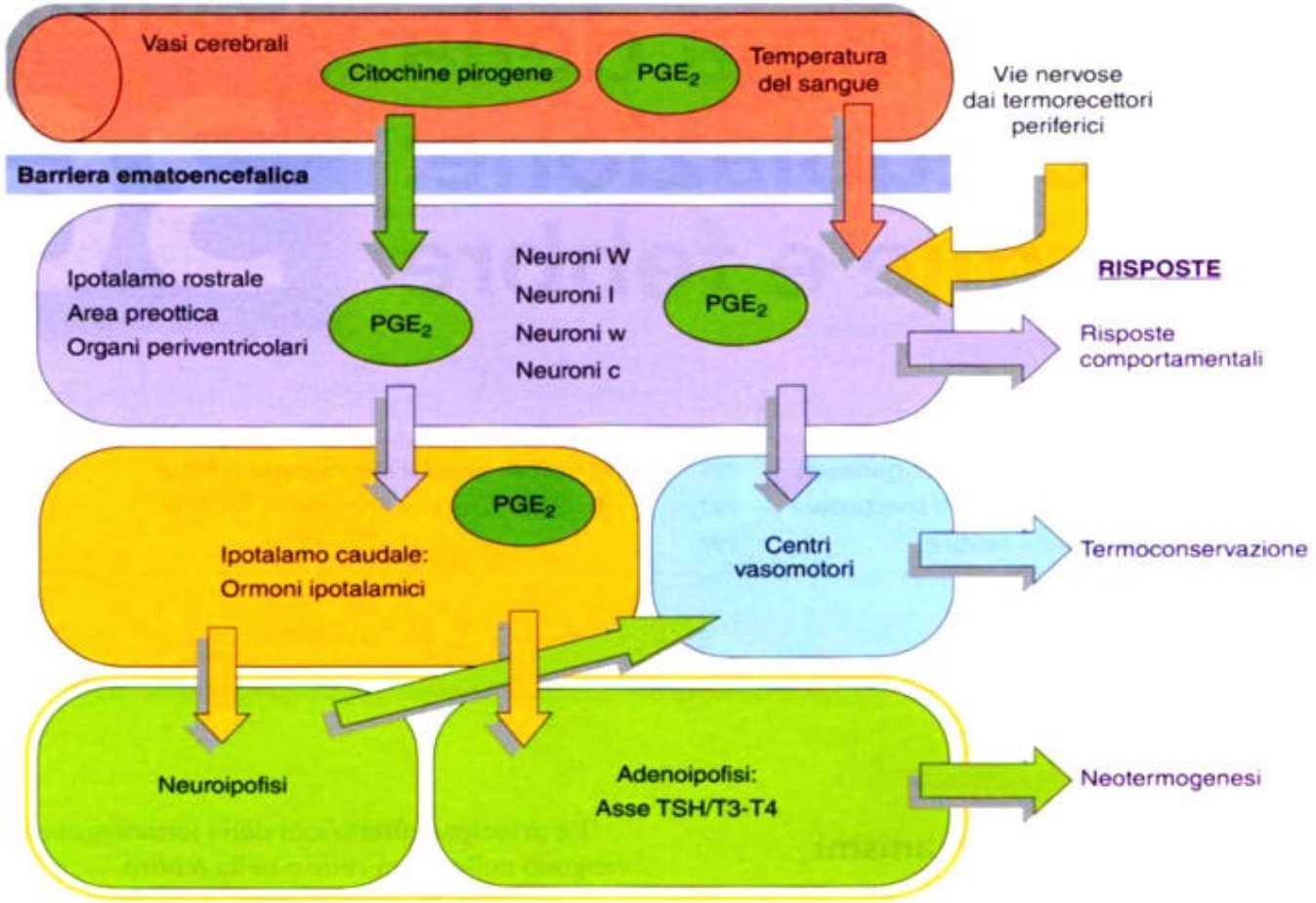
Does coprescribing nonsteroidal anti-inflammatory drugs and oral anticoagulants increase the risk of major bleeding, stroke and systemic embolism?

Leonie S. Penner[1,2] | Sean P. Gavan[1] | Darren M. Ashcroft[2,3] | Niels Peek[2,4] | Rachel A. Elliott[1]

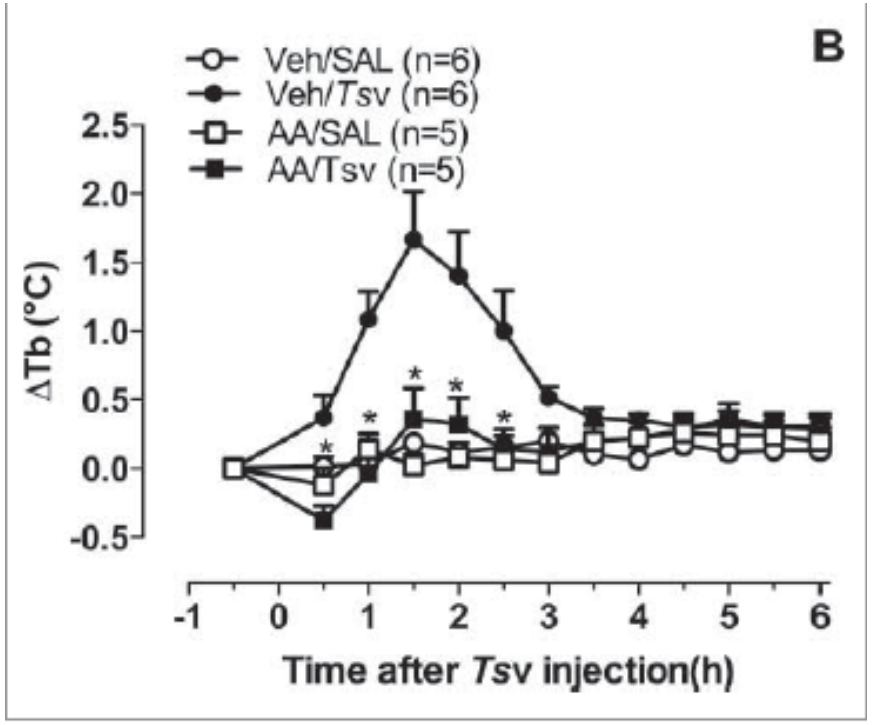
Conclusion: When OACs are coprescribed with NSAIDs, the risk of adverse bleeding events increases and, simultaneously, the protective effect of OACs to prevent strokes reduces. There is a need for interventions that reduce hazardous prescribing of NSAIDs in people receiving OAC therapy.


Agenti infettivi
Danno ai tessuti
Rilascio delle Citochine
PGE2
Brividi
Vasocostrizione
Adipe bruno aumenta il calore
Aumento dell'attività metabolica
Ipotalamo

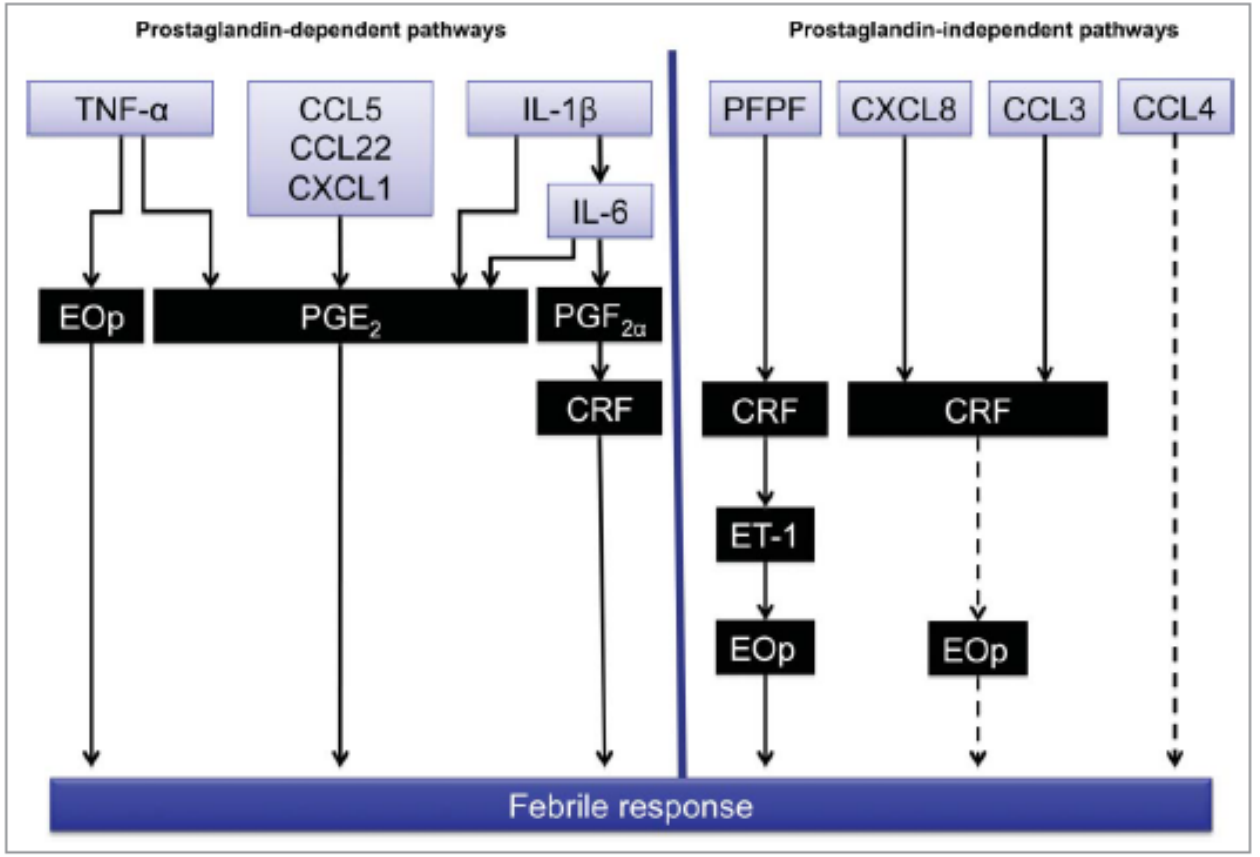
Patogenesi della febbre

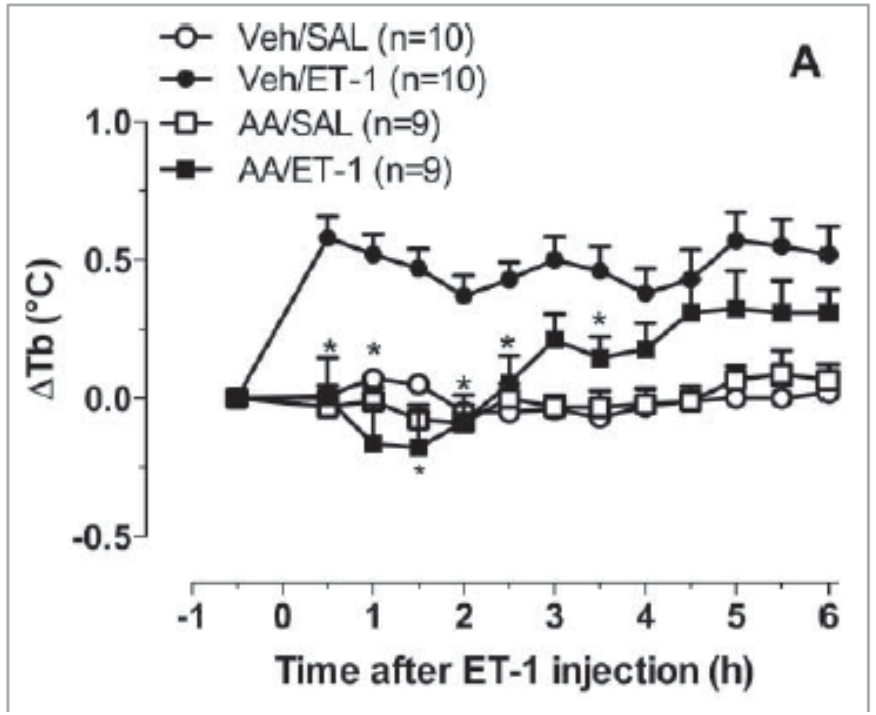


TITYUS SERRATULUS



Temperature 2:4, 506--521; October/November/December 2015


Prostaglandin-dependent pathways
Prostaglandin-independent pathways
TNF-α
CCL5
CCL22
CXCL1
IL-1β
IL-6
PFPF
CXCL8
CCL3
CCL4
EOp
PGE2
PGF2α
CRF
CRF
CRF
ET-1
EOp
EOp
Febrile response


Veh/SAL (n=10)
Veh/ET-1 (n=10)
AA/SAL (n=9)
AA/ET-1 (n=9)
A
1.0
0.5
0.0
-0.5
ΔTb (°C)
-1
0
1
2
3
4
5
6
Time after ET-1 injection (h)

Grazie per l'attenzione